Dewhurst's Textbook of Obstetrics & Gynaecology

Dedication

This book is dedicated to our families and their unerring support.

Dewhurst's Textbook of Obstetrics & Gynaecology

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Contents

Colour plate section can be found facing pages 524 and 525.

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Preface to the Ninth Edition

After 45 years in publication, this text continues to provide postgraduate students of obstetrics and gynaecology with the basic knowledge they need to progress in the specialty and also reference for established practitioners who will always feel the need to enhance their knowledge. Although the field is now populated with many sub-specialists, and individual areas of study advance independently, there continues to be the need for coordinating knowledge so every aspect can be considered in the overall context of the specialty. It is the continuing philosophy of this book to try to adhere to an integrated approach, which helps to deliver the highest possible care to patients.

This ninth edition has two new co-editors, Christoph Lees and Tom Bourne, and this was deemed necessary in the light of diverse sub-specialist knowledge, which needs to be edited in a way that balances basic knowledge with up-to-date advances. Since the last edition, there have been a number of obstetric breakthroughs but we still strive to improve outcomes for women and their babies. Maternal and perinatal mortality remain somewhat unchanged in the Western world but, thankfully, there are improvements in developing countries, which are to be encouraged. However, there is still a very long way to go to achieve the Millennium Goals and we hope that this edition can contribute to these aims.

The ninth edition has been restructured to reflect the reality of clinical practice and we are indebted to the authors who have contributed to this book. We offer our thanks and gratitude for all their efforts. We hope that we have produced a textbook for current obstetricians and gynaecologists, which will help them on their way to making a significant contribution to women's health.

Finally, we would like to thank the editorial staff at Wiley for all their support and help, particularly Mirjana Misina.

Keith Edmonds
Christoph Lees
Tom Bourne

Preface to the First Edition

Our purpose in writing this book has been to produce a comprehensive account of what the specialist in training in obstetrics and gynaecology must know. Unfortunately for him, he must now know a great deal, not only about his own subject, but about certain aspects of closely allied specialties such as endocrinology, biochemistry, cytogenetics, psychiatry, etc. Accordingly we have tried to offer the postgraduate student not only an advanced textbook in obstetrics and gynaecology but one which integrates the relevant aspects of other subjects which nowadays impinge more and more on the clinical field.

To achieve this aim within, we hope, a reasonable compass we have assumed some basic knowledge which the reader will have assimilated throughout his medical training, and we have taken matters on from there. Fundamental facts not in question are stated as briefly as is compatible with accuracy and clarity, and discussion is then devoted to more advanced aspects. We acknowledge that it is not possible even in this way to provide all the detail some readers may wish, so an appropriate bibliography is provided with each chapter. Wherever possible we have tried to give a positive opinion and our reasons for holding it, but to discuss nonetheless other important views; this we believe to be more helpful than a complete account of all possible opinions which may be held. We have chosen moreover to lay emphasis on fundamental aspects of the natural and the disease processes which are discussed; we believe concentration on these basic physiological and pathological features to be important to the proper training of a specialist. Clinical matters are, of course, dealt with in detail too, whenever theoretical discussion of them is rewarding. There are, however, some clinical aspects which cannot, at specialist level, be considered in theory with real benefit; examples of these are how to palpate a pregnant woman's abdomen and how to apply obstetric forceps. In general these matters are considered very briefly or perhaps not at all; this is not a book on *how* things are done, but on how correct treatment is chosen, what advantages one choice has over another, what complications are to be expected, etc. Practical matters, we believe, are better learnt in practice and with occasional reference to specialized textbooks devoted solely to them.

A word may be helpful about the manner in which the book is set out. We would willingly have followed the advice given to Alice when about to testify at the trial of the Knave of Hearts in Wonderland, 'Begin at the beginning, keep on until you come to the end and then stop'. But this advice is difficult to follow when attempting to find the beginning of complex subjects such as those to which this book is devoted. Does the beginning lie with fertilization; or with the events which lead up to it; or with the genital organs upon the correct function of which any pregnancy must depend; or does it lie somewhere else? And which direction must we follow then? The disorders of reproduction do not lie in a separate compartment from genital tract disease, but each is clearly associated with the other for at least part of a woman's life. Although we have attempted to integrate obstetrics with gynaecology and with their associated specialties, some separation is essential in writing about them, and the plan we have followed is broadly this – we begin with the female child *in utero*, follow her through childhood to puberty, through adolescence to maturity, through pregnancy to motherhood, through her reproductive years to the climacteric and into old age. Some events have had to be taken out of order, however, although reiteration has been avoided by indicating to the reader where in the book are to be found other sections dealing with different aspects of any subject under consideration. We hope that our efforts will provide a coherent, integrated account of the field we have attempted to cover which will be to the satisfaction of our readers.

Sir John Dewhurst
1972

Section 1

Obstetrics

Part 1

Basic Science

1

Maternal Physiology

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The physiological changes of pregnancy are strongly proactive, not reactive, with the luteal phase of every ovulatory menstrual cycle 'rehearsing' for pregnancy. Most pregnancy-driven changes are qualitatively in place by the end of the first trimester, only maturing in magnitude thereafter [1]. This chapter gives a brief overview of the major changes.

Maternal response to pregnancy

Normal pregnancy evokes a systemic inflammatory response, which includes the endothelium [2]. This may explain the greater risk of cardiovascular disease in later life of parous women in comparison with nulliparous women. Markers of oxidative 'stress' rise progressively throughout the first and second trimesters, but plasma concentrations of some endogenous antioxidants, such as superoxide dismutase, rise in parallel. The free radical superoxide is generated through a variety of pathways, including placental ones, but is more damaging when converted to the peroxide radical, a reaction catalysed by free iron in the plasma. Increasing concern is being expressed about over-supplementation with iron, especially in conjunction with vitamin C (which increases absorption) in pregnant women without evidence of iron deficiency and several studies have shown evidence of increased oxidative stress in such women [3]. Conversely, the low dietary selenium intake in women in the UK may predispose to lower activity of the antioxidant glutathione peroxidase and thioredoxin systems in pregnancy.

Immunology

Only two types of fetal tissue come into direct contact with maternal tissues: the villous trophoblast and the extravillous trophoblast. Villous trophoblast, which is a continuous syncytium, is bathed in maternal blood but seems to be immunologically inert and never expresses HLA class I or class II molecules. Extravillous trophoblast is directly in contact with maternal endometrial/decidual tissues and does not express the major T-cell ligands, HLA-A or HLA-B; the HLA class I molecules which are expressed are the trophoblast-specific HLA-G and HLA-C and HLA-E. The decidual uterine natural killer (NK) cells, the main type of decidual lymphocyte, differ from those in the systemic circulation. They express surface killer immunoglobulin-like receptors (KIRs), which bind to HLA-C and HLA-G on trophoblast. HLA-E and HLA-G are effectively monomorphic, but HLA-C is polymorphic, with two main groups, HLA-C1 and HLA-C2. The KIRs are very highly polymorphic, but again fall into two main classes, KIR-A (non-activating) and KIR-B (multiply activating). Thus the very polymorphic KIR in maternal tissues and the polymorphic HLA-C in the fetus make up a potentially very variable receptor–ligand system.

The effect of this on implantation has been inferred from indirect evidence. Both recurrent miscarriage and pre-eclampsia are associated with poor trophoblast invasion. The maternal KIR genotype may be AA, AB or BB. Since the identifiable trophoblast HLA-C allotypes are HLA-C1 and HLA-C2, there are nine possible combinations. It has been shown that if the maternal KIR haplotype is AA, and the trophoblast expresses any HLA-C2, then the possibility of miscarriage or pre-eclampsia is significantly increased. However, even one KIR-B provides protection [4]. HLA-C2 is highly inhibitory to trophoblast migration, and thus appears to need 'activating KIR' to overcome it.

NK cells appear and disappear in the endometrial decidua every ovulatory menstrual cycle, and the populations are maintained should conception occur. When progesterone is at its peak, they associate with the spiral arteries and uterine glands. Human data are limited, and animal studies of immunological phenomena must be

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viewed with especial caution in pregnancy, so the precise role of NK cells is not yet known. However, timed human endometrial sampling at 8–10 weeks' gestation has shown them to be major producers of a variety of angiogenic factors, expressing transcripts of *VEGFC* (vascular endothelial growth factor C), *PlGF* (placental growth factor) and *ANG2* (angiopoietin 2). This has ceased by 12–14 weeks. It has been suggested that NK cells are essential for spiral artery remodelling (for a review see Zhang *et al.* [5]).

The uterus

The first-trimester human embryo appears to gain nutrients histiotrophically, from the endometrial glands. These glandular secretions are rich in carbohydrates, lipids and growth factors and can well support early growth while the conceptus is small [6]. The inner third of the myometrium, as well as the endometrium, is anatomically changed by pregnancy, and once a pregnancy has gone beyond the first trimester, these changes appear to be irreversible. The most striking change is in the spiral arteries, which undergo extensive remodelling. Extravillous trophoblast attacks these vessels as interstitial cells within the stroma, and as endovascular cells within the vascular lumen. In normal pregnancy, the summed effects are the conversion of these vessels into floppy thin-walled vessels, more closely resembling veins than arteries, that do not respond to vasoconstrictor stimuli, so allowing the maximum flow to reach the placenta. This remodelling is only completed in the early second trimester, but is impaired in both pre-eclampsia and normotensive intrauterine growth restriction.

The uterus must be maintained in quiescence until labour is initiated. The mechanisms responsible for this have not been fully elucidated, although progesterone plays a central role, but include locally generated nitric oxide, probably acting through cyclic GMP or voltage-gated potassium channels such as Kv7 and Kv11, while a number of hormones such as brain natriuretic peptide, prostacyclin, prostaglandin (PG)E_2 and calcitonin gene-related peptide act through G_s receptors, and are relaxatory.

The cardiovascular system

There is much less information about the normal functioning of the cardiovascular system in young women than in young men, partly because they have been perceived as being 'more difficult' to study as a result of the monthly ovulatory cycle. However, an increasing number of studies have been initiated prior to conception and continuing thereafter. These are very demanding, but also extremely valuable. Such studies also underline the inherent errors in using data obtained at the first antenatal clinic visit, often late in the first trimester, as true baseline.

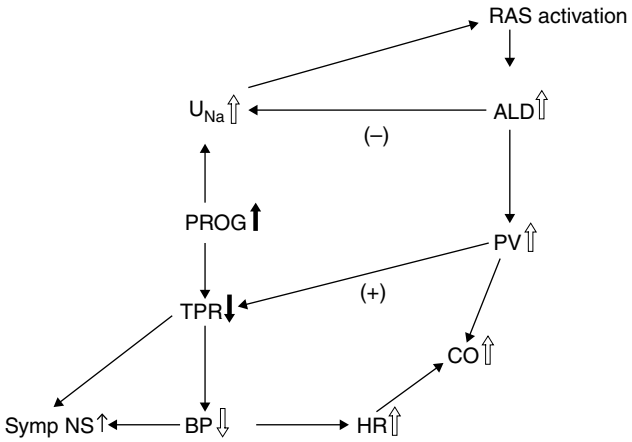

Fig. 1.1 Flow chart of the probable sequence of initial cardiovascular activation. ALD, aldosterone; BP, systemic arterial blood pressure; CO, cardiac output; HR, heart rate; PROG, progesterone; PV, plasma volume; RAS, renin–angiotensin system; Symp NS, sympathetic nervous system; TPR, total peripheral resistance; U_{Na}, urinary sodium excretion.

There is a significant fall in total peripheral resistance by 6 weeks' gestation to a nadir of about 40% by mid-gestation, resulting in a fall in afterload. This is 'perceived' as circulatory underfilling, which activates the renin–angiotensin–aldosterone system and allows the necessary expansion of plasma volume (PV) (Fig. 1.1) [7,8]. By the late third trimester, the PV has increased from its baseline by about 50% in a first pregnancy and 60% in a second or subsequent pregnancy. The bigger the expansion, the bigger, on average, the birthweight of the baby. The total extracellular fluid volume rises by about 16% by term, so the percentage rise in PV is disproportionate to the whole. The plasma osmolality falls by about 10 mosmol/kg as water is retained.

The heart rate rises synchronously, by 10–15 bpm, so the cardiac output begins to rise [9]. There is probably a fall in baroreflex sensitivity as pregnancy progresses, and heart rate variability falls. Stroke volume rises a little later in the first trimester. These two factors push the cardiac output up by 35–40% in a first pregnancy, and by about 50% in later pregnancies; it can rise by a further third in labour (Fig. 1.2). Table 1.1 summarizes the percentage changes in some cardiovascular variables during pregnancy [9].

Measuring brachial systemic arterial blood pressure in pregnancy is notoriously difficult, but there is now broad consensus that Korotkoff 5 should be used with auscultatory techniques [10]. However measured, there is a small fall in systolic, and a greater fall in diastolic, blood

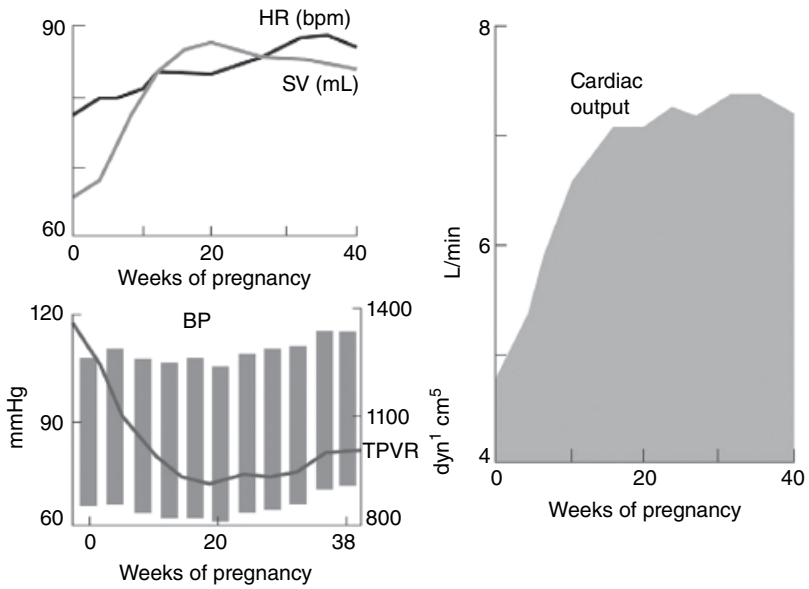

Fig. 1.2 Major haemodynamic changes associated with normal human pregnancy. The marked augmentation of cardiac output results from asynchronous increases in both heart rate (HR) and stroke volume (SV). Despite the increases in cardiac output, blood pressure (BP) decreases for most of pregnancy. This implies a very substantial reduction in total peripheral vascular resistance (TPVR).

Table 1.1 Percentage changes in some cardiovascular variables during pregnancy.

	First trimester	Second trimester	Third trimester
Heart rate (bpm)	+11	+13	+16
Stroke volume (mL)	+31	+29	+27
Cardiac output (L/min)	+45	+47	+48
Systolic blood pressure (mmHg)	−1	−1	+6
Diastolic blood pressure (mmHg)	−6	−3	+7
MPAP (mmHg)	+5	+5	+5
Total peripheral resistance (resistance units)	−27	−27	−29

MPAP, mean pulmonary artery pressure. Data are derived from studies in which pre-conception values were determined. The mean values shown are those at the end of each trimester and are thus not necessarily the maxima. Note that most changes are near maximal by the end of the first trimester.

pressure, initiated during the luteal phase, being mainly complete by 6–7 weeks' gestation, but continuing more slowlyto the late second trimester, resulting in an increased pulse pressure. The blood pressure then rises steadily, in parallel with an increase in peripheral sympathetic activity, and even in normotensive women there may be some late overshoot of non-pregnant values. Supine hypotension occurs in about 8% of women in late gestation as the uterus falls back onto the inferior vena cava, reducing venous return.

There is increasing interest in large artery function, measured as aortic pulse wave velocity (aPWV), and wave reflections, measured as the augmentation index (AIx). The central blood pressure can be estimated non-invasively, and has been suggested to be superior to the brachial blood pressure in predicting future adverse cardiovascular events outside pregnancy. Central blood pressure falls significantly more during the first 6 weeks of pregnancy than brachial blood pressure, but also reaches a nadir in the late second trimester. The AIx, adjusted for heart rate, falls significantly by 6–7 weeks' gestation, again reaching a nadir in the late second trimester; the aPWV, adjusted for mean blood pressure, does not change significantly [11].

The pressor response to angiotensin II is reduced in normal pregnancy but is unchanged to noradrenaline. The reduced sensitivity to angiotensin II presumably protects against the potentially pressor levels of angiotensin II found in normal pregnancy and is associated with lower receptor density; plasma noradrenaline is not increased in normal pregnancy. Pregnancy does not alter the response of intramyometrial arteries to a variety of vasoconstrictors. Nitric oxide may modulate myogenic tone and flow-mediated responses in the resistance vasculature of the uterine circulation in normal pregnancy.

The venous pressure in the lower circulation rises, for both mechanical and hydrodynamic reasons. The pulmonary circulation is able to absorb high rates of flow without an increase in pressure so pressure in the right ventricle, and the pulmonary arteries and capillaries, does not change. Pulmonary resistance falls in early pregnancy, and does not change thereafter. There is progressive venodilatation and rises in venous distensibility and capacitance throughout a normal pregnancy, possibly because of increased local nitric oxide synthesis.

The respiratory system

Tidal volume rises by about 30% in early pregnancy to 40–50% above non-pregnant values by term, with a fall in expiratory reserve and residual volume (Fig. 1.3) [12]. Neither forced expiratory volume in 1 s (FEV_1) nor peak expiratory flow rate are affected by pregnancy, even in women with asthma. The rise in tidal volume is largely driven by progesterone, which appears to decrease the threshold and increase the sensitivity of the medulla oblongata to carbon dioxide. Respiratory rate does not change, so the minute ventilation rises by a similar amount. This over-breathing begins in every luteal phase; the PCO_2 is lowest in early gestation. Progesterone also increases erythrocyte carbonic anhydrase concentration, which will also lower PCO_2. Carbon dioxide production rises sharply during the third trimester, as fetal metabolism increases. The fall in maternal PCO_2 allows more efficient placental transfer of carbon dioxide from the fetus, which has a PCO_2 of around 55 mmHg (7.3 kPa). The fall in PCO_2, together with an increased renal excretion of bicarbonate, results in a fall in plasma bicarbonate concentration (to about 18–22 mmol/L compared with the non-pregnant range of 24–28 mmol/L), which contributes to the fall in plasma osmolality and reduces buffering capacity. The peripheral venous pH rises slightly (Table 1.2 and Fig. 1.4).

The increased alveolar ventilation results in a much smaller proportional rise in PO_2 from about 96.7 to 101.8 mmHg (12.9–13.6 kPa). This increase is offset by the rightward shift of the maternal oxyhaemoglobin dissociation curve caused by an increase in 2,3-diphosphoglycerate (2,3-DPG) in the erythrocytes and the lower plasma bicarbonate concentration. This facilitates oxygen unloading to the fetus, which has both a much lower PO_2 (25–30 mmHg, 3.3–4.0 kPa) and a marked leftward shift of the oxyhaemoglobin dissociation curve, due to the lower sensitivity of fetal haemoglobin to 2,3-DPG.

There is an increase of about 16% in oxygen consumption by term due to increasing maternal and fetal demands. Since the increase in oxygen-carrying capacity

Table 1.2 The influence of pregnancy on some respiratory variables.

	Non-pregnant	Pregnant – term
PO_2 (mmHg)	93 (12.5 kPa)	102 (13.6 kPa)
O_2 consumption (mL/min)	200	250
PCO_2 (mmHg)	35–40 (4.7–5.3 kPa)	30 (4.0 kPa)
Venous pH	7.35	7.38

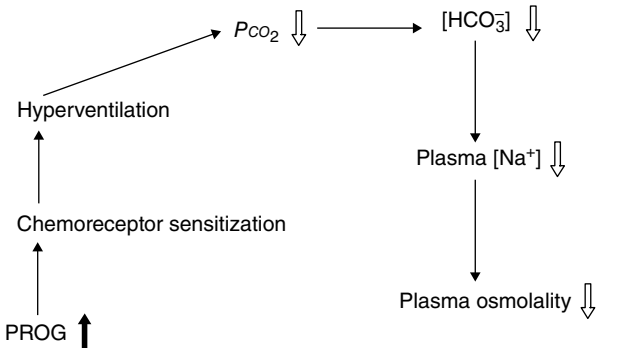

Fig. 1.4 Flow chart of the effects of over-breathing in pregnancy. HCO_3^-, bicarbonate; Na^+, sodium; PCO_2, carbon dioxide tension; PROG, progesterone.

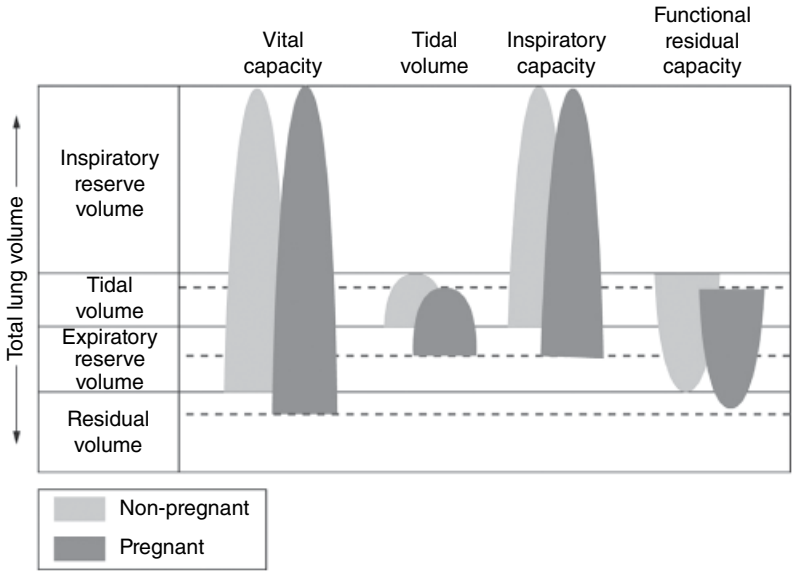

Fig. 1.3 Alterations in lung volumes associated with normal human pregnancy. In general terms, inspiratory reserve and tidal volumes increase at the expense of expiratory reserve and residual volumes.

Table 1.3 Although the increases in resting cardiac output and minute ventilation are of the same order of magnitude in pregnancy, there is less spare capacity for increases in cardiac output on moderate exercise than for increases in respiration.

	Resting	Exercise
Cardiac output	+33% (4.5–6 L/min)	+167% (up to 12 L/min)
Minute ventilation	+40% (7.5–10.5 L/min)	+1000% (up to ~ 80 L/min)

of the blood (see section Haematology) is about 18%, there is actually a fall in arteriovenous oxygen difference. Pulmonary blood flow, of course, rises in parallel with cardiac output and enhances gas transfer.

Pregnancy places greater demands on the cardiovascular than the respiratory system [13]. This is shown in the response to moderate exercise (Table 1.3).

Haematology

The circulating red cell mass rises by 20–30% during pregnancy, with increases in both cell number and size. It rises more in women with multiple pregnancies, and substantially more with iron supplementation (~29% compared with 17%). Serum iron concentration falls, the absorption of iron from the gut rises and iron-binding capacity rises in a normal pregnancy, since there is increased synthesis of the β_1-globulin transferrin. Nevertheless, 75% of diagnosed anaemia in pregnancy arises from iron deficiency. Plasma folate concentration halves by term, because of greater renal clearance, although red cell folate concentrations fall less. In the late 1990s, one-fifth of the female population aged 16–64 in the UK were estimated to have serum ferritin levels below 15 μg/L, indicative of low iron stores [14]; a similar proportion was reported in 2008 [15]. Pregnant adolescents seem to be at particular risk of iron deficiency. Even relatively mild maternal anaemia is associated with increased placental weight/birthweight ratios and decreased birthweight. However, inappropriate supplementation can itself be associated with pregnancy problems (see above) [16]. The National Institute for Health and Care Excellence (NICE) recommends that iron supplementation should be considered for women with haemoglobin concentrations below 110 g/L in the first trimester and 105 g/L at 28 weeks [17].

Erythropoietin rises in pregnancy, more so if iron supplementation is not taken (55% compared with 25%) but the changes in red cell mass antedate this; human placental lactogen may stimulate haematopoiesis.

Pro rata, the PV increases more than the red cell mass, which leads to a fall in the various concentration measures that incorporate the PV, such as the haematocrit, haemoglobin concentration and red cell count. The fall in packed cell volume from about 36% in early pregnancy to about 32% in the third trimester is a sign of normal PV expansion.

The total white cell count rises, mainly because of increased polymorphonuclear leucocytes. Neutrophil numbers rise with oestrogen concentrations and peak at about 33 weeks, stabilizing after that until labour and the early puerperium, when they rise sharply. Their phagocytic function increases during gestation. T and B lymphocyte counts do not change but their function is suppressed, making pregnant women more susceptible to viral infections, malaria and leprosy. The uterine NK cells express receptors that recognize the otherwise anomalous combination of human lymphocyte antigens (HLA-C, HLA-E and HLA-G) expressed by the invasive cytotrophoblasts. This is likely to be central to maternal recognition of the conceptus [18] (see above).

Platelet count and platelet volume are largely unchanged in most pregnant women, although their survival is reduced. Platelet reactivity is increased in the second and third trimesters and does not return to normal until about 12 weeks after delivery.

Coagulation

The changes in coagulation profile during pregnancy are most complex at the time of labour and delivery, with the urgent need to prevent life-threatening haemorrhage from the placental separation site, while avoiding excessive activation and thrombosis. Coagulation in pregnancy has recently been reviewed [19]. Continuing low-grade coagulopathy is a feature of normal pregnancy [20]. Several of the potent procoagulatory factors rise from at least the end of the first trimester [21] (Fig. 1.5). For example, factors VII, VIII and X all rise, and absolute plasma fibrinogen doubles, while antithrombin III, an inhibitor of coagulation, falls. The erythrocyte sedimentation rate rises early in pregnancy due to the increase in fibrinogen and other physiological changes. Protein C, which inactivates factors V and VIII, is probably unchanged in pregnancy, but concentrations of protein S, one of its cofactors, fall during the first two trimesters. An estimated 5–10% of total circulating fibrinogen is consumed during placental separation, and thromboembolism is one of the main causes of maternal death in the UK. Plasma fibrinolytic activity is decreased during pregnancy and labour, but returns to non-pregnant values within an hour of delivery of the placenta, suggesting strongly that the control of fibrinolysis during pregnancy is significantly affected by placentally derived mediators. Table 1.4 summarizes changes in some coagulation and fibrinolytic variables during pregnancy [22].

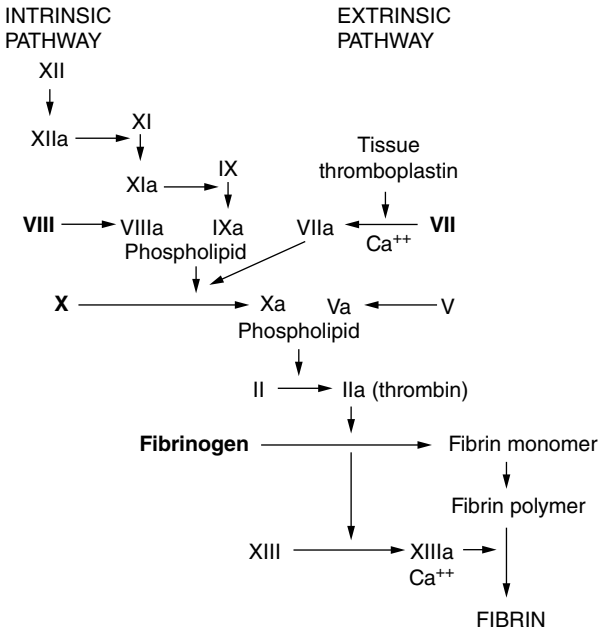

Fig. 1.5 Alterations in the coagulation pathways associated with human pregnancy. Factors which increase during normal pregnancy are in bold type. *Source:* Chamberlain, G. and Broughton Pipkin, F. *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Wiley, 1998. Reproduced with permission of John Wiley & Sons.

Table 1.4 Percentage changes in some coagulation and fibrinolytic variables and fibronectin levels are expressed from postpartum data in the same women. The mean values shown are those at the end of each trimester and are thus not necessarily the maxima. Note the very large rise in PAI-2 (placental type PAI) and TAT III complexes in the first trimester.

	First trimester	Second trimester	Third trimester
PAI-1 (mg/mL)	−10	+68	+183
PAI-2 (mg/mL)	+732	+1804	+6554
t-PA (mg/mL)	−24	−19	+63
Protein C (% activity)	−12	+10	+9
AT III (% activity)	−21	−14	−10
TAT III	+362	+638	+785
Fibronectin (mg/L)	+3	−12	+53

PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator antigen; AT III, antithrombin III; TAT III, thrombin–antithrombin III complex.
Source: Halligan A, Bonnar J, Sheppard B, Darling M, Walshe J. Haemostatic, fibrinolytic and endothelial variables in normal pregnancies and pre-eclampsia. *Br J Obstet Gynaecol* 1994;101: 488–492. Oxford: Elsevier. Reproduced with permission of Elsevier.

The renal system

The kidneys increase in size in pregnancy mainly because renal parenchymal volume rises by about 70%, with marked dilatation of the calyces, renal pelvis and ureters in most women [23]. Ureteric tone does not decrease, but bladder tone does. The effective renal plasma flow (ERPF) is increased by at least 6 weeks' gestation and rises to some 80% by mid-pregnancy falling thereafter to about 65% above non-pregnant values (Fig. 1.6). This increase is proportionally greater than the increase in cardiac output, presumably reflecting specific vasodilatation, probably via increased local prostacyclin or nitric oxide synthesis. The glomerular filtration rate (GFR) also increases, by about 45% by the ninth week, only rising thereafter by another 5–10%, but this is largely maintained to term, so the filtration fraction falls during the first trimester, is stable during the second, and rises thereafter, possibly to levels above non-pregnant. However, these major increments do not exhaust the renal reserve. The differential changes in ERPF and GFR in late pregnancy suggest a mechanism acting preferentially at the efferent arterioles, possibly through angiotensin II.

The filtered load of metabolites therefore increases markedly, and reabsorptive mechanisms frequently do not keep up (e.g. glucose and amino acids; see section Energy requirements). These changes have profound

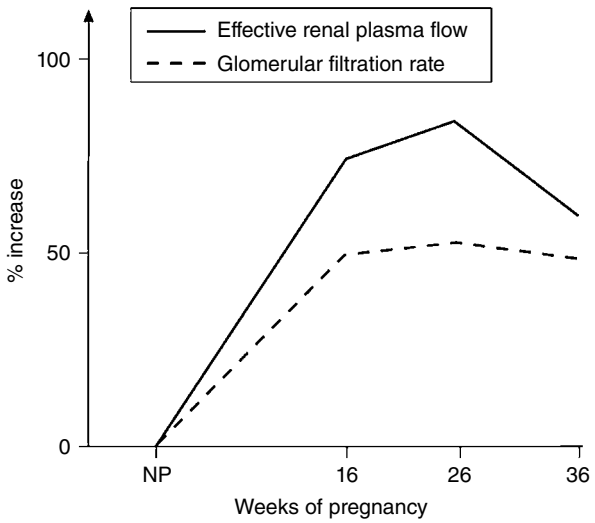

Fig. 1.6 The changes in renal function during pregnancy are largely complete by the end of the first trimester and are thus proactive not reactive to the demands of pregnancy. The filtration fraction falls during the first trimester but begins to return to non-pregnant levels during the third trimester. *Source:* Chamberlain, G. and Broughton Pipkin, F. *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Wiley, 1998. Reproduced with permission of John Wiley & Sons.

effects on the concentrations of certain plasma metabolites and electrolytes and 'normal' laboratory reference ranges may thus be inappropriate in pregnancy. For example, plasma creatinine concentration falls significantly by the fourth week of gestation and continues to fall to mid-pregnancy, to below 50 mmol/L, but creatinine clearance begins to fall during the last couple of months of pregnancy, so plasma creatinine concentration rises again.

Total body water rises by about 20% during pregnancy (~8.5 L) with a very sharp fall in plasma osmolality between weeks 4 and 6 after conception, possibly through the actions of human chorionic gonadotrophin (hCG). The volume-sensing arginine vasopressin (AVP) release mechanisms evidently adjust as pregnancy progresses, with a lowering of the osmotic threshold for AVP and thirst. As well as water present in the fetus, amniotic fluid, placenta and maternal tissues, there is also oedema fluid and increased hydration of the connective tissue ground substance with laxity and swelling of connective tissue.

The pregnant woman accumulates some 950 mmol of sodium in the face of high circulating concentrations of progesterone, which competes with aldosterone at the distal tubule. The potentially natriuretic prostacyclin also rises markedly, with a significant rise in atrial natriuretic peptide (ANP). This stimulates the renin–angiotensin system, with increased synthesis and release of aldosterone from the first trimester. The raised plasma prolactin may also contribute to sodium retention. It is assumed that glomerulotubular balance must also change in pregnancy to allow the sodium retention that actually occurs. There is a fall of some 4–5 mmol/L in plasma sodium by term, but plasma chloride does not change. Curiously, some 350 mmol of potassium are also retained during pregnancy, in the face of the much-increased GFR, substantially raised aldosterone concentrations and a relatively alkaline urine. Renal tubular potassium reabsorption evidently adjusts appropriately to the increased filtered potassium load.

Serum uric acid concentration falls by about one-quarter in early pregnancy, with an increase in its fractional excretion secondary to a decrease in net tubular reabsorption. The kidney excretes a progressively smaller proportion of the filtered uric acid, so some rise in serum uric acid concentration during the second half of pregnancy is normal. The developing fetus and placenta contribute to the load. A similar pattern is seen in relation to urea, which is also partly reabsorbed in the nephron.

Glucose excretion may rise 10-fold as the greater filtered load exceeds the proximal tubular T_{max} for glucose (~1.6–1.9 mmol/min). If the urine of pregnant women is tested sufficiently often, glycosuria will be detected in 50%. The excretion of most amino acids increases, which is curious since these are used by the fetus to synthesize protein. The pattern of excretion is not constant, and differs between individual amino acids. Excretion of the water-soluble vitamins is also increased. The mechanism for all these is inadequate tubular reabsorption in the face of a 50% rise in GFR.

Urinary calcium excretion is also twofold to threefold higher in normal pregnancy than in the non-pregnant woman, even though tubular reabsorption is enhanced, presumably under the influence of the increased concentrations of 1,25-dihydroxyvitamin D. To counter this, intestinal absorption doubles by 24 weeks, after which it stabilizes. Renal bicarbonate reabsorption and hydrogen ion excretion appear to be unaltered during pregnancy. Although pregnant women can acidify their urine, it is usually mildly alkaline.

Total protein and albumin excretion both rise during pregnancy, to at least 36 weeks, due to the increased GFR, and changes in both glomerular and tubular function. Thus in late pregnancy, an upper limit of normal of 200 mg total protein excretion per 24-hour collection is accepted. The assessment of absolute proteinuria in pregnancy using dipsticks has been shown to give highly variable data. Studies in which urinary protein/creatinine and albumin/creatinine ratios were measured in order to identify developing pre-eclampsia have also shown marked heterogeneity in test accuracy and thus diagnosis of the disease [24].

The cerebral circulation

The brain is responsible for approximately 20% of total oxygen consumption outside pregnancy. It has a relatively limited capacity to tolerate changes in blood flow, ion or water balance, and is enclosed by a rigid container. It is thus potentially very vulnerable. Its response to the substantial changes in PV and circulating hormone concentrations, both vasoconstrictor and vasodilator, is distinct from that of other vascular beds and is geared to maintaining the status quo through autoregulation. Cerebral blood flow does appear to be unchanged during pregnancy [25].

The gastrointestinal system

Taste often alters very early in pregnancy. The whole intestinal tract has decreased motility during the first two trimesters, with increased absorption of water and salt, tending to increase constipation. Heartburn is common as a result of increased intragastric pressure. Hepatic synthesis of albumin, plasma globulin and fibrinogen increases, the latter two sufficiently to give

increased plasma concentrations despite the increase in PV. Total hepatic synthesis of globulin increases under oestrogen stimulation, so the hormone-binding globulins rise. There is decreased hepatic extraction of circulating amino acids.

The gallbladder increases in size and empties more slowly during pregnancy but the secretion of bile is unchanged. Cholestasis is almost physiological in pregnancy and may be associated with generalized pruritus but only rarely produces jaundice. However, when cholestasis of pregnancy is severe, adverse pregnancy outcomes are increasingly likely [26].

Energy requirements

The energy cost of pregnancy includes 'stored' energy in maternal and fetal tissues, and the greater energy expenditure needed for maintenance and physical activity. The weight gained during pregnancy arises from the products of conception, the increased size of maternal tissues such as the uterus and breasts, and the greater maternal fat stores. The basal metabolic rate has risen by about 5% by the end of pregnancy in a woman of normal weight [27]. The average weight gain over pregnancy in a woman of normal body mass index (BMI) is about 12.5 kg. The average weight gain from pre-pregnancy values at 6–18 months after delivery is 1–2 kg, but in about one-fifth of women can be 5 kg or more [28]. Obese women usually put on less weight during pregnancy, but retain more post partum, partly dependent on the distribution of abdominal fat before pregnancy. A 5-year follow-up of nearly 3000 women found that parous women gained 2–3 kg more than nulliparous women during this time. They also had significantly greater increases in waist/hip ratio, an independent risk factor for future cardiovascular disease [29].

Carbohydrates/insulin resistance

Pregnancy is hyperlipidaemic and glucosuric. Although neither the absorption of glucose from the gut nor the half-life of insulin seem to change and the insulin response is well maintained, by 6–12 weeks' gestation fasting plasma glucose concentrations have fallen by 0.11 mmol/L, and by the end of the first trimester the increase in blood glucose following a carbohydrate load is less than outside pregnancy [30]. This increased sensitivity stimulates glycogen synthesis and storage, deposition of fat and transport of amino acids into cells. The uptake of amino acids by the mother for gluconeogenesis may also be enhanced. After mid-pregnancy, resistance to the action of insulin develops progressively and plasma glucose concentrations rise, though remaining below non-pregnant levels (Fig. 1.7). Glucose crosses the placenta readily and the fetus uses glucose as its primary energy substrate, so this rise is presumably beneficial to the fetus. Fetal and maternal glucose concentrations are significantly correlated.

The insulin resistance is presumably largely endocrine driven, possibly via increased cortisol or human placental lactogen. Plasma leptin concentrations are directly correlated with insulin resistance during pregnancy [31] while concentrations of glucagon and the catecholamines are unaltered. Serum adiponectin, which enhances insulin sensitivity and stimulates glucose uptake in skeletal muscle, is increased in early pregnancy, falling over the second half of gestation. Adiponectin concentrations are also low in other insulin-resistant states, but whether this is cause or effect is still uncertain. High concentrations of adiponectin in early pregnancy may enhance

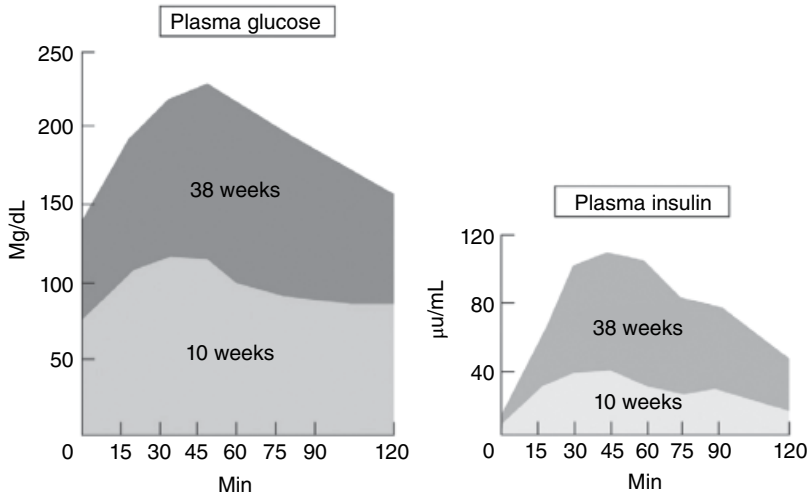

Fig. 1.7 Responses in normal pregnant women to a 50-g oral glucose load during early and late pregnancy. During early pregnancy there is a normal plasma insulin response with a relative reduction in plasma glucose concentrations compared with the non-pregnant state. In contrast, during late pregnancy plasma glucose concentrations reach higher levels after a delay despite a considerably enhanced insulin response, a pattern which could be explained by relative resistance to insulin.

maternal accumulation of nutrients, while the subsequent fall in adiponectin facilitates allocation of nutrients to the fetus. There is an inverse association between maternal serum adiponectin and fetal growth across the full range of birthweights [32].

Lipids

Serum total and low-density lipoprotein (LDL) cholesterol fall early in pregnancy, reaching their lowest levels at 6–8 weeks, but then rising to term; the early fall in AIx has been linked to the fall in LDL [11]. Conversely, high-density lipoprotein (HDL) cholesterol rises significantly by 6–8 weeks. There is a striking increase in circulating free fatty acids and complex lipids in pregnancy, with approximately threefold increases in very low density lipoprotein (VLDL) triglycerides and a 50% increase in VLDL cholesterol by 36 weeks [33], which is probably driven by oestrogens. Birthweight and placental weight are directly related to maternal VLDL triglyceride levels at term. The hyperlipidaemia of normal pregnancy is not atherogenic because the pattern of increase is not that of atherogenesis, although pregnancy can unmask pathological hyperlipidaemia.

Lipids undergo peroxidation in all tissues as part of normal cellular function. Excess production of lipid can result in oxidative stress, with damage to the cell membrane. During normal pregnancy, increases in plasma lipid peroxides appear by the second trimester in step with the general rise in lipids and may taper off later in gestation [34]. As the peroxide levels rise so do those of vitamin E and some other antioxidants; this rise is proportionately greater than that of peroxides so physiological activities are protected. Lipid peroxidation is also active in the placenta, increasing with gestation. Since the placenta contains high concentrations of unsaturated fats under conditions of low PaO_2, antioxidants such as vitamin A, the carotenoids and provitamin A carotenoids are required to protect both mother and fetus from free radical activity.

Early in pregnancy fat is deposited but from mid-pregnancy it is also used as a source of energy, mainly by the mother so that glucose is available for the growing fetus [35] and to provide energy stores for the high metabolic demands of late pregnancy and lactation. The accurate measurement of pregnancy-related fat deposition is technically difficult, but total accretion is estimated at about 2–6 kg. The absorption of fat from the intestine is not directly altered during pregnancy. The hormone leptin acts as a sensor, alerting the brain to the extent of body fat stores. Concentrations rise threefold during pregnancy and are directly correlated with total body fat; they are not related to the basal metabolic rate during gestation. Recent animal studies suggest that the hypothalamus, which contains the appetite-regulating centres, is desensitized to the effects of leptin in pregnancy. This allows the mother to eat more than she otherwise would consider doing, with consequent fat deposition.

Endocrine systems

The placenta is a powerhouse of hormone production from the beginning of gestation and challenges the mother's autonomy.

Placental hormones

hCG is the signal for pregnancy, but indirect effects, such as the oestrogen-driven increased hepatic synthesis of the binding globulins for thyroxine, corticosteroids and the sex steroids, also affect the mother's endocrinological function. The fetoplacental unit synthesizes very large amounts of oestrogens and progesterone, both probably being concerned with uterine growth and quiescence and with mammary gland development. However, they also stimulate synthesis of a variety of other important hormones. Oestrogens stimulate both the synthesis of the pro-angiogenic vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors (see below) and angiogenesis; the two are linked. VEGF appears to interact with other placentally produced hormones and angiopoietin 2 as major players in the development of the villous capillary bed in early human pregnancy. Trophoblasts express the transmembrane tyrosine kinase receptor Flt-1 which mediates the response to VEGF-A and placental growth factor (PlGF). The soluble isoform sFlt-1 also binds VEGF-A and PlGF, but antagonizes their pro-angiogenic actions due to lack of intracellular effector regions. Levels of sFlt-1 released to the maternal circulation rise during normal pregnancy. The oxygen-sensitive transcriptional activator hypoxia-inducible factor (HIF)-1 plays a major part in the response to hypoxic conditions and is a primary regulator of angiogenesis, acting synergistically with VEGF, PlGF and the angiopoietins [36].

The peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear receptor superfamily and has an important role in modulating expression of numerous other genes. It is expressed in human villous and extravillous cytotrophoblast. PPARγ binds to, and is activated by, natural ligands such as eicosanoids, fatty acids and oxidized LDLs. Studies in knockout mice have shown it to be essential for placental development.

The corpus luteum, uterus and placenta synthesize relaxin, structurally very similar to insulin, during pregnancy, plasma concentrations peaking at the end of the first trimester. It is thought to regulate VEGF in very

early pregnancy and, by its effects on extracellular matrix components, stimulate uterine growth and remodelling of the spiral arteries. It may also be concerned with the systemic vascular response to pregnancy. There is wide inter-species variability, and data from animal studies should be viewed with caution [37].

The hypothalamus and pituitary gland

The pituitary gland increases in weight by 30% in first pregnancies and by 50% subsequently. The number of lactotrophs is increased and plasma prolactin begins to rise within a few days of conception and by term may be 10–20 times as high as in the non-pregnant woman; the secretion of other anterior pituitary hormones is unchanged or reduced. hCG and the gonadotrophins share a common α-subunit, and the rapidly rising hCG concentration suppresses secretion of both follicle-stimulating hormone and luteinizing hormone, thus inhibiting ovarian follicle development by a blunting of response to gonadotrophin-releasing hormone. Thyroid-stimulating hormone (TSH) secretion responds normally to hypothalamic thyrotropin-releasing hormone (also synthesized in the placenta). Adrenocorticotrophic hormone (ACTH) concentrations rise during pregnancy, partly because of placental synthesis of ACTH and of a corticotrophin-releasing hormone and do not respond to normal control mechanisms.

The adrenal gland

Both the plasma total and the unbound cortisol and other corticosteroid concentrations rise in pregnancy, from about the end of the first trimester. Concentrations of cortisol-binding globulin double. Excess glucocorticoid exposure *in utero* appears to inhibit fetal growth in both animals and humans. However, the normal placenta synthesizes a pregnancy-specific 11β-hydroxysteroid dehydrogenase, which inhibits transfer of maternal cortisol. The marked rise in secretion of the mineralocorticoid aldosterone in pregnancy has already been mentioned. Synthesis of the weaker mineralocorticoid 11-deoxycorticosterone is also increased by the eighth week of pregnancy, and actually increases proportionally more than any other cortical steroid, possibly due to placental synthesis.

The measurement of plasma catecholamines has inherent difficulties, but there is now broad consensus that plasma catecholamine concentrations fall from the first to the third trimester. There is some blunting of the rise in noradrenaline (reflecting mainly sympathetic nerve activity) seen on standing and isometric exercise in pregnancy, but the adrenaline response (predominantly adrenal) is unaltered [38].

The thyroid gland

hCG may suppress TSH in early pregnancy because they share a common α-subunit. The thyroid remains normally responsive to stimulation by TSH and suppression by triiodothyronine (T3). There is a threefold rise in the thyroid's clearance of iodine, allowing the absolute iodine uptake to remain within the non-pregnant range. Thyroid-binding globulin concentrations double during pregnancy, but other thyroid-binding proteins do not increase. Overall, free plasma T3 and thyroxine (T4) concentrations remain at the same levels as outside pregnancy (although total levels are raised), and most pregnant women are euthyroid. Free T4 may fall in late gestation [39].

Calcitonin, another thyroid hormone, rises during the first trimester, peaks in the second and falls thereafter, although the changes are not large. It may contribute to the regulation of 1,25-dihydroxyvitamin D.

The parathyroid glands and calcium metabolism

Calcium homeostasis changes markedly in pregnancy [40,41]. Maternal total plasma calcium falls because albumin concentration falls, but unbound ionized calcium is unchanged. Synthesis of 1,25-dihydroxycholecalciferol increases, promoting enhanced gastrointestinal calcium absorption. Parathyroid hormone (PTH) regulates the synthesis of 1,25-dihydroxyvitamin D in the proximal convoluted tubule. There is a fall in intact PTH during pregnancy but a doubling of 1,25-dihydroxyvitamin D; PTH-related protein (PTHrP) is also present in the maternal circulation. The main sources of PTHrP are the fetal parathyroid gland and the placenta. It is presumably placentally derived PTHrP that is transferred into the maternal circulation and affects calcium homeostasis by acting through the PTH receptor.

Renal hormones

The renin–angiotensin system is activated from very early in pregnancy (see section Cardiovascular system). A vasodilator component to the renin–angiotensin system has recently been described in which angiotensin 1–7 is the agonist; angiotensin 1–7 rises during pregnancy and may stimulate release of both nitric oxide and prostacyclin. Synthesis of erythropoietin appears to be stimulated by hCG; its concentration rises from the first trimester, peaking in mid-gestation and falling somewhat thereafter. Prostacyclin is a potent vasodilator, synthesized mainly in the renal endothelium. Concentrations begin to rise rapidly by 8–10 weeks of gestation, being

fourfold higher than non-pregnant values by the end of the first trimester.

The pancreas

The size of the islets of Langerhans and the number of β cells increase during pregnancy, as does the number of receptor sites for insulin. The functions of the pancreas in pregnancy are considered above.

The endothelium

The endothelium synthesizes a variety of hormones, both vasodilator (e.g. prostacyclin, VEGF-A, nitric oxide) and vasoconstrictor (e.g. endothelin-1). The vasodilators are mostly upregulated in pregnancy, and allow the early fall in total peripheral resistance. Interestingly, although the lipid profile in pregnancy appears to be atherogenic, endothelial function in normal pregnancy, as assessed by flow-mediated dilatation, is not impaired. This may be due to the increased estradiol concentrations, which upregulate endothelial nitric oxide synthase.

Conclusion

This chapter attempts, very briefly, to outline the physiology of normal pregnancy. The changes mostly begin very early indeed, and it may be that two of the major problems of pregnancy – intrauterine growth retardation and pre-eclampsia – are initiated even before the woman knows that she is pregnant. Better understanding of the mechanisms of very early normal pregnancy adaptation may help us to understand the abnormal.

Summary box 1.1

- Each ovulatory menstrual cycle prepares the potential mother for the physiological changes of pregnancy. Progesterone is the prime mover, and before conception initiates such changes as increased tidal volume, heart rate and GFR, as well as endometrial priming. These changes are proactive, not reactive, and in normal pregnancy are greater than physiologically necessary.
- Early pregnancy is associated with a systemic inflammatory response. The mother's immune response is altered to allow implantation and placentation and the remodelling of the spiral arteries.
- Total peripheral resistance falls very early, followed by the peripheral and central blood pressure; plasma volume and cardiac output rise. Alveolar ventilation and oxygen-carrying capacity increase more than oxygen consumption. Even normal pregnancy is associated with low-grade coagulopathy.
- Renal filtration increases very early. The rise in filtered sodium load activates the renin–angiotensin system, allowing sodium retention and the increased plasma volume. Plasma concentrations of various analytes are reduced because of both increased filtration and plasma volume expansion. Aminoaciduria and glycosuria are common.
- The average weight gain over pregnancy in a woman of normal BMI is about 12.5 kg. Some of this is usually retained after delivery. Pregnancy is associated with insulin resistance and hyperlipidaemia; there is considerable fat deposition.
- The placenta is a powerhouse of hormone and cytokine synthesis, modifying the mother's physiology for the demands of pregnancy.

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2

The Placenta and Fetal Membranes

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The placenta was already recognized and venerated by the early Egyptians, while it was the Greek physician Diogenes of Apollonia (*c.* 480 BC) who first ascribed the function of fetal nutrition to the organ. Aristotle (384 to 322 BC) reported that the chorionic membranes fully enclose the fetus, but it was only in 1559 during the Renaissance that Realdus Columbus introduced the term 'placenta', derived from the Latin for a flat cake.

Structural characteristics of the human placenta

Placental shape

On the gross anatomical level, the placenta of eutherian animals can be classified according to the physical interactions between fetal and maternal tissues [1]. Such interactions may be restricted to specific sites or may be found covering the whole surface of the chorionic sac and the inner uterine surface. On this gross anatomical level, the human placenta is classified as a *discoidal* placenta, confining interactions to a more or less circular area (Fig. 2.1a).

Materno-fetal interdigitations

The next level of classification is based on the interdigitations between maternal and fetal tissues [1]. In the human placenta maternal and fetal tissues are arranged is such a way that there are three-dimensional tree-like structures called *villous trees* of fetallly derived tissues that float in a vascular space filled with maternal blood. Like the structure of a tree with leaves, the placental villi repeatedly branch into progressively smaller and slender gas-exchanging villi (Fig. 2.1b). On the maternal side blood vessels are eroded, resulting in an open circulation of maternal blood within the vascular space of the placenta. The placental villi are in direct contact with maternal blood with no intervening layer of maternal endothelial cells.

Materno-fetal barrier

Following implantation of the blastocyst within the decidualized endometrium, the outer trophoblast cells gradually erode into the surrounding maternal uterine stroma, breaching capillaries to direct maternal blood towards the placenta where the developing villi are forming. At the cellular level, this type of implantation is termed *invasive placentation* [1]. The fetally derived epithelial layer, termed villous trophoblast, covers the placental villi; it comes into direct contact with maternal blood and functions as the placental barrier between maternal and fetal tissues (Fig. 2.1c).

This type of placentation is termed *haemomonochorial* since on the maternal side blood makes direct contact rather than via blood vessels (haemo) while on the fetal side there is a single intact layer of trophoblast (monochorial) between maternal blood and the fetal vascular compartment (Fig. 2.1c).

Vascular arrangement

The diffusion efficiency of the human placenta depends on the extent of elaboration and development of the placental villi, with the more specialized terminal villi being the site of maximal diffusional exchange. An additional important determinant is the direction of maternal and fetal blood flows in relation to each other [1]. The optimal

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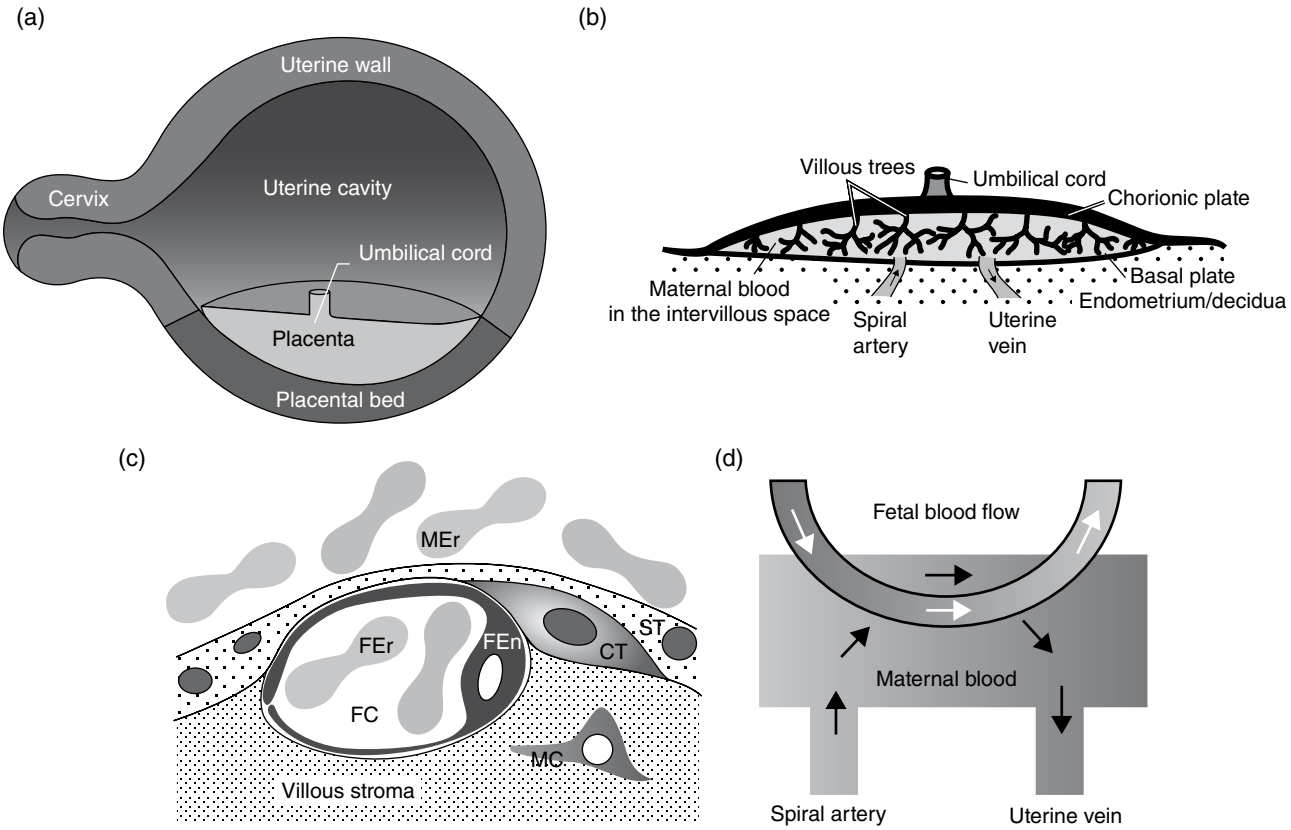

Fig. 2.1 Schematic representation of the structural characteristics of the human placenta. (a) The human placenta displays a discoidal shape. (b) The materno-fetal interdigitations are arranged in villous trees bathing in maternal blood that floats through the intervillous space. (c) The haemochorial type of placentation results in a materno-fetal barrier composed of villous trophoblast in direct contact with maternal blood. (d) Fetal and maternal blood flows are arranged in a multivillous flow. CT, cytotrophoblast; FC, fetal capillary; FEn, fetal endothelium; FEr, fetal erythrocyte; MC, mesenchymal cells; MEr, maternal erythrocyte; ST, syncytiotrophoblast.

design is counter-current, but due to the complex arrangement of the human placental villous trees, this is less efficient than in some other species, such as the guinea pig. The variable flow pattern in humans has been termed *multivillous flow* (Fig. 2.1d).

Summary box 2.1

- Macroscopically, the human placenta has a discoidal shape.
- The interdigitations between maternal and fetal tissues are arranged as follows: tree-like structures (villous trees) of the placenta are surrounded by a multivillous flow pattern of maternal blood.
- The epithelial covering of the villous trees, the villous trophoblast, represents the placental barrier between maternal blood and fetal tissues (haemomonochorial placentation).

Macroscopic features of the term placenta

Measures

The placenta displays typical macroscopic features after delivery at term [1]. The term placenta shows a round disc-like appearance, with the insertion of the umbilical cord in a slightly eccentric position on the fetal side of the placenta. The average measurements of a delivered placenta at term are as follows: diameter 22 cm, central thickness 2.5 cm, and weight 450–500 g. One has to keep in mind, though, that considerable variation in gross placental structure can occur in normal term pregnancies. In part, this is due to the fact that the human placenta comprises 30–50 operational units termed *placentomes*, whose aggregated shape may vary without compromise to the function of individual units.

Tissue arrangements

The tissues of the term placenta display a specific organization [1]. On the fetal side of the placenta, the *amnion* covers the *chorionic plate*. The amnion is assembled by a single-layered cuboidal epithelium fixed to an avascular layer of mesenchymal tissue. Beneath the amnion, the chorionic mesenchymal tissue layer contains the chorionic plate vessels that are direct continuations of those within the umbilical cord. These chorionic plate vessels penetrate to supply the fetally derived vessels within the villous trees where the capillary system, between arteries and veins, is located within the so-called gas-exchanging terminal villi. Hence, the chorionic vessels connect the fetal circulation (via the umbilical cord) with the placental circulation within the villous trees of the placenta. The villous trees hang down from the chorionic plate, floating within a vascular space filled with maternal blood. The villous trees are connected via a major trunk (stem villus) to the chorionic plate and display multiple sites of branching, finally ending in terminal villi. On the maternal side of the placenta, the *basal plate* is located (Fig. 2.1b). It is an artificial surface generated by separation of the placenta from the uterine wall during delivery. The basal plate is a colourful mixture of fetal trophoblasts and maternal cells of the decidua, all of which are embedded in trophoblast-secreted matrix-type fibrinoid, decidual extracellular matrices, and blood-derived fibrin-type fibrinoid. At the placental margin, chorionic plate and basal plate fuse with each other, thereby closing the intervillous space such that the remainder of the uterine cavity is lined by the *fetal membranes* or *chorion laeve*.

Summary box 2.2

The layers of a delivered placenta from the fetal to the maternal side comprise:

- avascular amnion (epithelium and mesenchyme)
- vascularized chorionic plate (mesenchyme with blood vessels)
- villous trees directly connected to the chorionic plate
- maternal blood in the intervillous space surrounding the villous trees
- basal plate with a mixture of fetal and maternal cells.

Placental development

Trophoblast lineage

At the transition between morula and blastocyst, the trophoblast lineage is the first to differentiate from the inner cell mass or embryoblast (Fig. 2.2) [1]. Following attachment of the blastocyst to the endometrial epithelium, further differentiation of the trophoblast occurs. Exact knowledge of the underlying molecular processes in the human is still lacking, but at this stage the first event is the creation of an outer layer of fused trophoblast cells, termed the *outer syncytiotrophoblast*. This outer syncytiotrophoblast generated by fused trophoblasts is in direct contact with maternal tissues and thus is the first layer from the conceptus to encounter and subsequently penetrate the uterine epithelium capillaries (Fig. 2.2).

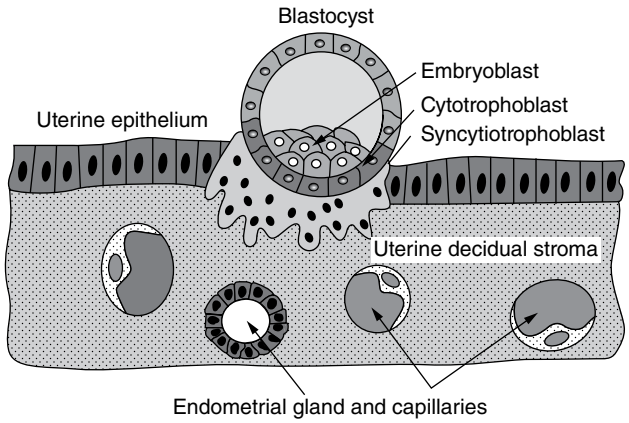

Fig. 2.2 During implantation of the blastocyst, trophoblast cells in direct contact with maternal tissues syncytially fuse and give rise to the syncytiotrophoblast. Only this multinucleated tissue is able to penetrate the uterine epithelium and to implant the developing embryo.

Prelacunar stage

At day 7–8 post conception, the blastocyst has completely crossed the uterine epithelium to become embedded within the decidualized endometrial stroma. The developing embryo is completely surrounded by the growing placenta, which at that stage consists of the two fundamental subtypes of the trophoblast. The multinucleated syncytiotrophoblast is in direct contact with maternal tissues, while the mononucleated cytotrophoblast as the stem cell layer of the trophoblast is directed towards the embryo.

All the differentiation and developmental stages of the placenta described so far take place before fluid-filled spaces within the syncytiotrophoblast develop. This is why this stage is termed 'prelacunar' [1].

Lacunar stage

At day 8–9 post conception, the syncytiotrophoblast generates a number of fluid-filled spaces within its mass (*lacunar stage*) [1]. These spaces flow together forming larger lacunae, and finally embed parts of the

syncytiotrophoblast (trabeculae) that cross the syncytial mass from the embryonic to the maternal side.

At the end of this stage, at day 12 post conception, the process of implantation is completed. The developing embryo with its surrounding extraembryonic tissues is completely embedded in the decidualized endometrium, and the syncytiotrophoblast surrounds the whole surface of the conceptus. Mesenchymal cells derived from the embryo spread over the inner surface of the trophoblast (extraembryonic mesoderm), thus generating an additional mesenchymal layer on top of the inner surface of the trophoblast, termed *chorion*.

The development of the lacunar system subdivides the placenta into its three compartments.

1) The embryonically oriented part of the trophoblast together with the extraembryonic mesoderm (chorion) will develop into the *chorionic plate*.
2) The trabeculae will become the anchoring villi, attaching the placenta proper to the uterine wall. The side branches growing out of the trabeculae will develop into *floating villi*. The lacunae surrounding the villi will turn into the *intervillous space* that will subsequently fill with maternal blood at the end of the first trimester.
3) The maternally oriented part of the trophoblast together with components of maternal decidual tissues will develop into the *basal plate*.

Early villous stage

Very early in pregnancy, specific types of villi develop as the forerunners of the placental villous tissues seen later in pregnancy [1]. Starting at day 12 post conception, proliferation of cytotrophoblast pushes trophoblasts to penetrate the syncytial trabeculae, reaching the maternal side of the syncytiotrophoblast by day 14. Further proliferation of trophoblasts inside the trabeculae (day 13) stretches the trabeculae, resulting in the development of syncytial side branches filled with cytotrophoblasts (*primary villi*).

Shortly after, the mesenchymal cells from the chorion follow the cytotrophoblast and penetrate the trabeculae and the primary villi, thus generating *secondary villi* with a mesenchymal core. At this stage, there is always a complete cytotrophoblast layer between penetrating mesenchyme and syncytiotrophoblast.

Around day 20–21 post conception, vascularization (development of new vessels from haemangioblastic precursor cells) within the villous mesenchyme gives rise to the formation of the first placental vessels (*tertiary villi*). Only later will the proximal connection to the vascular system of the embryo proper be established via the umbilical cord.

Placental villi are organized in villous trees that cluster together into a series of spherical units known as lobules or placentomes. Each placentome originates from the chorionic plate by a thick villous trunk stemming from a trabecula. Continuous branching of the main trunk results in the formation of floating villi that branch and end freely as terminal villi in the intervillous space.

Trophoblastic cell columns

During penetration of the syncytial trabeculae, the cytotrophoblasts reach the maternal decidual tissues while the subsequently penetrating mesenchymal cells do not infiltrate to the tips of the trabeculae [1]. Hence, at the tips of the anchoring villi multiple layers of cytotrophoblasts develop, referred to as trophoblastic *cell columns* (Fig. 2.3) [1]. Only those cytotrophoblasts remain as proliferative stem cells that are in direct contact with the basement membrane separating trophoblast from mesenchyme of the anchoring villi.

Subtypes of extravillous trophoblast

The formation of cell columns does not always result in a complete layer of trophoblastic shell but rather may be organized as separated columns from which extravillous trophoblasts invade into maternal uterine tissues (Fig. 2.3). All these cells migrate as *interstitial trophoblast* into the decidual stroma [1]. The interstitial trophoblast invades the whole thickness of the decidua and penetrates the inner third of the myometrium. Here, invasion normally stops and no extravillous trophoblast can be seen in the outer third of the myometrium.

Following this main direction of invasion, extravillous trophoblasts may invade via other specific routes. One subset of interstitial trophoblasts penetrates the walls of uterine spiral arteries and veins (*intramural trophoblast*), finally reaching the vessel lumen (*endovascular trophoblast*) (Fig. 2.3) [2]. Another subset of interstitial trophoblasts penetrates the walls of uterine glands, finally opening such glands towards the intervillous space (*endoglandular trophoblast*) (Fig. 2.4) [3]. Finally, some of the interstitial trophoblasts may fuse and thus develop into *multinucleated trophoblast giant cells* (Fig. 2.4) at the boundary between endometrium/decidua and myometrium [1].

Plugging of spiral arteries

Invasion of extravillous trophoblasts is the ultimate means to transform maternal arteries into large-bore conduits to enable adequate supply of oxygen and nutrients to the placenta and the fetus [1,2]. However, free transfer of maternal blood to the intervillous space is

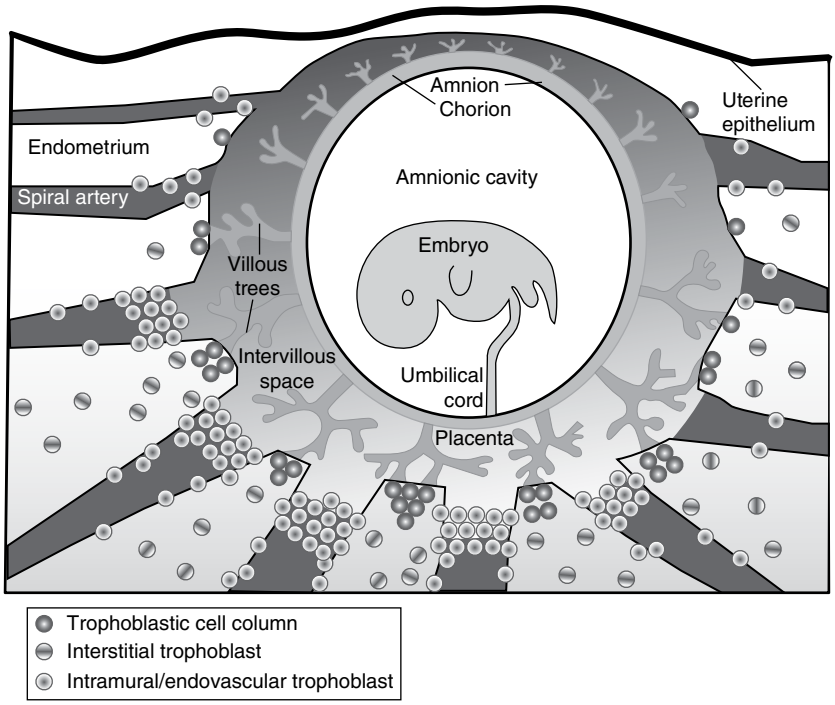

Fig. 2.3 Schematic representation of the developing embryo and its surrounding tissues at about 8–10 weeks of pregnancy. The amnionic cavity with the embryo inside is marked off by the amnion that has already contacted the chorion. From the chorion, villous trees protrude into the intervillous space where some villi have direct contact with the basal plate (anchoring villi). At these sites trophoblastic cell columns are the source for all extravillous trophoblast cells invading maternal tissues. Interstitial trophoblast cells derived from these columns invade endometrium and myometrium, while a subset of these cells penetrates the uterine arteries and veins first as intramural and then as endovascular trophoblast cells. Onset of maternal blood flow into the placenta starts in the upper regions of the placenta (the abembryonic pole) where development is slightly delayed. The locally high concentrations of oxygen contribute to the regression of villi at the abembryonic pole. This in turn leads to the formation of the smooth chorion, the fetal membranes.

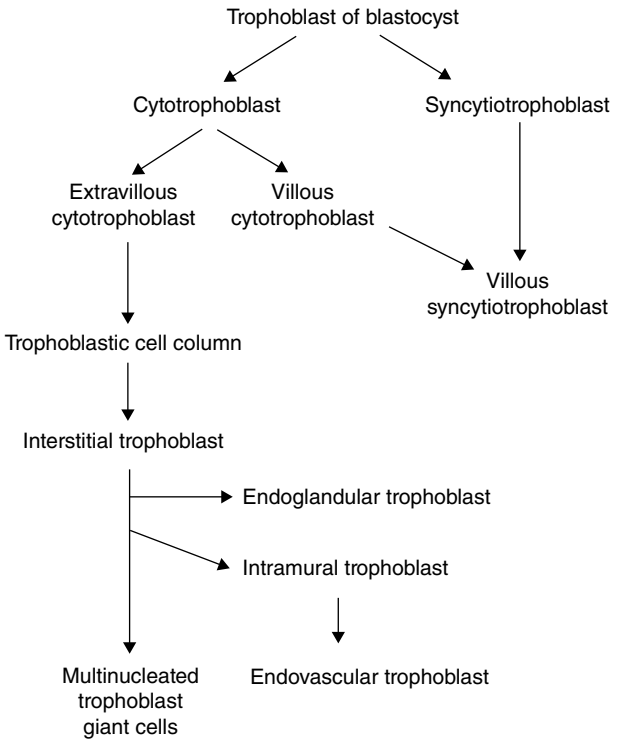

Fig. 2.4 Trophoblast differentiation and subtypes. The trophoblast lineage is the first to develop at the blastocyst stage. From this stage onwards, further differentiation leads to the generation of the syncytiotrophoblast and subsequently to the two main trophoblast types of placental villi, villous cytotrophoblast and villous syncytiotrophoblast. The trophoblast cells that start to invade maternal tissues are termed extravillous trophoblast. From the interstititat trophoblast all other subtypes of extravillous trophoblast develop.

only established at the end of the first trimester of pregnancy [4]. Before that, the extent of invasion and thus the number of endovascular trophoblasts is so great that the trophoblasts aggregate within the arterial lumen, plugging the distal segments of the spiral arteries (Fig. 2.3). Hence, before about 12 weeks of gestation, the intervillous space contains mostly a plasma filtrate that is free of maternal blood cells. To aid in nutritional support of the embryo, glandular secretion products from eroded uterine glands (*histiotrophic nutrition*) add to the fluids filling the intervillous space (Fig. 2.3) [3,5].

The reason for such paradoxical plugging of already eroded and transformed arteries may be because the lack of blood cells keeps the placenta and the embryo in a low oxygen environment of less than 20 mmHg in the first trimester of pregnancy. This low oxygen environment may be necessary to drive angiogenesis and at the same time reduce formation of free radicals that could damage the growing embryo in this critical stage of tissue and organ development [6].

Onset of maternal blood flow

At the end of the first trimester trophoblastic plugs within the spiral arteries break up to allow maternal blood cells to enter the intervillous space, thereby establishing the first arterial blood flow to the placenta (*haemotrophic nutrition*) [4]. The inflow starts in those upper parts of the placenta that are closer to the endometrial epithelium (the *abembryonic pole* of the placenta) (Fig. 2.3) [6]. These sites are characterized by a slight

delay in development since the deeper parts at the *embryonic pole* have been the first to develop directly after implantation (Fig. 2.3). Therefore, at these upper sites the plugs inside the vessels contain fewer cells, enabling blood cells to penetrate the plugs earlier, and blood flow starts at these sites first, maybe even weeks prior to the embryonic pole. Because of the massive increase in oxygenation at this time (around weeks 8–10) at the abembryonic pole, placental villi degenerate in larger parts and the chorion becomes secondarily smooth. The regression leads to the formation of the fetal membrane or *chorion laeve* [6]. The remaining part of the placenta develops into the *chorion frondosum*, the definitive disc-shaped placenta.

Summary box 2.3

- Blastocyst stage: differentiation of the trophoblast lineage.
- Day 7–8 post conception: prelacunar stage of placental development.
- Day 8–9 post conception: lacunar stage of placental development.
- Day 12 post conception: implantation completed, embryo completely surrounded by placenta.
- Day 14 post conception: differentiation of extravillous trophoblast.
- Day 20 post conception: development of placental vessels and blood cells independent of vessel development in the embryo proper.
- First trimester: histiotrophic nutrition.
- Week 12: onset of maternal flow within the intervillous space, development of the chorion laeve.
- Second and third trimester: haemotrophic nutrition.

Basic structure of villi

Villous trophoblast

The branches of the syncytial trabeculae are the forerunners of the placental villi [1]. Throughout gestation the syncytial cover remains and forms the placental barrier between maternal blood in the intervillous space and the fetal vessels within the mesenchymal core of the villi.

Villous cytotrophoblast

The layer of mononucleated villous cytotrophoblast cells is the basal layer of the villous trophoblast compartment resting on the basement membrane underneath the multinucleated layer of syncytiotrophoblast (see Fig. 2.1c) [1]. Villous cytotrophoblasts are a heterogeneous population: a subset proliferates throughout gestation (in contrast to the mouse, which terminally differentiates its chorionic trophoblast in mid-gestation), some exhibit a progenitor status because they can be induced to differentiate along the extravillous pathway, while others are in varying stages of differentiation, preparing for syncytial fusion directed by the transcription factor GCM1 (glial cell missing-1) [7].

The number of villous cytotrophoblasts continuously increases during pregnancy, from about 1×10^9 at 13–16 weeks to about 6×10^9 at 37–41 weeks of gestation [1]. These cells are gradually dispersed into a discontinuous layer in the third trimester due to the rapid expansion and specialization of the villous core that can mostly be found in combination with peripheral placental villi responsible for gas and nutrient exchange.

Villous cytotrophoblasts do not normally come into direct contact with maternal blood, unless focal damage occurs to the overlying syncytiotrophoblast: if focal areas of syncytiotrophoblast are lost, for example due to focal necrosis, the deficit is filled with *fibrin-type fibrinoid* (a maternal blood clot product) that covers the exposed cytotrophoblasts [1].

Villous syncytiotrophoblast

The *syncytiotrophoblast* is a multinucleated layer without lateral cell borders, hence there is a single syncytiotrophoblast covering all villi of a single placenta [1]. Microvilli on its apical surface provide amplification of the surface (sevenfold) and are in direct contact with maternal blood floating within the intervillous space (see Fig. 2.1c). Growth and maintenance of the syncytiotrophoblast is dependent on fusion with the underlying cytotrophoblasts, since syncytial nuclei do not divide and thus the syncytiotrophoblast does not proliferate.

Within the syncytiotrophoblast the incorporated nuclei first exhibit a large and ovoid shape, while during maturation they become smaller and denser. Finally, they display envelope convolution, increased packing density and increased heterochromatinization [8]. These are typical features of progression along the apoptosis pathway, a physiological process in the normal placenta. Interestingly, late apoptosis is extremely rare in the cytotrophoblast but may occur in a subset of cytotrophoblasts that fail to undergo syncytial fusion [9].

During gestation, syncytial fusion of cytotrophoblasts with the overlying syncytiotrophoblast more than meets the needs for growth of the placental villi [1]. Continuous syncytial fusion brings new cellular material into the syncytiotrophoblast including proteins related to apoptosis, such as caspase 8 or Bcl-2 and Mcl-1, the latter two of which focally retard apoptosis [9,10]. Those syncytial nuclei that have very recently entered the syncytial layer are still capable of RNA trancription [11,12]. However,

syncytial fusion remains critical for maintaining the functional and structural integrity of the syncytiotrophoblast, for example secretion of hormones such as chorionic gonadotrophin and the surface expression of energy-dependent transporters for the uptake of molecules such as glucose or amino acids. Consequently, nuclei that are incorporated into the syncytiotrophoblast remain within this layer for about 3–4 weeks. Then, the older nuclei accumulate and are packed into protrusions of the apical membrane known as *syncytial knots* [1,8].

Villous trophoblast turnover

Like every epithelium, the villous trophoblast exhibits the phenomenon of continuous turnover, comprising the following steps [8]:

1) proliferation of a subset of cytotrophoblast progenitor cells;
2) differentiation of post-proliferative mononucleated daughter cytotrophoblasts (2–3 days);
3) syncytial fusion of finally differentiated cytotrophoblasts with the overlying syncytiotrophoblast;
4) further differentiation and maturation of cellular components and organelles within the syncytiotrophoblast (3–4 weeks);
5) ageing and late apoptosis at specific sites of the syncytiotrophoblast;
6) packing of older material into syncytial knots; and finally
7) syncytial knots and smaller micro-particle fractions may be extruded or secreted into the maternal circulation [1].

Syncytial knots that complete the apoptosis cascade may be extruded from the syncytiotrophoblast surface into the maternal circulation [8]. In pathological pregnancies the molecular control of trophoblast differentiation may be altered. In cases of severe early-onset fetal growth restriction (FGR) this physiology is likely disturbed in favour of greater apoptotic shedding, while in cases of pre-eclampsia this physiology is disturbed in favour of both greater apoptotic shedding combined with the release of necrotic and aponecrotic material into the maternal circulation [13,14].

Trophoblast release

Throughout gestation, syncytial knots are released into the maternal circulation and may become lodged in the capillary bed of the lungs. Hence, they can be found in uterine vein blood but not in arterial or peripheral venous blood of a pregnant woman. It has been estimated that in late gestation up to 150 000 such corpuscles or 2–3 g of trophoblast material enter the maternal circulation each day [1].

Current knowledge places the multinucleated syncytial knots as products generated by apoptotic mechanisms [8]. As such, they are surrounded by a tightly sealed plasma membrane and do not release any content into the maternal blood. Hence, induction of an inflammatory response in the mother is not a normal feature of pregnancy. However, during placental pathologies with a disturbed trophoblast turnover such as pre-eclampsia, the release of syncytiotrophoblast material is altered. This necrotic or aponecrotic release of trophoblast material may well contribute to the systemic inflammation and widespread endothelial damage typical in severe pre-eclampsia [8,14].

Villous stroma

The stromal villous core comprises a population of fixed and moving connective tissue cells, including [1]:

- mesenchymal cells and fibroblasts in different stages of differentiation up to myofibroblasts;
- placental macrophages (Hofbauer cells); and
- placental vessels with smooth muscle cells and endothelial cells.

Oxygen as regulator of villous development

There is increasing recognition of the role that oxidative stress inside the placenta plays in the pathophysiology of pregnancy disorders, ranging from miscarriage to pre-eclampsia [1,4,14,15]. During the first trimester, villous trophoblast is well adapted to low oxygen, and it appears that trophoblast is more susceptible to raised oxygen rather than low oxygen [16]. The abembryonic part of the placenta is already oxygenated after mid first trimester (around week 8) by the onset of maternal blood flow [4,6]. Hence, villi at this site display increased evidence of oxidative stress, become avascular, and finally regress. These physiological changes result in the formation of the smooth chorion, the chorion laeve (Fig. 2.3) [4,6].

Maternal blood flow into the embryonic part of the placenta only starts at the transition from the first to the second trimester, at around week 12 [4]. At this time, signs of oxidative stress are obvious within the placenta; however, the placenta proper can cope with these oxygen changes and starts differentiation towards exchange of nutrients and gases. However, if early onset of maternal blood flow and consequently early onset of oxygenation also occurs in the embryonic part of the placenta, damage to the whole placenta will result [4,6]. The most severe cases end up in missed miscarriages, while less severe cases may continue but may lead to pathologies such as pre-eclampsia and IUGR [4,6]. It is becoming increasingly evident that the aetiology of pre-eclampsia

involves increased oxidative stress, mostly without changes in the extravillous subset of trophoblast [14]. Recent data point to hyperoxic changes or to the occurrence of fluctuating oxygen concentrations [17,18].

Summary box 2.4

Villous trophoblast as the outermost epithelial layer of placental villi

- Cytotrophoblast: progenitor cells to maintain the syncytiotrophoblast throughout pregnancy.
- Syncytiotrophoblast: multinucleated, in direct contact with maternal blood.
- Syncytiotrophoblast: shedding of apoptotic material into maternal blood, at the end of gestation about 3 g daily.
- Pre-eclampsia: quantity and quality of syncytial shedding are altered. More non-apoptotic fragments are released, mostly due to necrosis and aponecrosis.
- IUGR: poor development of placental villi reduces oxygen transfer to the fetus with relative placental hyperoxia (rather than placental hypoxia).

Villous stroma

- Mesenchymal cells and fibroblasts.
- Macrophages (Hofbauer cells).
- Vessels with media and endothelium.

Fetal membranes

During early embryonic development, the *amnionic cavity* increases in size and finally surrounds and encases the complete embryo [1]. Fluid accumulation within the amnionic cavity leads to complete separation of the embryo from surrounding extraembryonic tissues, leaving only the developing umbilical cord as the connection between placenta and embryo. The amnionic mesenchyme comes into direct contact with the chorionic mesoderm lining the inner surface of the chorionic sac (Fig. 2.3).

As described earlier, it is only at the implantation/embryonic pole that the definitive placenta develops. The rest of the surface of the chorionic sac (about 70%) displays regression of villi due to early increase in oxygen followed by collapse of the intervillous space at these sites. Subsequently, this results in merging of the early chorionic plate and the amnion on the fetal side with remnants of villi and the covering decidual tissues (*capsular decidua*). This multilayered compact structure is now termed the chorion laeve or fetal membranes [1].

Layers of the chorion laeve

The layers of the chorion laeve, from the fetal to the maternal side, are as follows (Fig. 2.5) [1].

1) *Amnionic epithelium*. A single cuboideal epithelium that secretes and resorbs the amnionic fluid and is involved in removal of carbon dioxide and pH regulation of the amnionic fluid.
2) *Amnionic mesoderm*. A thin layer of avascular connective tissue separated from the amnionic epithelium by a basement membrane.
3) *Chorionic mesoderm*. This second layer of connective tissue is separated from the amnionic mesoderm by slender fluid-filled clefts. It is continuous with the connective tissue of the chorionic plate, which contains the branching vessels to and from the umbilical and villous vessels.
4) *Extravillous trophoblast of the fetal membranes*. This specific type of extravillous trophoblast does not display invasive properties and is separated from the chorionic mesoderm by a basement membrane.
5) *Capsular decidua*. This layer of maternal cells is directly attached to the extravillous trophoblast. At the end of the implantation process, the decidua closes again over the abembryonic pole of the developing embryo, generating the capsular decidua. During the early second trimester, the capsular decidua comes into direct contact with the opposite wall of the uterus, causing obliteration of the uterine cavity.

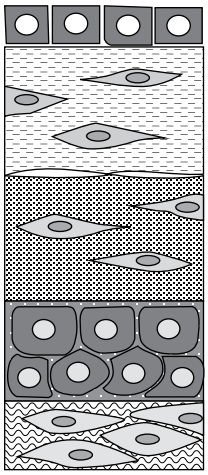

Fig. 2.5 Layers of the fetal membranes. The amnionic epithelium is a simple epithelium that secretes and resorbs the amnionic fluid. The two layers of connective tissues (amnionic and chorionic mesoderm) are separated by fluid-filled clefts. The extravillous trophoblast of the fetal membranes displays a non-invasive phenotype and is embedded in a self-secreted matrix, termed matrix-type fibrinoid. Finally, on the maternal side, the fetal membranes are covered by the capsular decidua of maternal origin.

Characteristics of the chorion laeve

After separation from the uterine wall, the fetal membranes have a mean thickness of about 200–300 μm at term. The presence of the capsular decidua on the outer surface of the fetal membranes after delivery indicates that separation of the membranes takes place between maternal tissues rather than along the materno-fetal interface. Because of the absence of vascular structures inside the connective tissues of the fetal membranes, all paraplacental exchange between fetal membranes and fetus has to pass the amnionic fluid.

Summary box 2.5

Layers of the fetal membranes, the chorion laeve

- Amnionic epithelium
- Amnionic mesoderm
- Chorionic mesoderm
- Extravillous trophoblast
- Decidua capsularis (maternal tissues)

Ultrasound

Transvaginal ultrasound can detect the gestational sac implanting within the decidualized endometrium at the 5–6 week postmenstrual stage of pregnancy. Developmental changes in the structure and organization of the placenta and membranes during the first trimester of pregnancy can be seen by ultrasound [19]. In the second trimester, the organization of the placenta and umbilical cord, together with its maternal blood supply, can be readily defined [20]. Minor anatomical variations, such as cysts and lakes, can readily be distinguished from lesions that destroy functioning villous tissue, such as infarcts and intervillous thrombi. Small placentas typically have eccentric cords, due to chorionic regression, and are a risk factor for early-onset FGR [21]. It is important to document placental location (for placenta praevia) and cord insertion (for vasa praevia) for ongoing management. Pathological placental invasion (placenta percreta), typically in association with placenta praevia and previous caesarean deliveries, may be suspected by ultrasound [22], and can be confirmed by magnetic resonance imaging (MRI) [23].

Doppler ultrasound

Pulsed and colour Doppler ultrasound are valuable techniques for placental assessment [24]. Umbilical cord flow can be visualized at 7–8 weeks, though end-diastolic flow (EDF) is not established until 14 weeks. Early-onset FGR may be characterized by absent EDF in the umbilical arteries even by 22 weeks, associated with small malformed placentas, and defective angiogenesis in the gas-exchanging terminal villi [21].

A major role for Doppler ultrasound in placental assessment is to determine impedance flow in the uterine arteries. This screening test is performed either at the 18–20 week anatomical ultrasound, or at a separate 22-week visit [19]. Integration of placental ultrasound, uterine artery Doppler and first and second trimester biochemistry screening tests (PAPP-A, hCG, PGF) is increasingly appreciated as an effective way of screening for serious placental insufficiency syndromes before achieving fetal viability, thereby directing ongoing care to a tertiary high-risk pregnancy unit [25]. However, in 2015 the American College of Obstetrics and Gynecology concluded that these resource-intensive placental health screening activities should not be adopted in low-risk women, opting instead for the utility of clinical risk assessment methods alone [26].

Subsets of high-risk pregnancies with multiparameter placental dysfunction in the 19–22 week window have up to a 40% positive predictive value for delivery before 32 weeks due to clinical complications of placental insufficiency (FGR, pre-eclampsia, abruption, stillbirth). Placental villous infarction complicates over 60% of such cases yet maternal thrombophilia is rare [25]. Since the normal healthy placenta expresses surface anticoagulant proteins, abnormal formation and perfusion of the placenta may be the underlying cause of multifocal placental infarction. If this is the case, multiparameter placental function testing in subsequent pregnancies may be a better determinant of future risk than maternal thrombophilia screening in the non-pregnant period.

Colour power Doppler

Colour power angiography (CPA) is an extented application in Doppler ultrasound and velocimetry. CPA can be used to map the vasculature within the placenta when combined with three-dimensional reconstruction (Fig. 2.6). This technique is able to identify red blood cells in vessels with a diameter of more than 200 μm [24]. Because the technique is three-dimensional, it can also be used to map the abnormal surface vascular arrangements that are typically seen in pregnancies with invasive placentation [22].

Summary box 2.6

Ultrasound (including Doppler and colour power Doppler ultrasound)

- Week 3: visualization of the gestational sac.
- Week 7–8: visualization of blood flow in the umbilical cord.
- Week 13 until delivery: visualization of placental vessels with a diameter larger than 200 μm.
- Week 14: establishment of EDF in the umbilical arteries.
- Week 18–22: screening of uterine arteries for pathological flow patterns.
- Week 22: early-onset FGR can be predicted by absent EDF in the umbilical arteries.

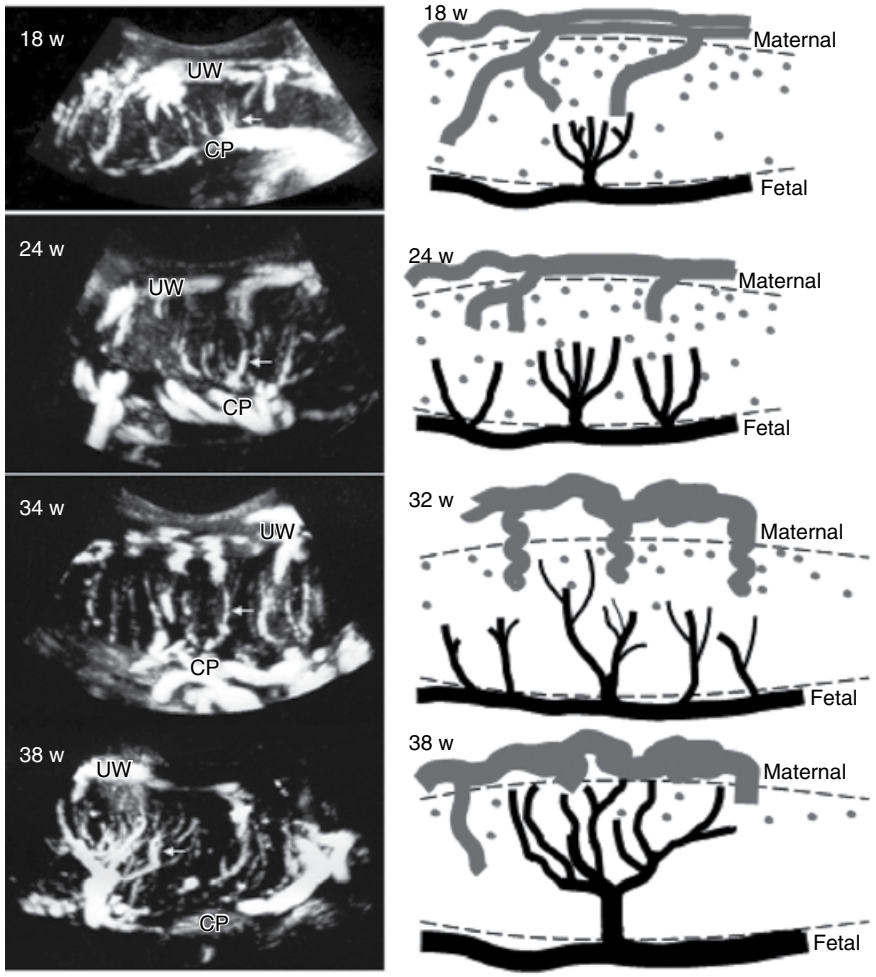

Fig. 2.6 Development of placental blood flow. *Left column*: Typical three-dimensional power Doppler scans from placentas of normal pregnant women at weeks 18, 24, 34 and 38. The flow signals within placental villi (white arrows) increase in extent, intensity, width and height with advancing pregnancy. At term (38 weeks) tree-like structures can be visualized. Since only anterior placentas have been used for these scans, the uterine wall (UW) is always at the top of the scan while the chorionic plate (CP) is always at the bottom of the scan. *Right column*: Synoptic view of characteristic features of placental blood flow throughout pregnancy as depicted by three-dimensional power Doppler. *Source:* Edmonds DK. *Dewhurst's Textbook of Obstetrics and Gynaecology*, 8th edn. Oxford: Wiley-Blackwell, 2012. Reproduced with permission of Justin Konje.

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Further reading

Structural characteristics of the placenta, see [1]
Definition of fibrinoid, see [1]
Trophoblast and its changes during pre-eclampsia, see [14]
Detailed descriptions of pathologies and their impact on macroscopic features of the placenta, see [1]
Classification of villi and the types of villi, see [1]
Stereological parameters of the growing placenta, see [27]
Syncytial fusion and the involvement of apoptosis, see [9,10]
Impact of oxygen on placental development and placental-related disorders of pregnancy, see [18]
Composition and characteristics of fetal membranes, see [1]
Rupture of fetal membranes, see [1]
Placental assessment by ultrasound, see [28]
Placental Doppler, see [19,25]
Developmental placental pathology, see [28]
Placental biochemistry in clinical practice, see [26,29]
Role of a placenta clinic, see www.mountsinai.on.ca/care/placenta-clinic
Trophoblast shedding in preeclampsia, see [30]

Part 2

Normal Pregnancy

3

Healthy Fetal Growth

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In healthy pregnancy, fetal growth follows distinct patterns. Initially, fetal weight increases mainly due to skeletal and muscle growth and is related to placental glucose and amino acid transport. After 20 weeks of gestation there is deposition of fetal adipose tissue, which occurs alongside increases in fatty acid transport; later, fetal growth and adipose tissue deposition coincide with increasing conversion of glucose into fat [1].

Assessment of fetal size (at one point during pregnancy) and fetal growth (a dynamic process that assesses change of size over a time interval) are key elements of pregnancy care. The aim of this assessment is to identify babies that are too small or too large, due to an abnormal growth pattern. This is because it puts them at higher risk of adverse pregnancy outcome and, in the case of poor fetal growth, increased rates of perinatal mortality.

In many epidemiological studies, small (or, to a lesser degree, large) babies are defined as being of below (or above) certain birthweight thresholds, for example babies of low birthweight (below 2500 g) or very low birthweight (1500 g) [2]. These are practical cut-offs and useful for international comparisons, and are linked to adverse outcome; for example, newborns weighing less than 2500 g are approximately 20 times more likely to die than heavier babies and are also at higher risk of a range of poor health outcomes [3].

However, the value of such cut-offs in monitoring and comparing perinatal health between countries or over time has been questioned. This is because they are unable to distinguish those babies that are small due to preterm birth from those that are small due to fetal growth restriction (FGR), or indeed whether the two conditions coexist. In order to discriminate between these phenotypes, the gestational age must be known. This allows the size to be defined according to gestational age: small for gestational age (SGA), average for gestational age (AGA) or large for gestational age (LGA). These are usually defined as below the 10th centile, between the 10th and 90th centiles, and above the 90th centile, respectively.

Thus, in order to differentiate the normally growing fetus from the abnormal, three things must be known: (i) accurate gestational age; (ii) measurement of the fetus; and (iii) whether the measurements of size (or growth) are within the normal range compared to a standard or reference.

Summary box 3.1

- Assessment of fetal size, at one point during pregnancy, is different from assessment of fetal growth (i.e. change of size over time).
- Using birthweight cut-offs to classify newborns (e.g. <2.0 kg) does not distinguish between preterm normal size babies from term small babies.

Estimation of gestational age

Accurate estimation of gestational age is not only important in the assessment of fetal size and growth, but also guides decisions regarding other obstetric interventions, such as prenatal testing, whether administration of prophylactic corticosteroids for fetal lung maturity and transfer to another healthcare setting is appropriate in cases of preterm labour, or when labour induction in prolonged pregnancy should occur [4]. It is also important in interpretation of results of first-trimester screening for chromosomal abnormalities using a combination of nuchal translucency, pregnancy-associated plasma protein-A and free β-human chorionic gonadotrophin (hCG) [5].

The typical length of gestation after conception is 266 days or 38 weeks (i.e. 'conceptual age'). However,

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gestational age is traditionally estimated from the last menstrual period (LMP), adding 2 weeks to 'postmenstrual age', giving 280 days or 40 weeks. This assumes that ovulation and conception occur 14 days after LMP. This is not always the case: irregular menses, unknown or uncertain dates, oral contraceptive use or recent pregnancy or breastfeeding may all influence the accuracy of this method, and this inaccuracy is significant in a large proportion of women [6,7]. Bleeding during the first trimester can also add to difficulty in confirming gestational age clinically based on the period of amenorrhoea.

Because of this, guidelines in most developed countries support the estimation of gestational age by first-trimester ultrasound using crown–rump length (CRL). Although this is more accurate at estimating gestational age at population level, it is important to recognize that this method too has limitations when interpreting individual results. For instance, there is an underlying assumption that all fetuses of the same size are of the same gestation, ignoring physiological differences and biological variability in size. In addition, aberrations in normal growth at very early stages of pregnancy exist and are associated with adverse outcome.

It is generally the case that assessment of gestational age in late pregnancy is less accurate than late pregnancy dating. This is because fetal ultrasound measurements are associated with a larger absolute error with advancing gestation, and because fetal growth disturbances become more prevalent, meaning that an abnormally small fetus could be misjudged to have lower gestational age (while a macrosomic fetus may be ascribed a more advanced gestational age). This limitation is of particular relevance in women who attend for their first antenatal care visit late in pregnancy and where no other reliable estimation of gestational age is available. It is known that unreliable reporting of LMP and late antenatal care are both associated with adverse pregnancy outcome; because of this, a clinically cautious approach is important when gestational age is assigned late, and particularly in the third trimester. Thus, the potential for error should be taken into account in order to ensure safe obstetric practice: for example, in preterm labour where late estimation of gestational age suggests a value above 34 weeks, prophylactic steroids or neonatal transfer should still be carried out as the gestational age may be lower by 2 weeks; in contrast, post-dates labour induction may be appropriate at 39 weeks after late assessment of gestational age, as this could be as late as 41 weeks [8].

Although a CRL measurement may be the most accurate measure of gestational age in most pregnancies, it has been argued that clinical judgement is required in practice to determine the best approximation of the true gestational age. First, the earliest reliable ultrasound scan should be used to ascribe an estimated due date and this should not be changed subsequently as this can lead to potential dating errors. Second, all information collected at the time of that first visit (including the reported LMP and assessment of its reliability) should be taken into account. When a reliable LMP and ultrasound estimate concur, small discrepancies with actual gestational age may still exist due to inherent CRL measurement variability. Conversely, an apparently reliable and accurate LMP with a substantial difference in estimated gestational age based on CRL should be considered as an indicator of possible growth disturbance or underlying pathology that may merit further assessment [9].

Summary box 3.2

Knowing the gestational age is important for:

- interpretation of prenatal screening tests;
- assessment of fetal growth;
- decision-making that requires knowledge of gestation, for example around the limits of viability, and post term.

Estimation of gestational age by first-trimester ultrasound using CRL is usually more accurate than menstrual history.

Measurement of the fetus

The most common methods for estimating fetal size at any one time are by measuring fetal biometry using ultrasound; or clinically, but also less accurately, by measurement of the maternal fundal height. It has been shown that universal third-trimester ultrasound (compared with selective ultrasound, which is only carried out based on risk factors or abnormal symphysis fundal height) is associated with greater diagnostic effectiveness as a screening test for SGA: those fetuses with reduced growth velocity were at increased risk of neonatal morbidity [10]. Nevertheless, meta-analysis of randomized trials has failed to demonstrate benefit of routine late pregnancy ultrasound in low-risk or unselected populations, in terms of perinatal mortality, preterm birth less than 37 weeks, caesarean section rates, and induction of labour rates [11]. It is possible that these two seemingly contradictory findings are the result of previous randomized trials lacking the use of an effective intervention after screening, or other flaws such as lack of statistical power [10].

Ultrasound

Estimation of the fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) is undertaken using standard ultrasonographic planes (Fig. 3.1).

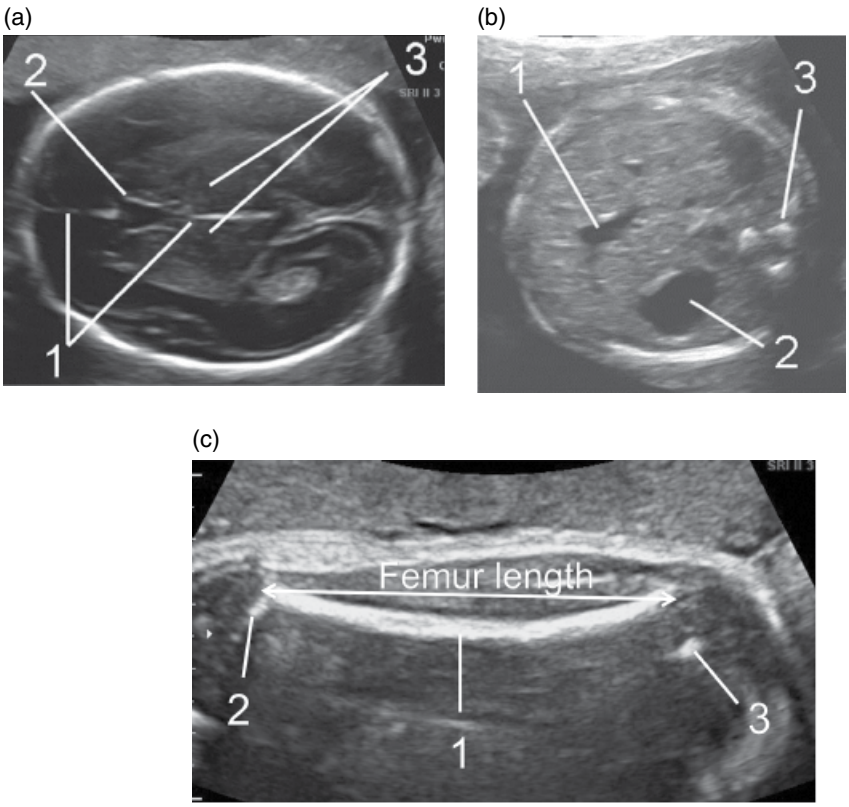

Fig. 3.1 (a) Correct ultrasound image for the measurement of the fetal head: the image is well magnified and the head is horizontal, oval in shape and symmetrical. The landmarks are (1) centrally positioned, continuous midline echo (falx cerebri); (2) midline echo broken anteriorly at one-third of its length by the cavum septum pellucidum; (3) thalami located symmetrically on each side of the midline. (b) Correct ultrasound image for the measurement of the fetal abdomen: the image is well magnified and the cross-section is circular. The landmarks are (1) a short segment of umbilical vein in the anterior third of the abdomen; (2) the stomach bubble is visible; (3) the spine is seen. Note that the bladder and kidneys should not be visible in this axial cross-section. (c) Correct ultrasound image of femur length: (1) the ossified diaphysis of the femur; in the third trimester the greater trochanter (2) and distal ossification centre (3) can be seen and this allows better orientation of the imaging plane.

Based on these parameters it is possible to calculate an estimated fetal weight (EFW). Although there are some advantages in using this estimation (for example, it is helpful in counselling parents and enabling paediatricians to make management decisions), there are disadvantages of using only a single summary measure of size. This is because individual measurement errors are compounded, resulting in 95% confidence intervals for random error in the region of 14% of birthweight. Importantly, this error is highest in exactly those pregnancies where accurate estimation is more important, namely babies with low and high birthweight [12]. Additional ultrasound measurements, including assessment of amniotic fluid and Doppler studies of uteroplacental and fetal blood flow, may aid in the clinical management of fetuses with (or at risk of) abnormal growth.

Fundal height

Depending on the availability of ultrasound, the setting and risk level of pregnancies, serial measurement of symphysis–fundal height (SFH) is often recommended as a simple, inexpensive, first-level screening tool. If this is abnormal, referral for ultrasound is then carried out. Observational cohort studies show that the use of SFH measurement is associated with very wide ranges of detection of SGA babies, from as low as 17% to as high as 93%. The marked heterogeneity in these studies is thought to be due to the variety of methodologies applied, including the use of different fundal height charts, varying thresholds for defining SGA, and a suggestion of publication bias [13]. The single randomized trial in the literature, involving 1639 women, showed no reduction in the incidence of SGA between those screened and not screened with SFH measurement, and no difference in the number of perinatal deaths [14]. Although the conclusion is that there is insufficient evidence to determine whether SFH measurement is effective, it has been argued that 'there is no suggestion that it should not be used as a screening tool', on the basis that the method is not resource intensive [15]. This view is upheld by a number of national guidelines [16,17].

Summary box 3.3

- Clinical assessment of fetal growth using SFH measurement is associated with very wide ranges of detection of SGA babies.
- Ultrasound assessment of fetal size is based on fetal HC, AC, and FL; these can be combined to calculate EFW.

Comparing the measurement to a standard or reference

Determining whether fetal growth is healthy or pathological can be challenging. This is not least because fetuses with SGA (i.e. those below the 10th centile of size) are not the same as those with FGR (i.e. those that fail to reach growth potential): it is possible for a fetus to be SGA but healthy, rather than FGR; conversely, it is possible for a fetus not to meet its growth potential yet remain in the AGA range. As it is not possible to accurately define growth potential, SGA is most often used as a surrogate. A more difficult scenario occurs in fetuses that exhibit a relative decrease in size over time by 'crossing centiles' but which remain above this cut-off of the 10th centile. In these cases careful clinical assessment is required; it is not known how many centiles (or standard deviations) can be crossed before the risk of adverse outcome increases significantly.

It is important here to highlight the difference between charts based on birthweight from those based on intrauterine EFW. Birthweight charts should not be used for assessment of fetuses. This is because in birthweight charts those with poor growth are over-represented at preterm gestations, even when excluding those births that are indicated for growth restriction; in other words, babies born prematurely are (by definition) not representative of healthy fetuses that remain *in utero* (Fig. 3.2).

One way to avoid this confusion is to assess the individual biometric variables, such as biparietal diameter (BPD), HC, AC and FL. However, this too is not straightforward, as there are a large number of available reference charts with differing results: in one study it was shown that, using three different charts, the proportion of fetuses classified with a BPD lower than the 5th centile at 20–24 weeks ranged from 6.6 to 23.7% [18]. In a systematic review of 83 fetal growth charts identified in 2012, Ioannou *et al.* [19] showed that differences in study design, data analysis and presentation contributed to these significant discrepancies between studies. A similar problem with a multitude of reference charts exists in EFW, SFH and newborn charts [20–22]. In order to overcome these issues, the concept of developing growth standards (rather than references) is discussed.

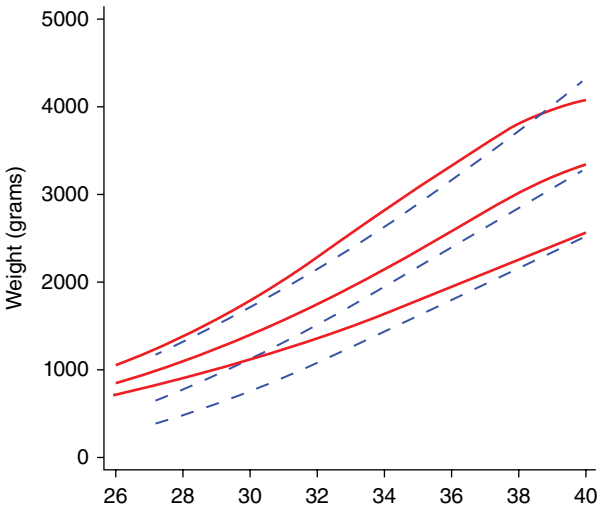

Fig. 3.2 Gestational age-specific centiles for estimated fetal weight (solid line) and birthweight of preterm born infants at the same gestation (dashed line). This demonstrates that at preterm gestations, birthweight is lower than EFW; at term these differences become very small.

Summary box 3.4

- Fetal growth charts should be based on ultrasound, not on charts of birthweight; this is because in birthweight charts, babies with poor growth are over-represented at preterm gestations.
- It is recommended that growth, including in fetuses, should be assessed using prescriptive standards which show how fetuses *should* grow when nutritional, environmental and health constraints on growth are minimal. This is different from references that represent the distribution of biometry within a population.

International standards of fetal growth and newborn size

The World Health Organization recommends the use of standards to assess human growth [23]. While references describe how fetuses (or newborns or infants) have grown at a particular time and/or place, standards describe how they *should* grow when nutritional, environmental and health constraints on growth are minimal. Thus, standards are prescriptive: they demonstrate how growth should occur under near optimal conditions. It is important to note that the distribution of biometry within a population does not constitute a standard; this is because populations at high risk may exhibit growth that is suboptimal and is associated with higher rates of adverse perinatal outcome. While the concept of growth standards has been widely accepted in paediatrics [24], until recently there has been a relative lack of knowledge regarding optimal fetal growth.

Since 2009, the INTERGROWTH-21st Project has undertaken a series of studies to address this gap in our understanding of early human growth. The overarching aim is to determine healthy fetal growth, newborn size, preterm postnatal growth and neurodevelopment in the

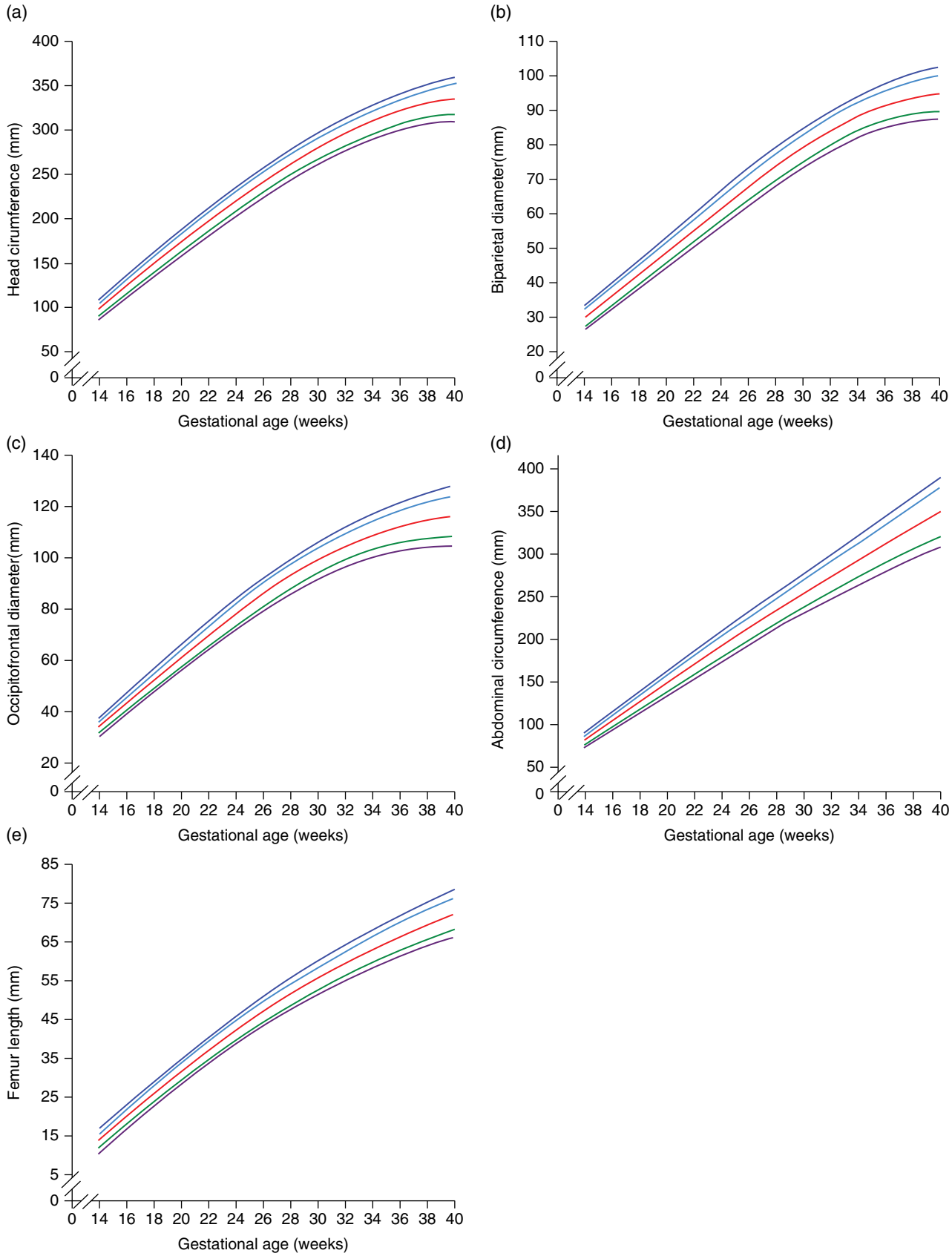

Fig. 3.3 International fetal growth standards, measured by ultrasound, from the INTERGROWTH-21st project: (a) head circumference, (b) fetal biparietal diameter, (c) fetal occipitofrontal diameter, (d) fetal abdominal circumference, and (e) fetal femur length. The lines show the 3rd, 10th, 50th, 90th and 97th smoothed centile curves.

first 1000 days of life in healthy mothers, under healthy conditions. Selection was firstly based at population level: eight diverse urban populations living in demarcated geographical or political areas were selected based on healthy environments free from pollutants, altitude less than 1600 m, and low perinatal morbidity and mortality (the selected sites were Pelotas, Brazil; Shunyi County, Beijing, China; Central Nagpur District, India; Turin, Italy; Parklands Suburb, Nairobi; Muscat, Oman; Oxford, UK, and Seattle, USA). Secondly, healthy women with a naturally conceived singleton pregnancy, and who met the individual inclusion criteria, were prospectively recruited from these healthy populations into the Fetal Growth Longitudinal Study from 9 weeks of gestation. Fetal biometry was measured every 5 weeks by ultrasound using highly standardized, blinded and scientifically rigorous protocols [25]. At birth, the same rigour was applied to measure the weight, length and head circumference of all newborns born in the entire population [26]. Infants were then followed up to the age of 2 years for detailed assessment of growth and neurodevelopment.

The studies of the INTERGROWTH-21st project have produced a uniquely detailed set of global tools and standards, based on the same healthy populations, and demonstrate healthy fetal growth (Fig. 3.3) and development from early pregnancy through to evaluation of fetal growth and EFW by ultrasound, fundal height, maternal weight gain, newborn size, as well as preterm postnatal growth. These standards challenge the perception of optimal fetal growth and also how growth problems should be identified and defined.

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4

Pre-conception Counselling

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A woman who enters pregnancy in a good state of health with a healthy diet and well-controlled medical disease is more likely to have a healthy pregnancy and a good outcome than a woman who enters pregnancy with an unhealthy lifestyle and uncontrolled medical disease. Pre-conception or pre-pregnancy counselling involves seeing women several months prior to conception in order to discuss and modify lifestyle choices and assess and improve medical health before pregnancy. The National Institute for Health and Care Excellence (NICE) has identified pre-conception counselling as an important area in their antenatal guidelines [1] and the importance of pre-conception health was highlighted in the Chief Medical Officer's Annual Report in 2014 [2].

Purpose of pre-conception counselling

All women considering having a baby should see their general practitioner (GP), and if they have a medical disease a specialist in the management of their particular disease, for pre-pregnancy counselling prior to conceiving. The purpose of these consultations is to:

- inform the woman and her partner of general advice, and advice about lifestyle behaviours including exercise, diet, smoking and drinking;
- detect any mental health or medical issues that will impact on pregnancy and advise if pregnancy should not be contemplated at present;
- assess any known medical conditions and optimize the state of the disease, in particular adjusting medications;
- discuss how the above may impact on the pregnancy, fetus and the mother;
- identify couples who are at risk of having babies with genetic disorders and refer them for genetic advice before they embark on pregnancy; and
- discuss contraception if it is considered that pregnancy is not advisable at present or if the woman prefers not to get pregnant yet.

Broadly, for any medical condition, there should be a discussion about whether becoming pregnant has risks for the mother or fetus.

- Mother: disease exacerbation (antenatally or postnatally), appropriate mode of delivery, maternal mortality.
- Fetus: malformations (genetic, teratogens), *in utero* fetal growth restriction, preterm delivery, stillbirth, neonatal morbidity and mortality.

Pre-pregnancy counselling will inform women of their risks, empowering them to make an informed decision whether or not to proceed with pregnancy. It will allow planning or prevention of pregnancy, and access to the appropriate multidisciplinary specialized services if necessary. Importantly, it is a conduit to influencing the health outcomes of the future generation, as improving maternal health and in particular obesity can impact on reducing the burden of some non-communicable diseases in the offspring.

Summary box 4.1

- All women should have pre-conception counselling to inform them of their own health, the health of their fetus in pregnancy, and the health of their offspring, empowering them to make an informed decision whether or not to proceed with pregnancy.
- It allows planning or prevention of pregnancy, and access to the appropriate multidisciplinary specialized services if necessary.

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Who needs pre-conception counselling?

All women will benefit from the general advice offered by GPs. The confidential enquiry reporting maternal deaths has specifically recommended that pre-conception counselling be provided for women of childbearing age with pre-existing serious medical or mental health conditions that may be aggravated by pregnancy, in particular the commoner conditions including epilepsy, diabetes, congenital or known acquired cardiac disease, autoimmune disorders, obesity with body mass index (BMI) of 30 or more, and severe pre-existing or past mental illness [3]. The recommendation especially applies to women prior to having assisted reproduction and other fertility treatments.

Timing of pre-conception counselling

This should ideally take place 3–6 months prior to conceiving; however, few women are sufficiently motivated to see a doctor prior to getting pregnant, even if they have a medical illness. Dedicated pre-pregnancy clinics or pre-pregnancy health check clinics would be ideal, but very few health authorities offer this service. Additionally, it is estimated that 25–40% of pregnancies are unplanned. Unplanned pregnancies are associated with adverse outcomes, including low birthweight babies, preterm delivery and postnatal depression [2]. Pre-conception advice should therefore occur opportunistically when women of childbearing age attend their GP for contraception or for baby and toddler checks, attend their specialist for review of their medical disease or if they are referred to infertility clinics.

The average age of first sexual intercourse is 16 years and 0.44% of girls under the age of 16 years in England and Wales get pregnant [4]. Two-thirds of these girls undergo a termination of pregnancy [3]. The UK has the highest teenage pregnancy rate in western Europe despite a fall of 25% in the last decade. Some medical conditions, such as complex congenital heart disease, would necessitate a discussion about pregnancy during adolescence (12–15 years old) depending on the degree of maturity of the child. This is not to encourage pregnancy in these teenagers, but to educate them of the risks that unintended pregnancy may hold for them.

Implicit in any discussion is the need for adequate contraception (see Chapter 65). Long-acting reversible contraceptive agents, including progesterone-containing implants, intrauterine devices and injections, are 20–100 times more effective in preventing pregnancy than contraceptive pills or barrier methods such as condoms [2].

Healthcare professionals who should undertake pre-conception counselling

GPs are best placed to do this as they have a long-term relationship with their patients and will usually be seeing them for contraceptive advice and for other medical conditions. Specialists also have a role, particularly diabetologists, neurologists and cardiologists, who will be seeing adolescents and women of reproductive age for regular checks of their diabetes, epilepsy or heart disease. Pre-conception counselling is vital in these groups as it can directly influence pregnancy outcome. Unfortunately some specialists may be reluctant to discuss the implications of medical disease and the associated medications in pregnancy because they are not up to date with current evidence in pregnancy, whereas some others may give incorrect advice despite not being up to date.

Misadvice is of significant concern and thus maternal medicine specialists and obstetric physicians are ideally placed to offer pre-conception advice to women with medical disease. They are well informed as to the effects of various medical diseases in pregnancy and are aware of the implications of drug use in pregnancy. Many will have dedicated pre-conception clinics in tertiary care. Many maternal medicine specialists will also be able to offer detailed contraceptive advice and in many instances are able to administer long-acting contraceptives, avoiding delay in gaining effective contraception.

General pre-conception advice

Diet

Women intending to conceive should be encouraged to eat fruit, vegetables, starchy foods (bread, pasta, rice and potatoes), protein (lean meat, fish, beans and lentils), fibre (wholegrain breads, fruit and vegetables) and dairy foods (pasteurized milk, yoghurt and hard, cottage or processed cheese) [1]. These will assist in increasing the stores of vitamins, iron and calcium. Continuing a healthy diet in pregnancy can have beneficial effects on childhood cardiovascular function [2].

The unpredictability regarding the exact moment a woman becomes pregnant leads to the recommendation that women trying to conceive should avoid the foods listed in Table 4.1, which may contain organisms or substances that can be harmful in early gestation. Even a planned pregnancy is not detected until 5–6 weeks of gestation, at which stage vulnerable organs, particularly the central nervous system, have already started developing and the neural tube is completely formed.

Table 4.1 Foods that can affect the fetus in very early pregnancy.

Food	Risk of containing	Fetal risk in early pregnancy
Unpasteurized milk Soft mould-ripened cheeses (e.g. Camembert, Brie, blue-veined cheese) Pâté (including vegetable pâté) Uncooked or under-cooked ready made meals	*Listeria*	Miscarriage
Raw shellfish (e.g. oysters)		
Uncooked or cured meat (e.g. salami)	*Toxoplasma*	Fetal CNS defects
Liver and liver products	Excess vitamin A	Cranial–neural crest tissue defects
Shark, swordfish and marlin	Methylmercury	Fetal CNS defects

CNS, central nervous system.

Vegetarians and vegans are at risk of nutritional deficiencies, particularly of vitamins B_{12} and D, and may benefit from advice from a dietitian.

Women who have a heavy intake of caffeine should be advised to cut down before pregnancy. The Food Standards Agency recommends that pregnant women should limit their consumption of caffeine in pregnancy to 300 mg daily or less (four cups of coffee, eight cups of tea, or eight cans of cola) [1]. High caffeine intake mildly increases the risk of fetal growth restriction.

Supplements

Folic acid

Folic acid 0.4 mg daily is recommended to all women trying to conceive and should be continued until 12 weeks' gestation along with an increase in folate-containing foods as this has been shown in randomized controlled trials to significantly reduce the incidence of fetal neural tube defects (NTDs) such as spina bifida and anencephaly [5]. A higher dose of folic acid (5 mg daily) is required in women:

- with a previous pregnancy affected by an NTD [6];
- who themselves are affected with an NTD;
- with a sibling or parent affected with an NTD;
- taking antifolate drugs (e.g. most antiepileptic agents, sulfasalazine);
- with diabetes [7];
- with a raised BMI (>35 kg/m^2);
- with thalassaemia trait throughout pregnancy;
- with thalassaemia or sickle cell disease throughout pregnancy.

Some countries have fortified certain foods (e.g. flour, cereals) with folate in order to help protect those women who cannot afford medical supplementation and those who have an unplanned pregnancy [8]. There is some evidence that the risk of other congenital malformations may be reduced with folate and multivitamin supplementation [9].

Vitamin D

Vitamin D 10 µg (400 IU) daily is recommended by the UK Department of Health for pregnant and breastfeeding women [10]. Vitamin D deficiency results in osteomalacia that can present with muscle and bony pain [1]. Vitamin D may play a role in early placental development, and subsequently the development of pre-eclampsia. Studies show that vitamin D levels are lower in women with pre-eclampsia compared with normotensive women, and meta-analyses have shown that women who received vitamin D supplements plus calcium compared with no supplements halve their risk of developing pre-eclampsia [11,12]. Maternal vitamin D deficiency can also result in fetal vitamin D deficiency, which is associated with hypocalcaemic seizures and childhood rickets [11].

The primary source of vitamin D is from exposure to sunlight, although it can be found in fatty fish, mushrooms, egg yolk and liver. Routine screening for vitamin D deficiency in pregnancy is not recommended. Women with the following risk factors will need to empirically take a higher dose of vitamin D (at least 1000 IU daily) [11]:

- skin pigmentation (melanin reduces the absorption of ultraviolet B sunlight and reduces cholecalciferol production by at least 90%);
- poor sun exposure (e.g. covered skin);
- factors affecting its absorption (gastrointestinal disease, phytates in chapatti flour);
- obesity (vitamin D is deposited in fat stores in obese individuals, making it less bioavailable);
- previous child with rickets or vitamin D deficiency;
- previous child who had neonatal fractures at delivery.

Women with renal disease may not metabolize vitamin D effectively and will require the use of active vitamin D metabolites instead [11].

Smoking

Women should be advised to stop smoking prior to pregnancy. They are usually aware of the risks to their own health, but are often less aware of the risks to the fetus, which include miscarriage, placental abruption, placenta praevia, premature rupture of membranes, preterm delivery, low birthweight, cleft lip and cleft palate, perinatal mortality, sudden infant death syndrome and

impaired cognitive development [1]. Discussion of these risks often provides a strong motivation to pregnant women to stop smoking. It is estimated that if all pregnant women stopped smoking there would be a 10% reduction in fetal and infant deaths. Advice from the doctor, smoking cessation programmes and self-help manuals have been shown to help women stop smoking. Nicotine replacement therapy including nicotine patches and e-cigarettes, can help wean women off tobacco.

Alcohol

The UK Department of Health advice recommends that women who are pregnant or planning pregnancy should be advised that the safest approach is not to drink alcohol at all [13]. In the first trimester there may be an increased risk of miscarriage. Thereafter, although there is no evidence of fetal harm with drinking one to two standard units of alcohol once or twice per week, there is no clear scientific evidence to support a quantified limit for drinking in pregnancy. The dangers to the fetus of drinking alcohol in pregnancy occur with greater consumption, so that women who binge drink (more than five standard drinks or 7.5 UK units on a single occasion) or drink heavily are at risk of subfertility, miscarriage, aneuploidy, structural congenital anomalies, fetal growth restriction, perinatal death and developmental delay [1,13]. Binge drinkers are more likely to have an unplanned pregnancy and hence may continue to drink erratically in the first trimester without knowing they are pregnant. Fetal alcohol syndrome occurs in 0.6 per 1000 live births (Canadian data) and is characterized by distinctive facial features, low birthweight, and behavioural and intellectual difficulties in later life. There is a further spectrum of fetal alcohol disorders [13]. Alcohol misuse can result in maternal ill health and is a significant cause of maternal death [3].

Body weight

Women should be advised to enter pregnancy with a normal BMI of 18.5–24.9 kg/m^2 [2].

Underweight

Women who are underweight (BMI <18.5 kg/m^2) may find it difficult to conceive due to anovulatory cycles. They are at risk of osteoporosis and nutritional deficiencies. They have an increased chance of fetal intrauterine growth restriction and low birthweight babies. They should be assessed for eating disorders.

Obesity

Overweight women (BMI 25–29.9 kg/m^2) and obese women (BMI ≥30 kg/m^2) should lose weight by dieting and exercise before conceiving. They may require referral to a dietitian. They should be informed of the adverse pregnancy outcomes associated with obesity (Table 4.2) [14].

Table 4.2 Risks of obesity to mother and her offspring.

Maternal risks of obesity
Subfertility
Miscarriage
Hypertensive disease
Gestational diabetes
Thromboembolism
Infection
Cardiac disease
Instrumental deliveries
Caesarean section
Postpartum haemorrhage
Maternal death
Risks to fetus of maternal obesity
Neural tube defects
Large for dates
Preterm delivery
Shoulder dystocia
Increase in birthweight
Stillbirth
Risks to offspring of maternal obesity
Neonatal hypoglycaemia
Obesity as children and adults
Diabetes
Hypertension

For women who are morbidly obese (obesity grade III) with a BMI of 40 kg/m^2 or more it is very difficult to achieve a normal BMI. In addition to referral to a dietitian, they should be assisted to lose weight by a variety of methods including prescription of weight reduction medication in a carefully supervised manner and referral for bariatric surgery. They should be strongly advised to defer pregnancy until they have lost weight.

Bariatric surgery results in weight loss either by reducing gastric capacity (e.g. sleeve gastrectomy, laparoscopic adjustable gastric banding) or by malabsorption (e.g. Roux-en-Y gastric bypass, biliopancreatic diversion) and this weight loss results in improved fertility [15]. However, women should be advised not to get pregnant whilst they are losing weight following surgery. They should use adequate contraception, preferably a non-oral method, and wait until their BMI stabilizes to prevent nutritional deficiencies affecting the fetus. Maternal and fetal outcomes improve following bariatric surgery, with reduced rates of gestational diabetes, pre-eclampsia, and large for gestational age babies. Studies have shown an increased incidence of small for gestational age babies and an increased chance of pretem birth following bariatric surgery [15]. Women should be recommended to remain on vitamin supplementation.

The method of bariatric surgery may influence outcomes, although few studies have compared pregnancy

outcomes after different types of surgery. There is less anaemia and vitamin and micronutrient deficiency with sleeve gastrectomy and gastric banding compared with Roux-en-Y gastric bypass or biliopancreatic diversion, which are more effective at achieving long-term weight loss [15].

Summary box 4.2

Women should modify their diet, stop or reduce smoking and alcohol intake, aim to enter pregnancy with a normal BMI and take folic acid supplementation peri-conceptionally.

Advice regarding medications

It is a misconception that most drugs are harmful in pregnancy. Unfortunately, this inaccurate belief is held by the public and many health professionals including doctors. Many women will discontinue vital medications as soon as they realize they are pregnant and risk a flare of their disease, which will cause harm to them and their babies.

Women with medical diseases on treatment should have a discussion regarding the safety profile of the medications in pregnancy before they conceive. There are valid concerns about the safety of some drugs in pregnancy, but most commonly used medications have good safety data and can continue to be taken in pregnancy. Even if a drug is known to have a risk of teratogenicity, the consequences of discontinuing it may be worse than the effects of taking it, justifying continuation of therapy (e.g. antiepileptic drugs). The smallest effective dose should be used. If a drug with a better safety profile is available, it should be used instead.

Drugs that are harmful to the fetus may have an effect depending on the time of exposure.

- Pre-embryonic stage (0–14 days after conception): can result in miscarriage, e.g. methotrexate, misoprostol, mifepristone, thalidomide, retinoids.
- First trimester: affect organogenesis, resulting in congenital malformation (teratogen), e.g. antiepileptic drugs, angiotensin-converting enzyme (ACE) inhibitors, warfarin.
- Second and third trimester: can cause growth restriction, affect neuropsychological behaviour (e.g. sodium valproate, dose related) or have toxic effects on fetal tissues (e.g. ACE inhibitors, tetracycline).

It is important to know when harmful drugs carry a risk of fetal harm as use of an individual drug at a different stage in pregnancy may have no effect on the fetus, for example a teratogen will bear the risk of congenital malformation with first-trimester use, but may be safe to use thereafter if required. A list of known teratogens and drugs that are safe to use in pregnancy is shown in Table 4.3.

Table 4.3 Drug safety in pregnancy.

Drugs that are harmful in pregnancy
NSAIDs after 28–30 weeks' gestation
Warfarin
Tetracycline, doxycycline, ciprofloxacin
Paroxetine
ACE inhibitors, angiotensin receptor blockers
Statins
Retinoids
Mycophenolate mofetil
Drugs that can be used in pregnancy (if clinically necessary: benefits outweigh risks)
Analgesics: paracetamol, codeine
Antacids, ranitidine, omeprazole
Most antibiotics (avoid trimethoprim in first trimester and avoid nitrofurantoin at term)
Most antidepressants (some SSRIs, tricyclic antidepressants)
Antihypertensives: methyldopa, nifedipine, labetalol, doxazosin, prazosin, hydralazine
Antiemetics: cyclizine, promethazine, prochlorperazine, metoclopramide, domperidone, ondansetron
Antihistamines
Beta-agonists
Inhaled and oral steroids
Hormones (insulin, thyroxine)
Laxatives
Low-dose aspirin
Some biologics

ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Summary box 4.3

- Most commonly used medications have good safety data and can continue to be taken in pregnancy in the smallest effective dose.
- Inform women of any risks to pregnancy of medications they are taking.
- Change teratogenic medications before pregnancy if possible.

Advice related to maternal age

Delaying childbirth is associated with worsening reproductive outcomes, with more infertility, miscarriage and medical comorbidity and an increase in maternal and fetal morbidity and mortality.

Table 4.4 shows the dramatic decline in fertility and rise in miscarriage rate in women over the age of 40 years [16]. The fertility rate is taken from 10 different populations that did not use contraception between the seventeenth and twentieth centuries. This provides the best approximation of the ability of women to conceive.

Table 4.4 Risk of infertility and spontaneous miscarriage with age [12].

Maternal age (years)	Fertility rate per 1000 married women	Spontaneous miscarriages (%)
20–24	470	11
25–29	440	12
30–34	400	15
35–39	330	25
40–44	190	51
≥45	40	93

Table 4.5 Risk of pregnancy-specific diseases with age [18].

	Maternal age	
Pregnancy-related disease	20–29 years	>40 years
Pre-eclampsia	3.4%	5.4%
Gestational diabetes	1.7%	7%

In current times, the fertility rate in older women is increasing as many older women resort to assisted reproductive technologies (ART) (see Chapter 52) such as *in vitro* fertilization in order to conceive. The risks of ART include an increased incidence of ovarian hyperstimulation syndrome and multiple pregnancies, which further compounds all maternal age-related risks.

The risk of pre-existing hypertension, obesity, diabetes, ischaemic heart disease and cancer all increase with age and are twofold to fivefold greater in women over the age of 40 compared with women in their twenties [17]. These risks need to be put into context, as the absolute incidences of these diseases are low. Table 4.5 shows how the risks of pre-eclampsia and gestational diabetes increase with maternal age. Maternal death in women over 40 years of age, though rare, is triple that of women in their early twenties [3].

Chromosomal abnormalities increase dramatically with increasing maternal age (Table 4.6). Women should be informed of these risks and advised that prenatal diagnosis, both screening and definitive testing, is available in pregnancy (see Chapter 6). The option of termination or continuation of pregnancy in the event of an affected fetus should be discussed.

Older mothers have poorer uterine contractility and a higher incidence of assisted vaginal deliveries and caesarean sections compared with younger mothers. The babies of older mothers are more likely to be of low birthweight and the stillbirth rate at all gestations is higher. At 41 weeks' gestation, the risk of a stillbirth in women aged 35–39 years is nearly double that of a woman in her twenties. The risk rises to 3.5-fold higher in women over 40 years [19]. However, it is important to remember that the absolute risk of stillbirth is still small.

Table 4.6 Risk of Down's syndrome (trisomy 21) with maternal age.

Maternal age (years)	Risk of chromosomal abnormality	Risk of Down's syndrome
15–24	1 in 500	1 in 1500
25–29	1 in 385	1 in 1100
35	1 in 178	1 in 350
40	1 in 63	1 in 100
45	1 in 18	1 in 25

The Royal College of Obstetricians and Gynaecologists states that women who start a family in their twenties or complete it by age 35 years face significantly reduced risks. Women contemplating delaying pregnancy should be told the health consequences of this and advised that completion of childbearing in their twenties will vastly reduce their obstetric and medical risks. If they do delay pregnancy to their forties for whatever reason, they should be supported. The absolute risks to the mother remain small, although risks of miscarriage and aneuploidy are high.

Summary box 4.4

Delaying childbirth is associated with worsening reproductive outcomes, with more infertility, miscarriage, chromosomal abnormalities and medical comorbidity and an increase in maternal and fetal morbidity and mortality.

Genetic counselling

Couples who have had a previous child with a chromosomal abnormality, an inherited disease such as cystic fibrosis or Fanconi's anaemia, or with a family history of a genetic disorder should be referred for genetic counselling so that they can be informed of the risks of recurrence and whether prenatal diagnosis is available for detection of the disorder. In some cases pre-implantation genetic diagnosis is available (see Chapter 52).

Advice regarding access to maternity care

The importance of accessing maternity care early should be emphasized to women of childbearing age contemplating pregnancy. They should aim to book for antenatal

care as soon as possible, particularly if they have a pre-existing medical disorder, but certainly by 10 weeks' gestation to allow the relevant screening tests to be performed.

Conditions where pregnancy is not recommended

There are some conditions where pregnancy is not recommended due to the high risks of maternal and fetal morbidity and mortality.

- Pulmonary arterial hypertension (mortality approximately 25%).
- Severe systemic ventricular dysfunction.
- Previous peripartum cardiomyopathy with any residual impairment of left ventricular function.
- Severe left heart obstruction, e.g. aortic/mitral stenosis with valve area <1 cm^2.
- Marfan syndrome with aortic dilatation >4 cm.
- Diabetes with HbA_{1c} >10%.
- Severe respiratory compromise, e.g. forced vital capacity <1 L.
- Breast cancer within last 2 years.
- Severe renal failure (creatinine >250 mmol/L).
- Recurrent uterine scar rupture.

The most effective contraceptive should be used in these circumstances. Other methods of having a family, including surrogacy and adoption, should be discussed if pregnancy is not recommended. If maternal life expectancy is limited, discussion on the appropriateness of having a baby (by pregnancy, surrogacy or adoption) as well as issues of childcare in the event of maternal mortality or severe morbidity should be discussed.

There may be women who choose, after full counselling, to conceive. They should be reassured that they will be looked after in a multidisciplinary team if this is their choice.

Summary box 4.5

If pregnancy is not recommended due to severe maternal or fetal risks:

- use the most effective contraceptive;
- discuss surrogacy and adoption if maternal life expectancy is not severely limited.

Specific medical diseases

In general, pregnancy outcome is better if women conceive when their medical disease is quiescent, for example connective tissue diseases such as systemic lupus erythematosus. Women who conceive when their disease is actively flaring are more likely to further clinically deteriorate in pregnancy, have a growth restricted baby or have a miscarriage or preterm birth compared with women whose disease is well controlled.

Diabetes

There are many international guidelines on pre-conception care of women with diabetes, the latest being from NICE [7] and the American Diabetes Association [20]. Pre-pregnancy control of diabetes directly influences miscarriage and congenital malformation rates. NICE recommends weight reduction for women with a BMI over 27 kg/m^2, monitoring of metabolic control and achieving an HbA_{1c} target of less than 6.1% before conception to help reduce these risks. Metformin and insulin are safe to use before conception and throughout pregnancy. All other blood glucose-lowering medications should be stopped before pregnancy and replaced with insulin. The woman and her partner should be taught about awareness and management of hypoglycaemia. Pregnancy is not recommended in women with HbA_{1c} over 10% and adequate contraception should be provided until target glucose and HbA_{1c} levels are achieved. Women should take a higher dose of folic acid around conception as diabetes is associated with an increased incidence of NTDs.

Diabetic complications should be reviewed and managed before pregnancy. Pre-existing retinopathy can progress rapidly in pregnancy and should be treated before pregnancy [7]. Urine should be tested for microalbuminuria. Women should be warned that diabetic nephropathy can progress in pregnancy, especially as ACE inhibitors need to be discontinued.

Pre-eclampsia

Women with a low dietary intake of calcium given calcium supplements at a dose of at least 1 g before and during pregnancy can halve their risk of developing pre-eclampsia [21]. Women who have had pre-eclampsia in a previous pregnancy have a 10% chance of recurrence. The recurrence is higher if the onset was early (<34 weeks' gestation), and in this group administration of low-dose aspirin from early pregnancy is associated with reduced risks of developing pre-eclampsia [22]. Women should be advised to start aspirin as soon as their pregnancy test is positive. They should not take it before conception as this may increase their risk of luteinized unruptured follicle syndrome, which can lead to female subfertility. Women at high risk of pre-eclampsia should also take at least 800 IU of vitamin D combined with calcium [11].

Hypertension

Women with pre-existing hypertension should have had secondary causes excluded and an assessment made of end-organ damage in those with long-standing hypertension. Their current drug treatment and blood pressure control needs to be reviewed, with replacement of teratogenic drugs (e.g. ACE inhibitors, angiotensin receptor blockers) with safer agents [23]. They should be informed of the increased risk of pre-eclampsia and how this can be reduced by taking low-dose aspirin once pregnant.

Renal impairment

Women with renal disease should be advised to conceive when their degree of renal impairment is mild to moderate. Delaying pregnancy may result in further loss of renal function. A pregnancy in these circumstances not only increases the risk of pre-eclampsia, fetal growth restriction and preterm delivery, but also the chances of accelerating the onset of end-stage renal failure. There are some women who conceive whilst on renal dialysis. However, maternal and fetal outcomes are much improved if they conceive 2 years following a renal transplant.

Cardiac disease

Women with cardiac disease should have a risk assessment, with full history, examination and investigations as appropriate (e.g. ECG, echocardiogram, MRI). The effects of the cardiac disease on pregnancy and the effects of the pregnancy on the cardiac disease should be assessed, particularly the risk of deterioration, the effect of treatment or intervention in pregnancy in the event of deterioration, and fetal and maternal mortality risk. Some cardiac conditions may require surgical correction prior to pregnancy, for example severe mitral stenosis requiring valvuloplasty or valve replacement. Other conditions may require planning for alteration of anticoagulation in early pregnancy (e.g. metal heart valves). Some conditions have such a high maternal mortality associated with them that pregnancy is not recommended (e.g. pulmonary arterial hypertension). A decision should be reached whether pregnancy should be contemplated, delayed or avoided, with adequate contraceptive advice [24].

The long-term prognosis following pregnancy is important. Despite one successful pregnancy, some conditions have a high recurrence risk (e.g. peripartum cardiomyopathy) and others can deteriorate with age, increasing the risk to future pregnancies. Referral should be made to a geneticist where there is a family history of heart disease with features suggesting an underlying genetic or chromosomal abnormality.

Summary box 4.6

Pre-existing medical disease

- Fully assess, and optimize medical and surgical treatment before conception.
- Discuss impact of disease and medications on the pregnancy, fetus and mother.
- Conceive when disease quiescent or well controlled.

Previous pregnancy-related disease

- Discuss recurrence risks and strategies for prevention of recurrence.

Previous poor obstetric history

Women who have had a previous traumatic delivery or adverse pregnancy outcome may benefit from a discussion with an obstetrician prior to conception. They should all have had a debrief following the delivery, but may have unresolved issues or uncertainties regarding the risks of another pregnancy. This visit would allow plans for frequency of antenatal care, requirements for fetal surveillance and delivery plans to be discussed, allowing couples to make an informed decision prior to contemplating further pregnancy.

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5

Antenatal Care

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The care of pregnant women presents a unique challenge to modern medicine. Most women will progress through pregnancy in an uncomplicated fashion and deliver a healthy infant requiring little medical or midwifery intervention. Unfortunately, a significant number will have medical problems that will complicate their pregnancy or develop such serious conditions that the lives of both themselves and their unborn child will be threatened. In 1928, a pregnant woman faced a 1 in 290 chance of dying from an obstetric complication related to the pregnancy; the most recent surveillance of maternal deaths between 2011 and 2013 put this figure at 1 in 34,394 [1]. Undoubtedly, good antenatal care has made a significant contribution to this reduction. The current challenge of antenatal care is to identify those women who will require specialist support and help while allowing uncomplicated pregnancies to progress with minimal interference. The antenatal period also allows the opportunity for women, especially those in their first pregnancy, to receive information from a variety of healthcare professionals regarding pregnancy, childbirth and parenthood.

Aims of antenatal care

Antenatal education

Provision of information

Women and their partners have the right to be involved in all decisions regarding their antenatal care. They need to be able to make informed decisions concerning where they will be seen, who will undertake their care, which screening tests to have and where they plan to give birth. Women must have access to evidence-based information in a format they can understand. Current evidence suggests that insufficient written information is available especially at the beginning of pregnancy and information provided can be misleading or inaccurate. *The Pregnancy Book* [2] provides information on the developing fetus, antenatal care and classes, rights and benefits as well as a list of useful organizations. Many leaflets have been produced by the Midwives Information and Resource Service (MIDIRS) that helps women to make informed objective decisions during pregnancy. The Royal College of Obstetricians and Gynaecologists (RCOG) has also produced many pregnancy-related patient information leaflets, most of them accompanying the relevant 'Green-top guidelines' for clinicians. Written information is particularly important to help women understand the purpose of screening tests and the options that are available and to advise on lifestyle considerations including dietary recommendations. Available information needs to be provided at first contact and must take into account cultural and language barriers. Local services should endeavour to provide information that is understandable to those whose first language is not English and to those with physical, cognitive and sensory disabilities. Translators will be frequently required in clinics with an ethnic mix.

There will be greater emphasis in the future in providing electronic sources of information. Women will want to be able to access their medical records digitally on smartphones and relevant information on pregnancy and childbirth through apps. While this would allow women to access up-to-date information enabling informed choices, it will require careful governance to ensure personal data safety, the accuracy of the information and availability for all.

Couples should also be offered the opportunity to attend antenatal classes. Ideally such classes should discuss physiological and psychological changes during pregnancy, fetal development, labour and childbirth and how to care for the newborn baby. Evidence

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

shows a greater acquisition of knowledge in women who have attended such classes compared with those who have not.

Lifestyle concerns

At an early stage in the pregnancy women require lifestyle advice, including information on diet and food, work during pregnancy and social aspects, for example smoking, alcohol, exercise and sexual activity.

Women should be advised of the benefits of eating a balanced diet that contains plenty of fruit and vegetables, starchy foods such as pasta, bread, rice and potatoes, protein, fibre and dairy foods. They should be informed of foods that could put their fetus at risk. Listeriosis is caused by the bacterium *Listeria monocytogenes* which can present with a mild flu-like illness but is associated with miscarriage, stillbirth and severe illness in the newborn. Contaminated food is the usual source including unpasteurized milk, ripened soft cheeses and pâté. Toxoplasmosis contracted through contact with infected cat litter or undercooked meat can lead to permanent neurological and visual problems in the newborn if the mother contracts the infection during pregnancy. To reduce the risk, pregnant women should be advised to thoroughly wash all fruits and vegetables before eating and to cook all meats thoroughly, including ready-prepared chilled meats. Written information from the UK Food Standards Agency (*Eating While you are Pregnant*) can also be helpful. For example, the Food Standards Agency advises women to reduce the consumption of caffeine to 200 mg/day (equivalent to two mugs of instant coffee), because of its association with low birthweight and miscarriage.

Women who have not had a baby with spina bifida should be advised to take folic acid 400 μg/day from preconception until 12 weeks of gestation to reduce the chance of fetal neural tube defects (NTDs). However, research analysis of the population incidence of NTDs has failed to show the efficacy of this strategy. This may be due to inadequate pre-conceptual intake of folate and/or poor compliance. Suggestions of adding folate to certain foods (e.g. flour) to ensure population compliance (already occurring in some countries including the USA and Canada) remain debatable.

Current evidence does not support routine iron supplementation for all pregnant women and can be associated with some unpleasant side effects such as constipation. However, any woman who is iron deficient must be encouraged to take iron therapy prior to the onset of labour as any excess blood loss at delivery will increase maternal morbidity. The intake of vitamin A (liver and liver products) should be limited in pregnancy to approximately 700 mg/day because of fetal teratogenicity.

Women should be informed at the booking visit about the importance for their own and their baby's health of maintaining adequate vitamin D stores during pregnancy and while breastfeeding. Women are advised to take 10 μg of vitamin D per day as found in the Healthy Start multivitamin supplement. This is particularly important in those most at risk, including women with limited exposure to sunlight, a body mass index (BMI) above 30 kg/m^2, those of South Asian, African, Caribbean or Middle Eastern family origin and those with poor dietary intake of vitamin D.

Because alcohol passes freely across the placenta, women should be advised not to drink excessively during pregnancy. The current UK Chief Medical Officer's advice for pregnant women is that if a woman is pregnant or planning a pregnancy, the safest approach is not to drink alcohol at all, to keep risks to the baby to a minimum. Binge drinking and continuous heavy drinking cause the fetal alcohol syndrome, characterized by low birthweight, a specific facies, and intellectual and behavioural difficulties later in life. Although the evidence of harm from low levels of alcohol consumption is lacking, it is highlighted that 'the safer option is not to drink alcohol at all during pregnancy'.

Approximately 27% of women are smokers at the time of birth of their baby. Smoking is significantly associated with a number of adverse outcomes in pregnancy, including increased risk of perinatal mortality, placental abruption, preterm delivery, preterm premature rupture of the membranes, placenta praevia and low birthweight. While there is evidence to suggest that smoking may decrease the incidence of pre-eclampsia, this must be balanced against the far greater number of negative associations. The recent NHS England care bundle for reducing stillbirth recommends carbon monoxide testing of all pregnant women at the antenatal booking appointment followed by referral, as appropriate, to a Stop Smoking service/specialist, based on an opt-out system [3]. Although there is mixed evidence for the effectiveness of smoking cessation programmes, women should be encouraged to use local NHS Stop Smoking services and the NHS pregnancy smoking helpline [4]. Pregnant women who are unable to stop smoking should be informed of the benefits of reducing the number of cigarettes they smoke. A 50% reduction can significantly reduce the fetal nicotine concentration and is associated with an increase in the birthweight.

Women who use recreational drugs must be advised to stop or be directed to rehabilitation programmes. Evidence shows adverse effects on the fetus and its subsequent development.

Continuing moderate exercise in pregnancy or regular sexual intercourse does not appear to be associated with any adverse outcomes. Certain physical activity should

be avoided such as contact sports which may cause unexpected abdominal trauma. Scuba diving should also be avoided because of the risk of fetal decompression disease and an increased risk of birth defects.

Physically demanding work, particularly those jobs with prolonged periods of standing, may be associated with poorer outcomes such as preterm birth, hypertension and pre-eclampsia, and small-for-gestational-age babies but the evidence is weak and employment per se has not been associated with increased risks in pregnancy. Women require information regarding their employment rights in pregnancy and healthcare professionals need to be aware of the current legislation.

Help for the socially disadvantaged and single mothers must be organized and ideally a one-to-one midwife allocated to support these women. The midwife should be able to liaise with other social services to ensure the best environment for the mother and her newborn child. Similar individual help is needed for pregnant teenagers and midwife programmes need to provide appropriate support for these vulnerable mothers.

Common symptoms in pregnancy

It is common for pregnant women to experience unpleasant symptoms in pregnancy caused by the normal physiological changes. However, these symptoms can be quite debilitating and lead to anxiety. It is important that healthcare professionals are aware of such symptoms, can advise appropriate treatment and know when to initiate further investigations.

Extreme tiredness is one of the first symptoms of pregnancy and affects almost all women. It lasts for approximately 12–14 weeks and then resolves in the majority.

Nausea and vomiting in pregnancy is one of the commonest early symptoms. While it is thought that this may be caused by rising levels of human chorionic gonadotrophin (hCG), the evidence for this is conflicting. Hyperemesis gravidarum, where fluid and electrolyte imbalance and nutritional deficiency occur, is far less common, complicating approximately 3.5 per 1000 pregnancies. Nausea and vomiting in pregnancy varies in severity but usually presents within 8 weeks of the last menstrual period. Cessation of symptoms is reported by most by about 16–20 weeks. Various non-medical treatments have been advocated but the ones which appear to be effective are ginger and P6 (wrist) acupressure. According to the NICE antenatal care guideline, antihistamines (prochlorperazine, promethazine and metoclopramide) appear to be the pharmacological agents of choice, as they reduce nausea and are safe in relation to teratogenicity (metoclopramide has insufficient safety data to be recommended as a first-line agent but no association with malformations has been reported), although they are associated with drowsiness [4]. However, the recent Cochrane review concludes there is a lack of high-quality evidence to support any particular intervention [5].

Constipation complicates approximately one-third of pregnancies, usually decreasing in severity with advancing gestation. It is thought to be related in part to poor dietary fibre intake and reduction in gut motility caused by rising levels of progesterone. Diet modification with bran and wheat fibre supplementation helps, as well as increasing daily fluid intake.

Heartburn is also a common symptom in pregnancy but, unlike constipation, occurs more frequently as the pregnancy progresses. It is estimated to complicate one-fifth of pregnancies in the first trimester, rising to about 75% by the third trimester. It is due to the increasing pressure caused by the enlarging uterus combined with the hormonal changes, leading to gastro-oesophageal reflux. It is important to distinguish this symptom from the epigastric pain associated with pre-eclampsia which will usually be associated with hypertension and proteinuria. Symptoms can be improved by simple lifestyle modifications such as maintaining an upright posture especially after meals, lying propped up in bed, eating small frequent meals and avoiding fatty foods. Proprietary antacid formulations, histamine H_2-receptor antagonists and proton-pump inhibitors are all effective, although it is recommended that the latter be used only when other treatments have failed because of their unproven safety in pregnancy.

Haemorrhoids are experienced by 1 in 10 women in the last trimester of pregnancy. There is little evidence for either the beneficial effects of topical creams in pregnancy or indeed their safety. Diet modification may help and in extreme circumstances surgical treatment considered, although this is unusual since the haemorrhoids often resolve after delivery.

Varicose veins occur frequently in pregnancy. They do not cause harm and while compression stockings may help symptoms they unfortunately do not prevent varicose veins from appearing.

The nature of physiological vaginal discharge changes in pregnancy. However, if it becomes itchy, malodorous or is associated with pain on micturition, it may be due to an underlying infection such as trichomoniasis, bacterial vaginosis or candidiasis. Appropriate investigations and treatment should be instigated.

Backache is another potentially debilitating symptom, with an estimated prevalence of up to 61% in pregnancy. There is limited research on effective interventions for backache, but massage therapy, exercise in water and back care classes may be helpful in symptom relief.

Domestic violence

The UK Government defines domestic violence as:

> Any incident or pattern of incidents of controlling, coercive, threatening behaviour, violence or abuse, between those aged 16 or over who are or have been intimate partners or family members regardless of gender or sexuality. The abuse can encompass, but is not limited to: psychological, physical, sexual, financial or emotional (Home Office 2013).

This includes issues of concern to black and minority ethnic communities, such as so-called honour-based violence, female genital mutilation and forced marriage. Family members are defined as mother, father, son, daughter, brother, sister and grandparents, whether directly related, in-laws or stepfamily.

Whatever form it takes, domestic abuse is rarely a one-off incident and should instead be seen as a pattern of abusive and controlling behaviour through which the abuser seeks power over their victim. Typically the abuse involves a pattern of abusive and controlling behaviour which tends to get worse over time. The abuse can begin at any time – in the first year or after many years together. It may begin, continue or escalate after a couple have separated and may take place not only in the home but also in a public place.

Domestic abuse occurs across society regardless of age, gender, race, sexuality, wealth and geography. However, the figures show that it consists mainly of violence by men against women. Children are also affected both directly and indirectly, and there is also a strong correlation between domestic violence and child abuse, with suggested overlap rates of between 40 and 60%.

At least one in four women have experienced domestic violence and this figure is likely to be an underestimate because all types of domestic violence and abuse are under-reported in health and social research, to the police and to other services.

Pregnancy represents a particularly vulnerable time for women. A woman who is experiencing domestic abuse may have difficulties using antenatal care services because the perpetrator of the abuse may try to prevent her from attending appointments. The woman may be afraid that disclosure of the abuse will worsen her situation. Every hospital should have a domestic violence policy promoting the safeguarding welfare of adults at risk of harm, children and young people, and the unborn baby. All healthcare professionals should be alert to the symptoms or signs of domestic violence and have a clear understanding of local safeguarding policies to support vulnerable patients.

Women should be given the opportunity to disclose domestic violence in an environment in which they feel secure. This can be encouraged by making available information and support tailored to women suspected to be experiencing domestic abuse and providing more flexible appointments if needed. Sources of support for women, including addresses and telephone numbers for social services, the police, support groups and women's refuges, should be displayed in appropriate areas. A telephone number that is agreed with the woman and on which it is safe to contact her should be obtained from those at risk.

When domestic violence is either suspected or known, an opportunity must be provided for discussions about individual circumstances in a quiet and private environment, and where the woman can be seen alone. The presence of a partner or a relative may constrain discussion of domestic violence and could place the woman in greater danger. The limitations of confidentiality must be clearly explained at the outset of the discussion. Women often find it difficult to disclose abuse even when they are asked about it and may deny that it is happening. Asking about abuse sends a clear message that abuse is wrong, and that the healthcare professional concerned takes the subject very seriously, giving a clear message that she can come back to the service when she feels ready to disclose. Practitioners may need to screen for domestic violence more than once and this should be a routine part of good clinical practice.

In asking questions it is important that practitioners remain non-judgemental, are empathetic, and listen and be aware of the woman's reaction.

If a woman discloses domestic abuse, immediate safety actions to reduce and manage the risk may be necessary. Actions will depend on whether the practitioner is present with the woman and she is safe in the immediate future, or whether she is still in a vulnerable location (e.g. with the perpetrator). Actions may include the following.

- Calling hospital security or the police in the event of an emergency.
- Is the person in need of immediate treatment for an injury?
- Are there children or vulnerable adults present? Consider if you need to make an onward safeguarding referral: contact the hospital safeguarding team for advice.
- Does the woman have somewhere safe to stay tonight?
- Can she stay with friends or family?
- Does she need temporary accommodation?

A supportive action plan should be discussed and agreed with the woman. The healthcare professional will need

to ensure that the risks to the individual and any children are not increased following disclosure and should discuss their immediate and longer-term safety and the options available and appropriate for them.

The plan of follow-up and action should be documented to provide clarity around any actions to be taken. If an agreed action plan is not followed up, the individual may feel that she has not been listened to. If the individual is unable to follow through with actions discussed, this should be documented and further follow-up and support offered.

Such women need to be supported in their use of antenatal services by training healthcare professionals in the identification and care of at-risk women. All hospital staff should be aware of their responsibilities in relation to safeguarding, including domestic violence. They will be able to achieve this through full compliance with the policy and procedures of their employing organization and attendance at appropriate mandatory training days. Recognition of the signs of domestic violence are now a required competency in Core Module 8: Antenatal Care in the RCOG Curriculum for Trainees. In addition, those undertaking the Advanced Training Skills Module in Forensic Gynaecology will be required to demonstrate significant skill in the recognition and management of domestic violence.

Female genital mutilation

Female genital mutilation (FGM) is defined by the World Health Organization (WHO) as 'all procedures involving partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons' [6]. The WHO classification of FGM is shown in Table 5.1.

FGM is a human rights violation and a form of child abuse because it breaches the United Nations Convention on the Rights of the Child. FGM is practised in 29 African countries but is also performed in non-African countries. It is estimated that over 125 million women and girls have undergone FGM worldwide [7]. In England and Wales it is estimated that there are 137 000 women and girls living with FGM, as they were born in countries where FGM is practised.

Table 5.1 WHO classification of female genital mutilation.

Type 1	Partial or total removal of the clitoris and/or the prepuce (clitoridectomy)
Type 2	Partial or total removal of the clitoris and the labia minora, with or without excision of the labia majora (excision)
Type 3	Narrowing of the vaginal orifice with creation of a covering seal by cutting and appositioning the labia minora and/or the labia majora, with or without excision of the clitoris (infibulation)
Type 4	All other harmful procedures to the female genitalia for non-medical purposes, for example pricking, piercing, incising, scraping and cauterization

FGM is associated with many complications, both short term (e.g. bleeding and infection) and long term (e.g. genital scarring, urinary problems, dyspareunia, menstrual problems and obstetric complications). In 2015, the RCOG published the second edition of the Green-top guideline on FGM and its management [8].

The obstetric complications include prolonged labour, perineal trauma, postpartum haemorrhage, increased risk of caesarean section, increased need for neonatal resuscitation and risk of early neonatal death and stillbirth. Given the potential severity of the obstetric complications, it is important that women with FGM are identified in the antenatal period. This is equally important for the protection of the unborn female child as she will be at risk of FGM as a child.

All women should be asked about a history of FGM at their booking visit, irrespective of the country of origin. Ideally, they will be referred to a dedicated multidisciplinary service and the majority will require consultant-led care. Some will require psychological support and some may require antenatal de-infibulation, especially women with FGM type 3, if it is considered that vaginal assessment in labour is likely to be difficult. The RCOG Green-top guideline also recommends screening for hepatitis C in addition to the routine antenatal infection screening tests. All women should have a documented plan of care for the antenatal, intrapartum and postnatal periods.

FGM is illegal in the UK and many other countries. UK healthcare professionals have certain responsibilities when women with FGM are identified in the antenatal period or at other times. They must explain the UK law on FGM to the woman and be familiar with the requirements of the Health and Social Care Information Centre (HSCIC) FGM Enhanced Dataset. This requires the submission of non-anonymized personal data and this must be explained to the woman. The recording of the data is different to reporting of the woman to the police or social services. The latter is not mandatory unless there is risk to the unborn child or existing children. The UK Department of Health has produced safeguarding risk assessment tools for this purpose (https://www.gov.uk/government/publications/safeguarding-women-and-girls-at-risk-of-fgm). If FGM is confirmed in a girl under the age of 18, reporting to the police is mandatory [8].

Screening for maternal complications

Anaemia

Maternal iron requirements increase in pregnancy because of the demands of the developing fetus, the formation of the placenta and the increase in the maternal red cell mass. With an increase in maternal plasma volume of up to 50% there is a physiological drop in the haemoglobin (Hb) concentration during pregnancy. It is generally recommended that an Hb level below 110 g/L up to 12 weeks' gestation or less than 105 g/L at 28 weeks signifies anaemia and warrants further investigation. A low Hb (85–105 g/L) may be associated with preterm labour and low birthweight. Routine screening should be performed at the booking visit and at 28 weeks' gestation. While there are many causes of anaemia, including thalassaemia and sickle cell disease, iron deficiency remains the commonest. Serum ferritin is the best way of assessing maternal iron stores and if found to be low, iron supplementation should be considered. Routine iron supplementation in women with a normal Hb in pregnancy has not been shown to improve maternal or fetal outcome and is currently not recommended.

Blood group and red cell alloantibodies

Identifying the maternal blood group and screening for the presence of atypical antibodies is important in the prevention of haemolytic disease, particularly from rhesus alloimmunization. Routine antibody screening should take place at booking in all women and again at 28 weeks' gestation irrespective of their rhesus D (RhD) status. Detection of clinically significant atypical antibodies should prompt referral to a specialist fetal medicine unit for further investigation and management. In the UK, 15% of women are RhD negative and should be offered anti-D prophylaxis after potentially sensitizing events (e.g. amniocentesis or antepartum haemorrhage) and routinely at either 28 and 34 weeks' gestation or once at 32 weeks depending on the dosage of anti-D immunoglobulin used [4]. Consideration should also be given to offering partner testing, as anti-D prophylaxis will not be necessary if the biological father is RhD negative. In the future, all RhD-negative women may have routine diagnosis of fetal RhD status by analysing free fetal DNA in the maternal plasma. This will allow targeted anti-D administration to women with RhD-positive fetuses, which may result in cost savings and allow many women to avoid an unnecessary blood product. An observational service implementation pilot in three NHS units showed that at least 35% of RhD-negative women can avoid unnecessary anti-D administration and this service could be implemented with little additional cost and probably a saving, if the cost of the fetal DNA test is less than the cost of each anti-D injection [9].

Haemoglobinopathies

Screening for sickle cell disease and thalassaemias is important and each country will have a different screening strategy depending on the prevalence of these conditions. In the UK, this screening should be offered to all women as early as possible in pregnancy. If the regional sickle cell disease prevalence is high, laboratory screening should be offered. If the regional sickle cell disease prevalence is low, the initial screening should be based on the Family Origin Questionnaire; if this indicates high risk, then laboratory screening should be offered.

Infection

Maternal blood should be taken early in pregnancy and with consent screened for hepatitis B, HIV and syphilis. Identification of women who are hepatitis B carriers can lead to a 95% reduction in mother-to-infant transmission following appropriate postnatal administration of vaccine and immunoglobulin to the baby. Women who are HIV positive can be offered treatment with antiretroviral drugs which, when combined with delivery by caesarean section (unless undetectable viral load) and avoidance of breastfeeding, can reduce maternal transmission rates from approximately 25% to 1% [10]. Such women need to be managed by appropriate specialist teams. Routine screening for rubella ended in England in April 2016, primarily because rubella infection levels in the UK are so low that they are defined as eliminated by the WHO criteria.

Although the incidence of infectious syphilis is low, there have been a number of recent outbreaks in England and Wales. Untreated syphilis is associated with congenital syphilis, neonatal death, stillbirth and preterm delivery. Following positive screening for syphilis, testing of a second specimen is required for confirmation. Interpretation of results can be difficult and referral to specialist genitourinary medicine clinics is recommended. Current evidence does not support routine screening for cytomegalovirus, hepatitis C, toxoplasmosis or group B *Streptococcus*.

Asymptomatic bacteriuria occurs in approximately 2–5% of pregnant women and when untreated is associated with pyelonephritis and preterm labour. Appropriate treatment will reduce the risk of preterm birth. Screening should be offered early in pregnancy by midstream urine culture.

Hypertensive disease

Chronic hypertension pre-dates pregnancy or appears in the first 20 weeks, whereas pregnancy-induced hypertension develops in the pregnancy, resolves after delivery and is not associated with proteinuria. Pre-eclampsia is defined as hypertension that is associated with proteinuria occurring after 20 weeks and resolving after birth. Pre-eclampsia occurs in 2–10% of pregnancies and is associated with both maternal and neonatal morbidity and mortality [11]. Risk factors include nulliparity, age 40 years and above, family history of pre-eclampsia, history of pre-eclampsia in a prior pregnancy, BMI greater than 35, multiple pregnancy and pre-existing diabetes or hypertension. Hypertension is often an early sign that pre-dates the development of serious maternal and fetal disease and should be assessed regularly in pregnancy. There is little evidence as to how frequently blood pressure should be checked and so it is important to identify risk factors for pre-eclampsia early in pregnancy. In the absence of these, blood pressure measurement and urine analysis for protein should be performed at each routine antenatal visit and mothers should be warned of the advanced symptoms of pre-eclampsia (frontal headache, epigastric pain, vomiting and visual disturbances). However, when risk factors are present, more frequent blood pressure measurements and urine analyses should be considered in addition to low-dose aspirin prophylaxis (see Chapter 7).

Gestational diabetes

Currently there is little agreement as to the definition of gestational diabetes, whether and how we should screen for it and how to diagnose and manage it. However, there has been increasing evidence that 'treating' gestational diabetes is more beneficial than expectant management [12]. Consequently, the National Institute for Health and Care Excellence (NICE) recommends screening for gestational diabetes using risk factors (such as BMI >30 kg/m^2 or previous gestational diabetes) in a healthy population [4]. Women with risk factors should be tested for gestational diabetes using the 2-hour 75-g oral glucose tolerance test.

Psychiatric illness

The importance of psychiatric conditions related to pregnancy was highlighted in the 2000–2002 Confidential Enquiry into Maternal and Child Health [13]. A significant number of maternal deaths due to or associated with psychiatric causes were also reported in the most recent enquiry [1]. At booking, women should be asked about history of significant mental illness, previous psychiatric treatment or a family history of perinatal mental health illness. If mental illness is suspected, further referral for assessment should be made. Good communication, particularly with primary care, is paramount.

Screening for fetal complications

Confirmation of fetal viability

All women should be offered a 'dating' scan. This is best performed between 10 and 13 weeks' gestation and the crown–rump length measured when the fetus is in a neutral position (i.e. not curled up or hyperextended). Current evidence shows that the estimated day of delivery predicted by ultrasound at this gestation will reduce the need for induction of labour at 41 weeks when compared with the due date predicted by the last menstrual period. In addition, a dating scan will improve the reliability of Down's syndrome screening, diagnose multiple pregnancy and allow accurate determination of chorionicity and diagnose up to 80% of major fetal abnormalities. Women who present after 14 weeks' gestation should be offered a dating scan where the estimated date of delivery is calculated by the ultrasound measurement of the head circumference.

Screening for Down's syndrome

Current recommendations from NICE advocate that all women in the UK are offered the combined screening test for Down's syndrome between 11 weeks and 13 weeks 6 days of gestation. Those that book later should be offered serum screening between 15 and 20 weeks' gestation. The National Screening Committee further refined these guidelines in 2010, stating that the detection rate should be 90% for a screen-positive rate of 2%. Because screening for Down's syndrome is a complex issue, healthcare professionals must have a clear understanding of the options available to their patients. Unbiased, evidence-based information must be given to the woman at the beginning of the pregnancy so that she has time to consider whether to opt for screening and the opportunity to clarify any areas of confusion before the deadline for the test passes. Recognizing the importance of this, NICE currently recommends that the first two antenatal appointments take place before 12 weeks' gestation to allow the woman adequate time to make an informed decision about whether to have screening. Following a 'screen-positive' result the woman needs careful counselling to explain that the test result does not mean the fetus has Down's syndrome and to explain the

options for further testing. A positive screen test does not mean further testing is mandatory. Likewise, a woman with a 'screen-negative' result must understand that the fetus may still have Down's syndrome.

The recent introduction of fetal DNA non-invasive prenatal testing (NIPT) allows another option prior to or instead of invasive testing because of the high sensitivity and low screen-positive rate. Universal screening with NIPT may increase the detection rate to above 99% for the screened population but it has cost implications for publicly funded healthcare systems and has a significant failure rate. Contingent screening (offering NIPT to women with high-risk combined screening) would have lower cost at the expense of lower detection rate. The detection rate would depend on the chosen cut-off value of risk (e.g 1 in 150) for offering NIPT. With either strategy, the number of invasive procedures would be lower and hence there would be fewer miscarriages of healthy fetuses as a result of screening. The UK National Screening Committee commissioned a systematic review and cost-consequence assessment of fetal DNA testing (https://legacyscreening.phe.org.uk/policydb_download.php?doc=552) and recommended offering NIPT to pregnant women whose chance of having a baby with Down's, Edwards' or Patau's syndrome is greater than 1 in 150 [14].

Screening for structural abnormalities

The identification of fetal structural abnormalities allows the opportunity for *in utero* therapy, planning for delivery, for example when the fetus has major congenital heart disease, parental preparation and the option of termination of pregnancy should a severe problem be diagnosed. Major structural anomalies are present in about 3% of fetuses screened at 20 weeks' gestation. Detection rates vary depending on the system examined, skill of the operator, time allowed for the scan and quality of the ultrasound equipment. Follow-up data are important for auditing the quality of the service. Women must appreciate the limitations of such scans. Local detection rates of various anomalies such as spina bifida, heart disease or facial clefting should be made available. Written information should be given to women early in pregnancy explaining the nature and purpose of such scans, highlighting conditions that are not detected such as cerebral palsy and many genetic conditions. It is important to appreciate that the fetal anomaly scan is a screening test which women should opt for rather than have as a routine part of antenatal care without appropriate counselling. In 2010 the NHS Fetal Anomaly Screening Programme published a document for national standards and guidance for the mid-trimester fetal anomaly scan; this was updated in 2015 [15]. These standards set out the basis for the ultrasound screening service in England, describing what can and, importantly, what cannot be achieved.

Screening for fetal growth restriction

Each antenatal clinic attendance allows the opportunity to screen for fetal well-being. Auscultation for the fetal heart will confirm that the fetus is alive and can usually be detected from about 14 weeks of gestation. While hearing the fetal heart may be reassuring, there is no evidence of a clinical or predictive value. Likewise there is no evidence to support the use of routine cardiotocography in uncomplicated pregnancies. Physical examination of the abdomen by inspection and palpation will identify approximately 30% of small-for-gestational age fetuses [16]. Measurement of the symphysis–fundal height in centimetres starting at the uterine fundus and ending on the fixed point of the symphysis pubis has a sensitivity and specificity of approximately 27 and 88%, respectively, although serial measurements may improve accuracy. A risk stratification algorithm is recommended by the recent NHS England care bundle for reducing stillbirth [3] as well as the RCOG Green-top guideline [16]. Women with one or more risk factors should have serial ultrasound scans to assess fetal growth, whereas low-risk women should have growth assessment by antenatal symphysis–fundal height charts (customized or other established growth chart). Customized growth charts make adjustments for maternal height, weight, ethnicity and parity. However, there is no good-quality evidence that their use improves perinatal outcomes [4].

Traditionally, women have been advised to note the frequency of fetal movements in the third trimester and report reduced fetal movements. Raising awareness of reduced fetal movement has been another element of the NHS England care bundle for reducing stillbirth [3]. Women should be given information and advice leaflet by week 24 of pregnancy and reduced fetal movements should be discussed at every subsequent visit. A protocol based on the relevant RCOG guideline should be in place for these women; this will lead to ultrasound scan for fetal growth, amniotic fluid and umbilical artery Doppler assessment if there are additional risk factors for fetal growth restriction or stillbirth.

Organization of antenatal care

Antenatal care has been traditionally provided by a combination of general practitioners, community midwives, hospital midwives and obstetricians. The balance has depended on the perceived normality of the pregnancy at booking. However, pregnancy and childbirth is to a

certain extent an unpredictable process. The frequency of antenatal visits and appropriate carer must be planned carefully, allowing the opportunity for early detection of problems without becoming over-intrusive.

Who should provide the antenatal care?

A meta-analysis comparing pregnancy outcome in two groups of low-risk women, one with community-led antenatal care (midwife and general practitioner) and the other with hospital-led care, did not show any differences in terms of preterm birth, caesarean section, anaemia, antepartum haemorrhage, urinary tract infections and perinatal mortality. The first group had a lower rate of pregnancy-induced hypertension and pre-eclampsia, which could reflect a lower incidence or lower detection [17]. However, clear referral pathways need to be developed that allow appropriate referral to specialists when either fetal or maternal problems are detected.

There is little evidence regarding women's views on who should provide antenatal care. Unfortunately, care is usually provided by a number of different professionals often in different settings. Studies evaluating the impact of continuity of care do not generally separate the antenatal period from labour. The studies consistently show that with fewer caregivers women are better informed and prepared for labour, attend more antenatal classes, have fewer antenatal admissions to hospital and have higher satisfaction rates. Differences in clinical endpoints such as caesarean section rates, postpartum haemorrhage, admission to the neonatal unit and perinatal mortality are generally insignificant [4]. While it would appear advantageous for women to be seen by the same midwife throughout pregnancy and childbirth, there are practical and economic considerations that need to be taken into account. Nevertheless, where possible, care should be provided by a small group of professionals.

Documentation of antenatal care

The antenatal record needs to document clearly the care the woman has received from all those involved. It will also serve as a legal document, a source of useful information for the woman and a mechanism of communication between different healthcare professionals. There is now good evidence that women should be allowed to carry their own notes. Women feel more in control of their pregnancy and do not lose the notes any more often than the hospital! In addition, useful information will be available to clinicians should the woman require emergency care while away from home. Many areas of the UK are endeavouring to work towards a standard format for the records. This would be of benefit to those women who move between hospitals so that caregivers would automatically be familiar with the style of the notes. If we are to move to an electronic patient record, there must be general agreement in a minimum dataset and a standard antenatal record would be a step in this direction.

Frequency and timing of antenatal visits

There has been little change in how frequently women are seen in pregnancy for the last 50 years. In 2003, NICE produced a clinical guideline entitled *Antenatal Care: Routine Care for the Healthy Pregnant Woman*, which was revised in 2008 [4] and updated in 2013. This document recognized the large amount of information that needs to be discussed at the beginning of pregnancy, particularly with regard to screening tests. The first appointment needs to be early in pregnancy, certainly before 12 weeks if possible. This initial appointment should be regarded as an opportunity for imparting general information about the pregnancy such as diet, smoking and folic acid supplementation. A crucial aim is to identify those women who will require additional care during the pregnancy. A list of conditions for which additional care will be needed is provided at the NICE website (https://www.nice.org.uk/guidance/cg62/chapter/Appendix-C-Women-requiring-additional-care). A urine test should be sent for bacteriological screen and a dating ultrasound scan arranged. Sufficient time should be set aside for an impartial discussion of the screening tests available, including those for anaemia, red-cell antibodies, syphilis, HIV and hepatitis. Because of the complexity of Down's syndrome screening, this too should be discussed in detail and supplemented with written information. Ideally another follow-up appointment should be arranged before the screening tests need to be performed to allow further questions and to arrange a time for the tests following maternal consent.

The next appointment needs to be around 16 weeks' gestation to discuss the results of the screening tests. In addition, information about antenatal classes should be given and a plan of action made for the timing and frequency of future antenatal visits, including who should see the woman. As with each antenatal visit, the blood pressure should be measured and the urine tested for protein. The 20-week anomaly scan should also be discussed and arranged and women should understand its limitations.

At each visit the symphysis–fundal height is plotted, the blood pressure measured and the urine tested for protein. At 28 weeks' gestation, blood should be taken for haemoglobin estimation and atypical red-cell antibodies. Anti-D prophylaxis should be offered to women who are rhesus negative. A follow-up appointment at 34 weeks will allow the opportunity to discuss these results.

At 36 weeks, the position of the baby needs to be checked and if there is uncertainty an ultrasound scan arranged to exclude breech presentation. If a breech is confirmed, external cephalic version should be considered. For women who have not given birth by 41 weeks, both a membrane sweep and induction of labour should be discussed and offered. Additional appointments at 25, 31 and 40 weeks are proposed for nulliparous women.

In summary, a total of 10 appointments is recommended for nulliparous women and seven appointments for multiparous women, assuming they have uncomplicated pregnancies.

Summary box 5.1

- The administration of folic acid 400 µg/day is recommended to reduce the incidence of NTDs.
- Women should be informed of the harmful effects of smoking in pregnancy.
- Nulliparous women require more antenatal appointments.
- Women with risk factors should be referred to specialist obstetric care.
- At booking, women should be asked about history of significant mental illness, previous psychiatric treatment or family history of perinatal mental illness.
- Women with FGM should be referred to a specialist multidisciplinary service.
- Dating scan should be performed between 10 and 13 weeks' gestation by measuring the crown–rump length.
- All women in the UK should be offered the combined screening test for Down's syndrome between 11 and 14 weeks' gestation.
- Antihistamines (prochlorperazine, promethazine and metoclopramide) appear to be the pharmacological agents of choice for nausea and vomiting in pregnancy.
- It is recommended that women are offered estimation of fetal size by symphysis–fundal height measurement at each antenatal visit; when there is suspicion of a small fetus, they are referred for formal ultrasound assessment.

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6

First Trimester Antenatal Screening

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A large part of normal obstetric care consists of a series of screening tests designed to identify those pregnant women who are at risk of various maternal, obstetric or fetal complications so that early interventions can be initiated so as to minimize maternal and fetal mortality and morbidities. This series of 'screening' tests includes not just blood tests and ultrasound scans but also history-taking and physical examination. Many of these screening tests have been discussed in other chapters in this book under specific conditions and therefore will not be repeated here. This chapter focuses on the antenatal screening of chromosomal abnormalities.

In deciding what diseases to screen for, one should balance the potential benefits and harms that a screening test may result in people who are otherwise well. The most widely used set of principles at present is the one described by Wilson and Jungner in a 1968 report commissioned by the World Health Organization (WHO). These principles are as follows.

1) The condition sought should be an important health problem.
2) There should be an accepted treatment for patients with recognized disease.
3) Facilities for diagnosis and treatment should be available.
4) There should be a recognizable latent or early symptomatic stage.
5) There should be a suitable test or examination.
6) The test should be acceptable to the population.
7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8) There should be an agreed policy on whom to treat as patients.
9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10) Case-finding should be a continuing process and not a 'once and for all' project.

A screening test will categorize the testing population into a high-risk (or test-positive) group and a low-risk (or test-negative) group. Further investigations and diagnostic tests should be considered for those in the high-risk group. There are four important parameters in assessing the performance of a screening test, namely the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Sensitivity, or detection rate or true positive rate, refers to the proportion of affected subjects that are correctly identified by the screening test, while specificity refers to the proportion of negatives that are correctly identified as such. Specificity, or true negative rate, equals (1 – false-positive rate). Sensitivity and specificity are determined by the screening test itself. A high sensitivity indicates a lower chance of missing an affected subject, while a high specificity will lead to less false alarms and therefore less harm. PPV refers to the proportion of screened high-risk subjects who are indeed affected by the condition or disease, while NPV refers to the proportion of screened low-risk subjects who are indeed free of the condition. Both PPV and NPV are not only affected by the sensitivity and specificity of the test but also by the prevalence of the condition in the testing population. For example, the PPV for a screening test with a sensitivity of 95% and a specificity of 95% will be 1.87% (1 in 53), 16.1% (1 in 6) and 67.9% (1 in 1.5) when the disease prevalence in the testing population is 0.1, 1 and 10%, respectively.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Summary box 6.1

- The effectiveness of a screening test is determined by its sensitivity and specificity.
- The majority of screen-positive subjects are false positives. The PPV is affected by the prevalence of the condition.

First-trimester Down's syndrome screening

Overview

Screening for fetal Down's syndrome has become part of routine antenatal care in many countries. Down's syndrome has been considered the commonest genetic cause of intellectual disability. Without screening, the incidence is about 1 in 600 to 1 in 800 live births. The incidence of Down's syndrome increases with maternal age, being relatively stable before age 30 but increasing exponentially after age 35. About 30% of affected pregnancies result in miscarriage or intrauterine fetal death and therefore the incidence of Down's syndrome decreases with advancing gestational age.

In over 95% of individuals with Down's syndrome the condition is due to trisomy 21 – the presence of one extra chromosome 21 – which is typically due to an error, namely non-disjunction, during cell division. About 95% of the non-disjunctions are meiotic errors, of which over 90% are maternal in origin. The remaining 5% of non-disjunctions are due to mitotic errors. Although trisomy 21 is not an inherited condition, a history of an affected pregnancy increases the chance of having another affected pregnancy by about 0.75%. Previous trisomy 21 not only increases the risk of trisomy 21 (relative risk or RR, 2.2) but also other different trisomies such as trisomy 13 or 18 (RR 1.4) in subsequent pregnancies [1]. This suggests that some individuals are more prone to non-disjunction during meiosis, or some trisomies are due to underlying maternal gonadal mosaicism.

About 2–3% of Down's syndrome cases are due to Robertsonian translocations, in which part of chromosome 21 is translocated to another chromosome, most commonly chromosome 14. About two-thirds of these cases are *de novo* events, while one-third are inherited from one of the parents who is a carrier of a balanced translocation. If the mother is the carrier, there is about a 10–15% chance of recurrence in future pregnancies. If the father is the carrier, the risk is much lower, estimated to be at most 3% although some believe that the additional risk is negligible. If an individual is a carrier of a very special form of balanced Robertsonian translocation involving two chromosomes 21, there will be 100% risk of having pregnancies with Down's syndrome.

About 2–3% of Down's syndrome are mosaic. The phenotype may be milder, especially among those with low percentage of the abnormal cell line.

All individuals with Down's syndrome have similar facial characteristics and some degree of intellectual disability, most common in the moderate degree range. About 40% are in the mild range with IQ between 50 and 70. Other medical problems are common, including hearing loss (up to 70%), obstructive sleep apnoea (50%), congenital heart diseases (50%), hypothyroidism, otitis media, cataracts and visual problems. They are at higher risk of developing leukaemia and Alzheimer's disease.

In the past, the outcome of individuals with Down's syndrome was poor, mostly due to the lack of medical care and support. In the early 1900s, affected individuals seldom survived to their teenage years. However, the prognosis of individuals with Down's syndrome has improved significantly over the last century. Currently in developed countries the average lifespan of affected individuals is already over 50, and many of them are living with their families or independently with varying degree of support.

Such improvement relies on the availability of appropriate and adequate medical care, early interventional programmes, education, financial support, social support and employment opportunities. Such interventions not only are important determining factors for the prognosis of affected individuals, but also affect the well-being of the family as a whole. In developed countries with adequate medical and social support, most families with children with Down's syndrome are able to find enough resources to help them in coping with the additional demands and challenges, resulting in an ordinary family life in themselves. However, about 30–40% of families still have significant stress and distress.

Even with all necessary social and medical support, Down's syndrome remains a condition with multiple medical problems that poses significant stress and challenges to the family. At present, it is medically possible to identify affected pregnancy in the antenatal period, and pregnancy termination of affected pregnancies is legal in many countries. Almost all published studies have confirmed that prenatal Down's syndrome screening is cost-effective. On the other hand, Down's syndrome is a non-lethal condition, and there is continuous debate about the ethics of terminating affected pregnancies. It is beyond the scope of this chapter to elaborate on the ethics of Down's syndrome screening. The discussion will therefore focus on the scientific basis and details of implementation of Down's syndrome screening in the first trimester of pregnancy.

Uptake of screening and ethical issues

Not all women want to undergo screening so any programme must recognize those wishing to 'opt out'. In the UK this group comprises 10–40% of the pregnant population, depending on local demographics. In this case these women can have an early scan but the fetal nuchal translucency (NT) is not measured.

First-trimester combined screening programmes

First-trimester combined screening test, or first-trimester combined screening (FTCS), is the commonest form of first-trimester screening, in which the risk of Down's syndrome is estimated based on the measurement of fetal NT and maternal serum markers, including pregnancy-associated plasma protein A (PAPP-A) and free β-human chorionic gonadotrophins (fb-hCG). The typical changes associated with fetal Down's syndrome are increased NT and maternal fb-hCG, and a reduction in maternal PAPP-A.

Most first-trimester combined screening programmes are performed between 11 and 13^{+6} weeks of gestation, or at a crown–rump length of 45–84 mm.

Down's syndrome screening is a risk estimation process. This starts with the estimation of the a priori risk or pre-test odds of Down's syndrome of a test subject based on her age, gestational age and history of affected pregnancies. Then, multiple markers are measured. The deviation of each marker from the expected value of a normal pregnancy is calculated, based on which a likelihood ratio (LR) is estimated. The LR tells how much more likely a pregnancy is affected by Down's syndrome given the value of the measurement. LR of 1 means that there is no change in risk. LR above 1 denotes an increased risk, while LR below 1 denotes a reduced risk. An individualized risk or post-test odds is calculated based on the following formula:

$$\text{Post-test odds} = \text{pre-test odds} \times \text{LR}_{\text{NT}} \times \text{LR}_{\text{PAPP-A}} \times \text{LR}_{\text{fb-HCG}} \cdots$$

Most Down's syndrome screening algorithms use a similar approach, although more complicated mathematical modelling may be involved to take into account the interactions between different markers.

A cut-off value of the individualized risk is chosen to categorize a test subject as high or low risk. There are many ways to determine the cut-off value. Moving the cut-off will change the sensitivity and specificity at the same time. For example, assuming that the sensitivity and specificity are 75% and 95%, respectively, at a cut-off of 1 in 250, moving the cut-off to 1 in 400 may increase the sensitivity to 85% but also reduce the specificity to 80%. Moving the cut-off to 1 in 100 may reduce the sensitivity to 65% but also increase the specificity to 98%. These numbers are only hypothetical, and the true effect in a screening programme can be analysed by the ROC (receiver operating characteristic) curve. The choice of cut-off is therefore a compromise between high sensitivity and high specificity.

It is important to realize that using the same screening test with the same cut-off in populations with different maternal age may result in different sensitivities and specificities. For example, using a fixed cut-off, the same screening test will result in higher sensitivity and lower specificity among those aged 35 or above compared to those aged 25 or below. Some argue that there should not be a recommended cut-off, and screened subjects should simply make their own judgement based on their own individualized risk to determine if further diagnostic tests are necessary. However, most screened subjects would probably be less confused with a suggested cut-off and a simple result of high or low risk.

NT is one of the best single markers of fetal Down's syndrome. NT is due to a thin layer of fluid beneath the fetal nuchal skin. It is present in all fetuses in the late first and early second trimester, and then gradually disappears. NT must be differentiated from nuchal fold thickness, which is a mid-second trimester marker measuring the fetal nuchal skin but not fluid collection. When properly performed, NT alone enables the detection of 70–80% of pregnancies affected by Down's syndrome at a 5% false-positive rate (FPR). Increased NT is also detected in about 70–75% of fetuses with trisomy 13 and trisomy 18, and 80–90% of those with Turner's syndrome. Overall, about 5–8% of those with increased NT will have chromosomal abnormalities.

Risk assessment by NT should only be undertaken by those who have been trained and accredited, with continuous auditing of performance and recertification. The most commonly used protocol is listed in Table 6.1, which should be followed strictly. Unlike maternal biochemistry, NT is not significantly affected by maternal characteristics.

Risk assessment by maternal serum biochemistry using PAPP-A and fb-hCG alone has a performance comparable to that of screening using NT alone, with a sensitivity of about 70% at 5% FPR. Maternal serum markers are significantly affected by maternal characteristics, including ethnicity, maternal weight, medical disease such as diabetes and the mode of conception. Most risk calculation algorithms provide adjustment for these factors, to maximize the test performance. All laboratories performing Down's syndrome screening biochemistry should have continuous internal and external quality assurance programmes (such as the United Kingdom National External Quality Assessment Service,

Table 6.1 The standard protocol for proper first-trimester nuchal translucency (NT) measurement used in prenatal Down's syndrome screening.

The measurement must be taken at a gestation between 11 weeks and 13 weeks 6 days
The measurement must be taken when the fetal crown–rump length is between 45 and 84 mm
The image must be taken in a good sagittal section, with the baby lying horizontally
The image must be magnified to include the fetal head and upper thorax only
The measurement should be taken when the neck is in a neutral position
The NT must be clearly shown
The calliper is placed *on* the line that defines the NT thickness: the crossbar of the calliper should be such that it is hardly visible as it merges with the white line of the border, not in the nuchal fluid
The measurement should be taken where the NT is thickest
The NT should be measured three times and the largest one is taken as the NT of the fetus
The amnion should not be confused with the skin, which will overestimate the NT

UKNEQAS) in place to ensure the stability of their assay. It is important for all clinicians involved in prenatal screenings to ensure that the biochemical laboratories they are using are well qualified and have satisfactory quality control.

Combining NT, PAPP-A and fb-hCG as the FTCS, the sensitivity is about 90% at 5% FPR. Screening centres should participate in appropriate quality assurance programmes.

Variations of first-trimester combined screening

The common variations include the following.

Approach using ultrasound markers alone

In addition to thickened NT, other sonographic markers, including absence of nasal bone (NB), tricuspid regurgitation (TR), abnormal waveform of ductus venosus (DV), increased frontomaxillary facial angle, the presence of aberrant right subclavian artery and many others, have been found to be associated with fetal Down's syndrome. Algorithms have been developed to use solely sonographic markers in calculating the individualized risk of Down's syndrome, commonly incorporating NT, NB, DV, TR and fetal heart rate, achieving a test performance similar to that of the FTCS programme. The advantage of this approach is that the test result is immediately available, and the assessment is fetus-specific. It is particularly useful in cases of multiple pregnancies, or a vanished twin pregnancy. The disadvantage is that ultrasound is a highly operator-dependent test, for which quality control is more difficult than for biochemistry-based tests. Since the throughput of an accredited sonographer is much lower than that of an accredited biochemical laboratory, an ultrasound-only approach is more difficult to implement in populated-based screening programmes. Furthermore, this approach has not been tested as vigorously in different ethnic populations as the FTCS. The effect of ethnicity on some of the markers, such as NB, is substantial.

Biochemistry-based approach

FTCS is not feasible if there are insufficient accredited sonographers for NT measurement. Under such circumstances, first-trimester screening can only be performed based on biochemistry alone. Compared with second-trimester screening, this offers earlier screening but there is no major additional benefit in terms of test performance. Even with biochemistry alone, a simple dating scan will improve the screening performance by confirming the number of fetuses and accurate dating.

Integrated or sequential screening

Different markers, both sonographic and biochemical, are tested at different gestational ages, typically in both first and second trimesters. Only one individualized risk is calculated when information from all markers is available. The advantage is improved performance, with estimated sensitivity above 90% and specificity above 98%. However, this approach involves more visits, more complicated logistic and administrative arrangements, higher chance of dropout, and high chance of deviation from protocol based on results from the first part of the study.

Special conditions

1) *Multiple pregnancies*. First-trimester combined screening can be used in twin pregnancies, although both sensitivity and specificity are lower, 75% and 90–97%, respectively. The chorionicity must be known for proper risk calculation. For higher-order pregnancies, no reliable data are available for adjustment of biochemistry. Ultrasound-based screening is the only available option.
2) *Vanished twin*. At the time of first-trimester combined screening, the presence of an empty second gestational sac does not appear to significantly affect the serum level of biochemical markers and therefore these pregnancies can be tested as singleton. However, if the second sac contains a dead fetus, the serum marker levels are affected unpredictably and no reliable adjustment can be made. In such situations, only ultrasound-based screening test should be performed.

3) *First-trimester vaginal bleeding*. This does not appear to significantly affect the serum biochemistry and therefore first-trimester combined screening can be performed even with such history.
4) *NT of 3.5 mm or above*. It is well known that increased NT is not only associated with chromosomal abnormalities, but also increased risk of intrauterine death, miscarriage, and fetal structural or genetic anomalies, in particular fetal cardiac defects. Overall, about 20% of those with increased NT but normal karyotype have an adverse outcome. This incidence varies with the initial NT value, being 8% for NT up to 3.5 mm, 20% for NT of 3.5–4.4 mm, 30% for 4.5–5.4 mm, 40% for 5.5–6.4 mm and 80% for those with NT above 6.5 mm [2]. When NT is 3.5 mm or above, the majority will be screened positive even when combined with biochemistry. Therefore, those with NT of 3.5 mm or above may be given a choice either to complete the FTCS by taking the biochemical test, or to have a diagnostic test directly. In any case, they should be referred for a detailed sonographic examination to exclude cardiac and other structural abnormalities. For those with additional abnormalities, specific genetic tests, such as Noonan syndrome tests, may be necessary. However, pregnant women can be reassured that if a detailed second-trimester scan is completely normal, the chance of having a healthy normal baby is about 96%.

Common questions and misconceptions about first-trimester screening of Down's syndrome

1) Using a single cut-off of NT: since the NT value in normal pregnancies increases with gestational age even between 11 and 13^{+6} weeks, a single cut-off of NT should not be used to define high-risk or low-risk groups. Increased NT should be defined by an NT measurement above the 95th percentile based on a gestation-specific reference chart. Incidentally, the 99th percentile of NT is roughly stable at 3.5 mm.
2) NT larger than +2SD (standard deviation) indicates Down's syndrome: many doctors and couples are horrified by an NT measurement that is above the +2SD level. Although a value above the 2SD level is usually defined statistically as abnormal, most individuals in this group are in fact normal. This is particularly true if the NT is below 3.5 mm. Most individuals will still be screened negative when combined with biochemistry, and have a normal baby.
3) Increased NT indicates cardiac defects: there is no doubt that there is a positive relationship between NT and the incidence of congenital heart defect (CHD), being 1.5% at NT of 2.5–3.4 mm, 3.4% at 3.5–4.4 mm, 7.5% at 4.5–5.4 mm, 15% at 5.5–6.4 mm, 19% at 6.5–8.4 mm and 64% at 8.5 mm or above. Unfortunately, the detecting rate of CHD using NT as the sole screening test is disappointing, being 31% if the NT cut-off is set at 3.5 mm which corresponds to the 99th percentile, or 37% if the cut-off is set at the 95th percentile [3]. In other words, the incidence of CHD is still below 2% among those with an NT between +2SD and the 99th percentile. Even with NT of 3.5–4.4 mm, over 95% will still have a normal heart. Irrespective of the NT value, every pregnancy should have a proper fetal structural assessment in the mid-trimester. Using NT as a screening tool for CHD should not be considered if there are insufficient competent sonographers able to perform first-trimester fetal echocardiography.
4) Absence of nasal bone: many couples interpret this as a malformation of the nose. Absence of nasal bone is a misnomer. It is not a structural anomaly. It only refers to the lack of calcification of the nasal cartilage, making the nasal bone less echogenic than usual. Absence of nasal bone does not imply abnormalities of the nose, or facial abnormalities. In fact, those with absence of nasal bone generally have a normal external appearance. In the majority of such cases, the nasal bone will become visible with increasing gestation. Although absence of nasal bone is a strong marker for fetal Down's syndrome, the great majority of those with absence of nasal bone are still normal fetuses. If the fetal karyotype is normal, there is no clinical significance associated with this sonographic marker.
5) Reliability of blood tests using maternal serum biochemical markers: the reliability of these assay results relies not only on the quality of the laboratory, but also the way blood samples are collected, stored and transported before they reach the laboratory. Some markers such as fb-hCG are particularly vulnerable to external factors, including ambient temperature and duration of storage [4]. All screening centres and health professionals should carefully prepare blood samples according to standard protocols to ensure best screening performance.

Screen-positive results

All women who are screened positive should be counselled and referred for a confirmatory diagnostic test. The final decision whether to have a diagnostic test or not is wholly a decision of the couple, which is a balance between the risk of losing a normal baby due to the diagnostic test and the chance of having an affected child. This balance could be difficult for many couples and is influenced by many factors, including (i) their reproductive history, (ii) how high the individualized risk

is, (iii) how the result of the diagnostic test will affect their decision and well-being, (iv) the risk of the diagnostic test, (v) the type of diagnostic test and (vi) the reporting time. There are two diagnostic tests to choose from, amniocentesis and chorionic villous sampling.

Summary box 6.2

- Clinicians have a duty to ensure that all sonographic markers are measured only by accredited sonographers, and that biochemical laboratories they are using are well qualified and have satisfactory quality control.
- NT is the best single marker for fetal Down's syndrome.
- Increased NT is associated with CHD, but the performance of NT as a screening test for CHD is inadequate.

First-trimester screening of aneuploidies other than Down's syndrome

Trisomy 13 and 18 are serious chromosomal abnormalities, usually with multiple structural abnormalities detectable by ultrasound examination in the first or early second trimester. Since the majority of pregnancies with trisomy 13 and 18 results in either spontaneous pregnancy losses or early neonatal death, a dedicated screening programme solely for these conditions is not justified and is not cost-effective.

However, both trisomy 13 and 18 are associated with increased NT, low PAPP-A and low fb-hCG. Therefore, these conditions can be identified by FTCS for Down's syndrome. Trisomy 13 is also associated with an increased fetal heart rate, and 85.2% have a heart rate above the 95th percentile. The detection rate for trisomy 13 and 18, using FTCS markers and an algorithm optimized for trisomy 21 detection, are 78 and 79% respectively at 5% FPR. The detection rate can be increased to 95% for trisomy 18 and 87% for trisomy 13, using similar markers but different algorithms optimized for the detection of these two types of trisomies [5]. In fact the role of biochemistry is limited for these two types of trisomy if a detailed first-trimester scan is performed. The median NT is 4.8 mm and 6.8 mm in trisomy 18 and 13 fetuses, respectively [6]. In expert hands, 100% of trisomy 13 and 82.5% of trisomy 18 pregnancies have at least one structural anomaly detectable in the first trimester [6]. These common defects include central nervous system (CNS) anomalies, facial defects, cardiac defects, and abnormal limbs.

Turner's syndrome (45X) is a common chromosomal abnormality but the majority of cases result in early pregnancy failure. Over 85% are detectable during the NT scan as part of the FTCS for Down's syndrome, and present with very thickened NT or cystic hygroma, together with generalized oedema and fetal hydrops. For those with 45X who survive, the major problems are ovarian failure, amenorrhoea, infertility and short stature. However, intelligence is normal. Therefore, a dedicated screening programme for this condition alone is not justified.

Summary box 6.3

- First-trimester screening for Down's syndrome can also detect other aneuploidies, including trisomy 13, trisomy 18 and 45X.
- Ultrasound plays a significant role in detecting trisomy 13 and 18, and those with 45X with unfavourable outcome.

Diagnostic tests

Amniocentesis and chorionic villous sampling

Amniocentesis is typically performed at or after 15 weeks of gestation. Amniocentesis at earlier gestation is not recommended as a routine test because of higher associated fetal loss rate, but may be offered in exceptional situations after careful counselling. Amniocentesis should be performed under strict aseptic techniques and should be under continuous ultrasound guidance. A small needle, most commonly 22G, is inserted into the amniotic cavity, avoiding the placenta and the fetus whenever possible. About 10–20 mL of amniotic fluid is aspirated depending on the test required.

Chorionic villous sampling (CVS) is typically performed between 11 and 14 weeks of gestation to obtain a placental tissue sample for further study. The transabdominal approach is the most common and preferred approach because transcervical CVS is associated with a higher incidence of post-procedural bleeding and miscarriage. In cases where transabdominal CVS is not possible or where it may be associated with significant risk of maternal internal organ damage, transcervical CVS may be considered for an early diagnosis. Ultrasound guidance is essential. CVS requires a higher level of skill than amniocentesis. CVS samples also require meticulous treatment in the laboratory to isolate pure chorionic villi to avoid maternal contamination.

CVS should preferably be performed after 11 weeks of gestation but not before 10 weeks of gestation. Early CVS

has been associated with fetal limb reduction defects. The risk and the severity are highest when CVS is performed before 9 weeks of gestation. When performed after 10 weeks, the relative risk of limb reduction defect is 2.4 with an absolute risk of 0.07%. The excess risk is negligible after 11 weeks of gestation.

Cytogenetic and molecular cytogenetic tests

Both amniotic fluid and CVS samples may be sent for cell culture and full karyotyping, or rapid karyotyping, or both. Karyotyping, which examines all 23 pairs of chromosomes to exclude aneuploidies or large chromosomal rearrangements, used to be the gold standard prenatal test. The major disadvantage is the long reporting time, 10–14 days or longer in most laboratories. Two types of rapid karyotyping techniques are in common use: quantitative-fluorescent polymerase chain reaction (QF-PCR) or fluorescence *in situ* hybridization (FISH). Both FISH and QF-PCR enable the exclusion or confirmation of aneuploidy of selected chromosomes, usually 13, 18, 21 and the sex chromosomes. The major advantages of rapid karyotyping are the short reporting time, usually 1–2 days, and the low cost. The major disadvantage is that other chromosomal abnormalities are not examined. In publicly funded services, it is increasingly common that rapid karyotyping is only performed for cases in which amniocentesis and CVS are indicated solely for high risk of Down's syndrome without fetal structural anomalies. However, the limitation of such practice needs to be explained clearly to the couples concerned and they should be given a chance to request a full karyotyping or chromosomal microarray if they are willing to pay for that additional information.

If rapid karyotyping confirms aneuploidy, karyotyping should always be performed to determine if the aneuploidy is due to typical trisomy or Robertsonian translocation. For typical trisomy 21, the risk of recurrence is about 0.75% in addition to the age-specific risk. For Robertsonian translocations, the recurrent risk is low for *de novo* events, and is 10–15% if maternally inherited.

Discordance in genetic constitution between amniocentesis and CVS samples

In a normal pregnancy, both the placenta and the fetus develop from the same fertilized egg. Therefore, theoretically, they should all have the same genetic composition. Mosaicism refers to the presence of two or more population of cells with different genetic or chromosomal constitutions in one individual. Mosaicism is detected in 1–2% of all CVS samples, and in at least 4.8% of term placentas. Based on a study of 1317 mosaic results from 60 347 CVS samples, it was found that mosaicism was confined to the placenta (CPM) in 87%, while fetal mosaic was confirmed in only 13% [7]. Uniparental disomy (UPD) was confirmed in 2% of the fetuses [7].

Mosaicism occurs either because of post-fertilization mitotic non-disjunction of a normal gestation, or in a trisomic gestation due to meiotic error with trisomic rescue. Depending on the distribution of normal and abnormal cell populations, the ultimate pregnancy may result in CPM or true fetal mosaicism. In the majority of cases, discordances between fetal and placental chromosomal status are accompanied by mosaicism in CVS. Therefore, amniocentesis should be considered whenever mosacisim is detected on CVS. In the most extreme scenario, there could be complete discordance in chromosomal constitution between the fetus and the placenta, in which the CVS result is non-mosaic normal or abnormal while the fetus has the opposite non-mosaic status. This is an extremely rare situation but has been reported in the literature. This rare event should not prevent the use of CVS as a diagnostic test. However, if there is any uncertainty or suspicion, such as a negative CVS result in a fetus with multiple sonographic markers, further confirmation by amniocentesis should be considered.

Risks of amniocentesis and CVS

Procedure-related fetal loss is probably the only significant complication of amniocentesis and CVS. Other major complications, such as bowel perforation, internal bleeding or haemorrhage, have been reported but are extremely rare. The most commonly quoted figure for amniocentesis-related fetal loss is 1%, based on a single randomized trial published in 1986 by Tabor *et al.* [8]. However, most recent studies have suggested a much lower complication rate. A recent systematic review of 42 716 amniocentesis and 8899 CVS tests estimated that the procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% and 0.22%, respectively [9].

Diagnostic tests in multiple pregnancies

Both amniocentesis and CVS can be performed safely in multiple pregnancies. However, these procedures should only be performed by experienced operators. The position of placenta and gestational sac, the fetal sex and the presence of any markers of structural anomalies should be recorded clearly to avoid sampling of the same gestational sac or placenta twice and to allow correct identification of the abnormal fetus when fetal reduction is required subsequently. The associated risk of miscarriage is higher than in singleton pregnancy, and has been estimated to be about 1% for both amniocentesis and CVS [10].

Summary box 6.4

- The risk of amniocentesis and CVS is commonly overstated. Risk is likely to be about 0.2% or lower in both.
- CVS is an acceptable diagnostic test, but the possibility of CPM should always be considered.

Non-invasive prenatal testing

Non-invasive prenatal testing (NIPT) is not a first-trimester screening test in the conventional sense because it can be done at any gestation. It is included here because it can be performed in the first trimester and it is going to replace conventional first-trimester screening for Down's syndrome. NIPT, also called non-invasive prenatal screening (NIPS) or non-invasive DNA testing (NIDT), is a newly developed technology which is still evolving. It is a highly accurate screening test for fetal Down's syndrome, with both sensitivity and specificity over 99%. It can be performed at any time during pregnancy after the minimal gestational age. It is a relatively simple test from the perspective of clinicians and pregnant women. The major limitation of using NIPT as a primary screening tool is the cost, which nevertheless is likely to be comparable to current first-trimester screening tests in the very near future.

All NIPT tests available today in clinical use are based on the study of cell-free DNA (cfDNA) fragments in maternal plasma instead of intact fetal cells in the maternal circulation. DNA is not only present in the nucleus of cells but also in plasma. During pregnancy, the presence of fetal cfDNA in maternal plasma can be detected as early as week 4 of pregnancy [11] and can be used for accurate fetal sex determination from 7 weeks onwards. From 10 weeks onwards, on average approximately 10% of maternal cfDNA is of fetal origin.

cfDNA is fragmented. It has been shown that the relative contribution of each chromosome of a genome is maintained in the cfDNA compartment. If a fetus is affected by trisomy 21, the fetal cfDNA will also have a higher contribution of fragments from chromosome 21, about 50% more. After being diluted by the normal maternal cfDNA background, an affected pregnancy will still lead to a slight increase in the proportion of chromosome 21 fragments in the maternal plasma. Such small difference can be detected using the latest molecular technologies.

It is now known that the principal source of fetal DNA in maternal plasma is from the trophoblastic cells of the placenta. Therefore, NIPT is just like examining the chromosomal status of a mixture of maternal and trophoblastic DNA fragments. Fetal chromosomal status is inferred based on the assumptions that (i) the fetal and trophoblastic chromosomal constitutions are identical and (ii) maternal constitution is normal (if the counting method is used, see following section). These assumptions are generally correct, but exceptions do occur which will result in false-positive NIPT results. The issue of CPM is particularly important for autosomal trisomies involving chromosomes other than 13, 18 and 21, and the issue of false positives due to maternal contribution is particularly important in sex chromosomal aneuploidies and microdeletion syndrome (see subsequent sections for more details).

NIPT methods for screening of fetal Down's syndrome

The commonest method is by simple counting, using either genome-wide massively parallel sequencing (MPS) or targeted MPS. With MPS, millions of DNA fragments within a maternal plasma sample are sequenced, and then compared against the human genome to determine their original chromosomal locations. The percentage representation of chromosome 21 is calculated, and compared against the expected value, or compared against the percentage representation of a reference chromosome. Different bioinformatics pipelines have been developed to determine if the chromosome 21 percentage is higher than expected, which signifies that the fetus is at high risk of having Down's syndrome. The advantage of this approach is simplicity in bioinformatics. However, this method does not differentiate fetal from maternal cfDNA and the NIPT result could be affected by the chromosomal status of the pregnant woman herself.

Another NIPT method that has been used clinically is the SNP (single nucleotide polymorphism) approach. SNPs are variations in a single nucleotide that occurs in a specific position in the human genome. There are about 10 million SNPs in the human genome. Most SNPs locate between genes and have no known biological effect. Different individuals have different SNP patterns. Using a panel of selected SNPs, fetal and maternal DNA fragments can be differentiated, and by studying the SNP pattern the trisomy or disomy status of the fetus can be estimated. This approach is attractive in that it differentiates fetal from maternal DNA. However, there is no evidence that this approach provides any superiority in performance as a screening test for fetal Down's syndrome. It does enable the detection of vanished twin, dichorionic twin or triploidy pregnancies, that the counting method is unable to do. This method is not suitable for donor egg pregnancies, and may not be feasible in couples who have highly similar SNP patterns, such as marriage between close relatives.

Other NIPT methods have been investigated and reported, including quantitative methylation-specific

PCR, methylated DNA immunoprecipitation, microarray-based methods and RNA-based methods. In general, relevant clinical data are either lacking or limited and will not be elaborated further here.

Performance of NIPT as a screening test for fetal Down's syndrome

The majority of published data are based on the counting method, although with much variations in methodology. The most recent systematic review showed a sensitivity and specificity of 99.3% and 99.9%, respectively, very similar to the results of early experimental studies [12].

It must be emphasized that NIPT is only a screening test. It is highly sensitive but definitely not diagnostic. Furthermore, there is still rapid development and modification of NIPT procedures, and the performance of NIPT using different methodologies requires further confirmation.

NIPT is highly sensitive. It is likely it will detect more placental mosaicisms and lower levels of maternal mosaicisms than conventional screening tests, which could contribute to false positives.

Implementation of NIPT as a Down's syndrome screening tool

Scientifically, it is beyond doubt that the performance of NIPT is far superior to any other existing Down's syndrome screening test. The only barrier for its clinical use at present is the relatively high cost in most countries. However, there is no reason why pregnant women cannot use NIPT as the primary screening test at their own cost, with the balance between cost and benefit being their personal preference.

Similarly, there is no reason why pregnant women cannot use NIPT as a secondary screening test in a sequential or contingent manner at their own cost. In the sequential model, NIPT is offered to those who are tested high risk by traditional screening tests, which in general have a lower detection rate and higher FPR. The sequential model will substantially reduce the overall FPR and the number of invasive tests needed. In other words, using NIPT sequentially cannot improve the overall detection rate, which is limited by the primary screening test. This approach will be useful to those who are satisfied with the detection rate of the traditional screening tests, but would like to avoid invasive tests as much as possible. In the contingent screening model, NIPT is also used as a second-line test but includes those who are screened high risk or borderline risk by the primary test, thereby increasing the overall sensitivity and specificity.

The incorporation of NIPT into publicly funded programmes requires solid proof of cost-effectiveness. All published studies on cost-effectiveness support the use of NIPT as a secondary screening test but not as a primary screening test at the current cost. In the Chinese territory of Macau, NIPT as a secondary screening test has already been incorporated into their screening programme. When the cost of NIPT is reduced to the level equivalent to traditional screening tests, there will be no reason not to replace them by NIPT even in publicly funded programmes. This situation is imminent. In fact in mainland China, some provinces have started, or are about to start, offering NIPT as a primary screening test at a cost (not user price) as low as RMB500, which is lower than the cost of traditional screening tests in many developed countries. It is foreseeable that NIPT will become the most cost-effective primary screening test for Down's syndrome within the next 5 years if not earlier.

Most commercial NIPT providers accept a test request from 10 weeks or even 9 weeks of pregnancy onwards. There is no upper gestational limit. However, most published studies include pregnant subjects at 12 weeks or beyond. There are very limited published data before 12 weeks of gestation, in particular at 10 weeks of gestation. It is possible that the detection rate may be lower in the first trimester, by about 1.3% for trisomy 21 [12].

Diagnostic tests for those who are high risk for NIPT

If pregnancy is at or after 15 weeks, amniocentesis should be the diagnostic method of choice. If pregnancy is at 14+ weeks, it is preferable to advise the woman to wait for an amniocentesis at 15 weeks.

Before 14 weeks, CVS is an acceptable diagnostic test, in particular if sonographic markers of Down's syndrome are present. This allows earlier diagnosis and intervention. If there is no sonographic marker present, the woman may choose CVS, mid-trimester amniocentesis or early amniocentesis. CVS could still be used since non-mosaic trisomy confined only to the placenta without affecting the fetus is a very rare event for chromosome 21 but the pregnant women must fully understand the implication. Delaying to 15 weeks for an amniocentesis could be psychologically stressful during the period of waiting, but this approach will completely avoid the possibility of trisomy confined to the placenta resulting in termination of a normal fetus. Early amniocentesis can be performed at the same gestation as CVS, and it avoids the disadvantage of both CVS and mid-trimester amniocentesis. However, early amniocentesis is associated with a higher risk of miscarriage and increased risk of fetal talipes.

In general, a detailed ultrasound scan should be performed when NIPT is high risk, and the ultrasound findings may assist the patient in deciding which diagnostic test to have.

Confirmatory test is essential

Although the sensitivity and specificity of NIPT are both greater than 99%, it is still a screening test and therefore confirmation by a diagnostic test is essential before pregnancy termination. With sensitivity of 99% and specificity of 99.9%, the PPV is 66.7% and 83.4% at disease prevalences of 0.2% and 0.5%, respectively (Table 6.2), indicating that one in three and one in six test-positive subjects are in fact false positives. This estimation is very close to the published PPV of NIPT on clinical datasets, i.e. approximately 70–80%. It is predicted that when NIPT is being used more extensively in average-risk populations, the PPV will reduce further to around 60–70%. Although a PPV of 80% is very high already, the one in six chance of being false positive warrants a diagnostic test before pregnancy termination. The only exception to this rule is when pregnancy termination is medically acceptable irrespective of the karyotype findings, such as the presence of major structural abnormalities.

Causes of positive NIPT

A positive NIPT for trisomy 21 may be due to (i) a truly affected fetus; (ii) a fetus affected by mosaic trisomy 21; (iii) CPM; (iv) vanished twin; (v) abnormalities of the maternal chromosome if the counting method is used, such as mosaic of an aneuploidy, asymptomatic carrier of a microdeletion or presence of cell-free tumour DNA from an underlying malignancy; and (vi) false positive related to the nature and limitation of the technology. With meticulous examination, it is usually possible to identify a biological cause in most cases with positive NIPT result.

In daily clinical practice, it may not be feasible to exclude all possible causes due to the additional cost implication. But such sources of false positives must be considered during the post-test counselling and when making a decision for the type of diagnostic test.

Table 6.2 The positive predictive value (PPV) of a screening test with a sensitivity of 99%. The PPV changes with the specificity and the prevalence of disease in the screened population. The possibility of false positives is significant even at a specificity of 99.9%.

		PPV	
Specificity (%)	False-positive rate (%)	Prevalence 0.2%	Prevalence 0.5%
99	1.00	16.7%	33.4%
99.5	0.5	28.6%	50.1%
99.9	0.1	66.7%	83.4%
99.99	0.01	95.3%	98.1%

Extending NIPT to other chromosomal abnormalities

Although originally developed for trisomy 21, the same NIPT algorithm could be modified to detect trisomy 13, trisomy 18, 45X syndrome, and other aneuploidies. With further modifications, NIPT can be extended to detect large unbalanced chromosomal rearrangements, microdeletions, microduplications and even single gene disorders.

Performance of NIPT for trisomy 18 appears to be slightly lower than that for trisomy 21, with an estimated sensitivity of 97% [12]. Performance for trisomy 13 is more variable, with sensitivity of 90–97% [12,13]. Sensitivity for 45X syndrome in general is lower, reported to be 75–90% [14].

Extending NIPT to 45X syndrome is common but worth further consideration. For those with typical sonographic features of 45X syndrome, including very high NT, cystic hygroma or early hydrops, the prognosis is poor and diagnostic tests should be considered instead of NIPT because of the relatively low detection rate. Pregnancies with 45X syndrome and normal first-trimester ultrasound examination usually proceed normally and the majority of babies will be liveborn with normal intelligence. It is a non-lethal condition although ovarian failure is almost certain. The decision to continue with pregnancy is common even with confirmed 45X after prenatal diagnosis, and therefore it is controversial if prenatal screening is necessary. When counselling a woman who is high risk for 45X, the following should be considered:

1) in the absence of songoraphic abnormalities, the overall prognosis in general is good in terms of survival and function other than ovarian failure;
2) the implications of ovarian failure and the treatments available;
3) 10% are due to low-level maternal mosaicism (if the counting method is used), and is more common with advancing maternal age due to somatic changes;
4) a significant proportion, as high as 40%, are due to mosaicism, which could be simple X/XX mosaic, or more complicated such as X/XY [15].

Extending NIPT to other sex chromosomal abnormalities (SCAs) is common in commercially available NIPT

products. The true detection rate is uncertain because many of the affected individuals are asymptomatic at birth. Most individuals with SCA are normal, although some may have problems with fertility, ambiguous genitalia or increased risk of learning difficulties in specific areas. Although scientifically it is controversial whether screening of SCA is worthwhile, the great majority of pregnant women want to be informed if NIPT results in suspicion of SCA so that they can make informed choices and are better prepared [16].

Extending NIPT to aneuploidy involving other chromosomes appears logical if the genome-wide MPS method is used, since sequencing data is necessarily available. The laboratory cost for the additional bioinformatics analysis and reporting is minimal. Aneuploidy involving other chromosomes usually results in early pregnancy losses and in the majority of such cases the cause is CPM. However, about 30% of these cases will have early-onset fetal growth restriction that requires early delivery, and some may be accompanied by fetal mosaicism or UPD due to trisomic rescue. UPD may result in the expression of recessively inherited diseases, and UPD of specific chromosomes such as 11 or 15 may result in significant imprinting disorders. Therefore, the additional information on other chromosomes may be clinically important. However, it must be realized that patient counselling is particularly difficult, and couples may request pregnancy termination for uncertainty only, such as UPD. Therefore, the risks and benefits of disclosing information about other chromosomes need to be carefully considered.

Detection of large chromosomal rearrangements, microdeletions and single gene disorders are possible with NIPT. This application is rapidly changing and is beyond the scope of this chapter.

Failure rate

In early reports, NIPT generates no report in 1–10% of cases for various reasons; the figure is approximately 1–3% in more recent studies. There is some evidence that those who fail to have an interpretable NIPT result are at higher risk of aneuploidy. The management of these pregnancies may include repeat blood sampling or a diagnostic test.

Factors affecting NIPT accuracy

The methodology used, stringency in quality control and sequencing depth are important determining factors but this information is rarely available in sufficient detail to be useful to end users.

Fetal fraction is obviously an important factor. Fetal fraction is negatively correlated with maternal weight, being 11.7% at 60 kg and 3.9% at 160 kg. The fetal fraction was found to be below 4% in 0.7, 7.1 and 51.1% of samples from women weighing 60, 100 and 150 kg respectively [17]. Adequate fetal genetic material in the sample is the prerequisite for an interpretable and reliable result. However, the definition of 'adequate' is affected by other factors as well, in particular the nature of the molecular test, sequencing depth and the bioinformatics methodology used. The common belief that a fetal fraction of 4% is required for NIPT is simple, but was based on a specific testing algorithm only. For example, an early study showed that false-negative cases had a significantly lower fetal fraction, all below 7% [18], while a more recent study showed that mean fetal fraction was 10.2% among the false-negative cases and low fetal fraction was not a cause for false negativity [19].

Sample preparation, storage and transportation significantly affect the fetal fraction due to breakdown of maternal nucleated cells in the sample. Various methods have been implemented to stabilize the fetal fraction, and it is the duty of the physicians to ensure that such protocols are strictly followed.

Twin pregnancies

There are limited published data on the performance of NIPT in multiple pregnancies. The sensitivity for trisomy 21 detection in twin pregnancy may be lower than in singleton pregnancy but is likely to be 95–99% with FPR below 1% [20]. In comparison, conventional screening tests have much higher FPR and lower detection rate. Therefore there is no reason why NIPT cannot be used or offered to those with twin pregnancies.

Role of first-trimester ultrasound in NIPT

NIPT is just one of the components of first-trimester screening. A first-trimester scan should be part of the screening package. The ultrasound will provide important information, including viability and gestational age of the pregnancy, the number of fetuses, presence of vanished twin, presence of thickened NT, or structural anomalies. All this information will be significant after deciding whether NIPT is appropriate and the timing of NIPT.

For those women who decide not to have first-trimester Down's syndrome screening, they should still have at least a basic first-trimester ultrasound to confirm the location and number of gestations, estimate gestational age, and determine chorionicity and amnionicity in cases of multiple pregnancy.

Summary box 6.5

- NIPT is a highly sensitive and specific screening test for Down's syndrome.
- All NIPT-positive cases must be confirmed by a diagnostic test before pregnancy termination.

First-trimester screening of fetal structural anomalies

Approximately 60% of major structural abnormalities can be diagnosed in the first trimester of pregnancy, such as anencephaly, omphalocele or limb defects. The potential benefit is an earlier diagnosis which will provide more time for the couple to undergo further tests and to consider further management plans, allow early intervention including pregnancy termination, and possibly lead to better outcome or less physical or psychological trauma. Pregnant women should be given a chance to decide if they would like to have this extra examination. However, there are many potential problems that need to be considered.

1) The detection rate of fetal anomalies in the first trimester can never reach that of second-trimester scan. A proper mid-trimester scan is still essential. This must be explained clearly to the pregnant women to avoid misunderstanding.
2) Timing of the scan is important. An almost complete fetal morphological assessment is usually feasible towards the end of 13 weeks of gestation, but is much more technically challenging at 11 weeks of gestation.
3) Confirmation of anomalies at such early gestation may not be feasible after pregnancy termination, especially if a surgical method is used.
4) A first-trimester scan may detect suspicious findings that require further evaluation and assessment when the gestation is more advanced. This may result in significant psychological stress and emotional disturbance.

Further details of prenatal diagnosis of fetal structural anomalies is discussed in Chapter 20.

First-trimester screening of late obstetric complications

There is increasing interest in first-trimester screening of late obstetric complications, in particular hypertensive disorders and fetal growth restriction. In general, screening using single markers does not produce adequate sensitivity for routine clinical use. Recent studies have suggested that risk assessment based on algorithms combining previous obstetric and medical history, personal demographic data, sonographic signs and biochemical markers may be an effective screening tool [21]. Further details will be discussed under specific conditions.

First-trimester screening of single gene disorders

Expanded carrier screening (ECS) is still in the early stages of development. This will certainly become routine in the near future when the cost becomes more affordable. ECS is best performed before pregnancy. In reality, most pregnant women do not have a proper preconception assessment. The first trimester may be the first time to discuss ECS with them. For further details, refer to Chapter 4.

Conclusion

The arrival of NIPT radically changes first-trimester screening for fetal Down's syndrome. The technology is rapidly evolving, and is being expanded rapidly to cover other chromosomal, genomic and single gene disorders. By the time this book is published, some of the details stated here might have become outdated. However, the principle remains that pregnant women should be given adequate information for them to make their own choices concerning prenatal screening of genetic conditions.

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Part 3

Maternal Medicine

7

Hypertensive Disorders

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Pre-eclampsia is an idiopathic disorder of pregnancy characterized by proteinuric hypertension. Recent estimates indicate that over 30 000 women die worldwide each year because of pre-eclampsia and its complications, with 98% of these occurring in developing countries [1]. Globally, pre-eclampsia has been estimated to cause between 10 and 25% of perinatal loss [2,3]. In the UK, despite improvements over recent years, pre-eclampsia remains a significant cause of direct maternal death, with six cases reported in the latest triennial report [4]. Up to 5% of women will develop pre-eclampsia in their first pregnancy and although the overwhelming majority of these will have successful pregnancy outcomes, the condition can give rise to severe multisystem complications including cerebral haemorrhage, hepatic and renal dysfunction and respiratory compromise. The development of strategies to prevent and treat the disorder has been challenging due to an incomplete understanding of the underlying pathogenesis.

Pathophysiology

The pathogenesis of pre-eclampsia originates in the placenta. The disease can occur in the absence of fetal tissue (molar pregnancy) and manifestations of the disease will only resolve following delivery of the placenta. The blueprint for establishing pre-eclampsia is determined at the outset of pregnancy when placental trophoblast invades the maternal uterine spiral arteries at the time of implantation. In pregnancies destined to be complicated by pre-eclampsia, transformation of the spiral arteries is impaired, with suboptimal remodelling of small-capacitance constricted vessels into dilated large-capacitance conduits. The prevailing theory has been that the subsequent relative placental ischaemia causes release of vasoactive factors into the circulation which then give rise to endothelial-mediated end-organ damage and clinical manifestations of the disease. Scientific endeavours to determine these elusive vasoactive factors have largely been responsible for pre-eclampsia being known as the 'disease of theories'.

Several candidates have been considered in the role of a key circulating vasoactive factor, including interleukins, tumour necrosis factor (TNF)-α and components of the angiotensin pathway. Whilst all these elements are subject to modification in pre-eclamptic pregnancies, it has not been possible to demonstrate that any have an initiating role in the disease process. Pre-eclampsia is a disease of higher primates only and the lack of a clinically relevant animal model has been a significant research obstacle. The discovery of soluble fms-like tyrosine kinase (sFlt)-1 has been particularly exciting because it is the first candidate that has been demonstrated to cause a pre-eclampsia phenotype in an animal model [5].

sFlt-1 is variant of vascular endothelial growth factor receptor (VEGFR)-1, which has an extracellular ligand-binding domain but lacks the transmembrane and cytoplasmic domains. Circulating sFlt-1 is therefore able to competitively bind to VEGF and placental growth factor (PGF) and therefore reduce biologically active binding of these factors that usually promote angiogenesis and placentation. Women with pre-eclampsia have increased circulating levels of sFlt-1 and reduced circulating free VEGF and PGF. VEGF is important in maintaining normal fenestration of the glomerular endothelium [6,7] and it has been suggested that the early renal manifestations of pre-eclampsia may be a consequence of the particular sensitivity of the kidney to reduced levels of VEGF. In animals it has been shown that both VEGF and PGF must be reduced to cause a pre-eclampsia phenotype [5]. *In vitro* and *in vivo* studies [8] have shown that the hypoxic placenta produces increased levels of sFlt-1 and primate studies [9] indicate that this may be sufficient to produce

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a pre-eclampsia phenotype. Another factor in this story is endoglin (sEng), a modified form of the transforming growth factor (TGF)-β coreceptor. sEng is also increased in pre-eclampsia and has been shown to augment the effect of sFlt-1 and is particularly associated with hepatic endothelial damage [10]. Importantly, sFlt-1, PGF and sEng have been shown to be elevated in the serum of women destined to suffer pre-eclampsia several weeks in advance of clinically evident disease [11].

Summary box 7.1

- The pathogenesis of pre-eclampsia remains elusive but a greater scientific knowledge of the condition is emerging.
- Pre-eclampsia accounts for approximately 25% of all very low birthweight infants, a significant number of preterm births and has a high perinatal mortality.
- Pre-eclampsia is the second most frequent cause of direct maternal death.
- These deaths are avoidable as substandard care complicates 90% of these deaths.

An intriguing aspect of this hypothesis is its link to a potential explanation as to why smokers have a reduced incidence of pre-eclampsia. The combustible component of cigarette smoke induces haemoxidase (HO)-1. This is a stress response gene that has a cellular protective role, particularly against hypoxic injury. HO-1 degrades haem into biliverdin, carbon monoxide (CO) and free iron. Both biliverdin and CO have been demonstrated to reduce endothelial expression of sFlt-1 and sEng [12]. Appreciation of the potential role of the HO-1 pathway has led to the suggestion that pharmacological agents known to have HO-1 activity might be useful in ameliorating pre-eclampsia. Statins are widely used outside obstetrics to reduce serum lipids and forthcoming studies will evaluate whether their theoretical potential can be translated safely and usefully into pregnancy.

Defining hypertensive disease in pregnancy

There has always been considerable debate over the most appropriate definition of the hypertensive disorders in pregnancy. It has been recognized that there are benefits in having a broader clinical definition whilst retaining a very tight phenotypic research definition. Hypertension complicates 6–12% of all pregnancies [13], and includes two relatively benign conditions (chronic and gestational hypertension) and the more severe conditions of pre-eclampsia or eclampsia. Pre-eclampsia complicates 3–5% of all pregnancies, and is characterized by placental and maternal vascular dysfunction that may lead to adverse outcomes such as severe hypertension, stroke, seizure (eclampsia), renal and hepatic injury, haemorrhage, fetal growth restriction, or even death [14].

The diagnosis of pre-eclampsia, and hence the prediction of adverse events, is based on traditional but somewhat unreliable and non-specific clinical markers such as blood pressure, urine protein excretion, and symptoms. For example, more than 20% of women who have eclampsia will fail to meet the common diagnostic criteria of pre-eclampsia prior to their event, making the prediction of this adverse outcome extremely difficult [15]. Conversely, only 0.7–5.0% of women with classically defined pre-eclampsia will experience any composite adverse outcomes [16].

For this reason consistency is required both for clinical management and to allow the comparison of outcomes from clinical units/regions. The National Institute for Health and Care Excellence (NICE) Clinical Guideline 107 [17] has defined management pathways for hypertension in pregnancy in the UK. The list that follows outlines the NICE definitions associated with hypertension in pregnancy used in this chapter.

- *Gestational hypertension*: new hypertension presenting after 20 weeks without significant proteinuria.
- *Pre-eclampsia*: new hypertension presenting after 20 weeks with significant proteinuria.
- *Chronic hypertension*: hypertension present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.
- *Eclampsia*: a convulsive condition associated with pre-eclampsia.
- *HELLP syndrome*: haemolysis, elevated liver enzymes and low platelet count.
- *Severe pre-eclampsia*: pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
- *Significant proteinuria*: defined as a urinary protein/creatinine ratio of greater than 30 mg/mmol or a validated 24-hour urine collection result showing greater than 300 mg protein.
- *Mild hypertension*: diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg.
- *Moderate hypertension*: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg.
- *Severe hypertension*: diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.

Summary box 7.2

- Pre-eclampsia is a multisystem disease diagnosed by the characteristic appearance of gestational hypertension and gestational proteinuria.
- Gestational hypertension is a persistent *de novo* blood pressure >140/90 mmHg occurring after 20/40 gestation in pregnancy. On its own it carries little additional morbidity.
- Gestational proteinuria is a protein excretion above 300 mg per 24 hours (equivalent to a protein/creatinine ratio of 30 mg/mmol).
- There are errors associated with the measurement of both blood pressure and proteinuria in pregnancy which can be minimized by a combination of good technique and automated devices.
- All the above conditions can occur superimposed on chronic hypertension, making diagnosis difficult.
- Postnatal follow-up is essential to confirm the 'pregnancy diagnosis' and to advise about long-term risk.

Measuring blood pressure and proteinuria in pregnancy and pre-eclampsia

The errors associated with blood pressure measurement have been well described in both non-pregnant and pregnant populations. Care in taking these measurements will reduce false-positive and false-negative results and improve clinical care. Machine/device errors have led to strict validation protocols for automated blood pressure devices in specific populations and clinical settings [18] and the human errors inherent in manual readings have led to guidelines on the measurement of blood pressure with both manual and automated devices in clinical practice [19]. Digit preference (the practice of rounding the final digit of blood pressure to zero) occurs in the vast majority of antenatal measurements and simply taking care to avoid this will limit inaccurate diagnoses. Using a standard bladder in a sphygmomanometer cuff will systematically undercuff 25% of an average antenatal population. Having large cuffs available and using them will prevent the over-diagnosis of hypertension [20]. Keeping the rate of deflation to 2–3 mmHg/s will prevent over-diagnosis of diastolic hypertension, as will using Korotkoff 5, which is now universally recommended for diagnosing diastolic hypertension. Korotkoff 4 (the muffling of the sound) is less reproducible, and randomized controlled trials confirmed that it is safe to abandon it, except in those rare situations when the blood pressure approaches zero [21,22].

The reliable detection of proteinuria is essential in differentiating those pregnancies with pre-eclampsia from those with gestational or chronic hypertension and, in the process, identifying those pregnancies most prone to adverse outcome. The measurement of significant proteinuria, traditionally 300 mg excretion in a 24-hour period, is also prone to collection and measurement error. The collection of 24-hour urine samples is not practical as a routine test and so urine dipstick screening is employed as a first-line screening test with secondary tests employed to confirm positive dipstick diagnoses. Visual dipstick reading is unreliable [23] but the use of automated dipstick readers significantly improves the accuracy of dipstick testing and as such is recommended by NICE for use in pregnancy [24]. NICE also recommends that quantification of proteinuria should follow diagnosis. There are two methods that NICE supports. The first is the 24-hour urine protein estimation and this requires that an assessment of sample completeness is undertaken, with measurement of creatinine excretion being the most common. NICE also supports the use of the protein/creatinine ratio test. This test is done on a 'spot' urine sample and is therefore much quicker. This test has been shown in numerous studies to be comparable to the 24-hour urine protein estimation [25]. The threshold for defining significant proteinuria by this test is 30 mg protein/mmol creatinine.

Risk assessment and risk reduction

There have been attempts to screen the antenatal population for pre-eclampsia over the past 60 years, with over 100 potential biochemical, biophysical or epidemiological candidate tests. Despite not yet having a single universal test to apply, it is still possible to advise women regarding their risk of pre-eclampsia from their clinical history and some investigations.

NICE guidelines for routine antenatal care [26] emphasize that a woman's risk of pre-eclampsia should be evaluated. Several risk factors for pre-eclampsia are known and these have been incorporated into the NICE recommendations [27,28]. Table 7.1 outlines risk factors that should be identified at booking to identify women at risk of pre-eclampsia. Many of the risk factors listed in this table are modifiable and may lead to a reduction in risk either prior to or between pregnancies.

Individual risk is not a simple numerical addition. A family history of pre-eclampsia in a first-degree relative is significant and two relatives even more so, whilst

Table 7.1 Risk factors for identifying women at increased risk of pre-eclampsia.

Any single high-risk factor
Hypertensive disease during a previous pregnancy
Chronic kidney disease
Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
Type 1 or type 2 diabetes
Chronic hypertension
Or two or more moderate-risk factors
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years
Body mass index (BMI) of 35 kg/m^2 or more at first visit
Family history of pre-eclampsia
Multiple pregnancy

Table 7.2 Relative risks of developing pre-eclampsia.

	Relative risk	Confidence intervals
Antiphospholipid syndrome	9.72	4.34–21.75
Previous history of pre-eclampsia	7.19	5.83–8.83
Pre-existing diabetes	3.56	2.54–4.99
Multiple pregnancy	2.93	2.04–4.21
Nulliparity	2.91	1.28–6.61
Family history	2.90	1.70–4.93
Raised BMI		
Before pregnancy	2.47	1.66–3.67
At booking	1.55	1.28–1.88
Age over 40	1.96	1.34–2.87
Raised diastolic blood pressure (>80 mmHg)	1.38	1.01–1.87

exposure over time to paternal antigen through increased periods of cohabitation and non-barrier contraception can reduce risk as can prior miscarriage or termination of pregnancy. Pre-eclampsia is more common at the extremes of reproductive age and is increased further following *in vitro* fertilization (IVF) treatment, particularly with donor sperm. Other factors often associated with increasing age, such as obesity, gestational and pregestational diabetes, and any disease affecting the cardiovascular system are potent risk factors for pre-eclampsia. The relative risk for pre-eclampsia for some of these risk factors is shown in Table 7.2 [28].

Clearly, from the relative risks quoted, the majority of women who are high risk will still not develop pre-eclampsia whilst a considerable number of cases will arise *de novo* in the 'low-risk' population. Identifying women at risk will allow increase in surveillance and use of prophylactic therapies can be considered. If adequate preventive measures become available, then these screening tests will become increasingly important. Tests that might be employed to screen the population (high or low risk) for pre-eclampsia centre on the identification of poor placental function, which is an almost universal prerequisite for the clinical condition. Doppler assessment of the maternal uterine circulation is considered to be a promising test. This test when 'positive' demonstrates the high resistance in the uterine arteries as well as a 'notch' apparent within the Doppler waveform. These two features have been used in isolation and combination to screen low- and high-risk populations. Early studies suggested that approximately one in five women who have an abnormal Doppler at 20 weeks' gestation will develop pre-eclampsia [29], and at 24 weeks' gestation the prediction value is greater. In 2008, NICE recommended that uterine artery Doppler screening should not be employed universally for low-risk women [26]. More recently NICE Clinical Guideline 107 recommended that this test should not be universally employed in high-risk women based on the relatively poor quality of the studies performed to date. However, it did recognize its potential and made a research recommendation regarding its use in the management of high-risk women.

No other biophysical test other than accurate measurement of blood pressure in the first trimester has either any clinical application or is practical enough to employ in clinical practice. Numerous haematological and biochemical markers have been used to both predict and evaluate pre-eclampsia. For example, in women who have chronic hypertension the measurement of uric acid and platelets can help in determining those who suffer superimposed pre-eclampsia; again the tests lack sensitivity and specificity [30]. Furthermore, very few of these markers have been independently evaluated for their ability to separately predict the timing or severity of specific adverse outcomes such as placental abruption, severe hypertension, neurological injury and fetal growth restriction. The reason for this is that the biomarkers previously studied were mostly generic indicators of vascular activation and dysfunction, which arise late in the pre-eclamptic disease process and which are not specific to pre-eclampsia or even to pregnancy.

As outlined previously, recent advances have identified a class of pregnancy-specific angiogenic and anti-angiogenic factors (e.g. PlGF, VEGF) that are produced by the placenta and which closely correlate with the preclinical and clinical stages of pre-eclampsia [11,31–36]. Assays of these markers are currently under assessment as tools to predict and/or diagnose pre-eclampsia prior to the onset of clinical disease and significant morbidity. The FASTER trial of 2003 demonstrated that, when measured as part of the quadruple aneuploidy screen at 15–18 weeks'

gestation, the odds ratios for the development of pre-eclampsia when inhibin-A and β-human chorionic gonadotrophin (hCG) levels are above the 95th centile were 3.42 (95% CI 2.7 and 4.3) and 2.20 (95% CI 1.7 and 2.9), respectively [37].

In 2008, the Society of Obstetricians and Gynaecologists of Canada Genetics Committee, following systematic review, suggested that abnormal uterine artery Doppler in combination with an elevated α-fetoprotein (AFP), hCG and inhibin-A, or decreased pregnancy-associated plasma protein A (PAPP-A), identify a group of women at increased risk of intrauterine growth restriction and pre-eclampsia. They also stated that multiple maternal serum screening markers at present should not be used for population-based screening as false-positive rates are high, sensitivities are low and no protocols have shown improved outcome [38].

Screening is important to focus resources on high-risk women as well as to identify those in whom prophylactic therapies might have some benefit. Aspirin and calcium have been found to have a beneficial effect whilst other agents, most recently antioxidants, have not proven useful. NICE Clinical Guideline 107 recommends low-dose aspirin therapy (75 mg/day) for all high-risk women from 12 weeks' gestation. Antiplatelet agents were associated with statistically significant reductions in the risk of pre-eclampsia in moderate-risk women and in high-risk women (moderate-risk women: 25 studies, $N = 28\,469$, RR 0.86, 95% CI 0.79–0.95; high-risk women: 18 studies, $N = 4121$, RR 0.75, 95% CI 0.66–0.85).

A meta-analysis using individual-patient data from 32 217 women and their 32 819 babies found a statistically significant reduction in risk of developing pre-eclampsia (RR 0.90, 95% CI 0.84–0.97). The data from this study suggest that one case of pre-eclampsia would be prevented for every 114 women treated with antiplatelet agents. In addition to the 10% reduction in pre-eclampsia in high-risk women receiving antiplatelet agents, there was a 10% reduction in preterm birth. No particular subgroup of women in the high-risk group was substantially more or less likely to benefit from antiplatelet agents. There was no statistically significant difference between women who started treatment before 20 weeks (RR 0.87, 95% CI 0.79–0.96) and those who started treatment after 20 weeks (RR 0.95, 95% CI 0.85–1.06; $P = 0.24$). Of importance, there were no statistically significant differences between women receiving antiplatelet agents and those receiving placebo in the incidence of potential adverse effects such as antepartum haemorrhage, placental abruption or postpartum haemorrhage, but there was a reduction in the risk of preterm birth before 37 weeks (RR 0.93, 95% CI 0.89–0.98) [39].

Trials of calcium to prevent pre-eclampsia are more controversial. There is good evidence that in areas where the dietary intake of calcium is low, calcium supplementation reduces the risk of pre-eclampsia but this is also influenced by prior risk status. In studies conducted where dietary calcium intake is normal, supplementation was not found to be of benefit. No other intervention can be recommended, including magnesium, folic acid, antioxidants (vitamins C and E), fish oils or bed rest. Diet or lifestyle changes may be beneficial for general health and weight loss may reduce the prior risk of hypertensive disease but modifications such as a low-salt diet have no proven benefit.

Chronic hypertension

Women with chronic hypertension should receive pre-pregnancy care. This should aim to determine the severity and cause of the hypertension; review potentially teratogenic medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (three times the risk of congenital abnormality) and diuretics; inform women of the risk associated with pregnancy and of prophylactic strategies (all should receive low-dose aspirin in pregnancy); and to assess comorbidities such as renal impairment, obesity or coexistent diabetes.

The main risk is of superimposed pre-eclampsia, but even in its absence the perinatal mortality is increased. Drugs appropriate for treating hypertension in pregnancy include methyldopa, labetalol, nifedipine and hydralazine. Safety data on other antihypertensives are lacking but there are several where no association with congenital abnormality has been established and so they can be used when clinically indicated.

Blood pressure control should be tailored to the individual. Where the chronic hypertension is secondary to other disease, then the care should be multidisciplinary with the appropriate physician aiming to keep blood pressure below 140/90 mmHg and often at lower limits. When the chronic hypertension is uncomplicated (usually essential) the target should be 150–155/80–100 mmHg [17].

There is a recognized risk of fetal growth restriction (FGR) in this group and so serial fetal biometry is recommended and women should be seen with increased frequency to maintain blood pressure control and to screen for pre-eclampsia. Delivery should be for either fetal indications or for poor hypertension control once corticosteroids for fetal lung maturity have been given if less than 34 weeks' gestation.

At term, NICE recommends delivery after 37 weeks when agreed with the individual, so long as blood pressure control is maintained. Following delivery blood pressure should be maintained below 140/90 mmHg and medication should be reviewed and optimized for both blood pressure control and breastfeeding.

Gestational hypertension

Gestational hypertension is relatively common and as such most units will assess women identified in the community in their day unit. Here, the first assessment is of proteinuria to identify those with pre-eclampsia. In the absence of proteinuria NICE Clinical Guideline 107 recommends an integrated package of care dependent on blood pressure.

- If blood pressure 140–149/90–99 mmHg, then review weekly and test for proteinuria only (as described above).
- If blood pressure 150–159/100–109 mmHg, then treat with labetalol as first line and target blood pressure is 140–150/80–100 mmHg. Check urea and electrolytes, liver function tests and full blood count once, then review twice weekly testing for proteinuria only.
- If blood pressure >160/>110 mmHg, then admit until below 159/109 mmHg and treat as above. When controlled, review twice weekly as above. Test for proteinuria each visit and also retest bloods weekly.

The guideline also recognizes that the earlier the presentation, the greater the likelihood of progression to pre-eclampsia and the frequency of visits should be adjusted accordingly. Gestational hypertension does not require aspirin prophylaxis and patients do not require routine hospital admission if blood pressure is controlled.

Fetal monitoring is also controversial. The suspected small baby (from customized symphysis–fundal height measurment) should be investigated with fetal biometry. No benefit (reduction in perinatal mortality) has been shown in trials where additional monitoring is offered to women with gestational hypertension where FGR was absent. As such the generic advice given to all pregnant women regarding awareness of fetal movements is all that NICE Clinical Guideline 107 recommends.

CHIPS (Control of Hypertension in Pregnancy Study) [40] was a large international trial that has recently reported. Investigators randomized 987 women with non-severe, non-proteinuric hypertension presenting before 34 weeks to less-tight (target diastolic pressure 100 mmHg) or tight (target diastolic pressure 85 mmHg) control. The study found no significant differences between the two groups with regard to adverse perinatal outcome or serious maternal complications. Women in the less-tight control group had an almost twofold increased incidence of severe hypertension (40.6% vs. 27.5%), representing a significant number of women exposed to increased risk of stroke and requiring urgent antihypertensive treatment.

A large randomized controlled trial, the HYPITAT study [41], compared delivery at term (by induction of labour) with conservative care for gestational hypertension and mild pre-eclampsia. This study showed a reduction in severe hypertension in pre-eclamptic women but not gestational hypertension and no neonatal benefits were noted. Following this NICE suggests that women are not induced prior to 37 weeks unless blood pressure is uncontrolled and beyond 37 weeks that time of delivery is a balanced judgement of risk agreed between the obstetrician and the woman.

It is imperative that women with gestational hypertension are followed up with a postnatal visit where their blood pressure is checked. Those who remain hypertensive require specialist review and a percentage of these women will be found to have chronic hypertension and they require cardiovascular risk assessment and advice.

Summary box 7.3

- Pre-eclampsia requires admission to hospital but gestational hypertension does not.
- Blood pressure of 140–149/90–99 mmHg does not require pharmacological treatment.
- Blood pressure of 150–159/100–109 mmHg requires treatment to achieve a target blood pressure of 130–149/80–99 mmHg.
- Blood pressure of ≥160/≥110 mmHg requires urgent treatment to achieve target blood pressure as above.

Pre-eclampsia

Pre-eclampsia is diagnosed when there is significant proteinuria in the presence of gestational hypertension. The relationship between the level of proteinuria and maternal and fetal complications is poor. One systematic review [42] found that there was an increased risk of stillbirth with proteinuria and a reduced likelihood of stillbirth in the absence of proteinuria (at a level of 5 g per 24 hours). Because of this NICE recommends that when pre-eclampsia has been diagnosed women should be admitted to hospital, blood pressure should be treated as for gestational hypertension and proteinuria does not need to be requantified. NICE recommends conservative care up to 34 weeks' gestation with steroid administration for fetal lung maturity as well as individualized plans for fetal monitoring, recognizing the increased risk associated with coincident FGR. NICE recommends delivery with a stable blood pressure when hypertension is severe after 34 weeks and after 37 weeks when hypertension is mild or moderate. When women present late (after 37 weeks) they should be delivered after 24–48 hours of stabilization [41].

Planning delivery

Delivery of the placenta remains the only intervention which leads to resolution of both the clinical and biochemical manifestations of pre-eclampsia. Unfortunately, some women will initially deteriorate in the immediate postpartum period before the recovery phase and all the serious complications of pre-eclampsia can be encountered at this time. It is therefore important that women are delivered in an environment where they can be closely monitored and appropriately managed. In most cases this will be a consultant-led delivery facility able to provide continuing postnatal surveillance, although some women will require high dependency or intensive care particularly if systemic complications develop. The mode of delivery will depend upon gestation, severity of maternal disease, degree of fetal compromise as well as maternal and clinician preference.

Isolated controlled hypertension or mild pre-eclampsia

Women with treated hypertension or mild pre-eclamspsia at term who labour spontaneously or following induction of labour should continue their antihypertensive medication and have their blood pressure monitored hourly. Haematological and biochemical parameters should only be checked in women who have not previously been under surveillance or in whom those investigations are not up to date [17]. Cardiotocography is recommended during active labour, particularly if there is any suspicion of FGR and labour attendants should be vigilant for signs of abruption. Providing hypertension remains well controlled, there is no evidence to support routine limitation of the duration of second stage and many women should therefore be able to achieve delivery without instrumentation.

Active third-stage management is encouraged as women with pre-eclampsia will be less tolerant of postpartum haemorrhage. Ergometrine is associated with exacerbation of hypertension and should not be used routinely. Oxytocin is the recommended drug for routine management of the third stage in the UK and this also applies to hypertensive women. In the event of postpartum haemorrhage it should be remembered that pharmacological uterotonic alternatives to ergometrine such as misoprostol can also be associated with hypertension.

Severe pre-eclampsia

The diagnosis of severe pre-eclampsia is usually made along with a decision to deliver once the maternal condition has been stabilized. Women should be managed in a high-dependency environment by a multidisciplinary team of senior clinicians including high-risk midwifery staff, obstetricians and anaesthetists in a clinical setting where additional support can be obtained if needed from intensivists, nephrologists, haematologists, hepatologists, neurologists and neonatologists. Care is focused around careful fluid management, treatment of hypertension, prevention/treatment of eclamptic fits and prompt recognition and supportive management of any complications which arise prior to the recovery phase.

Treatment of hypertension

Uncontrolled hypertension, particularly persistent systolic pressures above 160 mmHg or mean arterial pressures sustained above 125 mmHg, lead to compromised cerebral autoregulation. The associated complications of cerebral haemorrhage and encephalopathy are the leading cause of maternal mortality in hypertensive pregnancies in the UK and it is for this reason that one of the key recommendations from the most recent MBRRACE report [4] was that severe hypertension should be more actively controlled. The aim of treatment is to gradually reduce blood pressure and sustain levels in the region of 150/80–100 mmHg.

The most common antihypertensive agents used in the UK for acute management of hypertension in pregnancy are labetalol (α- and β-receptor blocker), hydralazine (α-receptor blocker) and calcium channel blockers (nifedipine). The available meta-analyses have failed to demonstrate that one agent is a more effective antihypertensive in this population and the choice of drug therefore depends on the pharmacological profile and anticipated side effects in an individual clinical scenario. Labetalol can be administered by oral and intravenous routes, nifedipine is given orally and hydralazine is reserved for intravenous administration in UK obstetric practice. Prior to delivery it is important to prevent precipitous drops in blood pressure, which will be associated with a reduction in placental perfusion and can give rise to fetal distress, particularly in growth-restricted babies. Rapid reduction in blood pressure is most commonly seen following hydralazine and this has led some clinicians to recommend that a 500-mL bolus of colloid is given before or at the same time as the first dose of hydralazine. It is currently unclear if this practice reduces the incidence of fetal compromise or if the practice is associated with any increased maternal morbidity especially fluid overload. Certainly there is no role for fluid preloading following delivery of the baby. Precipitous drops in blood pressure can also be a feature of nifedipine, especially if they are coadministered with magnesium sulfate when potentiation of the vasodilative action can be problematic. Labetalol has therefore emerged as the first-line agent (in non-asthmatics) and is currently the only agent in this group to be licensed in the UK for the acute treatment of hypertension in pregnancy.

Prevention and treatment of eclamptic fits

Magnesium sulfate is the recommended drug to treat and prevent eclampsia. The Magpie (Magnesium Sulphate for Prevention of Eclampsia) trial [15] recruited 10 141 women with pre-eclampsia and randomized them to receive magnesium sulfate or placebo. The incidence of eclampsia was significantly lower in women who received magnesium sulfate. The greatest effect was seen in women who were at the highest risk: 63 women with severe pre-eclampsia needed to be treated to prevent a fit in contrast to 100 women with mild or moderate disease. No benefit was seen in other outcomes including maternal or neonatal morbidity or mortality.

Cochrane reviews have reported that magnesium sulfate is superior to diazepam or phenytoin for the treatment of eclampsia [43]. The incidence of recurrent maternal fits is reduced and improved neonatal outcomes, including reduced need for admission to special care baby unit or ventilation, are seen in women who delivered following magnesium sulfate.

The precise mechanisms by which magnesium sulfate acts to reduce cerebral irritability is unclear. It is a vasodilating agent and contributes to reduction of cerebral perfusion pressures but it also has other relevant properties including membrane stabilization. Magnesium sulfate is emerging as a potential agent to reduce rates of cerebral palsy in preterm infants, although the mechanism and optimal dose for this purpose remain unclear. These properties may contribute to improved neonatal outcomes in women who deliver preterm due to pre-eclampsia.

Magnesium is given intravenously as a 4-g loading dose over 5 min followed by an infusion of 1 g/hour which is usually maintained for 24 hours. Recurrent seizures should be treated with a further dose of 2–4 g over 5 min and diazepam should be reserved for use in women who continue to fit despite magnesium sulfate. The therapeutic range for magnesium plasma levels is 4–8 mg/dL; toxicity causes loss of deep tendon reflexes at 10 mg/dL and respiratory paralysis at 15 mg/dL. The drug is excreted in the urine and toxicity is therefore more likely in women who have renal manifestations of pre-eclampsia. Calcium gluconate 1 g (10 mL of 10% solution) over 2 min is administered to reverse magnesium toxicity with ventilatory support if required.

Summary box 7.4

- Magnesium sulfate is the drug of choice for the treatment of eclamptic seizures.
- Magnesium sulfate is the drug of choice for the prevention of eclamptic seizures.
- Over 25% of eclamptic seizures will occur postnatally.

Fluid management

The combination of vascular endothelial injury and the normal physiological fluid shifts during the early postpartum period make pre-eclamptic women particularly vulnerable to pulmonary oedema at this time. Six deaths were reported to the Confidential Enquiry into Maternal Deaths in the UK between 1994 and 1996 and in all women injudicious fluid management in pre-eclampsia was felt to be a significant contributory factor. Encouragingly, following recommendations made in that report for tighter fluid management there were no deaths in this group of patients in the following triennial report attributed to iatrogenic fluid overload.

The current recommended practice is to restrict fluid intake to 80 mL/hour until a postpartum diuresis is established. In women where there are ongoing losses or where persistent minimal urine output raises concerns about renal injury, invasive monitoring may help guide fluid replenishment whilst avoiding overload.

Anaesthetic issues

Both regional and general anaesthesia can be problematic in the pre-eclamptic patient. Epidural anaesthesia is often advocated for labouring pre-eclamptic women due to the belief that it will contribute to lowering of blood pressure by reducing both pain-associated anxiety and peripheral vasodilatation. Whilst there may be a modest antihypertensive effect there do not appear to be any significant improvements in maternal or fetal outcomes in women who have epidural anaesthesia for labour. As in the general obstetric population, epidural anaesthesia is associated with a longer second stage and increased incidence of instrumental delivery. There is therefore no evidence to recommend the routine use of epidural anaesthesia in labouring pre-eclamptic women and the diagnosis should not influence the woman's choice of analgesia for labour. An important exception to this is women who have severe pre-eclampsia with thrombocytopenia. A platelet count below 80×10^9/L is a contraindication to regional anaesthesia due to the increased risk of spinal haematoma.

General anaesthesia can be complicated by exacerbation of severe hypertension in response to intubation. Furthermore, laryngeal oedema can make intubation technically difficult and should only be undertaken by senior anaesthetic clinicians. The greatest risks are seen in women who have not been appropriately stabilized prior to anaesthesia.

Complications

Hepatic

Approximately 12% of women with severe pre-eclampsia will develop HELLP syndrome, characterized

by haemolysis, elevated liver enzymes and low platelet count. Not all components are necessarily evident at presentation and the diagnosis is not necessarily associated with the most severe hypertensive presentations. Many affected women will be asymptomatic or will present with non-specific malaise and nausea, although a few will describe classical epigastric and right upper quadrant tenderness. The diagnosis is based on laboratory investigations including a blood film, platelet count and measurement of liver transaminases. Treatment is largely supportive. High-dose steroids have been used to try to hasten the recovery of thrombocytopenia but this has not been shown to be associated with any improved maternal outcomes and is not recommended.

Rarely, liver ischaemia can cause intrahepatic haemorrhage and subcapsular haematoma. This complication is associated with a significant risk of maternal mortality. Conservative management with ultrasound surveillance may be appropriate in the postpartum patient who is haemodynamically stable and where the haematoma is not expanding. Measures described to achieve haemostasis at laparotomy include compression, haemostatic sutures, application of topical coagulation agents, embolization or lobectomy.

Renal

Although glomerular capillary endotheliosis is a classic pathological feature of pre-eclampsia and relative oliguria is common in the early postpartum period, these features usually resolve spontaneously. Acute renal failure is a rare complication of pre-eclampsia, with an estimated incidence of 1 in 10 000–15 000 pregnancies. Obstetric haemorrhage is a much more common precipitating factor in this population. Treatment is supportive; meticulous fluid management along with a high-protein, low-potassium diet and daily electrolyte monitoring will usually be sufficient whilst awaiting spontaneous resolution. Dialysis is rarely required in women who do not have pre-existing renal pathology.

Neurological

Neurological sequelae of pre-eclampsia, other than fits, include cerebral haemorrhage, encephalopathy and temporary blindness (amaurosis). Disruption of cerebral autoregulation, increased perfusion pressures and increased vascular permeability are contributory factors but the aetiology is complicated by haemoconcentration predisposing to thrombosis and vasospasm associated with fits. Any focal neurological signs should be investigated with cranial imaging to exclude other pathologies but no specific treatment is recommended.

Postnatal management

One-third of women who have had pregnancy-induced hypertension or pre-eclampsia will sustain hypertension in the postnatal period and this increases to over 75% in women who have had preterm delivery triggered by maternal hypertensive disease. Poorly managed hypertension causes anxiety for the woman and her carers, delays discharge to the community and can occasionally put her at risk of significant complications. There is little evidence to inform clinicians when managing postpartum hypertension and until such evidence is available a pragmatic approach has been recommended [17]. Women should remain in hospital until they are asymptomatic, their blood pressure is stable within safe limits and their biochemical indices are resolving.

All women who have been prescribed antenatal antihypertensives should have these continued in the postnatal period. Women who have been given methydopa should be changed to an alternative agent before the third postnatal day due to the association of methyldopa with postpartum depression. If the blood pressure is persistently below 140/90 mmHg, then reduce the dose. Most women will not require medication beyond 6 weeks. Commonly prescribed antihypertensive agents which have no known effects on breastfeeding infants include labetalol, atenolol, metoprolol, nifedipine, enalapril and captopril.

Women who have not previously been treated with antihypertensives should have their blood pressure monitored four times daily while an inpatient and should be treated if blood pressure is above 150/100 mmHg. Women in the community should have their blood pressure measured once between days 3 and 5 using a similar threshold for treatment. If medication is initiated, follow-up should be within 48 hours to ensure an appropriate response.

Over 25% of eclampsia will present in the postnatal period, often in women who have not been previously identified as having hypertensive disease [44]. Any woman describing severe headache or epigastric pain postnatally should have pre-eclampsia excluded. Women who have developed pre-eclampsia should be offered an obstetric review around 6 weeks after birth. This affords the opportunity to confirm that hypertension and proteinuria have resolved, or to arrange referral for further investigation if there are concerns about underlying pathology. Women should be made aware of their risk of developing pre-eclampsia in future pregnancies; overall the risk of recurrence is around 16% but this increases to 55% if they were delivered before 28 weeks' gestation due to hypertensive disease. This discussion should also identify any other modifiable risk factors which might be addressed prior to embarking on another pregnancy, for example weight management.

Finally, women should be made aware of the emerging evidence that pre-eclampsia identifies a group of women who are at increased risk of future cardiovascular morbidity. A single pregnancy complicated by pre-eclampsia doubles the risk of a future cardiovascular event [45]. Coexisting FGR or early-onset, severe or recurrent disease increases the risk further. The proposed pathogenic hypotheses include shared genetic risk factors for pre-eclampsia and cardiovascular disease causing pregnancy to reveal an underlying susceptibility [46], persistence of circulating factors that promote endothelial dysfunction [47] or altered endothelial progenitor cell function activity [48]. Alternatively, persistent subclinical impairment of cardiac function [49] may represent a premorbid state which over time manifests as heart failure. Both the American College of Obstetricians and Gynecologists [50] and NICE [17] recommend that women should be offered a postnatal cardiovascular risk assessment following a pregnancy complicated by pre-eclampsia. There remains a paucity of evidence as to which health professionals are best placed to carry out the assessment and what should be included beyond informing the woman of her increased risk. Whatever the underlying pathogenesis, it seems plausible that targeting monitoring and lifestyle modifications to this group of women might ameliorate future cardiovascular events.

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8

Heart Disease in Pregnancy

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Although pregnancies complicated by significant heart disease are rare in the UK, Europe and the developed world, cardiac disease remains the leading cause of maternal death in the UK [1]. There were 49 indirect deaths attributed to cardiac disease in 2011–2013, giving a death rate of 2.1 per 100 000 maternities [1]. The maternal mortality rate from cardiac disease has continued to rise since the early 1980s though may now be stabilizing. The major causes of cardiac deaths over the last 15 years are cardiomyopathy (predominantly peripartum), myocardial infarction and ischaemic heart disease, dissection of the thoracic aorta and sudden adult death syndrome [2]. In the UK, rheumatic heart disease is now extremely rare in women of childbearing age and mostly confined to migrants.

Women with congenital heart disease who have undergone corrective or palliative surgery in childhood and who have survived into adulthood are encountered more frequently. These women may have complicated pregnancies yet mortality remains low, probably due to extensive multidisciplanary pre-pregnancy counselling and clear pathways of care for those with adult congenital heart disease. Women with metal prosthetic valves face difficult decisions regarding anticoagulation in pregnancy and have a greatly increased risk of haemorrhage, valve failure and fetal loss.

Because of significant physiological changes in pregnancy, symptoms such as palpitations, fatigue and shortness of breath are very common and innocent findings. Not all women with significant heart disease are able to meet these increased physiological demands. The significance of orthopnoea and paroxysmal nocturnal dyspnoea as symptoms of pulmonary oedema may not be appreciated by maternity staff. The care of the pregnant and parturient woman with heart disease requires a multidisciplinary approach involving obstetricians, cardiologists, anaesthetists and specialist midwives, preferably in a dedicated antenatal cardiac clinic. This allows formulation of an agreed and documented management plan encompassing management of both planned and emergency delivery.

The most common and important cardiac conditions encountered in pregnancy are discussed in this chapter.

Physiological adaptations to pregnancy, labour and delivery

Blood volume starts to rise by the fifth week after conception secondary to oestrogen- and prostaglandin-induced relaxation of smooth muscle that increases the capacitance of the venous bed. Plasma volume increases and red cell mass rises but to a lesser degree, thus explaining the physiological anaemia of pregnancy. Relaxation of smooth muscle on the arterial side results in a profound fall in systemic vascular resistance and together with the increase in blood volume determines the early increase in cardiac output. Blood pressure falls slightly, but by term has usually returned to the pre-pregnancy value. The increased cardiac output is achieved by an increase in stroke volume and a lesser increase in resting heart rate of 10–20 bpm. By the end of the second trimester the blood volume and stroke volume have risen by between 30 and 50%. This increase correlates with the size and weight of the products of conception and is therefore considerably greater in multiple pregnancies as is the risk of heart failure in women with concomitant heart disease [3].

Although there is no increase in pulmonary capillary wedge pressure, serum colloid osmotic pressure is reduced. The gradient between colloid oncotic pressure and pulmonary capillary wedge pressure is reduced by 28%, making pregnant women particularly susceptible to pulmonary oedema. Pulmonary oedema will be precipitated if there

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is an increase in cardiac preload (such as infusion of fluids), increased pulmonary capillary permeability (such as in pre-eclampsia), or both.

In late pregnancy in the supine position, pressure of the gravid uterus on the inferior vena cava (IVC) causes a reduction in venous return to the heart and a consequent fall in stroke volume and cardiac output. Turning from the lateral to the supine position may result in a 25% reduction in cardiac output. Pregnant women should therefore be nursed in the left or right lateral position wherever possible. If the mother has to be kept on her back, the pelvis should be rotated so that the uterus drops forward and cardiac output as well as uteroplacental blood flow is optimized. Reduced cardiac output is associated with reduction in uterine blood flow and therefore placental perfusion; this can compromise the fetus.

Labour is associated with further increases in cardiac output (15% in the first stage and 50% in the second stage). Uterine contractions lead to autotransfusion of 300–500 mL of blood back into the circulation and the sympathetic response to pain and anxiety further elevate heart rate and blood pressure. Cardiac output is increased more during contractions but also between contractions. The rise in stroke volume with each contraction is attenuated by good pain relief and further reduced by epidural analgesia and the supine position. Epidural analgesia or anaesthesia causes arterial vasodilatation and a fall in blood pressure [4]. General anaesthesia is associated with a rise in blood pressure and heart rate during induction but cardiovascular stability thereafter. Prostaglandins given to induce labour have little effect on haemodynamics but ergometrine causes vasoconstriction and Syntocinon can cause vasodilation and fluid retention.

In the third stage up to 1 L of blood may be returned to the circulation due to the relief of IVC obstruction and contraction of the uterus. The intrathoracic and cardiac blood volumes rise, and cardiac output increases by 60–80% followed by a rapid decline to pre-labour values within about 1 hour of delivery. Transfer of fluid from the extravascular space increases venous return and stroke volume further. Those women with cardiovascular compromise are therefore most at risk of pulmonary oedema during the third stage of labour and the immediate postpartum period. All the changes revert quite rapidly during the first week and more slowly over the following 6 weeks, but even at 1 year significant changes still persist and are enhanced by a subsequent pregnancy [5].

Normal findings on examination of the cardiovascular system in pregnancy

These may include a loud first heart sound with exaggerated splitting of the second heart sound and a physiological third heart sound at the apex. A systolic ejection murmur at the left sternal edge is heard in nearly all women and may be remarkably loud and be audible all over the precordium. It varies with posture and if unaccompanied by any other abnormality reflects the increased stroke output. However, diastolic murmurs are virtually always pathological. Venous hums and mammary souffles may be heard. Because of the peripheral vasodilatation the pulse may be bounding and in addition ectopic beats are very common in pregnancy. Ankle swelling is common in the normal pregnant woman but if accompanied by hypertension consider pre-eclampsia.

Cardiac investigations in pregnancy

The ECG axis shifts slightly to the left (superiorly) in late pregnancy due to a more horizontal position of the heart. Small Q waves and T-wave inversion in the inferior leads are not uncommon. Atrial and ventricular ectopics are both common. Troponin is not affected by pregnancy and remains a valid test for myocardial ischaemia.

The amount of radiation received by the fetus during a maternal chest X-ray (CXR) is negligible and CXR should never be withheld if clinically indicated in pregnancy. Transthoracic echocardiography is the investigation of choice for excluding, confirming or monitoring structural heart disease in pregnancy. Transoesophageal echocardiography is also safe with the usual precautions to avoid aspiration. Magnetic resonance imaging (MRI) and chest computed tomography (CT) are safe in pregnancy. Routine investigation with electrophysiological studies are normally postponed until after pregnancy but angiography should not be withheld in, for example, acute coronary syndromes.

General considerations in pregnant women with heart disease

The outcome and safety of pregnancy are related to:

- presence and severity of pulmonary hypertension;
- presence of cyanosis;
- haemodynamic significance of the lesion;
- functional NYHA (New York Heart Association) class as determined by the level of activity that leads to dyspnoea [6].

Most women with pre-existing cardiac disease tolerate pregnancy well if they are asymptomatic or only mildly symptomatic (NYHA class II or less) before the pregnancy, but important exceptions are pulmonary hypertension, Marfan's syndrome with a dilated aortic root, and some women with mitral or aortic stenosis. Women with cyanosis (oxygen saturation below 80–85%) have an increased

risk of fetal growth restriction, fetal loss, and thromboembolism secondary to the reactive polycythaemia. Their chance of a live birth in one study was less than 20% [7].

A number of scores have been developed to predict cardiac events. The CARPREG score identified an increased risk of cardiac events if the woman was classified as above NYHA class II, had cyanosis, had a left ventricular ejection fraction less than 40%, or had signficant left heart obstruction [8]. The total score predicted the risk of events such as stroke, arrhythmia, pulmonary oedema and death complicating pregnancies in women with structural heart disease. This was followed by the Zahara I score which included the first three parameters but added the presence of valvular regurgitation, mechanical valve prosthesis, cyanotic heart disease and cardiac medication required before pregnancy [9].

Finally, the simple modified World Health Organization (WHO) criteria were developed and when tested in a clinical cohort of pregnant women [10] appeared to predict risk better than the former two scoring systems [11]. Whichever score is used, all risk estimations show increased risk for the women with increasing class, risk score or number of predictors. The presence of these identified factors therefore also act as reasons to refer to specialist centres for counselling and management of the pregnancy.

Women with the above risk factors for adverse cardiac or obstetric events should be managed and counselled by a multidisciplinary team including cardiologists with expertise in pregnancy, obstetricians with expertise in cardiac disease, fetal medicine specialists and paediatricians. There should be early involvement of obstetric anaesthetists and a carefully documented plan for delivery.

Specific cardiac conditions

Congenital heart disease

Asymptomatic acyanotic women with simple defects usually tolerate pregnancy well. Many defects will have been treated surgically or by the interventional paediatric cardiologist but others are first discovered during pregnancy. Women with congenital heart disease are at increased risk of having a baby with congenital heart disease and should therefore be offered genetic counselling if possible before pregnancy [12] and detailed scanning for fetal cardiac anomalies with fetal echocardiography by 18–20 weeks' gestation. The risk of congenital heart disease in the child is higher with left-sided lesions such as coarctation of the aorta and is 50% in women with Marfan's syndrome. Those lesions associated with a reduced cardiac output are associated with an increased risk of fetal growth restriction.

Acyanotic congenital heart disease

Atrial septal defect

After bicuspid aortic valve, secundum atrial septal defect (ASD) is the commonest congenital cardiac defect in adults. Paradoxical embolism is rare and arrhythmias do not usually develop until middle age. Mitral regurgitation caused by mitral leaflet prolapse develops in up to 15% of uncorrected ASDs. Pulmonary hypertension is rare.

No problems are anticipated during pregnancy but acute blood loss is poorly tolerated. It can cause massive increase in left-to-right shunting and a precipitous fall in left ventricular output, blood pressure and coronary blood flow and even lead to cardiac arrest.

Ventricular septal defect and patent ductus

Like regurgitant valve disease, these defects, which increase the volume load of the right ventricle, are well tolerated in pregnancy unless the defects are large and complicated by pulmonary vascular disease.

Pulmonary stenosis

Pulmonary stenosis does not usually give rise to symptoms during pregnancy. However, when severe and causing right ventricular failure, balloon pulmonary valvotomy has been successfully carried out during pregnancy. The procedure is best performed during the second trimester.

Aortic stenosis

Left ventricular outflow tract obstruction at any level can cause problems during pregnancy. Pre-pregnancy assessment is the ideal. Significant obstruction results if aortic valve area is less than 1 cm^2 or if the non-pregnant mean gradient across the valve is above 50 mmHg. Indications that pregnancy will be high risk include failure to achieve a normal rise in blood pressure without the development of ST- or T-wave changes during exercise, impaired left ventricular function, and symptoms including chest pain, syncope or pre-syncope.

The ECG will normally show left ventricular hypertrophy and the Doppler transaortic valve velocity will rise during pregnancy if the stroke volume increases in normal fashion. Therefore the measured gradients in pregnancy will increase and should always be compared to pre-pregnancy where possible. If left ventricular systolic function is impaired, the left ventricle may not be capable of generating a high gradient across the valve, and a low gradient may therefore be falsely reassuring.

Any patient who develops angina, dyspnoea or resting tachycardia should be admitted to hospital for rest. Administration of a β-adrenergic blocking drug will increase diastolic coronary flow time and left ventricular filling with resultant improvement in angina and left ventricular function. If despite these measures angina,

pulmonary congestion and left ventricular failure persist or progress, balloon aortic valvotomy needs to be considered [13]. These valves are intrinsically not ideal and severe aortic regurgitation may be created, but if successful the procedure may buy time and allow completion of the pregnancy.

Coarctation of the aorta

Most cases encountered will already have been surgically corrected, although residual narrowing is not uncommon and may not have been identified before pregnancy if the woman has not had regular follow-up. Ideally, any narrowing or pre- or post-stenotic dilatation or aneurysm formation should be assessed with MRI prior to pregnancy. Aortic coarctation may first be diagnosed during pregnancy and should always be considered when raised blood pressure is recorded at booking, especially if investigation for secondary causes of pre-existing hypertension has not previously been undertaken.

Although the blood pressure can be lowered, adequate control cannot be maintained during exercise, which increases the risk of cerebral haemorrhage or aortic dissection [14]. Women with uncorrected coarctation should therefore be advised to rest and avoid exertion. The risk of dissection is increased in patients with pre-existing aortic abnormality associated with coarctation, Marfan's syndrome or other inherited connective tissue disorders.

Hypertension should be aggressively treated, and to minimize the risk of rupture and dissection beta-blockers are the ideal agents. Left ventricular failure is unlikely in the absence of an associated stenotic bicuspid aortic valve or endocardial fibroelastosis with impaired left ventricular function. Normal delivery is usually possible, although severe coarctation would indicate a shortened second stage.

Marfan's syndrome

The majority (80%) of patients with Marfan's syndrome have some cardiac involvement, most commonly mitral valve prolapse and regurgitation. Pregnancy increases the risk of aortic rupture or dissection, usually in the third trimester or early after birth. The risk of type A aortic dissection in pregnant women with Marfan's syndrome is around 1%, even in the absence of a dilated aortic root [6]. Progressive aortic root dilatation and an aortic root dimension above 4 cm are associated with increased risk (10%) [15]. Women with aortic roots greater than 4.6 cm should be advised to delay pregnancy until after aortic root repair or root replacement with resuspension of the aortic valve [16].

Conversely, in women with minimal cardiac involvement and an aortic root of less than 4 cm pregnancy outcome is usually good, although those with a family history of aortic dissection or sudden death are also at increased risk, since in some families aortic root dissection occurs in the absence of preliminary aortic dilatation [6].

Management should include counselling regarding the dominant inheritance of the condition, echocardiography every 4–6 weeks to assess the aortic root in those with cardiac involvement, and beta-blockers for those with hypertension or aortic root dilatation. Vaginal delivery for those with stable aortic root measurements is possible but elective caesarean section with regional anaesthesia is recommended if there is an enlarged or dilating aortic root.

Cyanotic congenital heart disease

Cyanotic congenital heart disease in the adult is usually associated with either pulmonary hypertension (as in Eisenmenger's syndrome) or pulmonary stenosis (as in tetralogy of Fallot). Patients with single ventricle, transposition of the great arteries and complex pulmonary atresias with systemic blood supply to the lungs may all survive to adult life with or without previous palliative surgery.

Tetralogy of Fallot

Tetralogy of Fallot is the association of severe right ventricular outflow tract obstruction with a large subaortic ventricular septal defect (VSD) and overriding aorta causing right ventricular hypertrophy and right-to-left shunting with cyanosis. Pregnancy is tolerated well but fetal growth is poor with a high rate of miscarriage, prematurity and small-for-dates babies. The haematocrit tends to rise during pregnancy in cyanosed women because systemic vasodilatation leads to an increase in right-to-left shunting. Women with a resting arterial saturation of 85% or more, haemoglobin below 18 g/dL and haematocrit below 55% have a reasonable chance of a successful outcome. Arterial saturation falls markedly on effort so rest is prescribed to optimize fetal growth but subcutaneous low-molecular-weight heparin (LMWH) should be given to prevent venous thrombosis and paradoxical embolism. Most women will have had previous surgical correction of tetralogy of Fallot and do well in pregnancy providing they have no signficant pulmonary stenosis or right ventricular failure [17].

Postoperative congenital heart disease

Survivors of neonatal palliative surgery for complex congenital heart disease need individual assessment. Echocardiography by a paediatric or adult congenital cardiologist enables a detailed assessment to be made.

Following the Fontan operation for tricuspid atresia or transposition with pulmonary stenosis, the right ventricle is bypassed and the left ventricle provides the pump for

both the systemic and pulmonary circulations. Increases in venous pressure can lead to hepatic congestion and gross oedema but pregnancy can be successful. It is important that women with a Fontan circulation are kept well filled peripartum as without optimal preload the left ventricle cannot adequately drive the pulmonary circulation. These women are usually anticoagulated with warfarin outside pregnancy and LMWH in pregnancy.

Eisenmenger's syndrome and pulmonary hypertension

Pulmonary vascular disease, whether secondary to a reversed large left-to-right shunt such as a VSD (Eisenmenger's syndrome) or to lung or connective tissue disease (e.g. scleroderma) or due to idiopathic arterial pulmonary hypertension, is extremely dangerous in pregnancy and women known to have significant pulmonary vascular disease should be advised from an early age to avoid pregnancy and be given appropriate contraceptive advice [10]. Maternal mortality was around 25–40% [18], but with a highly specialized team managing these women with aggressive drug regimens, the reported mortality rate has fallen to around 17% [19]. This mortality rate is still high and therefore the advice to these women not to undergo a pregnancy still stands.

The danger relates to fixed pulmonary vascular resistance that cannot fall in response to pregnancy, and a consequent inability to increase pulmonary blood flow with refractory hypoxaemia. Pulmonary hypertension is defined as a non-pregnant elevation of mean (not systolic) pulmonary artery pressure of 25 mmHg or more at rest or 30 mmHg on exercise in the absence of a left-to-right shunt. Pulmonary artery systolic (not mean) pressure is usually estimated using Doppler ultrasound to measure the regurgitant jet velocity across the tricuspid valve. This should be considered a screening test. There is no agreed relation between the mean pulmonary pressure and the estimated systolic pulmonary pressure. If the systolic pulmonary pressure estimated by Doppler is thought to indicate pulmonary hypertension, a specialist cardiac opinion is recommended. If there is pulmonary hypertension in the presence of a left-to-right shunt, the diagnosis of pulmonary vascular disease is particularly difficult and further investigation including cardiac catheterization to calculate pulmonary vascular resistance is likely to be necessary. Pulmonary hypertension as defined by Doppler studies may also occur in mitral stenosis and with large left-to-right shunts that have not reversed. Women with pulmonary hypertension who still have predominant left-to-right shunts are at lesser risk and may do well during pregnancy, but although such women may not have pulmonary vascular disease and a fixed pulmonary vascular resistance (or this may not have been established prior to pregnancy), they have the potential to develop it and require very careful monitoring.

Modern management of pulmonary hypertension includes drugs such as sildenafil/tadalfil and bosentan/macitentan. With such therapies, pulmonary pressures can be reduced to within the normal range, and therefore pregnancy may be safely negotiated. Although bosentan is teratogenic in animals, the benefit of continuing therapy in pregnancy probably outweighs this risk. In the event of unplanned pregnancy a therapeutic termination should be offered. Elective termination carries a 7% risk of mortality, hence the importance of avoiding pregnancy if possible. If such advice is declined, multidisciplinary care, elective admission for bed rest, oxygen and thromboprophylaxis with LMWH are recommended [20]. Fetal growth should be carefully monitored.

Most fatalities occur during delivery or the first week after birth. There is no evidence that monitoring the pulmonary artery pressure before or during delivery improves outcome; indeed insertion of a pulmonary artery catheter increases the risk of thrombosis, which may be fatal in such women. Vasodilators given to reduce pulmonary artery pressure will (with the exception of inhaled nitric oxide and prostacyclin) inevitably result in a concomitant lowering of the systemic pressure, exacerbating hypoxaemia.

There is no evidence that abdominal or vaginal delivery or regional versus general anaesthesia improve outcome in pregnant women with pulmonary hypertension. Great care must be taken to avoid systemic vasodilatation. The patient should be nursed in an intensive care unit after delivery. Nebulized prostacyclin can be used to try to prevent pulmonary vasoconstriction. When sudden deterioration occurs (usually in the postpartum period) resuscitation is rarely successful and no additional cause is found at post-mortem, although there may be concomitant thromboembolism, hypovolaemia or pre-eclampsia. Death is usually preceded by vagal slowing, a fall in blood pressure and oxygen saturation, followed by ventricular fibrillation.

Acquired valve disease

Mitral valve prolapse

This common condition may also be called 'floppy mitral valve' and may be sporadic or inherited as a dominant condition in some families with variants of Marfan's syndrome. Pregnancy is well tolerated and for women with isolated mitral valve prolapse there are no implications for the mother or fetus in pregnancy.

Rheumatic heart disease

Mitral stenosis

Worldwide, mitral stenosis remains the most common potentially lethal pre-existing heart condition in

pregnancy. There are many pitfalls because (i) an asymptomatic patient may deteriorate in pregnancy, (ii) mitral stenosis may have increased in severity since a previous uncomplicated pregnancy, (iii) stenosis can recur or worsen after valvuloplasty or valvotomy, and (iv) mitral stenosis that may previously not have been recognized may be missed during routine antenatal examination because the murmur is low-pitched, usually quiet, diastolic and submammary.

Women may deteriorate secondary to tachycardia (related to pain, anxiety, exercise or intercurrent infection), arrhythmias or the increased cardiac output of pregnancy. Sinus tachycardia at rest should prompt concern. Tachycardia is the reflex response to failure to increase stroke volume and it reduces the time for left atrial emptying during diastole so that left ventricular stroke volume falls, the reflex sinus tachycardia accelerates and left atrial pressure climbs. This creates a vicious circle of increasing heart rate and left atrial pressure and can precipitate pulmonary oedema. The anxiety caused by the dyspnoea increases the tachycardia and exacerbates the problem (Fig. 8.1). Pulmonary oedema may also be precipitated by increased volume (such as occurs during the third stage of labour or following injudicious intravenous fluid therapy) [21]. The risks are increased with severe mitral stenosis (mitral valve area $<1\,cm^2$), moderate or severe symptoms prior to pregnancy, and in those diagnosed late in pregnancy.

The ECG in mitral stenosis shows left atrial P waves and right axis deviation. The CXR shows a small heart but with prominence of the left atrial appendage and left atrium and pulmonary congestion or oedema. The diagnosis is confirmed with transthoracic echocardiography.

Women with severe mitral stenosis should be advised to delay pregnancy until after balloon, open or closed mitral valvotomy, or if the valve is not amenable to valvotomy until after mitral valve replacement. Beta-blockers decrease heart rate, increase diastolic filling time and decrease the risk of pulmonary oedema [21] and should be given in pregnancy to maintain a heart rate of under 90 bpm. Diuretics should be commenced or continued if indicated. It is also important that the woman does not over-exert herself.

In the event of pulmonary oedema, the patient should be sat up, oxygen should be given and the heart rate slowed by relief of anxiety with diamorphine, and intravenous furosemide 20 mg administered. Digoxin should only be used if atrial fibrillation occurs as it does not slow the heart in sinus rhythm (because increased sympathetic drive easily overcomes its mild vagotonic effect).

If medical therapy fails or for those with severe mitral stenosis, balloon mitral valvotomy may be safely and successfully used in pregnancy if the valve is suitable [22], although this will require transfer to a hospital with major cardiac facilities. Percutaneous balloon valvotomy carries a risk of major complications of about 1%, whereas for surgical valvotomy the risks are as follows.

- Closed valvotomy: fetal mortality 5–15%, maternal mortality 3%.
- Open valvotomy: fetal mortality 15–33%, maternal mortality 5%.

If an open operation on the mitral valve is likely to be required, this should be deferred if possible until after delivery.

Women with mitral stenosis should avoid the supine and lithotomy positions as much as possible for labour and delivery. Fluid overload must be avoided; even in the presence of oliguria, without significant blood loss, the temptation to give intravenous colloid must be resisted. Cautious epidural analgesia or anaesthesia is suitable for the patient with mitral stenosis as is vaginal delivery but limitation of maternal effort with an instrumental delivery may be indicated.

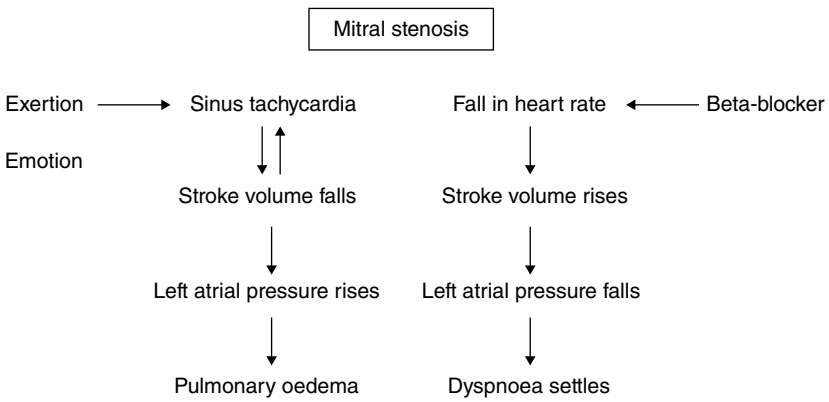

Fig. 8.1 Mitral stenosis.

Regurgitant valve disease

Patients with regurgitant valve disease, either mitral or aortic, tolerate pregnancy much better than patients with valvular stenosis. The systemic vasodilatation in pregnancy reduces regurgitant flow as does tachycardia in patients with aortic regurgitation. When the valve disease is of rheumatic origin the advent of sudden atrial fibrillation may precipitate pulmonary oedema. Similarly, monitoring of left ventricular function is important in those with severe mitral or aortic regurgitation.

Mechanical heart valves

Most women with prosthetic heart valves have sufficient cardiovascular reserve to accomplish pregnancy safely. The optimal strategy for anticoagulation in women with metal heart valve replacements in pregnancy is controversial since the interests of the mother and the fetus are in conflict. These women require lifelong anticoagulation and this must be continued in pregnancy because of the increased risk of thrombosis. However, warfarin is associated with warfarin embryopathy (chondrodysplasia punctata) if given during the period of organogenesis (6–12 weeks' gestation) [23] and with fetal intracerebral haemorrhage in the second and third trimesters.

Despite a maternal international normalized ratio (INR) within the therapeutic range, there is a greater anticoagulant effect on the fetus than on the mother because the immature fetal liver produces only low levels of vitamin K-dependent clotting factors and maternal procoagulants do not cross the placenta due to their large molecular size. The fetal risk from warfarin is dose dependent. Women requiring more than 5 mg daily are at increased risk of teratogenesis, miscarriage and stillbirth [24,25].

Heparin and LMWH do not cross the placenta and are therefore an attractive option. However, even in full anticoagulant doses, they are associated with an increased risk of valve thrombosis and embolic events [23,24,26]. Heparins can also cause retroplacental haemorrhage so the risk of fetal loss is not eliminated. Further disadvantages of unfractionated heparin include a need for parenteral administration, powerful but short duration of action, narrow therapeutic index, a steep dose–response curve, increasing dose requirement during pregnancy, and lack of agreed optimal test or target for safe and effective activity. Overshooting with incremental dosage brings a risk of bleeding. High doses of unfractionated heparin long term may also cause osteoporosis.

LMWHs have a better safety profile in pregnancy and provided there is close monitoring of anti-Xa levels with appropriate dose adjustments and good compliance with twice-daily injections, recent data would suggest a lower risk of thrombotic events [26,27]. Most clinicians use concomitant low-dose aspirin and many women need an increase in the LMWH dose in order to maintain peak anti-Xa levels of 0.8–1.2 IU/mL [27].

There are three basic options for anticoagulation management.

1) Continue warfarin throughout pregnancy, stopping only for delivery. This is the safest option for the mother [23,24].
2) Replace warfarin with high-dose LMWH from 6 to 12 weeks' gestation to avoid warfarin embryopathy but continue until prior to delivery when LMWH is used again.
3) Use high-dose LMWH throughout pregnancy.

Whilst the registry of pregnancy and cardiac disease (ROPAC) found a high rate of pregnancy loss in women using vitamin K antagonsists in the entire first trimester, no specific regimen turned out to be clearly safest [28]. Currently, therefore, the choice of regimen depends on several factors.

- *Type of mechanical valve*. The risk of thrombosis is less with the newer bileaflet valves (e.g. CarboMedics) than with first-generation ball and cage (e.g. Starr–Edwards) or second-generation single tilting disc (e.g. Björk–Shiley) valves.
- *Position of the valve replacement*. Valves in the aortic rather than the mitral position are associated with a lower risk of thrombosis [27].
- *Size of the mechanical valve*. If a valve was replaced before the woman had finished growing, it may be relatively small and this increases the risk of thrombosis.
- *Number of mechanical valves*. Two valves give a higher risk of thrombosis.
- *Dose of warfarin* required to maintain a therapeutic INR. If this is less than 5 mg, the risk to the fetus is reduced.
- Any previous history of embolic events.

If warfarin is used in pregnancy, serial fetal scans are indicated to detect embryopathy and intracerebral haemorrhage. Warfarin should be discontinued and substituted for LMWH for 10 days prior to delivery to allow clearance of warfarin from the fetal circulation. For delivery itself, LMWH therapy is interrupted.

Conversion from LMWH back to warfarin should be delayed for at least 5 days after delivery to minimize the risk of obstetric haemorrhage. There is a high risk of antenatal but particularly postpartum bleeding in women with mechanical valves [27].

In the event of bleeding or the need for urgent delivery in a fully anticoagulated patient, warfarin may be reversed with recombinant human factor VIIa, fresh frozen plasma and vitamin K, and heparin with protamine

sulfate. High doses of vitamin K should be avoided if possible since it renders the woman extremely difficult to anticoagulate with warfarin after delivery.

Thrombolytic treatment can be used for prosthetic valve thrombosis during pregnancy, and although it may cause embolism or bleeding or placental separation, the risks are lower than those of cardiothoracic surgery.

Coronary artery disease

Myocardial infarction and ischaemic heart disease are now seen more commonly in pregnant and postpartum women and pregnancy increases the risk of myocardial infarction [29]. When myocardial infarction occurs in pregnancy it often develops without a preceding history of typical angina. Pregnant women may present with atypical features as they often do outside of pregnancy. These include epigastric pain, nausea or dizziness as well as with more classical chest, neck and left arm pain. In pregnancy the underlying cause may be due to non-atherosclerotic conditions and thus can occur in a young individual without risk factors. These include spontaneous coronary artery dissection and coronary artery thrombosis, both of which are more common in pregnancy [2,30]. Most occur during late pregnancy or around or after delivery. Coronary ischaemia may also be associated with drug abuse from crack cocaine. Where there is thrombus on a normal coronary artery, embolic occlusion should always be considered and an embolic source such as mitral stenosis or infective endocarditis sought.

The risk factors for ischaemic heart disease in pregnancy are the same as those for the non-pregnant woman. The risk is increased in older multigravid women and in those who smoke and those with diabetes, obesity, hypertension, hypercholesterolaemia or a family history of coronary artery disease [29,31]. There should be a low threshold for investigating chest pain and other symptoms that could be due to acute coronary syndrome particularly in women with risk factors. Troponin is not affected by pregnancy and this should be requested along with serial ECGs in women in whom acute coronary syndrome is suspected. A raised troponin should therefore raise concern regarding an acute coronary syndrome and investigated appropriately.

The management of acute myocardial infarction and acute coronary syndrome is as for the non-pregnant woman. Coronary angiography should be undertaken without hesitation in order to define the pathology and determine management. Intravenous and intracoronary thrombolysis and percutaneous coronary intervention (PCI) and stenting have all been successfully performed in pregnancy. PCI is preferred as it has clinical superiority over thrombolysis outside of pregnancy but also coronary artery dissection is probably best treated with PCI. Both aspirin and beta-blockers are safe in pregnancy. Clopidogrel also appears to be safe but no data exist for the newer agents such as prasugrel or ticagrelor. The data for glycoprotein IIb/IIIa inhibitors are limited to case reports and these drugs are normally avoided where possible. It was thought statins should be discontinued for the duration of pregnancy as they are associated with an increased risk of malformations [32]. However, new safety data seem to be reassuring, but until we have more robust evidence, suspension of treatment is still advisable [33].

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease characterized by hypertrophy of the undilated left ventricle in the absence of an abnormal haemodynamic load and with underlying myocyte and myofibrillar disarray. Family studies, now sometimes aided by genetic identification of a responsible mutant gene, have indicated the broad spectrum of phenotypic abnormality that exists not only between individuals at different ages but within families. Patient series previously described from specialist centres represented a highly skewed population of high-risk patients referred because of disabling symptoms or a malignant family history. In the years before echocardiography only gross examples of the disorder could be identified but these patients formed the basis of many of the published natural history studies.

HCM is not infrequently first diagnosed in pregnancy when a systolic murmur leads to an ECG and echocardiographic study. Most patients are asymptomatic and do well. HCM used to be regarded as a rare disease with a high risk of sudden death but is now recognized to be relatively common, being found in 1 in 500 young adults in a recent study and in most patients the disorder is benign.

Patients with HCM respond well to pregnancy by a useful increase in their normally reduced left ventricular cavity size and stroke volume. The danger relates to left ventricular outflow tract obstruction that may be precipitated by hypotension or hypovolaemia. Symptoms of shortness of breath, chest pain, dizziness or syncope indicate the need for a beta-blocker [34]. Ventricular arrhythmias are commoner in older patients but uncommon in the young. Sudden death has only very rarely been reported during pregnancy. It is most important in all patients to avoid vasodilatation during labour and

delivery and during regional anaesthesia/analgesia. Any hypovolaemia will have the same effect and should be rapidly and adequately corrected. Equally, some HCM patients have a stiff ventricle and can therefore develop pulmonary oedema if they receive large volume loads. It is most unusual to find hypertrophy in the infants of mothers with HCM.

Peripartum cardiomyopathy

This pregnancy-specific condition is defined as the development of cardiac dysfunction towards the end of pregnancy or in the months following delivery, in the absence of an identifiable cause or recognizable heart disease prior to the last month of pregnancy, and left ventricular systolic dysfunction demonstrated by echocardiographic criteria [35]. The left ventricle may not be dilated but left ventricular ejection fraction is nearly always reduced (<45%). Echocardiography may show dilatation that usually involves all four chambers but is dominated by left ventricular hypokinesia, which may be global or most marked in a particular territory.

The condition is rare but the true incidence is unknown as mild cases undoubtedly go unrecognized. Recognized risk factors include multiple pregnancy, hypertension (pre-existing or related to pregnancy or pre-eclampsia), multiparity, increased age and Afro-Caribbean race.

Peripartum cardiomyopathy does not differ clinically from dilated cardiomyopathy except in its temporal relationship to pregnancy. The severity varies from catastrophic to subclinical, when it may be discovered only fortuitously through echocardiography. Diagnosis should be suspected in the peripartum patient with breathlessness, tachycardia or signs of heart failure. Pulmonary oedema is often a major feature and may be precipitated by the use of Syntocinon or by fluids given to maintain cardiac output during spinal anaesthesia for delivery. The CXR shows an enlarged heart with pulmonary congestion or oedema and often bilateral pleural effusions. Systemic embolism from mural thrombus may herald the onset of ventricular arrhythmias or precede the development of clinical heart failure and pulmonary embolism may further complicate the clinical picture.

The differential diagnosis includes pre-existing but undiagnosed dilated cardiomyopathy, pulmonary thromboembolism, amniotic fluid embolism, myocardial infarction and pulmonary oedema related to pre-eclampsia or β_2-agonist therapy for preterm labour. Echocardiography immediately implicates the left ventricle and excludes pulmonary embolism as the cause. Pre-eclampsia may rarely cause transient impairment of left ventricular function but this normally recovers rapidly after delivery.

Management is as for other causes of heart failure, with oxygen, diuretics, vasodilators and angiotensin-converting enzyme (ACE) inhibitors if post partum. Thromboprophylaxis is imperative. The cautious addition of a cardioselective β-adrenergic blocking drug may be helpful if tachycardia persists, particularly if the cardiac output is well preserved. The most gravely ill patients will need intubation, ventilation and monitoring with use of inotropes and sometimes temporary support from an intra-aortic balloon pump, ECMO (extracorporeal membrane oxygenation) or ventricular assist device. Heart transplantation may be the only chance of survival in severe cases.

More recently, the role of bromocriptine in peripartum cardiomyopathy has been investigated. Animal studies have suggested that oxidative stress raises the 16-kDa cleaved form of prolactin, which is angiostatic and pro-apoptotic, thus providing a plausible aetiology for the condition. A proof of concept pilot study was then undertaken which concluded that the addition of bromocriptine to standard heart failure treatment appeared to improve left ventricular ejection fraction and we now await a larger randomized trial [36].

Currently, about 50% of women make a spontaneous and full recovery. Most case fatalities occur close to presentation and cardiomyopathy is the cause of almost one-quarter of maternal cardiac deaths [2]. Recent data show a 5-year survival of 94% [37]. Patients should remain on an ACE inhibitor for as long as left ventricular function remains abnormal. Prognosis and recurrence depend on the normalization of left ventricular size, which may continue to improve for several years after delivery [38,39]. Those women with severe myocardial dysfunction (defined as left ventricular end-diastolic dimension ≥6 cm and fractional shortening ≤21%) are unlikely to regain normal cardiac function on follow-up [40]. Those whose left ventricular function and size do not return to normal within 6 months and prior to a subsequent pregnancy are at significant risk of worsening heart failure (50%) and death (25%) or recurrent peripartum cardiomyopathy in the next pregnancy. They should therefore be advised against pregnancy [38]. Women who have recovered normal left ventricular size and function should have their functional reserve assessed using stress (exercise) echocardiography. Even if this is normal there is a risk of recurrent heart failure in subsequent pregnancies [34].

Arrhythmias

Atrial and ventricular premature complexes are common in pregnancy. Many pregnant women are symptomatic from forceful heart beats that occur following a compensatory

pause after a ventricular premature complex. Most women with symptomatic episodes of dizziness, syncope and palpitations do not have arrhythmias [41].

A sinus tachycardia requires investigation for possible underlying pathology such as blood loss, infection, heart failure, thyrotoxicosis or pulmonary embolus. The commonest arrhythmia encountered in pregnancy is supraventricular tachycardia (SVT). First onset of SVT (both accessory pathway mediated and atrioventricular nodal re-entrant) is rare in pregnancy but exacerbation of symptoms is common in pregnancy [41]. Half of SVTs do not respond to vagal manoeuvres.

Propranolol, verapamil and adenosine have Food and Drug Administration approval for acute termination of SVT. Adenosine has advantages over verapamil, including probable lack of placental transfer, and may be safely used in pregnancy for SVTs that do not respond to vagal stimulation [42]. For prevention of SVTs, beta-blockers or verapamil may be used. Flecainide is safe and is used in the treatment of fetal tachycardias. Propafenone and amiodarone should be avoided [43], the latter because of interference with fetal thyroid function [44]. Temporary and permanent pacing, cardioversion and automatic implantable defibrillators are also safe in pregnancy. Care is needed when bipolar diathermy is used at caesarean section since this may be misinterpreted by the implantable defibrillator as ventricular fibrillation leading to deployment of a shock. The device is therefore usually inactivated during caesarean section.

Cardiac arrest

This should be managed according to the same protocols as used in the non-pregnant woman. Pregnant women (especially those in advanced pregnancy) should be 'wedged' to relieve any obstruction to venous return from pressure of the gravid uterus on the IVC. This can be most rapidly achieved by turning the patient into the left lateral position. If cardiopulmonary resuscitation is required, then the pelvis can be tilted while keeping the torso flat to allow external chest compressions. Emergency caesarean section may be required to aid maternal resuscitation.

Endocarditis prophylaxis

Infective endocarditis (IE) is rare in pregnancy but threatens the life of both mother and child. Fatal cases of endocarditis in pregnancy have occurred antenatally, rather than as a consequence of infection acquired at the time of delivery [2]. Treatment is essentially the same as outside pregnancy, with emergency valve replacement if indicated. As always, the baby should be delivered if viable before the maternal operation.

The current UK recommendations from the National Institute for Health and Care Excellence [45] are that antibiotic prophylaxis against IE is not required for childbirth. The British Society for Antimicrobial Chemotherapy [46] and the American Heart Association have recommended cover only for patients deemed to be at high risk of developing IE (such as women with previous IE) and for those who have the poorest outcome if they develop IE (such as those with cyanotic congenital heart disease). If antibiotic prophylaxis is used it should be with amoxicillin 2 g i.v. plus gentamicin 120 mg i.v. at the onset of labour or ruptured membranes or prior to caesarean section, followed by amoxicillin 500 mg orally (or i.m/i.v. depending on the patient's condition) 6 hours later. For women who are allergic to penicillin, vancomycin 1 g i.v. or teicoplanin 400 mg i.v. may be used instead of amoxicillin.

Summary box 8.1

- Cardiac disease is the commonest cause of death in pregnancy or the puerperium in the UK.
- Mortality of pulmonary hypertension in pregnancy is historically reported to be as high as 25–40%.
- Women with Marfan's syndrome are at risk of aortic dissection in pregnancy, particularly if they have a dilated aortic root.
- Women with mitral stenosis are at risk of pulmonary oedema in mid-pregnancy and during or immediately after delivery.
- If women with mechanical valves in pregnancy are managed with therapeutic doses of LMWH, this should be closely monitored and doses adjusted to maintain therapeutic levels. These women have an increased risk of bleeding, particularly after delivery.

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9

Diabetes in Pregnancy

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Diabetes in pregnancy poses major health risks to both the mother and the growing fetus, and influences the future health of the child [1–4]. The risk of diabetes to pregnancy outcome increases with increasing maternal hyperglycaemia [5,6], and thus the risk from pre-gestational diabetes, whether type 1 diabetes (type 1 DM) or type 2 diabetes (type 2 DM), is greater than gestational diabetes mellitus (GDM) which develops during the pregnancy [7].

In 1989 the St Vincent Declaration pledged to improve pregnancy outcomes for women with diabetes to those of non-diabetic women [8]. Despite major advances in obstetric, neonatal and diabetic care, this has not happened. While some improvement for women with type 1 DM have been reported, in general congenital abnormalities, stillbirths and perinatal deaths remain twofold to fourfold higher among women with pre-gestational diabetes [9]. Recent years has seen a rapid rise in type 2 DM among women of childbearing age who have additional risk factors that adversely affect pregnancy, including high maternal age, weight, parity, levels of social deprivation and belonging to non-white ethnic minority groups [6,10,11] (Fig. 9.1). These risk factors are similar to those associated with GDM. Because of changing demographics in European urban cities, women with pre-gestational type 2 DM now outnumber those with type 1 DM while those with GDM account for the majority of women attending an obstetric diabetes antenatal clinic [7,12].

The consequences of a diabetic pregnancy in women with type 1 DM, type 2 DM or GDM extend beyond the pregnancy. Approximately 40% of all births to women with pre-gestational diabetes have evidence of growth acceleration, with approximately half above the 90th percentile for gestational age. High birthweight and infant adiposity is associated not only with shoulder dystocia and caesarean section rates above 60% but also with early-onset obesity, metabolic dysfunction and diabetes in the child in later life [3,6,13–15].

Optimal glycaemic control prior to conception and throughout pregnancy improves pregnancy outcome [6,16,17]. All professionals caring for women of childbearing age with either known diabetes or at risk of GDM need to emphasize the importance of pregnancy planning and good glycaemic control prior to pregnancy and the need for GDM screening for those at risk.

This chapter covers the clinical management of pregnancies complicated by pre-gestational diabetes, as well as the screening and management of GDM. Finally, the long-term health consequences for the child of a diabetic pregnancy are discussed.

Classification of diabetes in pregnancy

The diabetic and obstetric management is influenced by the type of diabetes. The main types of diabetes seen in obstetric practice are shown in Table 9.1.

Diabetes in pregnancy can be defined as pre-gestational (i.e. pre-existing) diabetes or GDM. Most women with pre-gestational diabetes have type 1 or type 2 DM. However, a small percentage have monogenetic or mitochondrial forms of diabetes that require genetic screening for correct diagnosis. The importance of recognizing this cohort of women is that their pregnancy outcomes are determined as much by their genetic mutation as by their diabetic control [18–20]. GDM is defined as diabetes or glucose intolerance occurring or first recognized in pregnancy, a definition that includes those with previously unrecognized diabetes [21].

The numbers of women with pre-gestational DM and GDM is increasing, with the largest proportional

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

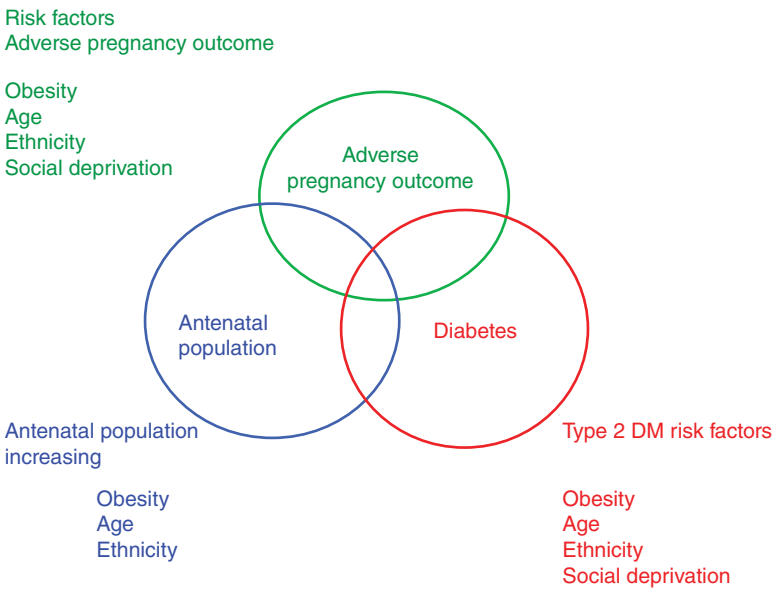

Fig. 9.1 Venn diagram illustrating the relationship between the demographics of the antenatal population and the risk factors for diabetes and those for adverse pregnancy outcomes.

Table 9.1 The types of diabetes encountered in obstetric practice.

Type 1 diabetes Absolute insulin deficiency due to autoimmune destruction of the pancreatic β-cell. Presents typically under the age of 20 years old, and only 10% have a first-degree relative affected. Not associated with obesity. Accounts for approximately 5% of all diabetes outside pregnancy
Type 2 diabetes Relative insulin deficiency and decreased insulin sensitivity. Presents typically over the age of 20 years, and >50% have a first-degree relative affected. Strongly associated with obesity. Accounts for approximately 90% of all diabetes outside pregnancy
Monogenetic diabetes Maturity-onset diabetes of the young (MODY). Results from a single gene mutation causing defects in pancreatic β-cell insulin secretion. Present from birth and typically diagnosed within the second and third decade. Autosomal dominant with approximately 95% having a first-degree relative affected. Not associated with obesity. Accounts for 1–2% of all diabetes outside pregnancy
Mitochondrial diabetes Arises from a mutation in mitochondrial DNA leading to a defect in insulin secretion. Associated with a number of other medical problems including neural sensory deafness, a tendency for stroke and lactic acidosis. Diabetes develops at approximately 35 years old, and is maternally inherited. Not associated with obesity. Accounts for less than 1% of all diabetes outside pregnancy
Secondary diabetes Diabetes due to other medical conditions, i.e. pancreatitis, cystic fibrosis, glucocorticoids and other drugs. Accounts for approximately 2% of all diabetes outside pregnancy

rise in those with pre-gestational type 2 DM and GDM, driven predominantly by the rise in obesity [22]. There is also a slower rise in the prevalence of type 1 DM, whose incidence is estimated at 3–4% per annum in Europe [23].

The prevalence of GDM across Europe in 2012 varied between 2 and 6% [24], influenced by the demographics of the antenatal population and the diagnostic criteria used [25]. This prevalence is anticipated to increase as more universal screening and testing for GDM is introduced. Annual audit data from England and Wales in 2015 estimated that approximately 35 000 pregnant women had either pre-gestational DM or GDM, the latter making up approximately 80% of cases [26].

While GDM typically arises in the late second trimester due to physiological changes in maternal carbohydrate metabolism [27], the number of women with undiagnosed type 2 DM becoming pregnant will increase as the age of onset of type 2 DM falls [28]. It is important to recognize this high-risk group as the clinical management needs to be similar to women with pre-existing type 2 DM.

Summary box 9.1

- Diabetes in pregnancy poses major health risks to both the mother and the growing fetus, and influences the future health of the child.
- Diabetes in pregnancy can be defined as pre-gestational (includes type 1 DM, type 2 DM and other rare forms of diabetes that precede pregnancy, i.e. monogenic diabetes) or gestational diabetes (glucose intolerance of diabetes first recognized in pregnancy).
- In general, congenital abnormalities, stillbirths and perinatal deaths remain twofold to fourfold higher among women with pre-gestational diabetes.
- Optimal glycaemic control prior to conception and throughout pregnancy improves pregnancy outcome.

Diagnosing diabetes and gestational diabetes

While the definition of GDM is not controversial, how and who to screen for GDM remains contentious [29]. Outside pregnancy the diagnosis of diabetes is made by [18]:

- fasting plasma glucose of 7.0 mmol/L or greater;
- 2-hour plasma glucose of 11.1 mmol/L or greater during a 75-g oral glucose tolerance test (OGTT);
- random plasma glucose of 11.1 mmol/L or greater in the presence of hyperglycaemic symptoms;
- HbA_{1c} of 6.5% (48 mmol/mol) or greater.

The distinction between type 1 and type 2 DM can usually be made clinically based on history and recognized risk factors; when there is uncertainty, testing for the specific pancreatic islet autoantibodies GAD, IA-2 and ZnT8 can help confirm the diagnosis of type 1 DM in approximately 80% of cases. It is increasingly recognized that new-onset type 1 DM after the age of 30 years may account for up to 50% of all type 1 DM in the white population.

Two large randomized controlled trials, one Australian and the other Canadian, have provided evidence that diagnosing and treating GDM improves pregnancy outcomes. These two randomized trials used different diagnostic criteria for GDM and randomized women between 24 and 34 weeks' gestation to active management with diet, glucose monitoring and insulin if required or to routine antenatal care [16,17]. The Australian trial of 1000 women diagnosed by World Health Organization (WHO) criteria for impaired glucose tolerance showed that serious perinatal complications were lower among the 490 pregnancies in the intervention group than among the infants of the 510 women assigned to routine care (1% vs. 4%; relative risk adjusted for maternal age, race or ethnic group, and parity). The intervention group had a 10% higher rate of induction of labour with a similar caesarean section rate compared with women receiving routine care [16]. The Canadian study of 958 women identified as having mild gestational diabetes showed that active treatment reduced mean birthweight (3302 vs. 3408 g), neonatal fat mass (427 vs. 464 g), frequency of large-for-gestational-age infants (7.1% vs. 14.5%), birthweight greater than 4000 g (5.9% vs. 14.3%), shoulder dystocia (1.5% vs. 4.0%), and caesarean delivery (26.9% vs. 33.8%). Active treatment was also associated with reduced rates of pre-eclampsia and gestational hypertension [17].

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed to establish internationally agreed diagnostic criteria for GDM [5]. This observational study analysed over 23 000 non-diabetic pregnant women between 2000 and 2006 from nine countries. All women underwent a 2-hour 75-g OGTT between 24 and 32 weeks' gestation. The results were analysed to clarify associations between maternal glucose values (below those diagnostic of diabetes) and four primary perinatal outcomes: macrosomia (corrected birthweight >90th centile), primary caesarean delivery, clinical neonatal hypoglycaemia and hyperinsulinaemia (assessed by cord serum C-peptide >90th centile for the whole study group). Analysis showed a continuous gradient between maternal glucose levels (at fasting, 1 hour and 2 hours post 75-g glucose load) and all four primary outcomes. Using these results new diagnostic criteria for GDM were drawn up by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) that have been subsequently endorsed by the American Diabetes Association (ADA) and WHO [30]. However, the IADPSG criteria for GDM differ from those recommended in 2015 by the National Institute of Health and Care Excellence (NICE) in England that proposed a higher fasting value, a lower 2-hour value, and no 1-hour value. The NICE criteria were based on published intervention studies and cost-effective analyses. The IADPSG and NICE criteria for GDM diagnosis are summarised in Table 9.2.

The decision to screen universally for GDM or only perform the test in women with recognized risk factors remains unresolved. The NICE criteria advocate using universal screening based on risk factors identified at the initial antenatal visit, which includes body mass index (BMI) above 30 kg/m^2, previous macrosomic baby weighing 4.5 kg or above, previous GDM, family history of diabetes (first-degree relative with diabetes) and a minority ethnic family origin with a high prevalence of diabetes. Only women with one or more of these factors are advised to have a 75-g OGTT between 24 and 28 weeks [26]. An OGTT at 16 weeks is also recommended

Table 9.2 The IADPSG and NICE criteria for GDM diagnosis.

	IADPSG criteria	NICE 2015 criteria
Screening	None	Risk factors at first antenatal clinic BMI >30 kg/m^2 GDM in a previous pregnancy Previous macrosomic baby ≥4.5 kg Family history (first-degree relative with diabetes) Ethnicity: family origin with a high prevalence of diabetes
75-g OGTT	Universal at 24–28 weeks	Selective testing 26–28 weeks Based on the presence of risk factors
Plasma glucose	IADPSG criteria: one or more of the following thresholds be met or exceeded:	NICE 2015 criteria: one or more of the following thresholds be met or exceeded:
0 min	5.1 mmol/L (92 mg/dL)	5.6 mmol/L (100 mg/dL)
60 min	10 mmol/L (180 mg/dL)	
120 min	8.5 mmol/L (153 mg/dL)	7.8 mmol/L (140 mg/dL)

for women with a history of GDM, which should be repeated at 24–28 weeks if the initial test is normal. The list of risk factors recommended by NICE is not exhaustive as they omit maternal age [31,32] and polycystic ovary syndrome [33]. This perhaps explains why using NICE risk factor screening alone can miss up to 25% of women identified with GDM on an OGTT [29,34]. The frequency of GDM among the original HAPO cohort using the IADPSG criteria was 17.8% (9.3–25.5%) depending on the country of origin [25]. The IADPSG criteria diagnose women with a fasting glucose between 5.1 and 5.6 mmol/L and these women are missed using the NICE criteria; 38% of these pregnancies result in a large-for-gestational-age infant despite the 2-hour value being below 7.8 mmol/L, this group of women tending to be obese [35]. The debate on the benefits of treating women with lesser degrees of glucose intolerance than identified by the NICE criteria continues [36].

Summary box 9.2

- GDM is defined as diabetes or glucose intolerance occurring or first recognized in pregnancy.
- GDM is diagnosed by a 75-g OGTT using the following criteria:
  - NICE 2015: fasting blood glucose ≥5.6 mmol/L and/or 120-min blood glucose ≥7.8 mmol/L.
  - IADPSG: fasting blood glucose ≥5.1 mmol/L, 60-min blood glucose ≥10 mmol/L and/or 120-min blood glucose ≥8.5 mmol/L.
- Risk factors for GDM include BMI >30 kg/m^2, GDM in a previous pregnancy, previous macrosomic baby ≥4.5 kg, family history (first-degree relative with diabetes) and family ethnic origin with a high prevalence of diabetes.

The significance of maternal type of diabetes

The 2002 CEMACH audit of 3800 pregnancies in England, Wales and Northern Ireland showed similar fetal complications (perinatal mortality, stillbirth and neonatal mortality) among women with type 1 and type 2 DM, emphasizing that the major determinant of fetal complications is maternal hyperglycaemia rather than type of diabetes [6] (Fig. 9.2). Maternal and social risk factors that can impact on pregnancy do nonetheless differ between women with type 1 DM and those with type 2 DM, and include being more obese, socially deprived and less prepared for pregnancy. This is especially true among adolescents and young adults with type 2 DM, a particularly vulnerable group whose pregnancy outcomes are extremely poor, with fetal malformation rates in excess of 20% [37]. Women with type 1 DM are at greater risk of recurrent and severe hypoglycaemia and retinopathy.

The principles of maternal glycaemic control

Maternal hyperglycaemia affects all aspects of pregnancy, from fertilization and implantation to birth (Fig. 9.3). There is growing evidence that maternal hyperglycaemia, via fetal programming, can cause changes in gene expression that increase the fetus's future susceptibility to obesity, diabetes and other health problems [3,38]. Hence a principal tenet for management of diabetes in pregnancy is to strive for euglycaemia throughout the whole of pregnancy. Congenital abnormalities, miscarriage,

accelerated fetal growth, late stillbirth, birth trauma and neonatal hypoglycaemia all increase as maternal glycaemia rises (Table 9.3). This risk can be further increased by the presence of obesity [39].

In a systemic review involving 1977 diabetic pregnancies from seven USA cohort studies between 1986 and 2006, the mean fetal malformation rate rose from 3% to 10% as peri-conception HbA_{1c} levels rose from two standard deviations (2SD) to 8SD above the normal 2% range, respectively (Fig. 9.4) [40]. This strong correlation between peri-conception glycaemic control and congenital anomaly was also seen in England among 1677 births to diabetic women between 1996 and 2008 [41]. High peri-conception HbA_{1c} values are also a predictor of stillbirth [2,6].

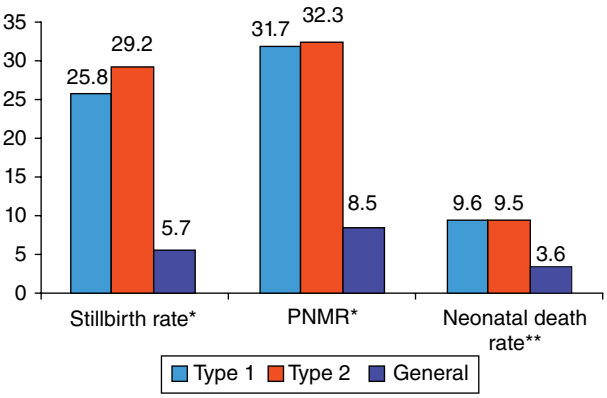

Fig. 9.2 Data from the Confidential Enquiry into Maternal and Child Health (CEMACH) Diabetes Audit. PNMR, perinatal mortality rates, stillbirth rates and neonatal death rates for mothers with type 1 and type 2 DM (delivered or booked between 1 March 2002 and 28 February 2003 in England, Wales and Northern Ireland). Maternal age adjusted: *, per 1000 total births; **, per 1000 live births [6].

Alongside glycaemic management, screening for and treating specific diabetic complications is also important. The association between pre-pregnancy levels of glycaemia and congenital malformations begins at the upper level of the normal non-diabetic range [41]. The teratogenic effect of hyperglycaemia occurs in the first 12 weeks of gestation at the time of blastocyst formation, embryogenesis and organogenesis. In order to significantly limit early fetal loss and congenital abnormalities women need optimal glycaemic control prior to pregnancy. To achieve this, women with pre-gestational diabetes ideally need to plan their pregnancies, be given pre-conception counselling and continue contraception until good glycaemic control has been achieved [26].

Pre-conception counselling

As half of all pregnancies are unplanned, discussing pregnancy planning should be an integral part of all diabetic reviews for women of childbearing age, whether in primary or secondary care [42]. Congenital malformations and preterm delivery are reduced when

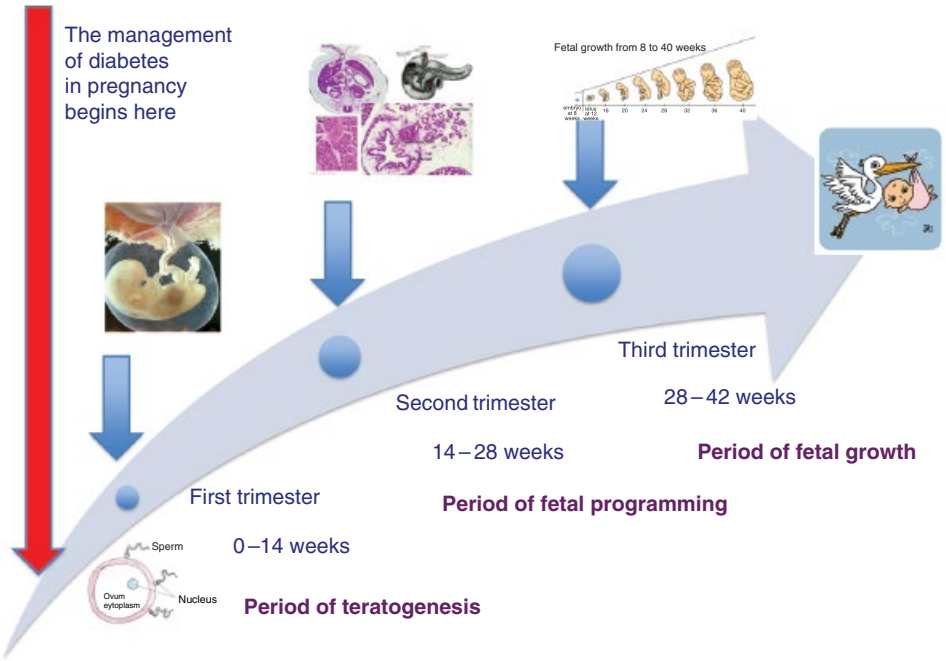

Fig. 9.3 Maternal hyperglycaemia affects all aspects of pregnancy from fertilization and implantation to birth.

Table 9.3 The role of maternal hyperglycaemia on maternal and fetal complications.

First trimester	
Implantation	Inhibits trophectoderm differentiation
Embryogenesis	Increases oxidative stress, affecting expression of critical genes essential for embryogenesis
Organogenesis	Activates the DAG–PKC cascade, increasing congenital defects
Miscarriage	Increases premature programmed cell death of key progenitor cells of the blastocyst
Second trimester	
Endocrine pancreas	Stimulates fetal β-cells
Fetal growth	Stimulates fetal hyperinsulinaemia, which results in growth acceleration seen on ultrasound by 26 weeks
Third trimester	
Fetal growth	Major fetal substrate and determinant of accelerated fetal growth
Adipose disposition	Stimulates hyperinsulinaemia, which promotes fat deposition including intra-abdominal fat
Lung maturation	Stimulates hyperinsulinaemia, which delays lung maturation by inhibiting surfactant proteins
Stillbirth	Is associated with defects in placental maturation that increase the risk of fetal hypoxia
Delivery	
Birth trauma	By causing accelerated fetal growth, there is an increased risk of shoulder dystocia, predisposing to birth trauma and asphyxia
Neonate	
Hypoglycaemia	Stimulates fetal hyperinsulinaemia, which predisposes to neonatal hypoglycaemia
Hypocalcaemia	Alters the placental expression of calbindin mRNA, which affects calcium status at birth
Polycythaemia	Stimulates fetal hyperinsulinaemia, which enhances antepartum haemopoiesis as does fetal hypoxia
Cardiomyopathy	Stimulates fetal hyperinsulinaemia, which predisposes to hypertrophic cardiomyopathy
Adolescence/adulthood	
Obesity	Intrauterine exposure predisposes to the metabolic syndrome, independent of any genetic susceptibility
Type 2 diabetes	Intrauterine exposure predisposes to type 2 diabetes, independent of any genetic susceptibility

DAG, diacylglycerol; PKC, protein kinase C.

women receive pre-conception counselling [43]. These clinics provide a supportive environment to discuss pregnancy care pathways, emphasize the need and timing for increased fetal and maternal surveillance, and offer reassurance that good glycaemic control can reduce the potential risks of a diabetic pregnancy. Glycaemic control can be intensified, high-dose folic acid supplements (5 mg) prescribed and potentially teratogenic drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and statins (HMG-CoA reductase inhibitor), stopped or switched to safer alternatives [44,45] (Table 9.4). Diabetic complications can be assessed as can the need for aspirin or heparin for women at high risk of pre-eclampsia or thrombophilia or who have significant proteinuria (>4 g per 24 hours) [26]. Unfortunately, women with type 2 DM, those from ethnic minority groups and those with the highest social deprivation scores are less likely to access these services [46].

Summary box 9.3

- The tetratogenic effects of hyperglycaemia occur in the first 12 weeks of gestation.
- Pre-conception planning is essential in women with pre-existing diabetes and should be integrated into every diabetic review for women of childbearing age.
- Congenital malformations and preterm delivery are reduced when women receive pre-conception counselling.
- Pre-conception care includes optimizing glycaemic control, prescribing folic acid 5 mg supplements and stopping all potentially teratogenic drugs or switching to safer alternatives.
- Aspirin or heparin may be required for women at high risk of pre-eclampsia or thrombophilia or if significant proteinuria is present.

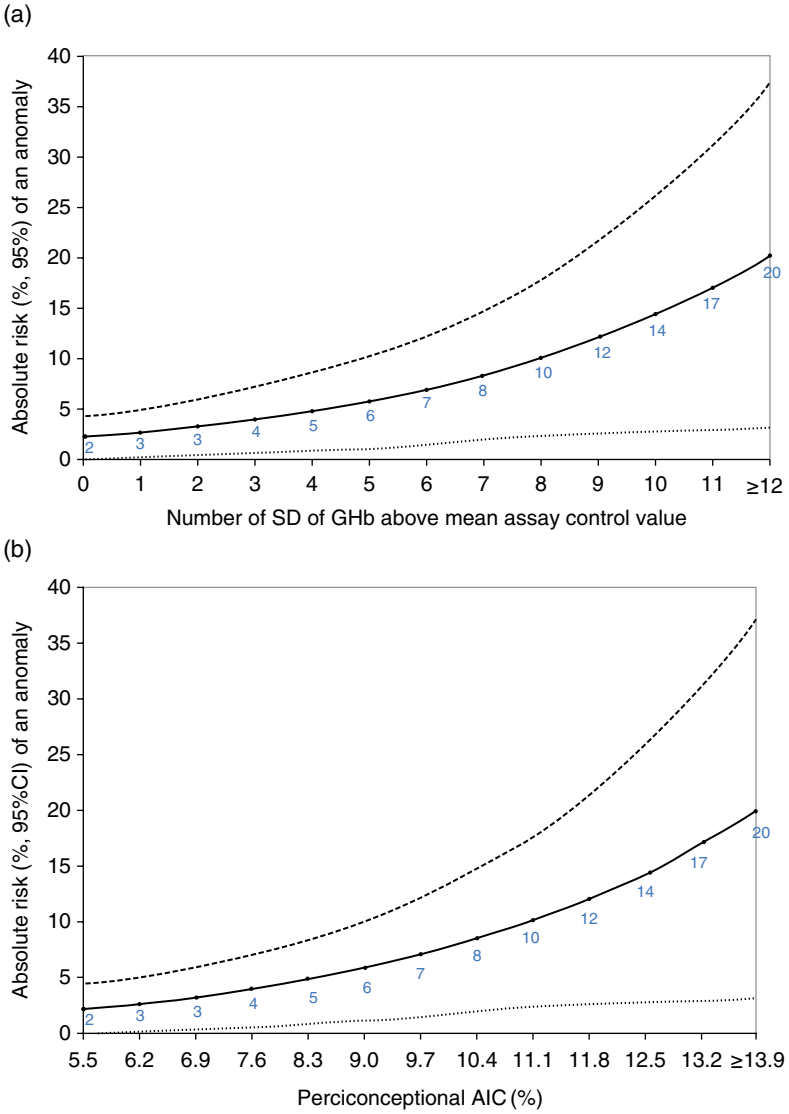

Fig. 9.4 The relationship between congenital abnormalities and antenatal glycosylated haemoglobin (HbA_{1c}).

Table 9.4 Key topics to discuss with all women of childbearing age with diabetes.

Optimizing glycaemia control
Reviewing all medications
Screening and management of diabetic complications
Information on optimal weight and weight gain
Information on pregnancy risk to the mother
Information on pregnancy risk to the baby

Achieving optimal glycaemic control

The level of glycaemic control required from pre-conception to birth mandates continual blood glucose monitoring and dose adjustment of insulin. Providing education and training to women with pre-gestational diabetes to enable them to self-manage and adjust their own insulin to match their carbohydrate intake is key to improving glycaemic control and reducing the risk of hypoglycaemia [47–52].

Based on the association between HbA_{1c} and major fetal anomalies, the 2015 NICE guidance strongly advises women with an HbA_{1c} above 86 mmol/mol (10%) not to become pregnant, while recommending an HbA_{1c} below 48 mmol/mol (6.5%) if achievable without causing problematic hypoglycaemia [6]. For women with type 1 DM, current recommended targets are as follows: fasting plasma glucose of 5–7 mmol/L on waking and a plasma glucose of 4–7 mmol/L before meals at other times. For women with type 1 DM to achieve this level of glycaemic

control requires four to five daily insulin injections (multiple-dose insulin, MDI) or a continuous subcutaneous insulin infusion (CSII) pump. With the MDI regimen, a long-acting basal insulin analogue is usually given at night or as a split morning and evening dose, with rapid-acting bolus insulin given with each meal. The recent advances in insulin pump technology, glucose monitoring and bolus insulin calculators that recommend a rapid-acting insulin dose based on the amount of carbohydrate may all assist women achieve better control. In the future, advances in the technologies of closed-loop insulin delivery, which combines real-time continuous glucose monitoring (CGM) with CSII using a computer algorithm, have the potential to normalize glycaemic control while reducing the risk of hypoglycaemia [53–55].

For women with type 2 DM, achieving an HbA_{1c} below 48 mmol/mol (6.5%) prior to pregnancy is easier, as these women are at less risk of hypoglycaemia [56]. While metformin can be continued in pregnancy, women previously on other oral hypoglycaemic agents, such as sulphonylureas, will need to be switched to insulin using MDI regimens.

Summary box 9.4

- A target HbA_{1c} below 48 mmol/mol (6.5%) should be set for women with pre-existing diabetes if achievable without problematic hypoglycaemia.
- For all women with diabetes, aim for fasting capillary blood glucose (CBG) levels to be <5.3 mmol/L and 1-hour postprandial CBG <7.8 mmol/L.
- Advise pregnant women with diabetes who are on insulin or glibenclamide to maintain their CBG level above 4 mmol/L.
- Target glycaemic control can be achieved by using metformin and an MDI regimen in women with GDM and type 2 DM.
- Women with type 1 DM should continue on an MDI regimen.
- Glibenclamide can be considered in women with GDM or type 2 DM where insulin initiation is problematic.

Screening for diabetic complications

Diabetic complications differ in women with type 1 DM and type 2 DM. Women with type 1 DM are more likely to have had diabetes for longer and since diabetic complications increase over time diabetic microvascular disease is more common in women with type 1 DM than those with type 2 DM. This may change as the onset of type 2 DM continues to fall. Pre-pregnancy counselling reduces the progression of both diabetic retinopathy and nephropathy in pregnancy. Women with long-standing type 1 DM and older obese women with type 2 DM and previous GDM are potentially at increased risk of diabetic macrovascular disease, including coronary heart disease.

Diabetic retinopathy

A dilated retinal examination should be performed prior to pregnancy, in early pregnancy and again at 28 weeks' gestation if no retinopathy was detected initially. However, in the presence of retinopathy a check is required at 16 weeks in addition to the one at 28 weeks' gestation. The risk factors for the development or worsening of retinopathy are pre-existing hypertension, duration of diabetes and a rapid fall in HbA_{1c} between the first and third trimester. However, diabetic retinopathy should not be considered a contraindication for rapid optimization of glycaemic control in pregnancy or a contraindication to pregnancy or a vaginal birth.

As duration of type 1 DM increases, background and proliferative diabetic retinopathy increases. Women with type 2 DM are more prone to diabetic maculopathy, which is less duration dependent. Rapidly improving glycaemic control during the pre-conception period and in pregnancy can worsen retinopathy, although long-term detrimental effects are rare post partum. Laser treatment before pregnancy protects against retinopathy progression in pregnancy and if needed should be performed before conception. When diabetic retinopathy develops *de novo* in pregnancy, it is usually not severe and laser treatment is safe if required [57–59].

Diabetic nephropathy

An assessment of renal function, comprising urinary protein/creatinine ratio and estimated glomerular filtration rate (eGFR), should be performed prior to pregnancy and in early pregnancy. The presence of proteinuria and/or reduced eGFR is a significant risk factor for nephrotic syndrome, hypertension, pre-eclampsia, placental insufficiency, preterm delivery and neonatal morbidity and mortality [60]. Intensive glycaemic control before and throughout pregnancy, low-dose aspirin from 12 gestational weeks, and intensive antihypertensive treatment can reduce these risks [61].

During a healthy non-diabetic pregnancy, structural, functional and hemodynamic changes to renal physiology occur; by term, eGFR is 40% higher, with an increase seen from 12 weeks alongside an associated rise in creatinine clearance and protein excretion rate [62]. Women with normal or mild renal impairment before pregnancy

usually preserve their renal function post partum and can anticipate a successful pregnancy outcome. When microalbuminuria is present that is not attributable to a urinary tract infection, serial urinary protein/creatinine ratios should be performed throughout the remaining pregnancy to quantify the degree of proteinuria. Those with moderate to severe diabetic nephropathy [serum creatinine >124 µmol/L (1.5 mg/dL) or proteinuria >3 g per 24 hours] are most at risk of perinatal death and irreversible deterioration in renal function after pregnancy (especially with serum creatinine >176 µmol/L). If accelerated progression of nephropathy occurs in pregnancy, renal intervention with dialysis may be required [61,63]. A pre-conception microalbumin measurement is also helpful as it assists with the diagnoses of pre-eclampsia, which can be difficult to distinguish from diabetic nephropathy in later pregnancy.

Diabetic neuropathy

Diabetic neuropathy can manifest as either a peripheral sensory neuropathy or an autonomic neuropathy and both increase with duration of diabetes [64]. Diabetic autonomic neuropathy can affect the cardiovascular, gastrointestinal and urogenital systems and sudomotor function. Cardiac involvement is associated with overall mortality while gastrointestinal involvement is a recognized cause of gastroparesis [64]. Historically, autonomic gastroparesis has been associated with poor pregnancy outcomes [65]. Gastroparesis causes erratic absorption of meals, resulting in episodes of hyperglycaemia and hypoglycaemia due to a mismatch between food intake and the short-acting pre-meal insulin. Although the suggestion that autonomic neuropathy causes hypoglycaemia unawareness has recently been challenged [66], the intensity of autonomic symptoms in response to hypoglycaemia decreases with duration of diabetes and this reduces the threshold at which hypoglycaemic symptoms occur [67]. Achieving good glycaemic control in early pregnancy, at a time when nausea and vomiting is common in women with autonomic gastroparesis, is challenging and hypoglycaemia is frequent.

Diabetic macrovascular disease

Diabetes is associated with premature cardiovascular disease. Women with over 20 years' duration of type 1 DM aged over 40 years are likely to have a degree of coronary artery calcification and coronary artery disease (CAD), independently of other risk factors. Older women with type 2 DM and GDM are also at increased risk of CAD. A previous history of CAD or its diagnosis in pregnancy is associated with significant maternal morbidity [68–70].

Hypoglycaemia

Hypoglycaemia affects up to 70% of pregnant women with pre-existing diabetes and is associated with excess maternal mortality. Hypoglycaemic symptoms change in pregnancy, especially if autonomic neuropathy is present. The risk of hypoglycaemia is greatest in the first 20 weeks of pregnancy and immediately post partum. Women with type 1 DM may benefit from an insulin pump and or continuous glucose sensors.

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a rare but a serious complication in pregnancy, with an associated fetal mortality in excess of 10% [71]. It usually occurs in women with type 1 DM, and can be the first presentation of type 1 DM; rarely it can occur in women with type 2 DM and even GDM. In pregnancy, DKA can occur at normal blood glucose levels (euglycaemic DKA), and thus it should be excluded in any pregnant woman with pre-gestational diabetes and persistent nausea and vomiting and considered in all cases of unexplained maternal acidosis. The risk of DKA is increased during pregnancy because of increased insulin demands and enhanced lipolysis. Other risk factors include infection, vomiting, use of beta-mimetic agents and insulin pump failures. The treatment of DKA is the same as for non-pregnant patients, with insulin administration, fluid replacement, correction of electrolyte imbalance and treatment of the underlying cause. Fetal monitoring and assessment should continue alongside maternal treatment.

Screening for non-diabetic comorbidities

Women with type 1 DM are at increased risk of autoimmune diseases. All women should be screened prior to pregnancy for thyroid disease; if they are already being treated for thyroid disease, this should be repeated in early pregnancy. There should be a high level of suspicion to screen for other autoimmune diseases if clinically indicated.

Women with type 2 DM are likely to have other metabolic risk factors, including obesity, hypertension, dyslipidaemia and insulin resistance as are those with a previous history of GDM. Obesity, independently of diabetes, is a risk factor for hypertension, late stillbirth, induction of labour, caesarean section, birth trauma and maternal complications post partum [72,73]. Advising obese and overweight women on weight management prior to pregnancy is an important part of pre-conception

counselling. The hypertriglyceridaemia associated with obesity is a source of glycerol and fatty acids, both fetal metabolic substrates that in excess can contribute to accelerated fetal growth, and therefore maternal weight management prior to pregnancy will help.

Risks to the fetus of a diabetic pregnancy

Maternal glucose crosses the placental barrier but insulin does not, so increases in maternal glucose stimulate fetal insulin production and hyperplasia of insulin-sensitive tissues [74,75]. Maternal hyperglycaemia also enhances production of human placental growth hormone, fetal insulin-like growth factor and tumour necrosis factor. As with insulin, these hormones act as fetal growth factors, resulting in accelerated fetal growth, macrosomia and organomegaly.

The commonest malformations secondary to maternal hyperglycaemia are cardiac and those involving the central nervous system [1]. Cardiac malformations include transposition of the great vessels, ventricular septal defect and dextrocardia, while the central nervous system anomalies include anencephaly, spina bifida, hydrocephaly and holoprosencephaly; malformations of the genitourinary system and the skeleton also occur [76]. Caudal regression, a rare malformation, has the strongest association with diabetes, occurring roughly 200 times more frequently in infants of diabetic mothers than in other infants [76].

Both liquor and fetal cord blood insulin or C-peptide at birth correlate with the risk of neonatal hypoglycaemia, respiratory distress, polycythaemia, hypocalcaemia and hyperbilirubinaemia, emphasizing the impact of maternal hyperglycaemia and secondary fetal hyperinsulinaemia on neonatal well-being. The long-term effects of a diabetic pregnancy on the child are only now being evaluated.

Table 9.5 A structured approach to the management of diabetic pregnancies.

Prior to pregnancy
Pre-conception counselling
Review of all medications
Folic acid 5 mg once daily
Screening for diabetic complications, including treatment of diabetic retinopathy
First trimester
Referral to a combined multidisciplinary diabetic obstetric antenatal clinic
Dating scan at 6–8 weeks, confirming viability and gestational age
Screening for diabetic complications
Screening for non-diabetic comorbidities
Assessment and optimization of glycaemia
Advice on hypoglycaemia prevention
Second trimester
Optimization of glycaemic control
Screening for diabetic complications
Repeat digital retinal assessment at 16 weeks if initial retinal screen was abnormal
Surveillance for medical obstetric complications, including hypertension
Screening for congenital abnormalities, including ultrasonographic examination of the fetal heart at 18–22 weeks
Assessment of fetal growth
Third trimester
Optimization of glycaemic control
Screening for diabetic complications, with repeat digital retinal screening
Assessment of fetal growth and amniotic fluid volume at 28, 32 and 36 weeks' gestation
Timing and mode of delivery to be discussed at 36 weeks' gestation
Document any changes to hypoglycaemic therapy during delivery and post partum, including breastfeeding
Delivery
Protocols for insulin during labour and delivery
Post partum
Adjustment of insulin dosage
Breastfeeding
Discuss contraception

Managing diabetes in pregnancy

First trimester

Referral to a combined multidisciplinary diabetic obstetric antenatal clinic

Pregnancy outcomes are improved when women with diabetes attend a hospital-based multidisciplinary consultant-led diabetic obstetric antenatal clinic working to locally agreed guidelines based on national and international guidelines (Table 9.5). The team comprises an obstetrician, diabetologist, specialist midwife, diabetes specialist nurse and dietitian and all are jointly involved in the care. Rapid access to this clinic is critical to ensure optimization of glycaemic control during the period of fetal organogenesis. Women need to be seen or phoned by the diabetes specialist nurse or midwife on a weekly basis throughout the first trimester, with access to the other members of the team as required.

Dating ultrasound scan

Ideally, a dating scan should be performed within the first 10 weeks of gestation to confirm viability of the pregnancy and to accurately assess gestational age. Relying on ultrasound scanning later in a diabetic pregnancy is less accurate because fetal growth restriction or growth promotion may be present.

Screening for chromosomal anomalies

Chromosomal abnormalities are not increased in women with diabetes. Routine antenatal blood tests plus nuchal translucency ultrasound scan for Down's syndrome between 11 and 14 weeks of pregnancy should be offered as part of routine antenatal care. Calculating the risk of Down's syndrome based on the standard formula of gestational age, mother's age and levels of unconjugated estriol, α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) is less accurate, as plasma levels of both AFP and unconjugated estriol are lower in diabetic pregnancies.

Summary box 9.5

- Women with pre-existing diabetes should have a dating scan at 6–8 weeks' gestation and ultrasonographic examination of the fetal heart at 18–22 weeks' gestation.
- All pregnant women with diabetes should have ultrasound monitoring of fetal growth and amniotic fluid volume every 4 weeks from 28 to 36 weeks.
- All women with pre-existing diabetes should have digital retinal assessment in the first and third trimesters, with an additional assessment at 16 weeks if the initial screen was abnormal.
- All women with pre-existing diabetes should have blood tests for renal function and urine albumin creatinine ratios in each trimester.

Assessment and optimization of glycaemia

Measurement of HbA_{1c} at booking assesses the risk of major congenital malformations [40,41]. Intensive capillary home blood glucose monitoring (HBGM) needs to be started once pregnancy is confirmed and continued throughout pregnancy. For women already on insulin, a minimum of a fasting value and 1-hour HBGM reading after each meal is required. Recent advances in CGM are increasingly available for clinical use and can provide semi-continuous interstitial fluid glucose measurements; some devices reduce the need for daily HBGM readings. However, the intermittent use of real-time CGM in pregnancy has not yet been shown to improve fetal or maternal outcomes [77,78]. However, the future development of CGM devices that signal wirelessly to insulin pumps to control the insulin infusion hold great promise [55,78].

The goal of glycaemic management is euglycaemia while avoiding hypoglycaemia [16]. NICE guidelines based on current evidence recommend maintaining fasting maternal plasma glucose levels below 5.3 mmol/L and 1-hour postprandial levels below 7.8 mmol/L [26], which has been shown in the first trimester to be associated with a reduced fetal malformation rate [79]. Achieving these targets during the first trimester is particular challenging for women with type 1 DM as insulin requirements actually drop by around 10% from week 7 through to week 15 gestation [80,81]. Even in the presence of nausea, vomiting and a reduced food intake, women with type 1 DM must never stop their insulin.

The majority of women with type 1 DM will already be on a basal bolus insulin regimen consisting of a basal analogue insulin and a rapid-acting analogue insulin with meals or a CSII insulin pump. These women can maintain their pre-pregnancy insulin regimens once pregnant, and adjust as needed. Women with type 2 DM may not be on insulin but will require insulin at some time during their pregnancy. Most women will have become pregnant while on the oral agent metformin and current advice is that this can be continued while other oral agents, especially the newer drugs such as the thiazolidinediones, DPP-IV inhibitors and SGLT2 inhibitors, must be discontinued as no safety data are available for their use in pregnancy. The majority of women on two or more oral hypoglycaemic agents will need to start a basal bolus insulin regimen once pregnancy is confirmed.

Women with a previous history of GDM should be offered the opportunity to start HBGM in the first trimester and to receive dietary and physical activity advice. Should this fail to achieve HBGM targets, then an oral hypoglycaemic agent with or without insulin should be started.

The oral hypoglycaemics metformin and glibenclamide (known as glyburide in the USA) are considered safe and efficacious in pregnancy [26,82,83]. Metformin improves insulin sensitivity, increases peripheral glucose uptake and inhibits hepatic gluconeogenesis. Metformin is generally well tolerated, easy to use, has a low risk of hypoglycaemia and is inexpensive; it also limits maternal weight retention post partum [82]. Although not licensed for pregnancy, experience of its use in treating pregnant women with polycystic ovaries, type 2 DM and GDM is increasing and there is growing evidence for its effectiveness and safety in pregnancy [84]. It forms part of the NICE guidelines for glycaemic control in type 2 DM and GDM [26]. Theoretical concerns about the use of metformin continue because it crosses the placenta, so despite good short-term results long-term follow-up studies are required [85]. Glibenclamide does not currently have UK marketing authorization for use in pregnancy, although it can be used if a women is reluctant to start insulin [26].

All women with type 1 DM should be aware of the risk of DKA and to know how to test for blood ketones and when to seek urgent medical attention if unwell with persistently raised blood ketones [71].

Advice on prevention of hypoglycaemia

Women need to be aware of the risk of hypoglycaemia as they intensify their insulin management. Severe hypoglycaemia is three times as frequent in early pregnancy than prior to pregnancy and is more frequent during the first trimester than during the rest of pregnancy [86–88]. While hypoglycaemia is not harmful to the fetus it can be life-threatening for the woman [81]. During the last 30 years in the UK, the Confidential Enquiry into Maternal Deaths and Morbidity has continued to report hypoglycaemia as a cause of death among type 1 diabetic women. The greatest risk factors for severe hypoglycaemia are previous hypoglycaemia and poor hypoglycaemic awareness [87]. Long duration of type 1 DM, autonomic neuropathy, gastroparesis, renal impairment and sleeping alone are other recognized risk factors. The use of rapid analogue insulin is associated with fewer severe nocturnal hypoglycaemic episodes in pregnancy [89].

Individual advice on meal and snack timing and exercise to minimize hypoglycaemia needs to be given and family members instructed on how and when to administer glucagon. Women should carry identification cards specifying that they are taking insulin and what to do if they become hypoglycaemic. Specific advice on driving should be given, including not to drive if experiencing hypoglycaemic episodes without warning signs.

Second trimester

Optimization of glycaemic control

By the start of the second trimester in non-diabetic pregnancies there is a fall in fasting glucose and a rise in postprandial glucose values. By the middle of the second trimester maternal insulin resistance starts to increase due to high concentrations of circulating maternal fatty acids and placental hormones. Women whose diabetes is well controlled may not need to increase their overall insulin dosage until 20 weeks' gestation when insulin requirements begin to rise and continue to rise throughout the rest of the pregnancy. Insulin requirements are frequently threefold higher by the end of pregnancy than at the start [27,81]. Women need the knowledge and confidence to self-adjust their insulin in response to HBGM. As the basal night-time insulin is increased, it may be necessary to give half this dose in the morning to avoid nocturnal hypoglycaemia.

Women with type 2 DM are usually insulin resistant at the start of pregnancy. By the second trimester, when insulin resistance starts to increase, oral hypoglycaemic agents are usually unable to achieve adequate glycaemic control. By the end of pregnancy, daily insulin doses in women with type 2 DM may exceed 300 units daily. Metformin potentially has the beneficial effect of reducing the total insulin dose required through its effect on hepatic glucose output and on insulin-sensitive tissues.

Screening for congenital abnormalities

A detailed ultrasound scan that includes a four-chamber view of the heart and the ventricular outflow tracts should be offered at 18–20 weeks' gestation to look for major congenital abnormalities.

Surveillance for medical obstetric complications

Women with diabetes have an increased risk of hypertension in pregnancy, including pre-eclampsia. In addition to serial clinic blood pressure measurements and urinalysis for protein, uterine Doppler waveform analysis at 20 weeks may be helpful in identifying those women most at risk.

Assessment of fetal growth

Ultrasound scans for assessment for fetal growth usually start at the end of the second trimester and are repeated every 4 weeks, or more frequently if needed. Baseline measurement of fetal abdominal circumference at 28 weeks expressed as a percentile can be compared with later scans to provide evidence for growth acceleration or restriction. Measurement of liquor volume should also be serially recorded as polyhydramnios is more common in diabetic pregnancies.

Third trimester

Optimization of glycaemic control

During the third trimester maternal insulin resistance continues to increase along with insulin requirements. Glycaemic control tends to become easier as the insulin resistance protects women from severe hypoglycaemic episodes. If insulin requirements begin to fall in the late third trimester, this can be a sign of marked fetal hyperinsulinaemia lowering maternal blood glucose levels secondary to an increased glucose gradient across the placenta [90] or to placental dysfunction [91]. A fall in insulin requirements is potentially a stimulus to consider advancing the timing of birth.

When glucocorticoid steroids are required for lung maturation, insulin requirements over the following 72 hours may double. For example, if two 12-mg beclometasone injections are given at 24-hour intervals, either the insulin dose needs to be proactively increased or the woman admitted and a variable-rate intravenous insulin infusion (previously termed insulin sliding scale) administered over the 72 hours, which can be given in addition to her normal insulin dose.

Assessment of fetal growth

Evidence on serial ultrasound scans of a rising abdominal circumference (AC) percentile in relation to the head circumference or biparietal diameter is indicative of accelerated fetal growth due to fetal hyperinsulinaemia. Excessive fat deposition within the abdomen and enlargement of the liver and heart are a direct result of excess fetal insulin. While the term 'macrosomia' is used clinically and in the literature to describe infants of diabetic mothers, the precise definition of macrosomia remains poorly characterized, with definitions varying from an absolute birthweight of less than 4 kg, 4.5 kg or greater than 5 kg, to a percentile birthweight in excess of 90%, 95% or 97.5%. As birthweight is dependent on gestational age, sex, ethnic origin, parental height and maternal weight, any definition based on absolute weight is best avoided. In clinical practice it is the trend of fetal growth rather than the absolute or percentile birthweight that is important. The influence of maternal obesity alone accounts for the high birthweights of many of the infants of mothers with type 2 DM and GDM [39].

Serial ultrasound can also help identify those women who have an infant with fetal growth restriction or asymmetrical growth restriction (poor increase in AC centile growth compared with head circumference). Such growth patterns are suggestive of uteroplacental insufficiency and may be seen in type 1 diabetic women with renal impairment, vascular disease or hypertension. If detected, early delivery may be necessary.

Timing and mode of delivery

Women with diabetes should be made aware early in pregnancy that it is potentially harmful to the baby for the pregnancy to go beyond term. While women should be encouraged to be actively involved in their birth plans, they need to appreciate that the exact timing and mode of delivery is best deferred to after the 36-week growth scan when a more informed discussion can take place based on maternal and fetal well-being.

The risk of late unexpected stillbirth among women with diabetes is approximately fourfold higher than for the non-diabetic population [2,6,92]. It is for this reason that most authorities advocate delivery between 38 and 39 completed weeks for women on insulin. Induction at 38 weeks' gestation in a nulliparous woman with type 1 DM is often slow and/or unsuccessful. Caesarean section following failed induction is therefore high among these women and this contributes to the greater than 50% caesarean rate among women with type 1 DM [6]. In contrast, women with type 2 DM are more likely to be multiparous and induction of labour before term is more likely to be successful. Women with GDM controlled on metformin or diet alone, with otherwise uncomplicated pregnancies, may be able to go safely to term (40 completed weeks) with the hope of achieving a spontaneous labour.

The risk of birth trauma increases with increasing birthweight. Maternal diabetes mellitus increases the likelihood of shoulder dystocia several fold over that of the non-diabetic population [93]. This is partly explained by the chest-to-head and shoulder-to-head ratios being increased in fetuses of women with diabetes. The risk of shoulder dystocia is approximately 3% for birthweights of 4–4.5 kg, and is 10–14% for birthweights above 4.5 kg. However, a caesarean section policy based purely on estimated birthweight by ultrasound (4000 or 4500 g) would result in an unacceptable caesarean section rate. For the diabetic mother of a large baby detected on ultrasound, planning the delivery needs to be an obstetric decision based on maternal obstetric history, her own size and personal preference [13,93].

Birth

Protocols for insulin during labour and delivery

High maternal glucose levels during labour are associated with neonatal hypoglycaemia [94]. Therefore, the 2015 NICE guidelines recommend monitoring capillary plasma glucose during labour and birth in women with diabetes to ensure that maternal glucose levels are maintained between 4 and 7 mmol/L [26].

As most women with diabetes will be given a date for delivery, be it induction or caesarean section, there needs to be clear written guidelines for both the woman and the labour ward on how insulin requirements are managed during labour. While there is no absolute right or wrong way to give insulin during this period, it is usual hospital policy to start a variable-rate intravenous insulin infusion (VRIII) with 5% dextrose during active labour and during an operative delivery that is carried on into the perioperative period before the mother starts taking meals. During this time, hourly blood glucose monitoring should be performed. Once delivered, for women who were on insulin before pregnancy, the insulin dose must be reduced, as insulin requirements drop to approximately 20–30% below pre-pregnancy values immediately after birth. As most pregnant women prior to delivery are taking a night-time long-acting basal insulin and quick-acting basal insulin with their evening meal, women being admitted for a planned induction should be encouraged to take their normal insulin doses the night before. Once admitted, they should continue with their short-acting bolus insulin to cover meals, only switching to VRIII once in labour or a decision has been

taken to perform a caesarean section. The increased use of insulin pumps and continuous glucose sensors in labour will help to maintain blood glucose levels within target [95].

Most women with GDM, particularly women on diet or metformin alone, will not require intravenous insulin. Insulin-treated women with GDM requiring less than 1.0 unit/kg daily of insulin can usually be monitored without intravenous insulin, with a VRIII commenced only if required [94].

Ideally, elective caesarean section should be planned for early morning, with the woman instructed to take her normal bolus insulin with her evening meal and two-thirds of her usual basal insulin the night before admission. Once on the ward, a VRIII can be started, with the dose reduced straight after delivery.

Postpartum care

Insulin requirements drop immediately to below pre-pregnancy values following delivery of the placenta. Women with type 1 DM can recommence their pre-pregnancy insulin as soon as they are eating and drinking normally, although the dose needs to be decreased by at least 25%. In women who are well controlled prior to pregnancy, the drop in total daily insulin dose after birth may be even greater, with the biggest reduction seen in the bolus insulin [96].

The dose of insulin after birth should be clearly written in the notes as part of the delivery plan. Women with type 2 DM previously on oral agents can restart these following pregnancy if choosing not to breastfeed; if these women were not previously taking these agents, then insulin can be stopped. Insulin is not excreted into breast milk and is considered completely safe for use during breastfeeding. Insulin requirements often fall in mothers with type 1 DM who breastfeed, due to the small increase in metabolic rate that occurs with lactation. The use of metformin by breastfeeding mothers is also considered safe, as very little of the drug is excreted in breast milk [97]. The sulphonylurea oral agents are highly protein bound, and as this binding is non-ionic these agents are unlikely to be displaced by other drugs and to pass into breast milk. Theoretically, oral secretagogue agents could cause neonatal hypoglycaemia, but the evidence for this is poor [97]. Currently, metformin and glibenclamide are the only oral agents endorsed by the 2015 NICE guidelines for glycaemic control while breastfeeding [26].

The postpartum period is also a time when contraceptive advice should be offered.

The management of gestational diabetes

The glycaemic targets set for GDM in pregnancy should be similar to those for all diabetic women, namely a fasting blood glucose below 5.3 mmol/L and a 1-hour postprandial glucose below 7.8 mmol/L [26]. While some women with GDM can be controlled by lifestyle changes to diet and exercise, many require insulin to reach these targets. The exact role of oral hypoglycaemic agents remains controversial in some countries. Although the newer sulphonylurea agents appear safe when given after 15 weeks' gestation [97,98], their use with or without metformin is still felt by many to be less effective and flexible than prescribing insulin. However, in parts of the world where access to insulin is limited, oral hypoglycaemic agents provide a necessary alternative therapeutic option [99,100].

Women identified as having GDM, who do not have previously undiagnosed diabetes, usually revert to having normal glucose tolerance after delivery. However, over the subsequent 20 years the majority will develop type 2 DM [101]. GDM is one of the most predictive factors for the development of type 2 DM later in life. All women with GDM should therefore be offered postnatal assessment for diabetes, with a fasting blood sugar or HbA_{1c} 6 weeks after delivery and repeated yearly thereafter [26].

Lifestyle intervention that minimizes weight gain and encourages physical activity has been shown to reduce the progression rate to diabetes over the subsequent 4–5 years [102,103]. It is therefore important that women who have GDM receive basic lifestyle advice post partum and are informed about the need to be screened annually for diabetes.

Neonatal and longer-term consequences of a diabetic pregnancy

The neonate of the diabetic mother, in addition to the increased risk of congenital abnormalities, is at increased risk of a number of neonatal metabolic conditions (Table 9.3) [104,105]. The commonest of these, neonatal hypoglycaemia, is a consequence of persistent postnatal fetal hyperinsulinaemia when the maternal transfer of glucose has ceased. This and the other neonatal metabolic conditions can be attributed to excess transfer of fetal metabolic substrates from mother to fetus and fetal hyperinsulinaemia and are usually transient. Another common problem is neonatal hypertrophic cardiomyopathy, although this is frequently transient and

asymptomatic but can occasionally lead to severe morbidity and even mortality [105].

Recent studies on children of both type 1 and type 2 diabetic mothers have shown that there is an increased risk of childhood obesity and metabolic disturbances in adolescence, including an increased risk of glucose intolerance [3,15,106]. This risk increases among children of poorly controlled diabetic mothers. As young adults, children of diabetic mothers have an increased risk of type 2 DM. The emergence of diabetes in these children is at an earlier age than that of their mother [37].

The children of women who have had GDM are also at increased long-term risk of developing obesity, type 2 DM and the metabolic syndrome. The association of childhood obesity and gestational diabetes is also seen in the multi-ethnic EPOCH study, where children of mothers with primarily GDM had a higher increase in BMI and growth velocity than unexposed controls, with the increase starting at the age of 10–13 years. Offspring of Caucasian women with GDM have a twofold increased risk of developing obesity and a fourfold increased risk of the metabolic syndrome compared with the background population, suggesting that genetics plays a major role in the development of the metabolic syndrome and obesity together with an effect of intrauterine hyperglycaemia [107].

Animal studies have convincingly shown that intrauterine exposure to maternal diabetes is associated with an increased risk of abnormal glucose tolerance, diabetes and obesity in offspring. Although it is difficult to study the effect of intrauterine hyperglycaemia separately from a genetic effect in humans, there is evidence to suggest an epigenetic mode of diabetes transmission from mother to child due to perinatal programming of the fetus, and further strengthens the need to optimize glycaemic control in all diabetic pregnancies.

Summary box 9.6

- The risk of late unexpected stillbirth among women with diabetes is approximately fourfold higher than for the non-diabetic population.
- Women on insulin should be delivered between 38 and 39 completed weeks.
- Women controlled on metformin or diet alone with otherwise uncomplicated pregnancies may be able to go safely to 40 completed weeks.
- Immediately after delivery, women with pre-gestational diabetes must reduce their insulin dose to 25–30% of their pregnancy dose.
- After birth-, women with GDM will most likely be able to stop the diabetic medications; some women with type 2 DM will be able to stop insulin.
- Metformin, glibenclamide and insulin are safe for women who are breastfeeding.
- Women with GDM require a fasting blood glucose level or HbA_{1c} 6 weeks post partum and then yearly thereafter.

Conclusion

Diabetes in pregnancy is increasing and this requires an increase in awareness of the associated health risks for the mother, the growing fetus and the impact poorly controlled diabetes may have on the future child. This chapter has highlighted the essential aspects of the management of diabetic pregnancies, from before conception to the postpartum period, including screening for gestational diabetes. Integral to this is the use of the consultant-led multidisciplinary team and the implementation of national evidence-based clinical guidelines to optimize glycaemic control and mimimize the risk of maternal diabetic complications.

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10

Liver and Endocrine Diseases in Pregnancy

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LIVER DISEASE IN PREGNANCY

Normal physiological changes in pregnancy

In pregnancy, physiological changes occur that mimic the changes seen in decompensated chronic liver disease and cirrhosis. These changes peak in the second trimester. Blood volume increases by 50% yet blood flow to the liver remains constant and typically the liver is not palpable during the pregnancy. Examination changes of telangiectasia, spider angiomas and palmar erythema are normal, and may be confused with the presence of cirrhosis. There is an increased tendency to bile lithogenicity and there is an increased incidence of gallstone formation as a consequence [1,2]. Similarly, the contractility of the gallbladder is reduced. These findings are all related to increasing oestrogen.

In a normal pregnancy, plasma volume results in a fall in many serum markers including albumin levels. Alkaline phosphatase activity increases due to placental secretion. Aminotransferase levels (alanine aminotransferase, ALT, and aspartate aminotransferase, AST), bilirubin and gamma-glutamyl transpeptidase (GGT) all remain normal throughout pregnancy. When abnormalities exist in these parameters, further investigation is warranted. Liver histology typically is normal.

Table 10.1 summarizes the laboratory changes occurring in pregnancy.

Investigation of liver disease in pregnancy

Imaging of the liver is a frequent requirement. Ultrasound is the safest modality but should further imaging be required, magnetic resonance imaging (MRI) without contrast is safe. Gadolinium-enhanced MRI should be avoided unless essential due to transplacental transfer and the unknown effects on the fetus, although increasing evidence suggests that in the third trimester it is possible to do this safely. Computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) can also be used during pregnancy. However, precautions should be taken to shield the fetus from radiation or to provide dosimetry estimates if significant exposure is likely.

Approach to the patient with suspected liver disease in pregnancy

The presence of liver enlargement is always an abnormal finding in pregnancy, and hepatomegaly if identified may signify an infiltrative process ranging from acute fatty liver of pregnancy in the correct context to viral hepatitis, or even an infiltrative process such as lymphoma or cancer. Since pregnancy itself is a procoagulant state, consideration also needs to be given to outflow obstruction of the hepatic veins in the form of Budd–Chiari syndrome. Jaundice and scleral icterus are abnormal findings and always warrant further evaluation.

It is very rare that a liver biopsy is actually needed in the management of patients with liver disease in pregnancy. It is unusual for a liver biopsy to influence the timing or decision to proceed with delivery. However, liver biopsy can be undertaken if clinically indicated.

Pregnancy-related liver disease

The typical biochemical features of pregnancy-specific liver diseases are summarized in Table 10.2.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 10.1 Liver function test results in normal pregnancy.

Test	Not pregnant	First trimester	Second trimester	Third trimester
AST (IU/L)	7–40	10–28	11–29	11–30
ALT (IU/L)	0–40	6–32	6–32	6–32
Bilirubin (μmol/L)	0–17	4–16	3–13	3–14
GGT (IU/L)	11–50	5–37	5–43	5–41
Alkaline phosphatase (IU/L)	30–130	32–100	43–135	130–418
Bile acids (μmol/L)	0–9	0–9	0–9	0–9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.
Source: adapted from Girling *et al.* [1] and Walker *et al.* [19].

Table 10.2 Characteristic timings and diagnostic laboratory features in the liver diseases unique to pregnancy.

Disease	Trimester	Diagnostics
Hyperemesis gravidarum	1, 2	↑ Bilirubin (×5) ↑ ALT/AST (×2–4)
Intrahepatic cholestasis of pregnancy	2, 3	↑ ALT/AST (×6) ↑ Bile acids
Pre-eclampsia	2, 3	↑ Bilirubin (×2–5) ↑ ALT/AST (×10–50) ↑ Platelets
HELLP syndrome	2, 3	↑ ALT/AST (×10–20) ↑ LDH ↑ Platelets ↑ Urate
Acute fatty liver of pregnancy	2, 3	↑ Bilirubin (×5–10) ↑ ALT/AST (×5–10), rarely >20×

HELLP, haemolysis, elevated liver enzymes and low platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

Hyperemesis gravidarum

Nausea and vomiting are common in pregnancy. However, exact estimates vary in relation to the prevalence of hyperemesis gravidarum (HG). Reports range from 0.3 to 2% of all pregnancies, typically within the first trimester [3,4]. Under-reporting of symptoms may in fact account for the variation in incidence in the literature.

One of the most frequently used definitions of HG is intractable vomiting, resulting in ketosis, dehydration and weight loss of 5% or greater of body weight. The aetiology remains unclear but a combination of abnormal gastric motility, hormonal factors and changes in the autonomic nervous system are all thought to play a key role. Risk factors include increased body mass index (BMI), psychiatric illness, molar pregnancy, pre-existing diabetes and multiple pregnancies whilst hyperthyroidism is identified in an estimated 60% of cases [5–8]. Higher serum concentrations of human chorionic gonadotrophin (hCG) may stimulate the thyroid in pregnancy, accounting for this finding [8].

Clinical features, diagnosis and management

HG typically occurs from the fourth week of gestation, resolving by week 18. Although AST and ALT may be elevated by as much as 20 times the upper limit of normal, this is rare, as is jaundice. Dehydration can contribute to raised serum urea and creatinine levels, and there may be associated hypophosphataemia, hypomagnesaemia and hypokalaemia. Abnormalities in biochemistry typically resolve on resolution of vomiting. Failure to resolve abnormalities in liver biochemistry should alert the physician to alternative diagnoses such as viral hepatitis. Liver biopsy is not indicated, but if performed shows non-specific changes. Persistence of symptoms beyond 18 weeks should warrant consideration of a gastroscopy to exclude mechanical obstruction.

Management

Overall management of HG is supportive and includes intravenous rehydration, antiemetics and gradual reintroduction of oral intake. Vitamin supplementation, especially thiamine, is mandatory to prevent Wernicke's encephalopathy. Most patients will require 5–8 days of hospital admission, but relapse is common. Recurrence in subsequent pregnancies is also common. Attention should be given to the development of refeeding syndrome for patients that have a protracted clinical course.

Overlap syndromes with liver dysfunction

Pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome, acute fatty liver of pregnancy (AFLP), and liver rupture are separate but similar conditions that usually occur during the third trimester and after delivery. Often associated with hypertension, elevated liver enzymes are common. Low platelets may occur irrespective of the presentation and these conditions typically recover following delivery. In

some situations, progressive disease may occur with multisystem organ failure and in the extreme maternal death. HELLP syndrome is most often considered a variant of severe pre-eclampsia since hypertension and proteinuria are generally accompanying features. To complicate matters, there may also be overlap clinically and biochemically between AFLP and pre-eclampsia, and up to 50% of patients with AFLP will have pre-eclampsia [9,10]. It is essential for the clinician to recognize and differentiate the overlap syndromes from unrelated conditions which do not improve after delivery. For severe cases, a multidisciplinary team approach is warranted.

Fatty acid oxidation pathways

Disorders of fatty acid oxidation play a key role in the aetiology of AFLP, HELLP syndrome and pre-eclampsia. In the presence of oxygen, fatty acids are metabolized to carbon dioxide and water, and approximately 40% of the free energy produced in this process is conserved as adenosine triphosphate (ATP), whereas the remainder is released as heat within the mitochondrion.

An enzyme that plays a central role in this pathway is long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) [11,12]. It is part of an enzyme complex that constitutes the mitochondrial trifunctional protein (MTP), located on the inner mitochondrial membrane. In LCHAD deficiency, there is accumulation of long-chain hydroxyl-acylcarnitines, free plasma hydroxyl-long-chain fatty acids, and dicarboxylic acids, which results in cell toxicity. Defects in the trifunctional protein are inherited as autosomal recessive conditions and cause non-ketotic hypoglycaemia and hepatic encephalopathy in early infancy that may progress to coma and death if untreated [12]. They can also cause cardiomyopathy, peripheral neuropathy, myopathy and sudden death, although the latter clinical features are not characteristically seen in isolated LCHAD deficiency [12]. It is important to diagnose MTP disorders because the clinical complications can be avoided with dietary manipulation.

An increased prevalence of AFLP, HELLP syndrome and severe pre-eclampsia has been identified among heterozygous mothers of children who are homozygous for LCHAD deficiency [11–13]. A subsequent study of 27 pregnancies complicated by AFLP demonstrated that five women had fetuses with MTP mutations and that at least one copy of the common E474Q mutation was present in each case [14]. The study authors recommended that the neonates of women whose pregnancies are complicated by AFLP should be screened for MTP disorders or for the E474Q mutation. Routine screening of offspring of women whose pregnancies are complicated by HELLP syndrome is not recommended since MTP disorders are not common in the fetuses [14–16].

Outwith mitochondrial β-oxidation defects, other defects such as short-chain and medium-chain defects have been described in AFLP; in a series of 50 infants whose mothers had severe liver disease, long-chain defects were 50 times more likely than in controls and defects in short-chain and medium-chain pathways were 12 times more likely to be present [17].

Acute fatty liver of pregnancy

AFLP is a rare, potentially life-threatening, pregnancy-related disease that affects 1 in 7000 to 1 in 16 000 pregnancies [18]. It is more likely to occur in a first pregnancy, multiple pregnancies, and pregnancies carrying a male fetus [18,19]. In two case series of 32 and 16 affected women admitted to tertiary centres, the maternal mortality rate was 12.5% [9]. Perinatal mortality rates are reported as approximately 10% in the latest series, [9,10,20], although other series report higher mortality possibly related to premature delivery [17].

Pathogenesis

The pathogenesis of AFLP is not completely understood. It is clear that fatty acid oxidation disorders contribute to approximately 20% of cases of AFLP [14]. In these cases, it is likely that the heterozygous mother has a reduced hepatic ability to metabolize long-chain fatty acids. Although there is sufficient capacity in the non-pregnant state, when a heterozygous woman becomes pregnant, her liver is required to metabolize fatty acids from the placenta as well as her own circulation. Accumulation of fatty acids and the increased metabolite load likely results in hepatotoxicity. This may be further compounded by the alterations in lipid metabolism that occur in normal pregnancy.

Diagnosis

AFLP typically manifests in the third trimester with symptoms of nausea and anorexia. Other later symptoms include vomiting and abdominal pain whereas polydipsia and polyuria may also occur. Liver function tests should be requested for any pregnant woman reporting these symptoms because rapid diagnosis of an acute fatty liver allows stabilization of the patient and rapid delivery.

It is often difficult to differentiate AFLP from HELLP syndrome. Patients with AFLP more commonly have high levels of bilirubin, creatinine, uric acid and neutrophils; a prolonged prothrombin time (PT); acidosis; and hypoglycaemia. Patients frequently exhibit disseminated intravascular coagulation. Although levels of liver transaminases can be markedly increased, this can be variable. Moreover, the level of ALT or AST does not reflect disease severity since hepatocytes cannot release transaminases if they have already been destroyed by severe injury. Diagnostic criteria for AFLP have been created and are summarized in Table 10.3.

Table 10.3 Swansea criteria for the diagnosis of acute fatty liver of pregnancy.

Six or more criteria required in the absence of another cause:
• Vomiting
• Abdominal pain
• Polydipsia/polyuria
• Encephalopathy
• Elevated bilirubin >14 μmol/L
• Hypoglycaemia <4 mmol/L
• Elevated urea >340 μmol/L
• Leucocytosis $>11 \times 10^9$/L
• Ascites or bright liver on ultrasound scan
• Elevated transaminases (AST or ALT) >42 IU/L
• Elevated ammonia >47 μmol/L
• Renal impairment; creatinine >150 μmol/L
• Coagulopathy; prothrombin time >14 s or APPT >34 s
• Microvesicular steatosis on liver biopsy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT activated partial thromboplastin time.
Source: adapted from Ch'ng *et al.* [21].

Imaging modalities that have been used to diagnose AFLP include liver ultrasound, MRI and CT. Liver biopsy may be used to obtain a definitive diagnosis using an oil red stain, although delivery should not be delayed to facilitate biopsy. It is also pertinent to consider alternative diagnoses even in patients with suspected AFLP. In a series of 32 patients, six had an additional diagnosis, two patients having malignancy, one alcohol-induced fatty liver, another veno-occlusive disease with antiphospholipid syndrome, and another acute viral hepatitis A infection [9]. Poisoning with acetaminophen can produce a clinical presentation that is hard to distinguish from AFLP and should always be considered in the context of an AST or ALT level above 1000 IU/L.

Management

Women with AFLP should be managed by a multidisciplinary team that includes obstetricians, hepatologists, anaesthetists, obstetric physicians, neonatologists and intensivists. In severe disease, the mother should be cared for in an intensive care unit (ITU). Biochemical and haematological monitoring is critical. It is essential to monitor the international normalized ratio (INR) or PT and other markers of coagulopathy. Similarly, plasma glucose levels, platelets, creatinine, liver function test results, and arterial blood gases including lactate are appropriate. Fresh-frozen plasma should be given as required. Women often require large amounts of glucose intravenously to correct hypoglycaemia. If multisystem failure develops, it may be necessary to use dialysis and support with mechanical ventilation. *N*-Acetylcysteine is often used by liver units to treat AFLP, and we advocate its use.

Patients with AFLP should be assessed regularly for encephalopathy. It is advisable to consult with a liver unit specialist at the time of presentation of patients who have severe AFLP, hypoglycaemia and/or encephalopathy for advice on detailed management of fulminant liver failure and because assessment of suitability for liver transplantation may be necessary. In a study of 56 admissions to a liver failure unit in the UK, the presence of encephalopathy in conjunction with the presence of an elevated blood lactate level was highly associated with a poor prognosis and a need for liver transplantation [20]. The most important management strategy is delivery of the infant. The decision about the mode of delivery is often complex because the mother is likely to have a coagulopathy. Although vaginal delivery reduces the risk of haemorrhage, induction of labour often takes longer and prompt delivery can improve the maternal outcome. Regional anaesthesia should be avoided or used with caution and in conjunction with close monitoring. Blood tests should be performed frequently to ensure that coagulopathy is rapidly corrected in the days after delivery.

Prevention

AFLP does not commonly recur in subsequent pregnancies, although there are recurrent cases reported in the literature. In women who are heterozygous for disorders of fatty acid oxidation, it may be possible to establish whether the fetus is affected, and this can indicate the magnitude of the mother's risk. Mothers who deliver an affected fetus have a greater chance of recurrence. For heterozygous mothers who do not have affected fetuses and for others who do not have a fatty acid oxidation disorder, the recurrence risk is lower. However, the disease has potentially disastrous consequences, and women who have had one affected pregnancy should be managed in an obstetric clinic specializing in high-risk pregnancies.

Pre-eclampsia and HELLP syndrome

Liver involvement often occurs in the context of severe pre-eclampsia. Although severe hypertension may be absent in women with HELLP syndrome, in most instances there is some degree of accompanying hypertension that helps to differentiate this disorder from other diseases. Similarly, as discussed earlier, there may be overlap between HELLP syndrome and AFLP yet isolated serum AST/ALT elevations in severe pre-eclampsia rarely exceed 500 IU/L. Bilirubin levels rise in women with the HELLP syndrome, partly as a consequence of liver damage and partly in response to haemolysis, but bilirubin levels are usually higher in AFLP [14].

Table 10.4 Classification systems used in HELLP syndrome.

Tennessee System	
AST >70 IU/L	
LDH >600 IU/L	
Platelets $<100 \times 10^9$/L	
All three components: complete	
One or two components: partial	
Mississippi System	
Class I: Platelets $<50 \times 10^9$/L	and AST >40 IU/L and LDH >600 IU/L
Class II: Platelets $50–100 \times 10^9$/L	
Class III: Platelets $100–150 \times 10^9$/L	

AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

Hepatic failure with encephalopathy and coagulopathy are uncommon in pre-eclampsia and should prompt consideration of a different diagnosis, including fatty liver and other causes of hepatic dysfunction. Table 10.4 summarizes classification systems for HELLP syndrome.

Hepatic involvement occurs in approximately 10% of women with severe pre-eclampsia [22]. The presence of right upper quadrant pain usually signifies liver involvement. Increased AST/ALT levels may occur several hours after the onset of pain and, where performed, liver biopsy shows periportal haemorrhage, sinusoidal fibrin deposition and cellular necrosis [23]. However, in practice, liver biopsy is rarely warranted.

Women with pre-eclampsia and liver involvement should usually undergo prompt delivery, with steroids administered as protocol to promote fetal lung maturity. Laboratory values improve within 1 week of delivery, but may persist for weeks. Because HELLP syndrome may develop during the postpartum period in 20% of cases, liver function testing and imaging should be undertaken if abdominal pain, thrombocytopenia or other clinical features suggesting pre-eclampsia occur after delivery.

Liver rupture and infarction

Epidemiology

Rupture of the liver during pregnancy is a rare but often catastrophic event, with substantial risk for fetal and maternal death [20,24]. The majority of cases during pregnancy occur with pre-eclampsia or HELLP syndrome [25]. Liver rupture occurs in only a small proportion of women with pre-eclampsia, 4 of 442 (<1%) in one series [26]. Hepatic haematoma and rupture may rarely also occur after uncomplicated pregnancy, in association with biliary disease, infection, aneurysm and hepatic neoplasm [26–29].

Pathogenesis and clinical features

Although the pathogenesis of hepatic rupture remains unclear, subcapsular haemorrhage is a common finding at post-mortem in cases of pre-eclampsia. Hypertension may not be present, and the presence of severe right upper quadrant pain and hypotension should trigger thoughts on this outcome. Other symptoms include nausea, vomiting, shoulder pain and headache. Haemoperitoneum produces peritoneal signs and hypovolaemic shock.

Diagnosis

Diagnostic imaging is required to establish a diagnosis [30]. CT or MRI is the preferred technique for visualizing liver haematomas. Paracentesis and the finding of blood may occasionally be helpful. Laboratory evaluation of women with subcapsular haematoma or rupture reveals thrombocytopenia, hypofibrinogenaemia or INR/PT. Anaemia and haemolysis are typically present, and levels of bilirubin, lactate dehydrogenase and liver transaminases are elevated. The differential diagnosis for unruptured liver haematoma includes AFLP, placental abruption with coagulopathy, thrombotic thrombocytopenic purpura, and cholangitis with sepsis.

Management

An intact haematoma without rupture may be managed conservatively, particularly if the patient is haemodynamically stable [30]. Patients should be managed in ITU, with serial imaging studies to define the extent of the subcapsular haemorrhage, its progression and whether leaking has occurred. Management options for hepatic rupture include embolization of the hepatic artery, hepatic resection, hepatic artery ligation, and exploration with digital compression of the hepatic artery and portal vein to temporarily arrest the haemorrhage (i.e. Pringle manoeuvre). Surgical exploration and evacuation of haematoma and temporary packing of the liver is often appropriate. Fluid replacement, multiple transfusions and correction of coagulopathy are necessary components in conjunction with an attempt to control the hepatic bleeding. In a patient who is relatively stable, angiography may be attempted while making preparations for potential laparotomy. Mortality rates approach 50% in cases of liver rupture. In a series of seven cases, the four survivors were managed with packing and drainage [24]. The three women undergoing hepatic lobectomy did not survive. In another series of 10 patients, nine were treated surgically with a combination of stitching of the lesion, omental patching, hepatic artery embolization, and ligation. The tenth patient was dead on arrival at hospital. Five patients were treated with hepatic artery ligation and all survived [31]. Evaluation of the literature suggests that patients who receive arterial embolization, whether performed with or without a laparotomy, have a better prognosis than patients managed by other strategies in isolation.

Death is often caused by massive blood loss and coagulopathy. Patients who survive commonly experience

respiratory insufficiency from adult respiratory distress syndrome or pulmonary oedema and acute liver failure. Hospital stay is significantly prolonged [22].

Liver infarction

Infarction involving many areas of liver parenchyma may be a feature of severe pre-eclampsia or HELLP syndrome [32]. Presenting signs usually include abdominal pain and fever. CT demonstrates clearly demarcated areas of poor vascularization involving many liver segments. Histological evaluation of these areas demonstrates haemorrhage and leucocyte infiltration in areas adjacent to haemorrhage. In the setting of HELLP syndrome, many adjacent areas of periportal haemorrhage most likely form these infarcted segments. Improvement after delivery can be expected, even in the face of laboratory evidence of severe liver inflammation.

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is the commonest liver-specific disorder in pregnancy [33]. It affects approximately 1 in 140 women in the UK, but there is geographical variability in prevalence, with higher rates in women from South America, particularly Chile, and Asia. The condition is more rarely seen in women of African/Caribbean origin.

Pathogenesis

The aetiology of ICP has a genetic component, with a 17-fold increase of developing the disease in parous first-degree relatives. Mutations have been identified in biliary transporters, most commonly in ABCB11/BSEP and ABCB4/MDR3, which transport bile acids and phosphatidylcholine from the hepatocyte into bile, respectively [34]. There is evidence that raised reproductive hormones in pregnancy impact the normal pathways of bile acid homeostasis resulting in the development of cholestasis, and this is likely to be more severe in genetically predisposed women.

Diagnosis

The commonest presenting symptom of ICP is pruritus. This has varying severity but can be sufficiently severe to result in marked excoriations (Fig. 10.1) and sleep deprivation. Most women develop pruritus in the third trimester, but ICP can present as early as 8 weeks' gestation. Women commonly also complain of dark urine and approximately 25% have pale stools secondary to steatorrhoea. If ICP is suspected, the liver function tests and serum bile acids should be checked. The condition is characterized by raised serum bile acids, and most women also have elevated liver transaminases. Approximately 10% have raised bilirubin concentrations, consistent with jaundice being a relatively rare symptom. Those with severe disease may have abnormal coagulation with a prolonged PT.

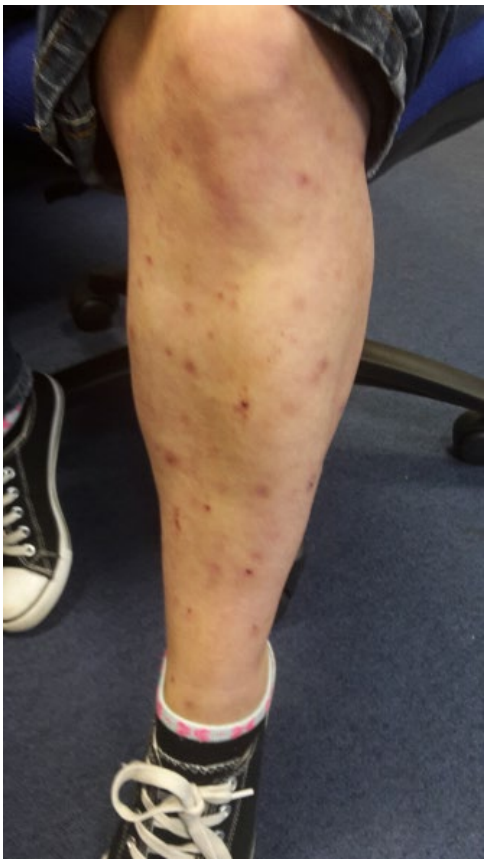

Fig. 10.1 Typical appearance of excoriations on skin in a woman with severe pruritus in ICP. Reproduced with permission of ICP Support.

The largest population studies in ICP, one in Sweden [35] and one in the UK [36], both demonstrated increased risk of adverse pregnancy outcomes in pregnancies in which the maternal serum bile acid concentration is 40 μmol/L or greater. The risk of spontaneous and preterm labour, stillbirth, meconium-stained amniotic fluid and prolonged admission to the neonatal unit were increased in these pregnancies. Both studies also demonstrated that the risk of an adverse outcome was greater as the maternal serum bile acid concentration became higher. Although liver transaminases were also raised in most cases, there was a less clear-cut relationship with adverse outcome compared with bile acids. The rise in serum bile acids can occur several weeks after onset of symptoms, and therefore it is advisable to continue to measure the serum bile acids weekly in women with ICP, including after making the diagnosis as otherwise severe cases (bile acids ≥40 μmol/L) may be missed.

ICP is a diagnosis of exclusion, and therefore other hepatic disorders must be discounted. Women should have blood tests to exclude hepatitis C and autoimmune hepatitis and an ultrasound scan to ensure they do not have gallstones.

Management

The drug with the best evidence to support its use is ursodeoxycholic acid (UDCA). Most studies demonstrate that UDCA treatment improves maternal pruritus and improves biochemical derangements [37]. There are currently no completed trials to establish whether UDCA treatment can reduce the frequency of adverse pregnancy outcome in ICP, although one meta-analysis [38] and a pilot trial of UDCA versus placebo [39] suggested that some adverse outcomes may be less frequent in ICP pregnancies in which the mother was treated. Specifically, the meta-analysis combined the data from eight trials of UDCA versus another treatment (placebo or another drug, e.g. cholestyramine, dexamethasone or *S*-adenosyl-methionine), and included data from 207 UDCA-treated and 70 placebo-treated ICP cases. This study reported reduced rates of all preterm labour (including iatrogenic), fetal distress and duration of admission to the neonatal unit [38]. The UDCA versus placebo pilot trial, although underpowered to investigate an effect on pregnancy outcome, did show reduced rates of meconium-stained liquor and a trend for reduction in neonatal unit admission and preterm labour in UDCA-treated women [39]. A large randomized controlled trial is currently underway with the aim of establishing whether UDCA treatment reduces adverse pregnancy outcome in ICP.

As most stillbirths have been shown to occur at later gestational weeks, it has been proposed that induction of labour at 37–38 weeks' gestation may reduce the risk of fetal death. There are no prospective studies to support or refute this practice. Several studies have recently evaluated the merits of elective delivery with the aim of reducing the risk of stillbirth in ICP, and all concluded that elective delivery at 36 weeks' gestation is associated with reduced risk. Specifically, a retrospective cohort study of 1 604 386 singleton pregnancies in California between 34 and 36 weeks' gestation with and without ICP demonstrated an increased risk of stillbirth in ICP at each gestational age from 34 weeks after adjusting for race, maternal age, hypertension, diabetes mellitus, parity and limited perinatal care [40]. This study also reported that the risk of mortality associated with delivery is lower than the risk of expectant management from 36 weeks' gestation. This was supported by retrospective reports of pregnancy outcomes in centres adopting a strategy of delivery at 36 or 37 weeks [41,42], and by the findings of a team that used a decision-analytic model to compare different decision strategies, which concluded that the optimal strategy for ICP pregnancies is immediate delivery at 36 weeks, without fetal lung maturity testing or steroid administration [43].

The pruritus and hepatic impairment usually resolve within a small number of weeks after delivery. Women should be advised that ICP has a high recurrence risk in subsequent pregnancies and they are at increased risk of hepatobiliary disease in later life, in particular gallstones. They should also be aware that they have an increased risk of cholestasis if they take the combined oral contraceptive pill. However, progesterone-containing contraception can be used.

Liver diseases incidental to pregnancy

Viral hepatitis in pregnancy

Viral hepatitis is the commonest cause of jaundice in pregnancy worldwide. Presentation, clinical features and general outcome for hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus or Epstein–Barr virus infection in pregnancy is similar to that in the non-pregnant state [44].

Hepatitis B virus

HBV can present in an acute or chronic form. For patients with acute hepatitis B, transmission of the virus to the child occurs in 50% of cases, with 70% of children infected if acute HBV infection occurs in the third trimester. For patients with chronic HBV, transmission of virus is dependent on the degree of viral replication and the quantity of HBV DNA detectable in the serum of the mother. Transmission rates above 90% have been reported from mothers who are HBV DNA positive and these are typically hepatitis B E antigen positive (HBeAg+).

Vaccination programmes throughout Southeast Asia and in the developed world have reduced transmission rates dramatically. Following vertical transmission, up to 80% of children become chronic carriers. Two strategies exist to reduce transmission rates. Firstly, the use of antiviral therapy such as tenofovir disoproxil fumarate (245 mg daily) that decreases HBV DNA level in the third trimester for appropriate patients reduces viral load and vertical transmission. Secondly, the use of hepatitis B immunoglobulin with hepatitis B vaccination in the neonate within 7 days of birth and at 1, 2 and 12 months of age also reduces the transmission rate significantly.

Hepatitis C virus

Chronic HCV infection in chronic carriers occurs in 8% of cases. Vertical transmission is highest in those patients with higher viral loads. Mother-to-child transmission of HCV has become the leading cause of paediatric infection, at an approximate rate of 5%, with maternal HIV co-infection a significant risk factor for mother-to-child transmission. However, anti-HIV therapy during pregnancy can reduce the transmission rate of both viruses. A high maternal viral load is an important but unpreventable risk factor since no anti-HCV treatment can currently be administered in pregnancy. With obstetric

procedures such as amniocentesis or internal fetal monitoring that could expose the fetus to maternal blood, caution should be undertaken, although evidence is lacking on the real risk of single obstetric practices. Mode of delivery and type of feeding do not represent significant risk factors for mother-to-child transmission. Therefore, there is no reason to offer elective caesarean section or discourage breastfeeding in HCV-infected patients. Antibody conversion of infants following transmission may take 6–12 months, although measurement of HCV RNA levels will allow for early diagnosis.

Hepatitis E virus

Hepatitis E virus is problematic in pregnancy, typically occurring in epidemic form in Southeast Asia, the Indian subcontinent and the Middle East. The development of acute liver failure in the second and third trimester can be associated with a mortality of up to 20%.

Pregnancy in patients with cirrhosis

Many patients with chronic liver disease and cirrhosis are infertile. However, patients with autoimmune liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis may become pregnant. Patients with autoimmune hepatitis should be maintained on baseline immunosuppression throughout pregnancy (azathioprine with or without prednisolone). For patients treated with mycophenolate mofetil before pregnancy, they should be converted to an alternative immunosuppressant such as azathioprine, tacrolimus or cyclosporin prior to planned pregnancy. A 20–25% risk of flare in autoimmune hepatitis occurs following delivery in the first 3 months post partum, and this is reduced if immunosuppressive treatment is maintained.

Since varices develop even in normal pregnancy as a consequence of changes in cardiac output, azygos blood flow, increased circulating blood volume and changes in splanchnic haemodynamics, an increased risk of variceal bleeding in cirrhotic patients can be anticipated. Patients with established cirrhosis should be screened for varices in the second trimester. This is to facilitate and guide appropriate peripartum care. The presence of small varices in otherwise well-compensated cirrhotic patients should not preclude a vaginal delivery. However, close monitoring in pregnancy is warranted.

For patients with non-cirrhotic portal hypertension, a bleeding rate in pregnancy of 13% has been reported. In cirrhotic patients contemplating pregnancy, pre-pregnancy screening and appropriate treatment of large varices should be undertaken. Propranolol is not contraindicated in pregnancy and episodes of variceal bleeding should be treated with normal endoscopic approaches including endoscopic band ligation or histoacryl glue, whereas transjugular intrahepatic shunts should be reserved for rescue therapy and field endoscopic treatment. There are limited safety data for vasoconstrictors such as terlipressin, but they may be used in women with life-threatening haemorrhage in pregnancy.

Pregnancy following liver transplantation

Successful pregnancy following liver transplantation has been widely reported and fertility will return typically within 6 months of transplant. Best outcomes are reported for pregnancies undertaken more than 1 year after the transplant operation since it reduces the risk of acute cellular rejection and other infective complications. Tacrolimus, cyclosporin, azathioprine and corticosteroid therapy are widely and safely used in pregnancy. Specific complications in pregnancy related to a higher prevalence of hypertension/pre-eclampsia and preterm delivery have been reported. Patients on mycophenolate should be converted to an alternative immunosuppressant prior to pursuing pregnancy.

Summary box 10.1

- Tests of liver function should be evaluated using normal ranges for pregnancy.
- Women with hyperemesis gravidarum should be treated with thiamine, and thromboprophylaxis should be considered in addition to correction of electrolyte disturbance and use of antiemetics with good safety data.
- It is advisable to discuss patients who have severe AFLP, hypoglycaemia and/or encephalopathy with a liver unit specialist at the time of presentation.
- In AFLP and HELLP syndrome the presence of encephalopathy in conjunction with an elevated blood lactate level is associated with a poor prognosis and a need for liver transplantation.
- Women with ICP with serum bile acids ≥40 µmol/L have an increased risk of adverse pregnancy outcome, including spontaneous preterm labour, stillbirth and prolonged neonatal unit admission.
- Women with cirrhosis should be screened for varices in the second trimester.
- Variceal bleeding should be treated with normal endoscopic approaches including endoscopic band ligation and histoacryl glue. Beta-blockers are not contraindicated, and terlipressin can be used in women with life-threatening haemorrhage in pregnancy, although there are more limited safety data.
- Pregnancy should be deferred for 1 year after liver transplantation, and women who have had a transplant and are planning pregnancy should be advised to change mycophenolate to an alternative immunosuppressant.

ENDOCRINE DISORDERS IN PREGNANCY

Thyroid disease

The normal ranges for thyroid function tests alter in pregnancy, in part related to elevation in hCG – and associated stimulation of the thyroid-stimulating hormone (TSH) receptor causing a transient increase in thyroxine and suppression of TSH in the first trimester – and also haemodilution in the second and third trimesters. Thyroid-binding globulin increases in pregnancy, likely secondary to elevated oestrogen levels, and therefore free thyroxine measurement should be used. The normal ranges of thyroid function tests in each trimester of pregnancy are summarized in Table 10.5.

Autoimmune hypothyroidism

Autoimmune hypothyroidism affects 1% of pregnancies. While well-controlled patients have good pregnancy outcomes, overt hypothyroidism is associated with increased risks of adverse pregnancy outcome, including miscarriage, pre-eclampsia, placental abruption and low birthweight [48], in addition to having an adverse impact on the subsequent intelligence of the baby [49]. Therefore it is important to ensure that affected women are adequately treated. However, it should be borne in mind that over-treatment is associated with iatrogenic maternal hyperthyroidism, and this should be avoided as well [50]. The impact of subclinical hypothyroidism on subsequent intelligence of the fetus is not clearly established, and a recent well-powered UK study that evaluated the impact of thyroxine replacement from the end of the first trimester for subclinical hypothyroidism did not show any difference in subsequent intelligence of the offspring at 3 years of age, nor was there any impact on birthweight or the rate of preterm birth [51]. Therefore, it is clearly important to ensure that women with hypothyroidism receive treatment with thyroxine to maintain their thyroid function tests in the normal range for pregnancy, but there is no evidence for treatment of women with normal thyroid function tests.

Table 10.5 Normal ranges for thyroid function tests in pregnancy.

Normal range*	FT4 (pmol/L)	TSH (mU/L)
Non-pregnant	11–23	0–4
First trimester	11–22	0–1.6
Second trimester	9–19	0.1–1.2
Third trimester	7–15	0.7–5.5

*Normal ranges may vary according to ethnic group.
Source: based on data from Parker [45], Chan & Swaminathan [46], Soldin *et al.* [47].

Management

As the thyroid-binding globulin concentration is elevated, some women will need an increase in thyroxine dose. However, it is not necessary to increase the dose in all women and this should be guided by testing the thyroid function tests before pregnancy and in each trimester. A study that addressed the need for increased dose of thyroxine in 100 pregnancies in women with autoimmune hypothyroidism found that 50% of women needed more thyroxine, but in the majority of cases this was due to inadequate replacement prior to pregnancy, poor compliance, or recent diagnosis with insufficient time to optimize treatment, rather than a consequence of a gestation-specific need for an increased dose [41]. The thyroxine dose should be adjusted in those that are deficient using normal ranges for pregnancy.

Occasionally a woman will present in early pregnancy with overt hypothyroidism and elevated TSH above the normal range for pregnancy. The principal concern in this group is whether the hypothyroidism will impact the subsequent intelligence of the child. Unfortunately, there are limited research data about this but it is likely that the impact will be minimal if thyroxine replacement is optimized in the second and third trimesters.

There is evidence that pregnant women positive for thyroid autoantibodies are more likely to have miscarriage and preterm delivery [52]. This may be partly due to coexisting autoimmune disorders, such as antiphospholipid syndrome.

Hyperthyroidism

Hyperthyroidism affects 1 in 800 pregnancies, and the majority of cases have Graves' disease. This may also be secondary to toxic nodule, thyroid adenoma, carcinoma or subacute thyroiditis. The presenting symptoms of hyperthyroidism include palpitations, heat intolerance and palmar erythema, all of which can also be seen in normal pregnancy. However, eye signs and pre-tibial myxoedema are specific to autoimmune thyroid disease and weight loss does not occur in normal pregnancy.

Management

There is some debate about the best drug to treat hyperthyroidism in pregnancy. Carbimazole and propylthiouracil are used to treat hyperthyroidism. Both drugs are associated with an approximately doubled risk of congenital abnormalities [53,54] and these have been more consistently reported in women treated with carbimazole. Propylthiouracil is known to be occasionally complicated by fulminant hepatic failure in 1 in 10 000 adults and 1 in 2000 children and therefore is not recommended as first-line therapy. However, the American

Thyroid Association has recommended that it could be preferable to carbimazole in pregnant women given that there are more data to suggest that carbimazole is teratogenic. However, it should be noted that propylthiouracil can also cause congenital abnormalities [53,54]. Therefore, a sensible management approach is to continue carbimazole in women who are already taking it prior to conception, while either carbimazole or propylthiouracil can be used for newly diagnosed cases in the first trimester of pregnancy, with appropriate advice about the risk of congenital malformations. Given that carbimazole is the preferred treatment outside pregnancy, this is important to consider and often will be the most sensible choice. It is important to ensure that women with hyperthyroidism are adequately treated, as untreated thyrotoxicosis is associated with increased risk of fetal loss, growth restriction and preterm labour while severe cases may develop the life-threatening complication of thyroid storm. As with other autoimmune conditions, many women with hyperthyroidism improve during pregnancy and in some the dose of antithyroid drugs may be reduced or even stopped. However, the requirement for treatment usually returns post partum.

Women with autoimmune thyroid disease should have TSH receptor antibodies checked as they can cross the placenta and stimulate the fetal thyroid. The impact of this often depends on whether the mother is taking antithyroid drugs. If she is, the drugs will also cross the placenta, so the maternal antibodies are unlikely to cause problems until after delivery, but there is a risk of neonatal thyrotoxicosis 2–4 days post partum. This is because the drugs will be cleared from the neonatal circulation rapidly, but the maternal antibodies will remain for approximately 3 months. As a consequence it is important to involve neonatologists in early fetal assessment. In contrast, if a woman is not taking antithyroid drugs, for example because she has previously had surgery or radioiodine treatment, her pregnancy should be closely monitored for fetal hyperthyroidism or goitre because TSH receptor antibodies can cross the placenta and there will be no antithyroid drugs to prevent fetal disease.

Carbimazole and propylthiouracil can be given to lactating women. There are no concerns about transfer to the baby with low, maintenance doses of either drug, but if high doses are used the baby's thyroid function should be monitored.

Pituitary disease

Pituitary tumours are often diagnosed in women of reproductive age as they cause menstrual irregularity. The commonest is prolactinoma, subdivided into microprolactinoma (<10 mm diameter) and macroprolactinoma (≥10 mm diameter). Both are treated with dopamine agonists, and this typically results in a return to normal menstruation and fertility. While microprolactinomas rarely undergo enlargement in pregnancy, symptomatic enlargement occurs in approximately 15% of women with macroprolactinoma [55]. Therefore, this latter group of women should have formal visual tests performed each trimester. Many clinicians also continue dopamine agonist treatment in women with macroprolactinomas. The next most common pituitary tumour that is identified in pregnant women is non-functioning tumour. These tumours can result in symptomatic visual impairment, likely secondary to gestational enlargement of surrounding pituitary tissue. Cushing's disease, acromegaly and TSH-oma are very rare and commonly result in visual impairment or cause symptoms secondary to hormone excess. Treatment should be coordinated in collaboration with an endocrinologist. Women with pituitary tumours may develop pituitary apoplexy. This medical emergency presents with visual impairment, headache and neurological defects.

Women with hypopituitarism who receive adequate hormone replacement can become pregnant. It is important to ensure that women who are deficient in glucocorticoids receive an increased dose at times of stress, when vomiting or at the time of delivery. Lymphocytic hypophysitis is an autoimmune disorder that can present with features of hypopituitarism and more commonly occurs in pregnancy. It responds to treatment with glucocorticoids or immunosuppression, but often recurs after treatment is stopped. It may resolve spontaneously. It is important to ensure that women with lymphocytic hypophysitis are not incorrectly diagnosed as having a pituitary tumour as surgery will make them worse. Diabetes insipidus secondary to vasopressin deficiency often requires additional treatment in pregnancy, likely a consequence of placental secretion of vasopressinase. If affected women increase the dose of desmopressin during pregnancy this should be reduced to the pre-pregnancy dose immediately after delivery.

Adrenal disease

Adrenal insufficiency affects approximately 1 in 3000 pregnant women. In developed countries this is most commonly caused by autoimmune destruction of the adrenal glands, a condition described as Addison's disease. Most women with adrenal insufficiency will have presented prior to pregnancy. Typical presenting symptoms are non-specific and include fatigue, hypotension, nausea, vomiting, weakness and hyperpigmentation. Affected women frequently also have hyponatraemia. Many of

these clinical features are reported in normal pregnancy, so *de novo* diagnosis can be difficult but is essential. Women with a prior diagnosis of adrenal insufficiency who are taking glucocorticoid replacement usually have good pregnancy outcomes providing they are able to continue adequate treatment doses. This can be a challenge if they develop hyperemesis gravidarum, and it may necessitate parenteral or intramuscular administration of glucocorticoids. Women will require an increased replacement dose of glucocorticoids to cover intercurrent illnesses and they should be given an increased dose to cover the stress of labour.

Adrenal tumours are very rare in pregnancy, but should be considered in women with atypical or severe hypertension [56]. Phaeochromocytoma can cause paroxysmal severe hypertension. Urinary or plasma catecholamines can be used for diagnosis. Management should involve a multidisciplinary team, and alpha-blockade should be started prior to beta-blockade. Other hormone-secreting tumours are primary hyperaldosteronism and adrenal Cushing's syndrome. Both cause severe hypertension. Primary hyperaldosteronism can also cause hypokalaemia and affected women often need potassium replacement as well as treatment with antihypertensive drugs. Surgical removal is the treatment of choice for Cushing's syndrome caused by an adrenal tumour. For the other hormone-secreting adrenal tumours in pregnancy, surgery may be performed in pregnancy or post partum, providing the disease is controlled with appropriate medical therapy.

Parathyroid disease

Hyperparathyroidism is usually caused by a parathyroid adenoma, but it may occur in women with parathyroid hyperplasia or carcinoma. Women develop hypercalcaemia, but this is usually less severe than in non-pregnant individuals due to reduced circulating albumin concentrations and transplacental transfer of calcium to the fetus. The mother may develop hypertension and nephrolithiasis, and treatment should be given if the corrected calcium concentration is persistently raised despite high fluid intake. Surgical assessment should be given as many women are cured by removal of the tumour. However, it is important to establish the location of the tumour as some women have mediastinal tumours that necessitate a much more complex surgical approach, and in these cases it may be more appropriate to defer surgery until after delivery. The concerns with medical management are intractable hypercalcaemia or increased risk of stillbirth [57]. This is thought to be due to fetal hypercalcaemia, as is the increased risk of neonatal tetany.

Summary box 10.2

- In women with autoimmune hypothyroidism, replacement doses of thyroxine should be monitored with the use of normal pregnancy reference ranges with the aim of staying within the normal range.
- Transplacental transfer should be considered in women with elevated titres of TSH receptor antibodies:
  - Women with previous radioiodine treatment or thyroid surgery for autoimmune hyperthyroidism are at risk of fetal hyperthyroidism, and their fetuses should be assessed for the presence of goitre or growth restriction.
  - Those treated with antithyroid drugs have babies at risk of neonatal hyperthyroidism and should have neonatology review.
- In women with macroprolactinoma (tumour diameter ≥10 mm), there is a 15% chance of symptomatic enlargement and visual fields should be assessed with perimetry.
- Pituitary apoplexy can occur in a small proportion of women with pituitary tumours in pregnancy and should be managed as a medical emergency.
- Women with adrenal insufficiency are at risk of life-threatening glucocorticoid deficiency if they develop hyperemesis gravidarum, and will also require increased doses of glucocorticoids to cover the stress of labour and delivery.
- Women with hyperparathyroidism in pregnancy often have less marked hypercalcaemia, in part due to enhanced transplacental transfer. Surgery should be considered as fetal hypercalcaemia may result in stillbirth.

Conclusion

Liver and endocrine diseases can cause serious maternal and fetal morbidity and mortality. With a multidisciplinary approach the pregnancy outcome for mother and child can be improved. If a woman has a known pre-existing disease, it is important to give informed pre-pregnancy counselling. Once women with potentially life-threatening hepatic or endocrine disorders of pregnancy are identified, they should be referred for review by physicians with training and experience in the management of these diseases in pregnancy.

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11

Renal Disease

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Providing care for women with underlying renal disease contemplating pregnancy or those already pregnant requires that the obstetrician has up-to-date knowledge about pregnancy physiology, antenatal care and the technology for fetal surveillance. It is essential to appreciate the need for multidisciplinary teamwork in a centre with all the necessary facilities for dealing with high-risk patients and their babies. It is estimated that chronic kidney disease (CKD) affects up to 6% of women of childbearing age in high-income counties, and has been estimated to affect 3% of pregnant women. This chapter focuses on CKD, women on dialysis and kidney transplant recipients, aiming to provide the busy clinician with information for counselling and judicious decision-making.

Summary box 11.1

- All women of childbearing age with CKD, including those on dialysis and kidney transplant recipients, should be made aware of the implications regarding reproductive health, contraception, modification of remedial risk factors and optimization of medications.
- Active preparation for pregnancy should be individualized to each woman's needs and should involve her partner.
- Multidiscplinary clinics are needed for the pre-pregnancy assessment and antenatal care of these women.

Pre-pregnancy assessment

The basic components should be analysis of risks as well as provision of health education and advice plus any interventions that might be considered helpful, all united under the banner of that much-used word 'counselling' [1]. The multidisciplinary team has to decide what is important so that active preparation for pregnancy is tailored to each woman's needs, with her being encouraged to involve her partner so that all the implications can be discussed, including potential areas of disagreement, even whether infertility treatment, if needed, would be made available.

What the woman wants to know

All healthcare professionals looking after women of childbearing age with kidney disease need to raise the issue of her plans, or not, for pregnancy. It may not be apparent to the woman that her kidney disease poses any issues for her or a baby. Once prompted, aside from what the team wants to discuss and achieve for the woman and her partner, she herself usually has four straightforward questions.

1) Should I get pregnant and when is the best time for me to get pregnant?
2) Will my pregnancy be complicated?
3) Will I have a live and healthy baby?
4) Will I have problems after my pregnancy?

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Most women focus on the third question but it is essential to ensure that all relevant information and even harsh realities are passed on, based on fact not anecdote.

What the patient needs to understand

She must understand the risks and the need to improve her own knowledge, so that she can best use the guidance and support to make any necessary changes in her behaviour, attitude and medication(s). However, knowledge, and even understanding, of the risks may not be sufficient to ensure the patient makes the changes because many other factors influence her behaviour. Even when there is an element of self-management (perhaps best exemplified with dialysis and/or diabetes) this will also be affected by the woman's repertoire of beliefs, skills, intuition and motivation and not just her so-called knowledge, however gained. The key is a strong, unwaivering, positive and supportive relationship with the team that allows pre-pregnancy advice to be included in the overall care agenda as a goal-orientated process. Thus a planned pregnancy is one that is desired well before conception, occurs when contraception is discontinued and where the woman attempts to achieve optimal health beforehand.

Even if some of the answers are not favourable, a woman, being an autonomous adult, may still choose to plan for (or proceed with) a pregnancy in an effort to re-establish a normal life in the face of chronic illness [2]. Indeed some women may not seek advice until already pregnant. Occasionally, there may be ethical dilemmas regarding the clinician's duty of care for women who ignore advice; interestingly, there are studies that have differentiated 'healthy' and 'pathological' levels of assumed risk and which have tried to understand the psychology of women who pursue parenthood despite big risks to their own health and the unborn child [3].

Normal pregnancy

The renal tract undergoes marked anatomical, haemodynamic, tubular and endocrine changes as part of the systemic upheaval of maternal adaptation to pregnancy [4,5]. The kidneys enlarge because both vascular volume and interstitial space increase but there is no accelerated renal growth nor morphological alterations akin to compensatory renal hypertrophy. The calyces, renal pelves and ureters dilate markedly, invariably more prominent on the right side, seen in 90% of women.

Glomerular filtration rate (GFR), measured as 24-hour creatinine clearance (C_{cr}), increases by 6–8 weeks' gestation. Serum creatinine (S_{cr}) and serum urea (S_{urea}), which average 70 μmol/L and 5 mmol/L respectively in non-pregnant women, decrease to mean values of 50 μmol/L and 3 mmol/L during pregnancy. Values for S_{cr} of 80 μmol/L and S_{urea} of 6 mmol/L, which are acceptable in the non-pregnant state, are suspect in pregnancy. At term, a 15–20% decrement in C_{cr} occurs, which affects S_{cr} minimally.

The 24-hour urinary total protein excretion (TPE) increases in normal pregnancy, and up to 300 mg per 24 hours can be regarded as normal [6]. So-called significant proteinuria (TPE >300 mg per 24 hours) may correlate with a protein concentration of 30 mg/dL in a 'spot' urine sample. Timed urine collections are no longer required since proteinuria can be reliably monitored with the use of 'spot' urine protein/creatinine ratios that equal 30 mg/μmol or more.

Chronic kidney disease

Renal impairment and the prospects for pregnancy and afterwards

A woman may lose up to 50% of her renal function and still maintain S_{cr} below 125 μmol/L because of hyperfiltration by the remaining nephrons; however, if renal function is more severely compromised, then further small decreases in GFR will cause S_{cr} to increase markedly [4,7–9]. In women with CKD, whilst the pathology may be both biochemically and clinically silent, the internal milieu may already be disrupted. Most individuals remain symptom-free until GFR declines to less than 25% of normal, and many serum constituents are frequently normal until a late stage of disease. However, degrees of functional impairment that do not appear to disrupt homeostasis in non-pregnant individuals can jeopardize pregnancy.

Assessment of renal impairment and its implications for CKD in pregnancy

Estimated GFR

Because a normal creatinine does not necessarily reflect normal kidney function, for the past few years it has become accepted practice to classify renal function in non-pregnant patients using estimated GFR (eGFR; units, mL/min per 1.73 m^2) calculated from a formula based on S_{cr} adjusted for age, gender and race (Black African descent or not). The so-called Modified Diet in Renal Disease (MDRD) formula was developed in the USA in a multiethnic population of women and men with moderate renal impairment and, most importantly, an eGFR below 60 mL/min per 1.73 m^2. The classification recognizes five stages of CKD (Table 11.1). In non-pregnant populations, eGFR is much less reliable in patients

Table 11.1 Stages of CKD classified according to the US National Kidney Foundation.

Stage		eGFR (mL/min per 1.73 m^2)
1	Kidney damage (structural or proteinuria) with normal or even increased GFR	≥90
2	Kidney damage (structural or proteinuria) with mild GFR decrease	60–89
3	Moderate GFR decrease	30–59
4	Severely low GFR	15–29
5	Kidney failure	<15 or dialysis

eGFR, estimated glomerular filtration rate.
Sources: Davison *et al.* [5], Rich-Edwards *et al.* [11], National Kidney Foundation [12], Davison & Lindheimer [13], and Imbasciati *et al.* [14].

with CKD stages 1 and 2 because of the poor correlation with actual GFR when it exceeds 60 mL/min [10]. In fact over 95% of women with underlying CKD becoming pregnant do have an actual GFR of 60 mL/min or more.

Unlike many prediction formulas, the MDRD equation is not individualized for body surface area and is therefore theoretically attractive for use in the obstetric population in whom increased surface area is not a reflection of increased muscle mass and therefore of increased S_{cr}. However, reports to date have not borne this out and during pregnancy the MDRD fomula substantially underestimates GFR compared with the gold standard of inulin clearance [15,16]. An important clinical concern deriving from the fact that eGFR tends to underestimate true GFR is that its use might signal to the clinician an exaggerated deterioration in GFR, perhaps promoting unnecessary delivery. Therefore, the use of the MDRD equation during pregnancy to estimate GFR in women who have known renal impairment prior to conception or who develop renal complications during pregnancy cannot be recommended. The same applies for the CKD-Epi formula [17]. In addition, the Cockroft–Gault formula, and many others, are inaccurate in pregnancy and there is disagreement about using cystatin C to monitor renal function [18]. However, in prospective studies of women with known renal function prior to pregnancy, outcomes are now being related to pre-pregnancy CKD stages based on eGFR rather than serum creatinine.

eGFR versus S_{cr}

It might seem that a system based on GFR would be superior to one based on S_{cr} and perhaps the database in the literature should be converted to this new CKD classification [13]. We would argue almost certainly not, as the great majority of pregnant women are those with mild disease (CKD stages 1 and 2) and, as mentioned already, the formulas for eGFR in women whose values are anticipated to be above 60 mL/min in the non-pregnant state are unreliable, though better with use of CKD-Epi. Furthermore, the traditional system has been easy to disseminate and is familiar to non-nephrology specialists. Whilst defending the use of S_{cr} it must nevertheless be mentioned that very small women may present with normal or mildly elevated S_{cr}, and clinicians should be suspicious of abnormal function if they see a pregnant woman with a serum creatinine greater than 80 µmol/L.

Summary box 11.2

- If pre-pregnancy renal function is normal or only mildly decreased (S_{cr} ≤125 µmol/L) and hypertension minimal and/or well controlled, then obstetric outcome is usually successful.
- There is an increased risk of antenatal complications such as pre-eclampsia, fetal growth restriction and preterm delivery.
- Offer low-dose aspirin as prophylaxis against pre-eclampsia, starting within first trimester.
- During pregnancy target blood pressure should be <140/90 mmHg, and in women with proteinuric renal disease ideally <130/80 mmHg but not less than 110/60 mmHg [19,20].
- Greater degrees of renal dysfunction (S_{cr} >125 µmol/L, and certainly >180 µmol/L) and/or the presence of poorly controlled hypertension are more ominous, at least for maternal outcome, especially long-term renal prognosis.
- The use of eGFR from the MDRD or CKD-Epi formula is not recommended for use in pregnancy.

The basic question for a woman with CKD must be: is pregnancy advisable? The timing of the pregnancy depends on whether the CKD is caused by relapsing remitting disease such as systemic lupus erythematosus (SLE) or is progressive and function likely to decline over time, for example adult polycystic kidney disease (APKD). In the latter scenario, it is clear that if all else is stable, then sooner is better as with time function will only worsen and risks increase. If the former, then disease should be inactive for several months prior to trying to conceive as active disease is associated with worse outcomes. Many women still present pregnant without prior counselling and then the question must be whether pregnancy should continue (Table 11.2).

Obstetric and long-term renal prognoses differ in women with different levels of dysfunction (for recent reviews of

pregnancy and CKD, see Hladunewich *et al.* [21] and Webster *et al.* [22]). Counselling is based on three functional parameters: the degree of renal insufficiency (Table 11.3), the presence or absence of hypertension and the underlying kidney disease. Until recently, all the data on outcomes of pregnancy in women with CKD were based on retrospective data, which traditionally and arbitrarily classified renal insufficiency solely by pre-pregnancy S_{cr}: 125 μmol/L or less as descriptive of 'mild' insufficiency, 125–250 μmol/L as 'moderate' insufficiency, and above these levels as severe insufficiency [23]. Their use has been the mainstay of pre-pregnancy counselling for over 25 years, consistently showing that normotensive women with intact or only mildly decreased but stable renal function generally do very well, experiencing more than 95% live births, about 75% of which are appropriate for gestational age. These excellent statistics also reflect a literature that has shown constantly improving perinatal outcomes from the 1980s onwards, indicative of the marked advances in both antenatal and neonatal care [24–31]. With mild insufficiency there is an increased incidence of superimposed pre-eclampsia or late pregnancy hypertension, as well as increased proteinuria, exceeding the nephrotic range (3 g per 24 hours) in 50% of women in the second half of pregnancy. Pregnancy does not appear to adversely affect the course of the CKD. However, there are exceptions to this optimistic outlook [31,32]. Indeed, the earliest prospective study of women with baseline CKD stages 3–5 covering 23 years assessed the rate of decline of maternal renal function during pregnancy in 49 white non-diabetic women with CKD stages 3–5 before pregnancy (eGFR <60 mL/min per 1.73 m^2 pre-pregnancy) to average 39 months after delivery [14]. This multicentre Italian network effort confirmed earlier observations that such women have complicated pregnancies with poor perinatal outcomes as well as an accelerated decline in renal function [33]. The main conclusion was encouraging because while the group as a whole lost function during pregnancy, the rate of loss was not affected by pregnancy. Also, 95% of the fetuses survived, albeit many were born preterm and/or growth restricted. The best outcomes were to women whose pre-pregnancy eGFR was between 60 and 40 mL/min per 1.73 m^2, corresponding to S_{cr} values between 125 and 141–150 μmol/L or proteinuria less than 1 g/day. On the other hand, women with eGFR below 40 mL/min per 1.73 m^2 and proteinuria above 1 g/day had poorer outcomes, the combination resulting in worse outcomes than either factor alone. Although these women developed renal failure faster than other groups, it was not possible to determine if pregnancy was a causal factor.

Recently however, prospective data from the TOCOS study [35] have suggested even women with CKD stage 1 (eGFR >90 mL/min and S_{cr} probably much lower than 125 μmol/L) without baseline hypertension, proteinuria above 1 g/day, or systemic disease before pregnancy had an increased risk of a combined adverse outcome (preterm, neonatal intensive care or small for gestational age) (odds ratio, OR 1.88; CI 1.27–2.79) versus women with no CKD. Additionally, the risks for preterm delivery rose further for women with CKD stage 1 associated with baseline hypertension (OR 3.42)/proteinuria (OR 3.69)/systemic disease (OR 3.13). Thus, all women with CKD should be considered high risk and be assessed for risk of adverse pregnancy outcomes.

Prognosis is poorer when there are greater degrees of renal dysfunction (reviewed in Hladunewich *et al.* [21]

Table 11.2 Pre-pregnancy considerations in chronic kidney disease.

Renal pathology under consideration
Good general health
Review and optimize pre-pregnancy drug therapy
Diastolic blood pressure ≤80 mmHg or well-controlled hypertension with 'safe' medication(s)
S_{cr} ideally <125 μmol/L, at least ≤180 μmol/L, and very concerning from 180 to ≤250 μmol/L
No or minimal proteinuria
'Well-controlled' comorbidities (e.g. diabetes mellitus, infections)
Relevance of obstetric history

Table 11.3 Pre-pregnancy kidney function (S_{cr}) in CKD patients with estimates for obstetric outcome and renal functional loss.

Renal status Dysfunction	S_{cr} (μmol/L)	Problems in pregnancy (%)	Successful obstetric outcome (%)	Permanent loss of kidney function* (>25% increment in S_{cr}*) (%)	ESRF within 1 year post partum (%)
Mild	≤125	26	96	<2	
Moderate	≥125	42	95	15	1
Severe	≥180	80	74	52	38

Estimates are based on a 26-year literature review of pregnancies (1984–2010) which attained at least 24 weeks' gestation. ESRF, end-stage renal failure.

*Compared with pre pregnancy serum creatinine.

Source: Lindheimer & Davison [34].

and Webster *et al.* [22]). With moderate impairment, live births still approach 90%, but the incidence of pre-eclampsia, fetal growth restriction and/or preterm delivery exceeds 50%. With severe dysfunction, outlook is more drastically curtailed. Although there is a paucity of data for analysis in both these categories, what has become obvious is that a cut-off S_{cr} of 250 μmol/L is too high for moderate impairment, with 180 μmol/L more appropriate, and thus there is a tendency to designate these patient groups 'moderate to severe' (Tables 11.3 and 11.4). This literature is slowly increasing and the message could not be clearer: hypertension is common by term (60%) as is significant proteinuria (50%) as well as deterioration in renal function (at times rapid and substantial) and although infant survival rates are good (80–90%), rates of premature delivery (60%) and fetal growth restriction (40%) underscore the very high potential for obstetric complications in these women [36–39]. Not previously so obvious are the facts that 30–50% of women with moderate insufficiency experience functional loss more rapidly than would be expected from the natural course of their renal disease and that poorly controlled hypertension might be a harbinger of poor outcome [40–43]. Once S_{cr} rises above 250 μmol/L there are even bigger risks of accelerated loss of renal function, and even terminating the pregnancy may not reverse the decline (Table 11.3).

Temporary dialysis

Temporary or acute dialysis has been advocated during pregnancy in the face of overall deterioration in renal function (especially when S_{urea} exceeds 20 mmol/L and/or there is refractory hyperkalaemia), severe metabolic acidosis, pulmonary oedema responding poorly to diuretics, and danger of volume overload with heart failure [5,31,39,44]. Dialysis may increase the chance of successful outcome by 'buying time' for fetal maturation but it does not arrest the inexorable decline in renal function, ultimately to end-stage failure. In trying to avoid extreme prematurity in this way, it has to be asked whether such life-threatening effects on the mother's renal prognosis can be justified. Nevertheless, the awareness by some women of progress in antenatal care and neonatal provision encourages them to anticipate good outcomes and they will say that they are prepared to take a chance and even seek assisted conception in the face of their infertility. Of importance in all the current controversies is that the literature that forms the basis of our views is primarily retrospective, with most patients only having mild dysfunction and women with severe to moderate disease being limited in number. Confirmation of guidelines and prognoses therefore requires adequate prospective trials. The prospective TOCOS study only had 10 women with advanced CKD (pre-pregnancy eGFR <30 mL/min per 1.73 m^2); however, 90% of these had adverse pregnancy outcomes and 80% had severe adverse outcomes [35]. Additionally, 20% progressed to a worse stage of kidney function at the end of pregnancy.

Antenatal strategy and decision-making

These women ideally will have had pre-pregnancy counselling to ensure optimal timing, that disease is quiescent, medications and blood pressure control optimized and that they understand the risks of pregnancy. Once pregnant, they must be seen as early as possible. Thereafter assessments should usually be performed at least every 4 weeks until 28 weeks' gestation and then every 1–2 weeks depending on the clinical circumstances [8,45].

1) Assessment of renal function by serum creatinine and by protein excretion (see Chapter 7) by a spot protein/creatinine ratio ideally on a first morning void.

Table 11.4 Pre-pregnancy kidney function (S_{cr}) in CKD patients with estimates for obstetric complications and outcome and renal functional loss.

					Loss of >25% renal function		
S_{cr} (μmol/U)	Fetal growth restriction (%)	Preterm delivery (%)	Pre-eclampsia (%)	Perinatal deaths (%)	Pregnancy (%)	Persists post partum (%)	End-stage failure in 1 year (%)
≤125	25	30	22	1	2	–	–
125–180	45	70	40	6	40	20	3
≥180	70	>90	60	12	70	55	35

Estimates are based on literature from 1985 to 2009, with all pregnancies attaining at least 24 weeks' gestation (Davison & Winfield, unpublished data). Modified and supplemented from Williams & Davison [8].

Note that from more recent analyses of women with severe CKD it is now apparent that an S_{cr} cut-off of 250 μmol/L is too high a level for 'moderate' renal impairment, a cut-off of 180 μmol/L now being recommended [1,13].

2) Careful blood pressure monitoring for early detection of hypertension (and assessment of its severity) and pre-eclampsia, with most women being offered low-dose aspirin in early pregnancy (before 12 weeks) to reduce the risk of pre-eclampsia.
3) Early detection and treatment of anaemia, usually by oral/intravenous iron therapy. Blood transfusion should be avoided as much as possible due to the risk of sensitizing a woman who may subsequently need a renal transplant. If anaemia is persistent and resistant to iron, recombinant human erythropoietin can be used but may exacerbate hypertension.
4) Early detection of covert bacteriuria or confirmation of urinary tract infection (UTI) and prompt treatment; if there are recurrent UTIs, then antibiotic prophylaxis should be given throughout pregnancy.
5) Many women with significant renal disease will have proteinuria; this may well increase due to cessation of renin–angiotensin blockers before or definitely during the first trimester. Proteinuria increases the risk of thrombosis and in the face of significant proteinuria (usually in the region of 2–3 g per 24 hours) and especially if serum albumin is low for pregnancy, women should be offered prophylactic low-molecular-weight heparin. Bear in mind that the dose should be reduced if S_{cr} is above 120 μmol/L or the patient weighs less than 50 kg.
6) Biophysical/ultrasound surveillance of fetal size, development and well-being.
7) The clinician must bear in mind the balance between maternal prognosis and fetal prognosis: the effect of pregnancy on a particular disease and the effect of that disease on pregnancy. The clinical watchpoints associated with specific renal diseases are summarized in Table 11.5.

Impact of underlying renal disease

Women with certain types of CKD face particularly increased risks with pregnancy, including those with lupus and especially those with prior lupus nephritis. In addition, women with scleroderma and classical periarteritis nodosa do poorly (particularly when there is marked renal involvement and associated hypertension and/or pulmonary hypertension) and thus should be counselled to avoid pregnancy. Furthermore, there is some disagreement about whether pregnancy adversely influences the natural history of IgA nephropathy, focal segmental glomerulosclerosis and reflux nephropathy. It seems likely that prognosis with these renal lesions is actually similar to that of women with mild impairment in general, provided pre-pregnancy function is preserved and high blood pressure absent (Table 11.5).

Reflux nephropathy often presents for the first time during pregnancy as women have recurrent UTIs and hypertension. Ultrasound may reveal scarred kidneys, hydronephrosis and function may or may not be normal. It is important to make the diagnosis not just to ensure optimal care of the woman during pregnancy but so that her baby will be appropriately screened in the first year of life – there is a strong genetic influence on the presence of reflux and early diagnosis may prevent renal scars [46].

Because SLE most commonly affects women of childbearing age and since about 60% of people with SLE will develop lupus nephritis, this is one of the commoner forms of renal disease seen in pregnant women. Recent data from a prospective cohort of 385 women with well-controlled SLE (with or without prior lupus nephritis, proteinuria <1 g/day, creatinine <106 μmol/L and taking less than 20 mg oral prednisolone at baseline) showed, in the absence of baseline hypertension or a lupus anticoagulant, that 81% of the women had successful pregnancies and flares were infrequent [47]. Moroni *et al.* [48] reported recently on 71 pregnancies in 61 Italian women all of whom had prior or active lupus nephritis and had undergone pre-pregnancy counselling. The majority (78.9%) were in complete remission and the rest had mild active lupus nephritis. Flares were seen in 19.7% of women and all responded to treatment. Pre-eclampsia was seen in 8.4% (a figure very consistent with the Mayo group systematic review published in 2010 [49]) and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) in 2.8%; both pre-eclampsia and HELLP were predicted by prior lupus nephritis, longer disease duration and baseline hypertension. Fetal loss occurred in 8.4%, preterm delivery in 28.2%, and 16.4% of babies were small for gestational age (SGA). Importantly, the use of the antimalarial hydroxychloroquine appeared to significantly reduce the probability of having an SGA baby [50]. In addition, it is known from other studies that hydroxychloroquine almost certainly reduces the risk of congenital heart block and neonatal lupus in babies born to mothers with anti-Ro antibodies. The following recommendations apply to all CKD patients.

Renal function

If renal function deteriorates significantly at any stage of pregnancy, then reversible causes, such as UTI, volume depletion or electrolyte imbalance (occasionally precipitated by inadvertent diuretic therapy), should be sought. Near term, as in normal pregnancy, a decrease in function of 15–20%, which affects S_{cr} minimally, is permissible. Failure to detect a reversible cause of a significant decrement may be an indication for early delivery. However, this will depend on the underlying renal disease, whether progression of renal impairment was expected and whether dialysis during pregnancy is an option. When proteinuria occurs and persists, but blood

Table 11.5 Chronic renal disease and pregnancy.

Renal disease	Clinical watchpoints
Chronic glomerulonephritis and focal segmental glomerular sclerosis (FSGS)	In the absence of hypertension and abnormal renal function, most of these women will have normal pregnancies though probably have a higher risk of late hypertension and pre-eclampsia. In the presence of hypertension and/or renal impairment, there may be accelerated loss of renal function possibly due to podocyte stress during pregnancy
IgA nephropathy	Some cite risks of sudden escalating or uncontrolled hypertension and renal deterioration. Most note good outcome when renal function is preserved
Chronic pyelonephritis (infectious tubulointerstitial disease)	Bacteriuria in pregnancy, recurrent urinary tract infections (often requiring prophylactic antibiotics) and frequent hypertension
Reflux nephropathy	Some have emphasized risks of sudden escalating hypertension and worsening of renal function. Consensus now is that results are satisfactory when pre-pregnancy function is only mildly affected and hypertension is absent. Vigilance for urinary tract infections is necessary
Urolithiasis	Ureteral dilatation and stasis do not seem to affect natural history, but infections can be more frequent. Stents have been successfully placed and sonograpically controlled ureterostomy has been performed during gestation
Polycystic kidney disease	Outcomes largely predicted by baseline function and hypertension. Women should be advised to have their pregnancies before they have lost function
Diabetic nephropathy	Proteinuria is likely to increase significantly during pregnancy and if nephropathy is advanced, salt and water retention may predominate. Most women with diabetes do not have overt nephropathy during their childbearing years; however, this is becoming more common as women have children later in life and the rates of type 2 diabetes in younger women increase. Increased frequency of infections, oedema or pre-eclampsia
Human immunodeficiency virus with associated nephropathy (HIVAN)	Renal component can be nephrotic syndrome or severe impairment. Need to ensure anti-retroviral treatment is optimised pre-pregnancy
Systemic lupus erythematosus	Prognosis is most favourable if disease is in remission 6 months before conception, the woman does not have lupus anticoagulant, and if non-white does not have hypertension at baseline. If the mother has anti-Ro antibodies she should be offered fetal echocardiography at 18/40 to look for early signs of congenital heart block
Systemic vasculitis (granulomatous or microscopic polyangiitis)	If in remission will have little impact on pregnancy. However, flares can occur and if severe may mandate early termination of pregnancy to allow adequate treatment of aggressive renal disease. Rare
Scleroderma	If onset during pregnancy, there can be rapid overall deterioration. Reactivation of quiescent scleroderma can occur during pregnancy and after delivery
Previous urologic surgery	Depending on original reason for surgery, there may be other malformations of the urogenital tract. Urinary tract infection is common during pregnancy and renal function may undergo reversible decrease. No significant obstructive problem, but caesarean section might be necessary for abnormal presentation or to avoid disruption of the continence mechanism if artificial sphincters or neourethras are present
After nephrectomy, solitary and pelvic kidneys	Pregnancy is well tolerated. Might be associated with other malformations of the urogenital tract. Dystocia rarely occurs with a pelvic kidney

pressure is normal and renal function preserved, pregnancy can be allowed to continue under closer scrutiny. With nephrotic-range proteinuria, prophylactic low-molecular-weight heparin is needed and should be continued for 6 weeks after delivery. The use of acute dialysis has been mentioned earlier.

Blood pressure

The conventional dividing line for obstetric hypertension has been 140/90 mmHg. Most of the specific risks of hypertension in pregnancy appear to be related to superimposed pre-eclampsia (see Chapter 7). There is confusion about the true incidence of superimposed pre-eclampsia in women with CKD. This is because the diagnosis cannot be made with certainty on clinical grounds alone: hypertension and proteinuria may be manifestations of the underlying CKD, and chronic hypertension alone has an increased pre-eclampsia risk fourfold that of normotensive pregnant women. Treatment of mild hypertension (diastolic blood pressure <95 mmHg in

the second trimester or <100 mmHg in the third) was not previously necessarily considered mandatory during normal pregnancy, but many would treat women with CKD more aggressively, believing that this preserves kidney function. The CHIPS study brought the obstetric community into closer alignment with the renal community by demonstrating fewer episodes of severe hypertension in the women assigned to the 'tight' control group (achieved blood pressure 133/85 mmHg). In non-pregnant women with renal disease, particularly those with proteinuric renal disease, the target blood pressure would be less than 130/80 mmHg so this would seem to be a reasonable target now in pregnant women [19].

Medications such as methyldopa, calcium channel blockers, labetalol and hydralazine are safe in pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers should not be prescribed and even if patients were taking either of these in early pregnancy (to continue the so-called renal protection from before pregnancy), they should not be continued or recommended beyond the early first trimester. We advise patients with minimal proteinuria to switch from ACE inhibitors or angiotensin receptor blockers before pregnancy. In those women with heavy proteinuria and progressive renal decline, the benefit of continued renal protection probably outweighs the low risk of early first trimester exposure. In those women we advise cessation as soon as pregnant in order to avoid months pre-pregnancy with no renal protection. Recent data suggest that the excess congenital abnormalities attributed to ACE inhibitors may in fact all be explained by hypertension rather than the medication [51]. ACE inhibitors and angiotensin receptor blockers are contraindicated (except in the rare instance of a woman having scleroderma) beyond the first trimester because of the risk of a fetopathy.

Fetal surveillance and timing of delivery

Serial evaluation of fetal well-being, with regular assessment of fetal growth, amniotic fluid and Doppler, is essential. In the absence of fetal or maternal deterioration delivery should be at or near term. If complications do arise, the judicious moment for intervention might be determined by fetal status (see Chapter 28). Regardless of gestational age, most babies weighing more than 1500 g survive better in a special care nursery than a hostile intrauterine environment. Planned preterm delivery may be necessary if there is impending intrauterine fetal death, if renal function deteriorates substantially, if uncontrollable hypertension supervenes, or if pre-eclampsia occurs. Obstetric considerations should be the main determinant for delivery by caesarean section.

Role of renal biopsy in pregnancy

Experience with renal biopsy in pregnancy is relatively sparse, mainly because clinical circumstances were considered to rarely justify the risks [5,9]. However, there are now case series reporting safety in selected cases in early pregnancy. Biopsy should be considered in the first trimester if there is a suspicion of rapidly progressive glomerulonephritis or a new presentation of nephrotic syndrome. In women with known renal disease (e.g. prior lupus nephritis or previous membranous glomerulonephritis), clinical judgement may well allow a biopsy not to be undertaken in pregnancy. However, 'blind' treatment with steroids or other immunosuppressants is not without risk and having a firm diagnosis is very helpful. Beyond 18–20 weeks most would not biopsy but use clinical status and blood tests to judge most likely diagnosis and treatment. In reality, biopsy during pregnancy remains a relatively infrequent event [52] but it is imperative that women presenting with new-onset proteinuria in early pregnancy are not lost to follow-up post partum as they may well need a biopsy in due course to ensure the correct diagnosis is made and appropriate therapy given. When renal biopsy is undertaken immediately after delivery in women with well-controlled blood pressure and normal coagulation indices, the morbidity is certainly similar to that reported in non-pregnant patients.

Long-term effects of pregnancy in women with renal disease

Readers are referred to earlier sections for advice regarding the impact of pregnancy on CKD. Whilst the recent TOCOS study suggests significant impact even of CKD stage 1 on renal outcomes, in the majority of women with normal eGFR, pregnancy does not cause deterioration or otherwise affect rate of progression of CKD beyond what might be expected in the non-pregnant state, provided pre-pregnancy kidney dysfunction was minimal and/or hypertension is absent or very well controlled before pregnancy [24,31,33,44]. An important factor in long-term prognosis could be the sclerotic effect that prolonged gestational renal vasodilatation might have in the residual (intact) glomeruli of the kidneys of these women. The situation may be worse in a single diseased kidney, where more sclerosis has usually occurred within the fewer (intact) glomeruli. Although the evidence in healthy women and those with mild renal disease argues against hyperfiltration-induced damage in pregnancy, there is little doubt that in some women with moderate, and certainly severe, dysfunction there can be unpredicted, accelerated and irreversible renal decline in pregnancy or immediately afterwards.

It is also now well recognized that both CKD and pre-eclampsia influence remote prognosis in both groups in terms of cardiovascular disorders and end-stage renal failure but there is debate about whether the superimposition of pre-eclampsia on CKD hastens progression to end-stage status [53–57]. It seems that pre-eclampsia is

not a risk factor ('marker' is a better term) for progression (see Chapter 7) but can lead to a stepwise decrease in renal function in those with underlying renal disease. The TOCOS study suggested strongly that, across all levels of baseline renal function, a proportion of women will develop worse renal function post partum.

Patients on dialysis

Dialysis and the prospects for pregnancy and afterwards

Despite reduced libido and relative infertility, women on long-term dialysis do conceive and must therefore use contraception if they wish to avoid pregnancy [14,21,58,59]. Although conception is not common (an incidence of 1 in 200 patients has been quoted), its true frequency is unknown because many pregnancies in dialysis patients probably end in early spontaneous abortion. The high therapeutic abortion rate in this group of patients (which has decreased from 40% in the 1990s to under 15% today) still suggests that those who become pregnant do so inadvertently, probably because they are unaware that pregnancy is possible. Recent data on improved fertility, likely due to normalization of the hypothalamic–pituitary–gonadal axis, as evidenced by the return of regular menstrual cycles [60] with increased dialysis, have persuaded some to consider increasing dialysis hours to assist conception in those women who wish to become pregnant and who have no prospect of a renal transplant in their fertile years.

Summary box 11.3

- Incidence of conception in chronic haemo dialysis patients of childbearing age is quoted as 1 in 200.
- Pregnancy poses big maternal risks but successful obstetric outcome is now 80%, leading to a reconsideration of counselling for these patients.
- Frequency of dialysis must be increased as soon as pregnancy is diagnosed and management of anaemia, nutritional issues and hypertension is very important.

Many authorities still do not advise patients on chronic dialysis to become pregnant or to continue a pregnancy if present. In the last two decades, however, fetal survival has significantly improved from 50% to almost 80%, with 90% attaining 36 weeks' gestation, which has led to a reconsideration of counselling for these patients [61,62,66]. Favourable prognoses for obstetric success include time on dialysis of less than 5 years, age under 35 years, residual urine production and absence of or well-controlled hypertension, as well as the early diagnosis of pregnancy thus facilitating increases in frequency and duration of dialysis. There are now clear data from the Toronto group and others that increasing dialysis hours and dose leads to significantly improved maternal and fetal outomes [61,62]. Pregnant women on dialysis should be offered increased hours of dialysis, aiming for at least 24 hours per week. All such pregnancies should be considered high risk, with increased potential for volume overload, threat of preterm labour, polyhydramnios (40–70%; directly related to adequacy of dialysis), major exacerbations of hypertension and/or superimposed pre-eclampsia (50–80%) and rarely, fortunately, placental abruption.

Antenatal strategy and decision-making

If women on dialysis become pregnant, they may present for care in advanced pregnancy because it was not suspected by either the patient or her doctors. Irregular menstruation is common and missed periods are usually ignored. Urine pregnancy tests are unreliable (even if there is any urine available). Thus ultrasound evaluation is needed to confirm and date pregnancy.

Dialysis policy

Some patients have gestational GFR increments despite renal function being insufficient to sustain life without dialysis [9,23,58,63–69]. The planning of dialysis strategy has several aims.

1) Maintain S_{urea} below 20 mmol/L (some would argue <15 mmol/L), as intrauterine fetal death is more likely if values are much in excess of 20 mmol/L. A lower S_{urea} is definitely associated with higher birthweight and gestational age at delivery. Total weekly dialysis should be 24 hours or more, ideally aiming for 30 hours or more, though this is often not feasible or achievable unless offering overnight dialysis. Use a dialysate with a higher potassium, lower calcium and lower bicarbonate. There is now good evidence that nocturnal dialysis (up to 36 hours per week) is associated with much better outcomes. Increased dialysis hours, however minimal, should make control of weight gain and dietary management easier. The potential disadvantage of more dialysis is electrolyte imbalance, hence the need to scrutinize serum chemistries at all times. Heparin can be used for anticoagulation.
2) Avoid hypotension and maternal volume depletion during dialysis, and a biocompatible small-surface-area dialysis to reduce ultrafiltration per treatment may be helpful in this regard. In late pregnancy the

enlarging uterus and supine posture may aggravate hypotensive episodes by decreasing venous return.
3) Ensure tight control of blood pressure throughout pregnancy, with the diastolic blood pressure ideally maintained at 80–90 mmHg.
4) Avoid rapid fluctuations in intravascular volume by limiting inter-dialysis weight gain to about 1 kg until late pregnancy.
5) Watch serum calcium closely to avoid hypercalcaemia and remember the potential for hypophosphataemia, hypokalaemia and depletion of water-soluble vitamins as well as the hazards of magnesium sulfate infusion, if required.
6) Scrutinize carefully for preterm labour, as dialysis and uterine contractions are associated.

Anaemia

Women with CKD, and particularly those on dialysis, are usually anaemic, invariably aggravated further in pregnancy. There is some evidence of a positive correlation between maternal haemoglobin and successful obstetric outcome; however, although haemoglobin of 100 g/L or more is advisable, the upper limit of an optimal haemoglobin level has yet to be determined. Where possible, blood transfusion should be avoided, since both pregnancy and blood transfusion can sensitize a woman, making future transplantation more difficult. If needed (especially before delivery), caution is necessary as it could exacerbate hypertension and impair the ability to control circulatory overload, even with extra dialysis. Fluctuations in blood volume can be minimized if packed red cells are transfused during dialysis. Recombinant human erythropoietin has been 'safely' used to treat anaemia during pregnancy in women with CKD and on dialysis, when requirements can be higher than in the non-pregnant state. The theoretical risks of hypertension and thrombotic complications have not been encountered, nor have adverse neonatal effects. Women should also be iron replete and intravenous iron can be used to maintain a serum ferritin around 200 mg/L.

Nutrition

Despite more frequent dialysis, uncontrolled dietary intake should be discouraged [21,59]. Daily oral intakes of 1.5 g/kg protein, 1.5 g calcium, 50 mmol potassium and 80 mmol sodium are advisable, with supplements of vitamin C, riboflavin, niacin, thiamine and vitamin B_6 as well as iron and folic acid supplements. Vitamin D supplements can be difficult to judge in patients who have had parathyroidectomy. Measurement of 25-hydroxyvitamin D levels should not be neglected, with supplementation if needed. In addition, oral phosphate supplements can be used if phosphate levels are low. Daily dialysis often leads to severe hypophosphataemia which may be associated with cervical shortening. Women can liberalize their low phosphate diet, stop their phosphate binders and may need intravenous phosphate during dialysis.

Fetal surveillance and timing of delivery

The same applies as with CKD. Preterm labour is common and it may even commence during dialysis. Caesarean section should be necessary only for obstetric reasons.

Peritoneal dialysis

Young women can be managed with this approach and successful pregnancies have now been reported [70]. Outcome is not dependent on mode of dialysis (haemodialysis vs. peritoneal) but there may be more infertility in women receiving continuous ambulatory peritoneal dialysis (PD).

With PD, although anticoagulation and some of the fluid balance and volume problems of haemodialysis are avoided, these women nevertheless face the same problems of hypertension, anaemia, term labour, sudden intrauterine death and placental abruption. During pregnancy the number of PD exchanges must be increased and the fill volumes of fluid may need reducing to less than 1.5 L, which might be best achieved by switching to automated PD. The size of the enlarging uterus in late pregnancy may make PD impossible and a temporary switch to haemodialysis may be necessary. It should be remembered that peritonitis can be a severe complication of chronic ambulatory PD, accounting for the majority of therapy failures but an increased incidence has not been reported in pregnancy. If caesarean section is needed, then theoretically it should be undertaken extraperitoneally with the traditional approach requiring a switch to haemodialysis.

Kidney transplant recipients

Transplantation and the prospects for pregnancy and afterwards

Renal, endocrine and sexual functions return rapidly after transplantation and assisted conception techniques are also available. About 1 in 50 women of childbearing age with a functioning transplant will become pregnant. Of the conceptions, about 25% do not go beyond the initial trimester because of spontaneous or therapeutic abortion, but of those pregnancies in well women that do, 97% end successfully [1,3,5,9]. In early gestation there may be increased risk of ectopic pregnancy, particularly for women with pancreas and kidney transplants, because of pelvic adhesions following surgery, PD,

intrauterine contraceptive device (IUCD) and/or pelvic inflammatory disease consequent to immunosuppression. Diagnosis of ectopic pregnancy may be delayed as irregular bleeding and pain may be wrongly attributed to deteriorating renal function and/or the presence of the pelvic allograft. A renal transplant has even been performed with surgeons unaware that the recipient was in early pregnancy. Obstetric success in such cases does not negate the importance of contraception counselling for all patients with renal failure and the exclusion of pregnancy prior to the surgery.

Summary box 11.4

- About 1 in 50 women of childbearing age with a functioning transplant becomes pregnant.
- Of those pregnancies that go beyond the first trimester, 97% have successful obstetric outcome.
- Serial assessment of renal function is essential along with early diagnosis and treatment of rejection (~2%), blood pressure control and treatment of infection.
- Some immunosuppressive drugs are contraindicated in pregnancy.
- There are no obstructive problems and/or mechanical injury to the transplant during vaginal delivery.

A woman should be counselled from the time the various treatments for renal failure and the potential for optimal rehabilitation are discussed [1,22]. As mentioned at the start of this chapter, couples who want a child should be encouraged to discuss all the implications, including the harsh realities of maternal survival prospects. Guidelines vary, with the European Best Practice Guidelines recommending a delay of 24 months before conception [71], whilst the American Society of Transplantation is less conservative and suggests that women should delay conception until at least 1 year after transplantation and only when they meet the following criteria: no rejection in the previous year; adequate and stable renal function (e.g. creatinine <1.5 mg/dL or 133 mmol/L); no or minimal proteinuria; no acute fetotoxic infections; and stable function with non-teratogenic immunosuppression [2]. Most centres recommend a wait of at least 1 year after transplantation. By then, the patient will have recovered from the surgery and any sequelae, graft function will have stabilized, and imunosuppression will be at maintenance levels. Also, if function is well maintained at 2 years, there is a high probability of allograft survival at 5 years (Table 11.6). As with CKD it is preferable if pre-pregnancy S_{cr} values are below 125 μmol/L, as above this level there can be more complications and problems (Table 11.7).

Antenatal strategy and decision-making

Management requires serial assessment of renal function, early diagnosis and treatment of rejection, blood

Table 11.6 Pre-pregnancy considerations in renal transplant recipients.

Good general health for about 1 year after transplantation
Stature compatible with good obstetric outcome
No or minimal proteinuria
No or well-controlled hypertension
No evidence of graft rejection
No pelvicalyceal distension on recent ultrasound or intravenous urography
Stable graft function: S_{cr} ≤160 μmol/L, preferably ≤125 μmol/L
Drug therapy at maintenance levels: prednisolone, azathioprine, cyclosporin and tacrolimus are 'safe'
Mycophenolate mofetil and sirolimus are contraindicated

Source: Newcastle upon Tyne 1976, revised 1987 and 2006. See Damjanov *et al.* [72] and Bramham *et al.* [73].

Table 11.7 Pre-pregnancy kidney function (S_{cr}) in kidney transplant recipients with estimates for obstetric complications and outcome and loss of graft function.

					Loss of >25% renal function		
S_{cr} (μmol/L)	Fetal growth restriction (%)	Preterm delivery (%)	Pre-eclampsia (%)	Perinatal deaths (%)	Pregnancy (%)	Persists post partum (%)	End-stage failure in 1 year (%)
≤125	30	35	24	3	15	4	–
125–160	50	70	45	7	20	7	10
≥160	60	90	60	12	45	35	70

Estimates based on literature review (1991–2007) from 1076 women in 1498 pregnancies, with all pregnancies attaining at least 24 weeks' gestation.
Source: Davison (unpublished data) and Bramham *et al.* [73].

pressure control, early diagnosis or prevention of anaemia, treatment of any infection, and meticulous assessment of fetal well-being (Table 11.8). As well as at least monthly renal assessments, including trough CNI levels, liver function tests, calcium and phosphate should be checked regularly throughout pregnancy. Haematinics are needed if the various haematological indices show deficiency.

Transplant function

The sustained increase in GFR characteristic of early normal pregnancy is evident in renal transplant recipients. Immediate graft function after transplantation and the better the pre-pregnancy GFR, the greater the increment in GFR in pregnancy. Transient 20–25% reductions in GFR can occur during the third trimester and do not usually represent a deteriorating situation with permanent impairment. However, significant renal functional impairment can develop in some patients during pregnancy, and this may persist following delivery, invariably being related to pre-pregnancy S_{cr} (Table 11.7). Because a gradual decline in function is common in non-pregnant patients, it is difficult to delineate the specific role of pregnancy. Most agree that pregnancy does not compromise long-term graft progression unless graft dysfunction was already present before pregnancy [22,74,75]. Proteinuria occurs near term in 40% of patients but disappears after delivery. Delineating late-onset proteinuria from pre-eclampsia remains a challenge but if hypertension is present, then it is usually safer to assume superimposed pre-eclampsia. In the future, angiogenic factor levels may assist in differentiating pre-eclampsia from other causes of proteinuria [76] though more recent reports have suggested it is lower e.g. [78]. Whether calcineurin inhibitors are more nephrotoxic in the pregnant compared with the non-pregnant patient is not known.

Transplant rejection

A systematic review and meta-analysis suggests that rejection during pregnancy is rare, with an overall pooled incidence of acute rejection in 2412 pregnancies being only 4.2% [77] though more recent reports have suggested it is lower e.g. [78]. This should be treated with high-dose steroids as the safety profile of antibody-mediated treatments is unknown and placental transfer is likely. Plasma exchange can also be considered.

Immunosuppressive therapy (Table 11.9)

It is important to note that this section is applicable to all women on immunosuppression for their kidney disease, not just renal transplant recipients.

Immunosuppressive therapy needs to be adjusted to ensure that teratogenic medications are ceased well before conception and that appropriate doses of others are used during pregnancy. A major issue for women with renal transplants and for women with lupus nephritis is that of mycophenolate mofetil (MMF). It is widely

Table 11.8 Management summary for a renal transplant patient (generalizable in most aspects for all women with CKD, particularly those on immunosuppression).

Before pregnancy
Patients should defer pregnancy for at least 1 year after transplant, with appropriate and reliable contraception
Assessment of graft function
Recent biopsy and/or organ-specific tests
Proteinuria
S_{cr}
Hepatitis B and C, cytomegalovirus, toxoplasmosis, and herpes simplex status
Maintenance immunosuppression: Azathioprine, Cyclosporine, Tacrolimus and Corticosteroids are all acceptable
Azathioprine
Cyclosporin
Tacrolimus
Corticosteroids
Mycophenolate mofetil and sirolimus contraindicated
Comorbidities (e.g. diabetes, hypertension) should be optimally managed
Vaccinations should be given if needed (e.g. hepatitis, tetanus, pneumococcus, human papillomavirus and influenza). No live vaccines can be given to any patient on immunosuppression.
Discuss the aetiology of the original disease and genetic issues, if appropriate
Discuss the effect of pregnancy on graft function
Discuss the risks of fetal growth restriction, preterm delivery and low birthweight
Antenatal
Early diagnosis and dating of pregnancy
Clincial and laboratory monitoring of the graft and immunosuppressive drug levels every 2–4 weeks until 32 weeks, then every 1–2 weeks until delivery
Surveillance for rejection, with transplant biopsy considered if it is suspected
Surveillance for bacterial or viral infection (e.g. cytomegalovirus, toxoplasmosis, hepatitis in first trimester and repeat if signs of rejection or tenderness over graft site)
Monthly urine cultures
Fetal surveillance from 24–28 weeks onwards (e.g. non-stress test, sonographic evaluation)
Monitoring of hypertension and management
Surveillance for pre-eclampsia
Screening for gestational diabetes: steroids and calcineurin inhibitors are diabetogenic which combine with the insulin-resistant state of pregnancy to increase the risk of GDM significantly. Offer GTT at 28 weeks
Delivery
Caesarean delivery for obstetric reasons
For kidney recipients: episiotomy on side opposite to graft; caesarean section may not be easy
Should discuss operative approach with transplant surgeon in advance and ideally he or she would be present at time of delivery to ensure kidney and/or pancreas transplant protected
Post partum
Monitor immunosuppressive drug levels for 3–4 weeks after delivery, with adjustment as needed
Breastfeeding is appropriate (unless mycophenolate mofetil restarted); monitor fetal drug levels if there are concerns e.g., in very pre-term infants
Contraception counselling is essential

GDM, gestational diabetes mellitus; GTT, glucose tolerance test.
Source: modified and supplemented from Armenti *et al.* [74].

Table 11.9 Pregnancy safety information for immunosuppressive drugs used in transplantation and other renal diseases.

	Animal reproductive data	Pregnancy category
Corticosteroids (prednisolone, methylprednisolone, others)	Yes	B
Azathioprine (Imuran)	Yes	D*
Cyclosporin (Sandimmun, Neoral, others)	Yes	C
Tacrolimus (FK506, Prograf, Adoport)	Yes	C
Antithymocyte globulin (Atgam, ATG)	No	C
Antithymocyte globulin (Thymoglobulin)	No	C
Muromonab-CD3 (Orthoclone OKT3)	No	C
Mycophenolate mofetil (CellCept)	Yes	D
Mycophenolic acid (Myfortic)	Yes	D
Basiliximab (Simulect)	Yes	B
Daclizumab (Zenapax)	No	C
Sirolimus (Rapamune)	Yes	C

*Azathioprine has known impact on fetal lymphocytes and possibly thymus development. However, azathioprine is widely used in pregnancy and is generally considered safe.
B, no fetal risk, no controlled studies; C, fetal risk cannot be ruled out; D, evidence of fetal risk.
Source: US Food and Drug Administration classification. Modified from Webster *et al.* [22], Armenti *et al.* [82,83] and Coscia *et al.* [84].

used in both settings but is undoubtedly teratogenic. The existence of an MMF-associated embryopathy has been proposed with consistent key features: cleft lip and palate, microtia with atresia of the external auditory canal, micrognathia and hypertelorum [79–81]. Ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations and diaphragmatic hernia could also be a part of the phenotypic spectrum, which is supported by experimental animal studies. To date, in the babies, psychomotor development and growth have been reported as normal. MMF is now classed as teratogenic by the FDA and there has been recent guidance on MMF use before pregnancy and in pregnancy prevention from the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-mycophenolic-acid-new-pregnancy-prevention-advice-for-women-and-men). Specifically, MMF should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Women should not have been using MMF for at least 6 weeks prior to pregnancy. Much less evidence-based is the parallel recommendation that men who are planning a pregnancy with their partner should stop MMF 90 days prior to attempting conception. All women on MMF, whether for transplant or lupus, should be advised when starting the medication about the risks of pregnancy and to use secure contraception. Women should be tested to ensure they are not pregnant before starting MMF and should be counselled as to the safety of switching (usually to azathioprine) in advance of conception.

There are many encouraging registry and single-centre reports of (non-complicated) pregnancies in patients taking cyclosporin and tacrolimus. Numerous adverse effects are attributed to calcineurin inhibitors in non-pregnant transplant recipients, including renal toxicity, hepatic dysfunction, chronic hypertension, tremor, convulsions, diabetogenic effects, haemolytic uraemic syndrome, and neoplasia. In pregnancy, some of the maternal adaptations that normally occur may theoretically be blunted or abolished by cyclosporin especially plasma volume expansion and renal haemodynamic augmentation. There was good evidence suggesting that patients had more hypertension and smaller babies [81,82], but it is possible that the women who originally used calcineurin inhibitors had worse kidney function and that may have been a confounding factor. In the current era, lower doses are used. A very practical problem is that of dosing of tacrolimus, a calcineurin inhibitor. Tacrolimus dosing is adjusted according to serum tacrolimus levels. Since tacrolimus metabolism increases in pregnancy, levels fall and doses may need to be increased by as much as 50% (and rapidly reduced post partum). However, there is some controversy as 'free' tacrolimus levels are not measured in standard assays and may be unchanged, exposing the woman to the risk of tacrolimus toxicity. This should be considered in the face of an otherwise inexplicable rise in creatinine in a pregnant woman with a transplant.

Hypertension and pre-eclampsia

Hypertension, particularly before 28 weeks' gestation, is associated with adverse perinatal outcome. This may be due to covert cardiovascular changes that accompany, and/or are aggravated by, chronic hypertension. The appearance of hypertension in the third trimester, its relationship to deteriorating renal function, and the possibility of chronic underlying pathology and pre-eclampsia poses a diagnostic problem. Pre-eclampsia is actually diagnosed clinically in about 20–30% of pregnancies in women with renal transplants [74].

Infections

Throughout pregnancy patients should be monitored carefully for bacterial and viral infection. Prophylactic antibiotics must be given before any surgical procedure, however trivial. Asymptomatic bacteriuria is common, should be treated and, if recurrent, merits prophylactic antibiotics during pregnancy.

Diabetes mellitus

In general, women are having their children at an older age, which makes it more likely that patients with type 1 diabetes mellitus have reached end-stage renal failure and hence have had a transplant before conceiving. Pregnancy complications occur with at least twice the frequency seen in the non-diabetic patient, and this may be due to the presence of generalized cardiovascular pathology, which is part of the metabolic risk factor syndrome. Successful pregnancies have been reported after combined pancreas–kidney allografts [86].

Fetal surveillance and timing of delivery

The points discussed under CKD are equally applicable to renal transplant recipients. Preterm delivery is common (45–60%) because of intervention for obstetric reasons and the common occurrence of preterm labour or preterm rupture of membranes. Preterm labour is commonly associated with poor renal function, but in some it has been postulated that long-term immunosuppression may 'weaken' connective tissues and contribute to the increased incidence of preterm rupture of membranes.

Vaginal delivery should be the aim; usually there are no obstructive problems and/or mechanical injury to the transplant [86]. Unless there are problems, spontaneous onset of labour can be awaited but most advise not exceeding 38–39 weeks' gestation. During labour careful monitoring of fluid balance, cardiovascular status and temperature is mandatory. Aseptic technique is essential for every procedure. Surgical induction of labour (by amniotomy) and episiotomy warrant antibiotic cover. Pain relief can be conducted as for healthy women. Augmentation of steroids should not be overlooked. If required, episiotomy should be performed on the opposite side to the transplant. Caesarean section should be undertaken for obstetric reasons only and may not be easy. The operative approach should be discussed with a transplant surgeon in advance and ideally he or she would be present at delivery to ensure that the kidney and/or pancreas transplant is protected.

Post-delivery management issues

Paediatric management

Over 50% of liveborns have no neonatal problems. Preterm delivery is common (45–60%), as is fetal growth restriction (20–30%), and occasionally the two problems coexist. Lower birthweights are seen in infants born to mothers who received their transplant less than 2 years previously and the use of calcineurin inhibitors can be associated with lower birth weights [84].

Breastfeeding

There are substantial benefits to breastfeeding. It could be argued that because the baby has been exposed to immunosuppressive agents and their metabolites in pregnancy, breastfeeding should not be allowed. For cyclosporin levels in breast milk are usually greater than those in a simultaneously taken blood sample. However, we have shown that breastfeeding – certainly of term infants – by mothers taking tacrolimus is safe and very little 'seen' by the baby; similarly with azathioprine. There is a view that mothers who want to breastfeed should be encouraged, so long as the baby is thriving [87,88] and monitoring fetal drug levels could be undertaken if there are concerns. If MMF is needed by the mother in the pueperium, the current advice is not to breastfeed.

Long-term assessment

There are theoretical worries about *in utero* exposure to immunosuppressive agents, with eventual development of malignant tumours in affected offspring, autoimmune complications and/or abnormalities in reproductive performance in the next generation. Thus paediatric follow-up is needed (Table 11.10). To date, information about general progress in early childhood has been good.

Table 11.10 Neonatal problems in the newborn of kidney allograft recipients.

Preterm delivery and/or small for gestational age
Respiratory distress syndrome
Adrenocortical insufficiency
Septicaemia
Cytomegalovirus infection
Depressed haematopoiesis
Lymphoid and thymic hypoplasia
Reduced T lymphocyte and immunoglobulin levels
Chromosome aberrations in leucocytes

Maternal follow-up after pregnancy for women with transplants or CKD

The ultimate measure of transplant success is the long-term survival of the patient and the graft. As it is only 40 years since this procedure became widely employed in the management of end-stage renal failure, few long-term data from sufficiently large series exist from which to draw conclusions. Furthermore, the long-term results for renal transplantation relate to a period when many aspects of management would be unacceptable by present-day standards. Average survival figures of large numbers of patients worldwide indicate that about 95% of recipients of kidneys from related living donors are alive 5 years after transplantation. With cadaver kidneys, the figure is approximately 89%. If renal function is normal 2 years after transplant, graft survival increases further. This is why women are counselled to wait about 2 years before considering a pregnancy even though a view is now emerging that 1 year would be sufficient.

A major concern is that the mother may not survive or remain well enough to rear the child she bears. Pregnancy occasionally and sometimes unpredictably causes irreversible declines in renal function. However, the consensus is that pregnancy, whilst often complicated, has little effect on long-term graft function or survival providing function is good at baseline, it is a first transplant and hypertension is not a major issue [72,87,89]. Similarly, repeated pregnancies do not adversely affect graft function or fetal development, provided that pre-pregnancy renal function is well preserved and hypertension minimal and/or well controlled.

Contraception

Oral contraception can cause or aggravate hypertension, thromboembolism and/or subtle changes to the immune system. This does not necessarily contraindicate its use but careful surveillance is essential. Generally, oestrogen containing contraceptives are not used due to the increased risk of thrombosis. However, progesterone only methods – the mini-pill, an implant or progesterone IUCD are all highly effective and safe alternatives. IUCDs may aggravate menstrual problems, which in turn may obscure symptoms and signs of early pregnancy abnormalities, such as threatened miscarriage or ectopic pregnancy. Current data suggest that immunosuppressed women have no increased risk of pelvic inflammatory disease compared to the general population of non IUCD users [78].

Gynaecological problems

There is a danger that symptoms secondary to genuine pelvic pathology may be erroneously attributed to the transplant because of its location near the pelvis [5]. Transplant recipients receiving immunosuppressive therapy have a malignancy rate estimated to be 100 times greater than normal and the female genital tract is no exception. This association is probably related to factors such as loss of immune surveillance, chronic immunosuppression allowing tumour proliferation (especially if virally driven) and/or prolonged antigenic stimulation of the reticuloendothelial system. Regular gynaecological assessment is therefore essential and any gynaecological management should be on conventional lines, with the outcome unlikely to be influenced by stopping or reducing immunosuppression, unless the pathology is thought to be virally driven.

Kidney donors

It has always been considered that living kidney donors are low risk for almost all medical conditions. However, recent data suggest that gestational hypertension and pre-eclampsia are about twice as common in those who have donated a kidney than in those who have not. Whilst these data need to be extended, it is worth considering whether possible donors have completed their family before allowing them to donate a kidney [90].

Summary

Women with kidney disease used to be discouraged from becoming pregnant. It is now clear that with adequate pre-pregnancy planning, the vast majority can have safe pregnancies with good outcomes for the mother and baby. Ideally, pregnancy should be planned for a time of normal or stable renal function, minimal proteinuria and well-controlled blood pressure on safe drugs. Women should be followed up post partum to ensure stability of renal disease, make the renal diagnosis if they have presented for the first time during pregnancy, and to ensure an appropriate long-term care plan is in place.

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12

Haematological Problems in Pregnancy

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Pregnancy is associated with physiological adaptation of the haematological system. An understanding of these changes is essential for distinguishing the normal from the pathological state. There is an increased likelihood of certain haematological complications, with thromboembolism and haemorrhage being leading causes of direct maternal deaths. This chapter covers the normal physiological changes, haematological complications of pregnancy and common haematological diseases which may impact on or be influenced by pregnancy.

Physiological changes to the blood in pregnancy

To accommodate the developing uteroplacental circulation, plasma volume increases by approximately 1250 mL (45%) and red cell mass by approximately 250 mL (10–20%) by the end of pregnancy. This produces a total blood volume increase of around 1500 mL but fall in haemoglobin concentration, as plasma volume is increased disproportionately to red cell mass (Table 12.1). Consequently, red cell count and haematocrit are lower in pregnancy. Other red cell indices remain largely stable except mean cell volume (MCV) which increases by about 4–6 fL, secondary to greater numbers of larger young red cells from the increase in red cell mass.

Expansion of red cell mass requires 450–600 mg of iron and approximately 300 mg is transferred to the fetus and placenta, mainly in the last 4 weeks. Coupled with 0.8 mg daily basal loss (240 mg over duration of pregnancy) and 250 mg average loss at delivery, this suggests that most women require 1250 mg of iron during pregnancy. Serum folate levels fall by around half, due to a twofold increase in folate requirements but red cell folate levels are relatively spared. Functional vitamin B_{12} levels change very little and it is extremely unusual for a woman to have genuine B_{12} deficiency in pregnancy, even though serum levels often appear low.

Typically, pregnancy causes a neutrophilia and therefore leucocytosis. There is usually an increase in circulating immature neutrophils (left shift) and evidence of toxic granulation. Levels may be markedly elevated after delivery but usually return to normal by 4 weeks post partum. Lymphocyte counts are often reduced, particularly in the first and second trimesters, and monocyte counts may be elevated, especially in the first trimester.

A reduction in platelet count, mainly secondary to hyperdestruction and shortened lifespan, is common and around 10% of pregnancies have a platelet count below 150×10^9/L in the third trimester. It is usually mild, with 80% of counts remaining above 115×10^9/L, and does not seem to have an adverse effect on platelet function, possibly due to increased fibrinogen levels in pregnancy.

Von Willebrand factor (vWF) and factors VII, VIII and X increase markedly with gestation and remain elevated in the early postpartum period. Factor IX remains unchanged. The natural anticoagulant protein S decreases with no change in protein C levels. This creates a prothrombotic state and activated partial thromboplastin time (APTT) is often shortened in pregnancy.

Summary box 12.1

Haematological changes in normal pregnancy

- Fall in haemoglobin concentration.
- Leucocytosis (mainly neutrophilia).
- Mild thrombocytopenia with no impairment of platelet function.
- Prothrombotic state predominantly due to increases in FVIII, vWF, fibrinogen and reduction in protein S.
- Significant requirements for iron and folate.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 12.1 Changes in blood composition with gestation.

		Gestation (weeks)		
	Non-pregnant	20	30	40
Plasma volume (mL)	2600	3150	3750	3850
Red cell mass (mL)	1400	1450	1550	1650
Total blood volume (mL)	4000	4600	5300	5500
Haematocrit	35	32	30	30

Anaemia in pregnancy

Anaemia is defined as a haemoglobin (Hb) two standard deviations below the mean for a healthy age-matched population. However, consensus on what is normal in pregnancy is lacking. The British Society of Haematology (BSH) and the US Centers for Disease Control and Prevention (CDC) use a value of less than 110 g/L in the first trimester but less than 105 g/L in the second and third trimesters as this takes into account the marked expansion in plasma volume at this stage. Postpartum anaemia is defined as Hb less than 100 g/L and African populations in general have lower Hb levels than Caucasians.

Iron deficiency anaemia

Iron requirements for pregnancy, the fetus and delivery are substantial, with the average woman requiring at least 1250 mg. Western diets typically provide 15 mg/day, of which 10% is absorbed. During pregnancy, absorption increases to around 30% by 30 weeks but this is often insufficient to meet demand. Furthermore, many women start pregnancy already iron depleted, due to poor diet, increased need, menstruation and previous pregnancies within 2 years.

Iron deficiency leads to anaemia and decreased tissue oxygen transport and affects iron-dependent enzymes in every cell. Iron deficiency anaemia is a significant problem worldwide, affecting 50% of pregnant women (56% in developing and 18% in developed countries).

The early stages of iron deficiency are often asymptomatic or show non-specific symptoms. These include fatigue, poor concentration and irritability. As the anaemia develops tiredness is common but patients also complain of headaches, palpitations, dizziness and shortness of breath. Signs, if any, are pallor of mucous membranes and a hyperdynamic circulation. Specific signs, such as angular cheilitis, glossitis and koilonychia, can occur in severe cases.

Iron deficiency may affect maternal morbidity. Cellular immunity and phagocytosis is impaired, rendering women more susceptible to infection, and its effect on iron-dependent enzymes of the nervous system may lead to poor work performance and emotional instability, especially in the postpartum period. There may also be a link between iron deficiency, low birthweight and preterm delivery but this is, as yet, unproven.

The fetus is relatively spared, as preferential delivery of iron is facilitated by upregulation of placental transferrin. However, infants born to iron-deficient mothers are more likely to develop iron deficiency in the first 3 months of life.

Diagnosis

Initially, as iron stores are depleted, serum ferritin levels fall. A low serum ferritin is diagnostic of iron deficiency but as it is an acute-phase reactant, it can be elevated in active inflammation or infection despite iron deficiency. Levels of transferrin, the iron transporter protein, increase as it attempts to deliver more iron to tissues. Anaemia develops as iron for erythropoiesis is reduced. MCV is an unreliable measure in pregnancy due to the physiological increase. Serum iron and total iron binding capacity (TIBC) are also unhelpful as they are affected by factors such as recent iron ingestion and infection.

The British Committee for Standards in Haematology (BCSH) [1] suggest the following.

- A trial of oral iron should be the first 'diagnostic test' for women with a normocytic or microcytic anaemia, with a check for Hb increase at 2 weeks.
  - Exceptions are women with known haemoglobinopathy, who should have a serum ferritin before starting iron, to confirm the diagnosis and exclude an iron loading state.
  - Anaemic women whose haemoglobinopathy status is unknown should commence a trial of iron therapy and simultaneous haemoglobinopathy screening.
- A serum ferritin level below 15 μg/L is diagnostic of established iron deficiency and a level below 30 μg/L should also prompt treatment.
- In those women at high risk of iron deficiency but who are not yet anaemic, ferritin levels should be checked and oral iron started in those with ferritin below 30 μg/L.

Treatment

The principles of treating iron deficiency are as follows:

1) establish cause;
2) correct deficiency;
3) replenish iron stores.

The recommended daily iron intake for pregnant women is 30 mg and all women should receive dietary advice on iron-rich foods and factors that aid or inhibit absorption (Table 12.2).

Table 12.2 Factors affecting iron absorption.

Factors increasing iron absorption
Haem iron (red meats, fish and poultry)
Acids, e.g vitamin C
Ferrous form (Fe^{2+})
Factors reducing iron absorption
Tannins in tea and coffee
Foods rich in calcium
Antacids

Table 12.3 Elemental iron content in oral iron preparations.

Iron preparation	Tablet size (mg)	Elemental iron per tablet (mg)
Ferrous sulfate	200	65
Ferrous fumarate	200	65
Ferrous gluconate	300	35

Iron deficiency in pregnancy cannot be corrected through diet alone so iron supplementation is necessary. Oral, intramuscular and intravenous preparations are available. For most women oral replacement is the best option because it is effective, safe and inexpensive and can be started in primary care. The optimal dose has not yet been established but the current recommendation in the UK is 100–200 mg elemental iron daily with Hb level checked in 2 weeks. Hb should rise by around 20 g/L every 3–4 weeks and treatment should continue for at least 3 months after Hb has normalized and until at least 6 weeks post partum. Non-anaemic women with low serum ferritin (<30 μg/L) should be started on 65 mg of elemental iron daily with a repeat Hb and ferritin in 8 weeks.

Postpartum women with Hb below 100 g/L who are haemodynamically stable with minimal symptoms should be offered 100–200 mg elemental iron daily for 3 months to replenish iron stores.

There are several different iron preparations available and choice should be based on dose of elemental iron and side-effect profile (Table 12.3). Around 10–20% of patients experience gastrointestinal side effects, which are mostly dose related.

To maximize absorption, patients should take tablets with orange juice on an empty stomach, avoid tea and coffee for an hour either side of the tablet and not take with other medications, especially antacids. However, if side effects do occur and lowering the dose does not help, it may be appropriate to take tablets with meals despite the reduction in absorption.

Intravenous iron is reserved for patients who fail to respond to oral iron or who are truly intolerant. Intravenous iron preparations have no licence for use in the first trimester due to concerns that oxidative free radicals could cause toxicity to placental membranes. They are relatively contraindicated in patients with chronic liver disease or active infection. The risk of anaphylaxis is exceedingly rare but other non-allergic reactions occur in around 1 in 200 000.

The older intravenous preparations do not raise Hb levels quicker than correctly taken oral iron. However, newer preparations such as iron carboxymaltose, which is given as a single dose over 15 min, produces a faster response (approximately 10 g/L improvement per week) so may be particularly beneficial for those women who present late in pregnancy.

Intramuscular iron is rarely used as it is painful, has variable absorption and can cause permanent skin staining if not given correctly.

With optimum care most women will no longer be anaemic at the point of delivery. However, women whose Hb is less than 100 g/L should deliver in hospital (<95 g/L in an obstetrician-led unit), have intravenous access, a group and save available, and active management of the third stage of labour to minimize bleeding.

Megaloblastic anaemia

Worldwide, megaloblastic anaemia during pregnancy secondary to folate deficiency is common due to poor diet and increased folate requirements. In the UK prevalence is less than 5% as many women take folate supplements to prevent neural tube defects. However, women with haemolytic disorders, malabsorption syndromes, myeloproliferative disorders and those on anticonvulsants are at high risk and should receive folate supplements.

Folate deficiency is suggested by an elevated MCV, although the physiological increase in MCV and possible coexisting iron deficiency make this an unreliable parameter for diagnosis. The blood film may show hypersegmented neutrophils and oval macrocytes, and if iron deficiency coexists a dimorphic picture (two populations of red cells). Red cell folate levels are usually reduced and unaffected by recent folate intake but sensitivity and specificity during pregnancy are poor. The gold standard is a bone marrow biopsy demonstrating megaloblastic erythropoiesis but a trial of folate supplementation with assessment of Hb response is more practical.

Patients at increased risk of folate deficiency should take 5 mg of folate daily as prophylaxis during pregnancy. Those with established folate deficiency should take 5 mg three times daily and all patients should be given dietary advice.

Vitamin B_{12} deficiency in pregnancy is extremely rare as body stores last for several years. The commonest

cause of B_{12} deficiency in the UK is pernicious anaemia, which typically affects older people. Furthermore, B_{12} deficiency is usually associated with infertility.

Summary box 12.2

- Iron deficiency in pregnancy is common.
- In established anaemia, in the absence of a known haemoglobinopathy, start oral iron supplements as both a diagnostic test and treatment.
- Oral iron is best for the majority of women and should be taken on an empty stomach, to optimise absorption.

Thrombocytopenia in pregnancy

A platelet count below 100×10^9/L occurs in less than 1% of pregnancies. Causes can be specific to or concurrent with pregnancy and can result in either isolated thrombocytopenia or thrombocytopenia in association with a systemic disorder. The majority of cases are secondary to the benign condition gestational thrombocytopenia (Fig. 12.1). However, causes may be life-threatening and thrombocytopenia has implications for mode of delivery and the bleeding risk of mother and neonate. EDTA in full blood count tubes can induce platelet clumping leading to pseudo-thrombocytopenia. Therefore, thrombocytopenia should always be confirmed with a repeat full blood count (FBC) and blood film and a citrate platelet count performed if clumping is present.

Gestational thrombocytopenia

Gestational thrombocytopenia is a benign condition. Its pathogenesis is unclear but likely reflects platelet consumption within the placental circulation, haemodilution and hormonal inhibition of megakaryocytopoiesis. It usually causes a mild thrombocytopenia in the third trimester with no symptoms of bruising or bleeding and no history of thrombocytopenia outside pregnancy. It has no pathological significance for mother or fetus. There is no diagnostic test except the platelet count normalizes within 6 weeks post partum. It is therefore a diagnosis of exclusion and may cause diagnostic difficulty with autoimmune thrombocytopenia, especially if there are no pre-pregnancy counts. It is extremely unusual for gestational thrombocytopenia to produce platelet counts below 70×10^9/L so levels below this should prompt consideration of alternative diagnoses.

Autoimmune thrombocytopenia

Immune thrombocytopenic purpura (ITP) is an autoimmune condition in which autoantibodies are directed against platelet surface glycoproteins (GPIIb/IIIa and/or GP1b/IX). This leads to premature clearance of platelets via Fc receptors in the reticuloendothelial system (mainly spleen). It is often chronic and presents a particular problem in pregnancy as the antibodies can cross the placenta rendering the fetus thrombocytopenic. It affects up to 5 in 10 000 pregnancies, two-thirds of these being women who have a previous diagnosis of ITP and one-third who have their diagnosis made during pregnancy. It is the most common cause of thrombocytopenia in the first trimester.

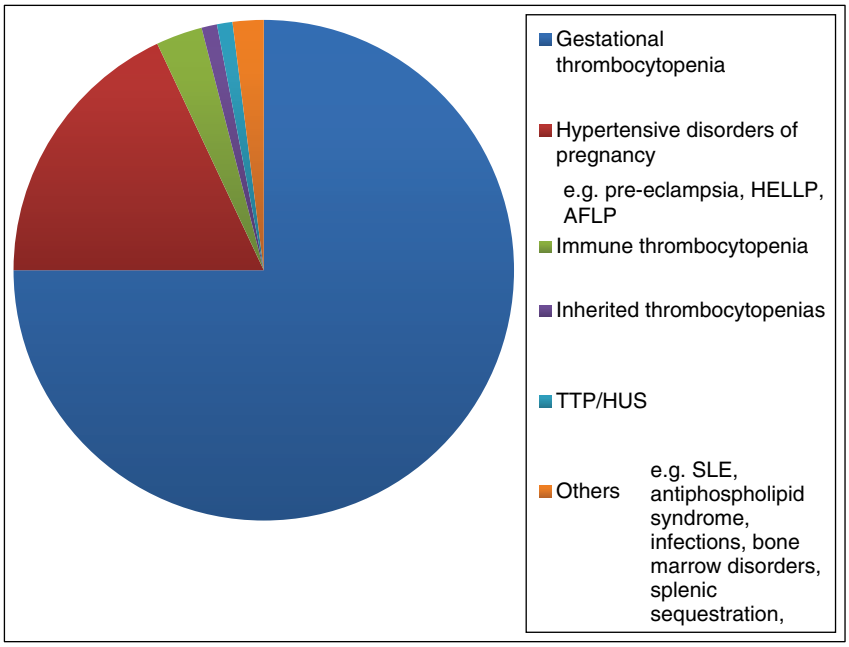

Fig. 12.1 Causes of thrombocytopenia in pregnancy. AFLP, acute fatty liver of pregnancy; HELLP, haemolysis, elevated liver enzymes, low platelet count; HUS, haemolytic uraemic syndrome; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

Table 12.4 Suggested platelet counts for immune thrombocytopenic purpura in pregnancy.

First and second trimesters of pregnancy: $>20 \times 10^9$/L
Vaginal delivery: $>40 \times 10^9$/L
Operative/instrumental delivery: $>50 \times 10^9$/L
Epidural: $>80 \times 10^9$/L

Platelet counts in ITP are usually less than 70×10^9/L and it is a diagnosis of exclusion. For women with a pre-pregnancy diagnosis of ITP, the accuracy of the diagnosis should be checked, response to treatments documented as well as the course and outcome of previous pregnancies, including neonatal platelet counts.

The aim of ITP treatment in pregnancy is to maintain the platelet count at a level that avoids haemorrhagic problems for the mother during pregnancy and allows a safe delivery. Suggested platelet counts are detailed in Table 12.4.

This approach minimizes maternal and fetal exposure to therapeutic agents. Women do not usually require treatment before 36 weeks, providing they are asymptomatic and platelet levels are above 20×10^9/L. For those that need treatment, the first line is usually oral corticosteroids, starting with prednisolone 20 mg daily and titrated to response, and/or intravenous immunoglobulin if a more immediate response is required. If a woman with ITP goes into labour with an uncorrected platelet count, intravenous immunoglobulin 1 g/kg should be given immediately and platelet transfusion if birth is imminent or haemorrhage occurs.

Mode of delivery should be led by obstetric indications. Rarely, transplacental transfer of maternal autoantibody can cause thrombocytopenia in the baby, increasing risk of intracranial haemorrhage at delivery. To minimize this risk, fetal scalp monitoring and blood sampling, ventouse and high/mid-cavity forceps should be avoided. Active management of the third stage of labour reduces bleeding risk in the mother and non-steroidal anti-inflammatory drugs should be avoided.

Because there is no correlation between maternal and fetal platelet counts, predicting which babies will have thrombocytopenia is difficult, unless the previous sibling was affected. Therefore all neonates born to mothers with ITP should have a cord blood count. If normal there is no need to repeat, but if abnormal a count should be repeated at 3–5 days of age, when the neonatal spleen has developed.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition characterized by thrombocytopenia and a microangiopathic haemolytic anaemia. Renal dysfunction, fever and neurological abnormalities also occur. Although rare, it is precipitated by pregnancy in 5–25% of cases. It can cause diagnostic confusion with other thrombotic microangiopathies such as HELLP (haemolysis, elevated liver enzymes, low platelets), pre-eclampsia and disseminated intravascular coagulation. Prompt plasma exchange can be life-saving.

Summary box 12.3

- Mild to moderate thrombocytopenia is common in pregnancy.
- A platelet count below 100×10^9/L should be investigated.
- Gestational thrombocytopenia is the commonest cause.
- ITP poses a risk to both mother and fetus and should have multidisciplinary management.

Sickle cell disorders

The sickle cell disorders (SCDs) are a group of conditions in which the sickle β gene is inherited with another abnormal haemoglobin. Sickle cell anaemia (HbSS) is the commonest and most severe, but the SCDs also includes HbSβthal and HbSC disease amongst others. HbS polymerizes at low oxygen tensions, which causes the red cells to sickle. Cells are inflexible in small blood vessels, contributing to vaso-occlusion and have a shorter lifespan, leading to a chronic haemolytic anaemia. The clinical phenotype is varied, with some patients experiencing an almost 'normal' life and others suffering frequent crises. These crises may be haemolytic, vaso-occlusive, visceral or aplastic and many patients develop chronic organ damage.

Pregnancies are high risk for both mother and fetus. Crisis frequency may increase, anaemia usually worsens, infections, especially urinary, are common (secondary to hyposplenism and a more complex immune defect), and pre-eclampsia occurs in around one-third of patients. There is also an increased thrombotic risk with both pregnancy and SCD. Patients have an increased risk of miscarriage, premature delivery and intrauterine growth restriction. Therefore, patients should be managed within a multidisciplinary team including midwives, haematologists, anaesthetists and obstetricians.

Ideally, pregnancy should be planned to allow women's health to be optimized. Patients should undergo pre-conception screening to assess end-organ damage, their vaccination status should be up to date and any medications that are potentially teratogenic should be stopped. These include hydroxycarbamide (used to control frequent crises), angiotensin-converting enzyme (ACE) inhibitors and iron chelators. Unless contraindicated,

women should continue penicillin V for infection prophylaxis and take folic acid 5 mg daily.

Antenatal care should particularly focus on continued education to avoid crisis triggers, such as dehydration from vomiting. Blood tests and monitoring for asymptomatic urinary infections, pregnancy-induced hypertension and pre-eclampsia should be carried out monthly, along with ultrasound scans to assess fetal growth and liquor volume [2]. Blood transfusions are not required routinely but regular transfusion programmes may be helpful in women with poor medical or obstetric histories in order to suppress HbS production. Examples include women previously on hydroxycarbamide, those with history of stroke or chest crisis and those with previous fetal loss or prematurity. Exchange transfusion may be preferred in these cases, depending on Hb. Acute chest crisis, pre-eclampsia or other emergencies may benefit from exchange Hb to allow more aggressive reduction in HbS levels. All patients should have an extended red cell phenotype; many will have red cell alloantibodies making it difficult to provide blood quickly and the fetus may be at risk of haemolytic disease of the newborn.

Severe crises in pregnancy are most frequent in the third trimester and may precipitate labour. The principles of treatment are the same as for a non-pregnant patient and include keeping the woman warmth, well hydrated and oxygenated, with adequate analgesia and screening for and treatment of any infection. Indications for transfusion should be discussed with a haematologist and the possibility of chest crisis should always be considered and treated as a priority. Patients are at risk of thrombosis so unless otherwise contraindicated should be on low-molecular-weight heparin (LMWH) and fetuses should be monitored with regular cardiotocography (CTG).

Mode of delivery should be led by obstetric indications and spontaneous vaginal delivery is usual. The mother should be kept warm, well hydrated and oxygenated and prolonged labour avoided. Continuous CTG monitoring is suggested and epidural anaesthesia is the pain relief of choice. There is an increased risk of postpartum haemorrhage, infection and thromboembolism so mothers should be closely monitored and attention paid to thromboprophylaxis.

Thalassaemia

The thalassaemias are a group of inherited disorders characterized by reduced or absent production of the α or β haemoglobin chains. This causes a relative excess of the remaining chain, resulting in ineffective erythropoiesis and chronic haemolysis. There are four α-globin genes and two β-globin genes. A complete absence of α-chains is incompatible with life but otherwise a wide variety of genetic abnormalities exist. For this reason thalassaemias are classified by their clinical phenotype into thalassaemia carriers, thalassaemia intermedia and thalassaemia major. The more severe intermedia patients and those with thalassaemia major are transfusion dependent and the main cause of morbidity and mortality is organ dysfunction caused by iron loading.

Carriers or those who have mild thalassaemia intermedia syndromes can be treated as 'normal' pregnancies, except that pre-conception counselling about a couple's risk of having a baby with a haemoglobinopathy should occur and women should have ferritin checked before starting on iron.

Pregnancies in women with β thalassaemia major and severe intermedia syndromes are high risk and should be managed in a multidisciplinary setting. Pre-conception counselling should be offered, covering the risk of subfertility due to hypogonadotrophic hypogonadism, fetal haemoglobinopathy and the risks pregnancy poses to life if patients have cardiac or hepatic dysfunction. Screening for iron-induced organ damage should be performed, including diabetic testing, thyroid function, cardiac and hepatic T2* MRI and echocardiography. Ideally, patients should have no myocardial and minimal liver iron before pregnancy, otherwise a pre-conception period of intensive iron chelation should be considered.

Teratogenic medications, including iron chelators, bisphosphonates and ACE inhibitors, should be stopped 3 months before conception. Folic acid 5 mg daily and calcium and vitamin D supplements, if bone density is reduced, should be taken. Extended red cell phenotyping and antibody screen should be performed.

Antenatal care should be multidisciplinary and individualized. Particular focus should be given to transfusion, cardiac and liver status, diabetes, thrombotic risk and bone problems.

Transfusion requirements often increase during pregnancy and patients who were not previously transfusion dependent may become so. Pre-transfusion haemoglobin should remain above 100 g/L and any red cell antibodies (e.g. Kell, rhesus) should be monitored and the risk of haemolytic disease of the newborn considered.

Between 6 and 8% of patients are diabetic due to iron overloading. They should be managed as per standard guidelines for diabetes in pregnancy. Transfusion-dependent patients are often osteoporotic and osteopenic and may worsen during pregnancy. Vitamin D, calcium supplements and analgesia should be given as necessary. Caesarean section is frequent as many patients have small stature due to cephalopelvic disproportion.

Thrombotic risk is significant, particularly in splenectomized transfusion-independent thalassaemia intermedia patients. The Royal College of Obstetricians and Gynaecologists guidelines recommend aspirin 75 mg/day in splenectomized patients or patients with a platelet

count above 600×10^9/L, and aspirin and LMWH prophylaxis if they have both.

Because cardiac failure and arrhythmias are the commonest cause of death, women with thalassaemia should see a cardiologist before pregnancy. Monitoring with regular echocardiography and iron chelation with desferrioxamine during pregnancy may be appropriate in those with cardiac decompensation or high liver iron (associated with significant myocardial iron).

An ultrasound scan at 7–9 weeks, for the high rate of fetal loss, and 4-weekly growth scans from 24 weeks are recommended. Delivery should be as per obstetric indications and individualized. Peripartum iron chelation to minimize the risk of iron free radicals causing myocardial damage during labour is suggested in transfusion-dependent patients. Regular iron chelation should restart post partum and breastfeeding is safe with this. Women with thalassaemia are high risk for venous thromboembolism.

Summary box 12.4

- Pregnancies in patients with haemoglobinopathies are high risk.
- A woman's health should be optimized prior to pregnancy, including discontinuation of teratogenic medication.
- Care should be multidisciplinary.
- Thromboembolism risk is increased.

Prevention of haemolytic disease of the fetus and newborn

Haemolytic disease of the fetus and newborn (HDFN) is caused by immune-mediated destruction of fetal red cells that have been 'sensitized' by maternal antibodies. Rapid haemolysis can occur, rendering the fetus hydropic, anaemic and at risk of kernicterus in the first few days of life. ABO incompatibility is common but this is usually mild. Severe HDFN is most frequent with anti-D but can occur with a variety of antibodies including anti-c, anti-E and anti-K. Antibodies are formed following exposure to non-self red cell antigens during transfusion or pregnancy. Fetomaternal haemorrhage, and therefore risk of iso-immunization, is greatest at delivery but other potentially sensitizing events are listed in Table 12.5.

Around 15% of pregnant women are RhD negative. Historically, many developed anti-D antibodies when pregnant with an RhD-positive fetus and developed HDFN in subsequent RhD-positive pregnancies. However, the use of anti-D immunoglobulin after sensitizing events and as prophylaxis, initially following delivery and then additionally during the third trimester, has all but eradicated the problem. Anti-D immunoglobulin binds to fetal RhD-positive cells and causes their removal by the reticuloendothelial system before anti-D is produced. Independent of sensitizing events, some fetal cells circulate in the maternal circulation, especially in the third trimester, providing the rationale for routine anti-D immunoprophylaxis.

Table 12.5 Potentially sensitizing events leading to iso-immunization.

Miscarriage/threatened miscarriage
Ectopic pregnancy
Hydatidiform mole
Termination of pregnancy
Amniocentesis/chorionic villous sampling
Abdominal trauma
Antepartum haemorrhage/uterine bleeding
External cephalic version
Intrauterine death
Delivery (all methods)

In the UK, all women have ABO, Rh grouping and antibody screening at booking and 28 weeks [3]. Therefore, RhD-negative mothers should be identified routinely, educated about sensitizing events and offered routine antenatal anti-D prophylaxis (RAADP). There are two schedules in use: 500 IU at 28 and 34 weeks or 1500 IU at 28 weeks. During early pregnancy, fetal blood volume is small, lessening the chance of sensitization but this risk increases throughout pregnancy. Therefore, for events up to 20 weeks 250 IU of anti-D immunoglobulin is given and there is no necessity to calculate the size of fetomaternal haemorrhage (FMH). After 20 weeks, 500 IU is given and a test for FMH performed (Kleihauer or flow cytometry). If greater than 4 mL, further anti-D should be administered (125 IU of anti-D immunoglobulin covers 1 mL of FMH). Doses should be given as soon as possible after the sensitizing event and definitely within 72 hours. However, there may be benefit up to 10 days after the event. Routine anti-D should be given regardless of recent doses for sensitizing events and at birth cord samples for ABO and Rh grouping should be sent. Mothers with RhD-positive babies should receive 500 IU anti-D, a test for FMH and more doses as necessary.

Until recently, all RhD-negative women were recommended to have anti-D immunoprophylaxis. However, approximately 40% of RhD-negative women will be carrying RhD-negative babies and therefore do not need anti-D immunoprophylaxis. It is now possible to determine fetal RhD status by detecting cell-free fetal DNA in the maternal circulation via a maternal blood test after 12 weeks' gestation. Therefore, the National Institute for Health and Care Excellence (NICE) recommends that this is routinely offered to RhD-negative women to avoid unnecessary anti-D.

Women noted to have a clinically significant antibody should be referred to a specialist, ideally before pregnancy,

Table 12.6 Risk of developing haemolytic disease of the fetus and newborn (HDFN) with clinically significant antibody levels.

Risk of developing HDFN	Anti-c	Anti-D	Anti-K
Mild	<7.5 IU/mL	<4 IU/mL	Severe fetal anaemia can occur even with low titres so refer once detected
Moderate	>7.5 to <20 IU/mL	>4 to <15 IU/mL	
Severe	>20 IU/mL	>15 IU/mL	
Level to refer to fetal medicine specialist	>7.5 IU/mL	>4 IU/mL	

to discuss HDFN risk and potential cross-matching difficulties. Despite RAADP, anti-D remains the commonest. Determining the father's red cell phenotype is useful for predicting the chances of the fetus carrying the relevant red cell antigen. However, it should be noted that the stated father may not be the biological father.

Once pregnant, if the father's antigen status is unknown or his red cells express the corresponding antigen, it is possible to determine fetal RhD, Rhc and Kell genotypes from free fetal DNA in maternal blood samples from 16 weeks. If the fetus is negative for the corresponding antigen, the parents can be reassured; if positive, the fetus and mother can be carefully monitored.

Once a clinically significant antibody is detected, an antibody titre will be determined. This correlates with the chance of developing HDFN (Table 12.6).

Anti-D, anti-c and anti-K titres should be performed every 4 weeks until 28 weeks and then fortnightly until delivery. Other antibodies should be retested at 28 weeks and referral to a fetal medicine specialist made if its presence dilutes at more than 1 : 32 or there is a previous history of HDFN. Once the antibody titre threshold is met, patients should undergo weekly ultrasound scans to assess the fetal middle cerebral artery peak systolic velocity. If this rises above 1.5 times the median threshold or there are other signs of fetal anaemia, consideration should be given to invasive treatment, i.e. intrauterine transfusion with red cells negative for the causative antigen.

Summary box 12.5

- HDFN is immune-mediated red cell destruction of fetal/newborn red cells and may cause hydrops, anaemia and kernicterus.
- The best 'treatment' is prevention and RAADP has greatly reduced the incidence.
- Anti-c, anti-D and anti-K are the most commonly encountered causes of significant HDFN.

Fetal/neonatal thrombocytopenia

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is analogous to HDFN but affects platelets rather than red cells. It is the most common cause of severe neonatal thrombocytopenia and is caused by immune-mediated destruction of fetal platelets by maternal antibodies. Human platelet antigens (HPAs) are expressed on fetal platelets from around 16 weeks' gestation and those which are paternally derived may cause maternal alloimmunization and placental transfer of maternal immunoglobulin. Approximately 80% of cases are due to HPA-1a incompatibility, detected in around 1 in 1000 live births but estimated to be considerably under-diagnosed. A further 15% are due to HPA-5b incompatibility and the remaining 5% are caused by antibodies against other HPAs.

Although it often affects first pregnancies (unlike HDFN), there is no programme for routine screening for anti-HPA antibodies in the UK and the diagnosis is considered on clinical grounds (Table 12.7) and confirmed with laboratory tests (Table 12.8).

Women with known HPA antibodies, or those whose sisters have had babies affected by FNAIT, should be referred to a haematologist and fetal maternal medicine unit, ideally before pregnancy, to discuss FNAIT risk and plans for antenatal management. Until a few years ago, this involved intrauterine assessment of fetal platelet count and transfusion of compatible platelets through the umbilical cord. Serial procedures were required for those with severe thrombocytopenia, increasing the chance of fetal death from haemorrhage or umbilical artery thrombosis from the concentrated platelet transfusion. Recent treatment strategies have been non-invasive and involve reduction of maternal immunoglobulin with intravenous immunoglobulin with or without steroids.

Table 12.7 Clinical suspicion of fetal/neonatal alloimmune thrombocytopenia.

Neonatal thrombocytopenia, unexplained by maternal autoimmune disease or drug ingestion, neonatal sepsis, DIC or congenital anomalies known to be associated with thrombocytopenia
Neonatal platelet count $<50 \times 10^9$/L
Intracranial haemorrhage in fetus or neonate
Unexplained hydrocephalus

DIC, disseminated intravascular coagulation.

Table 12.8 Laboratory tests required for diagnosis of fetal/neonatal alloimmune thrombocytopenia.

Detection and identification of the maternal HPA antibody
Determination of the HPA genotype of the mother, baby and father, depending on results and availability
Cross-match of maternal serum and paternal platelets

Summary box 12.6

- FNAIT is alloimmune-mediated destruction of fetal/newborn platelets.
- Treatment of affected pregnancies is non-invasive, with regular administration of intravenous immunoglobulin with or without steroids.
- Anti-HPA-1a and anti-HPA-5b are the most commonly encountered causes of significant FNAIT.

Haemostatic measures in obstetric haemorrhage

Major postpartum haemorrhage (>1000 mL blood loss after delivery) is a major cause of maternal death in the developed world. It has multiple aetiologies and requires a multidisciplinary team focusing on resuscitation, local control of bleeding, and haemostasis. This section considers the organizational and haemostatic measures only.

All delivery centres should have a major obstetric haemorrhage protocol. This should detail how to alert key staff, how to transport samples to the laboratory and obtain blood products quickly, the policy on non-cross-matched blood, recommended resuscitation measures and blood product use and haemostatic monitoring. Good communication is essential, with a designated team leader and person to liaise with the transfusion laboratory.

Blood component management in obstetric haemorrhage is similar to that for other causes of major haemorrhage, except that many patients have a group and save on record, enabling group-specific blood in advance, and fibrinogen replacement should be at a higher level. Fibrinogen levels rise throughout pregnancy and are around 4–6 g/L at delivery. A level of 2–3 g/L signifies significant loss and should prompt replacement with cryoprecipitate.

Initial resuscitation is with red cells and fresh frozen plasma (FFP) in a 2 : 1 ratio until bleeding is under control or coagulopathy monitoring results are available to guide product replacement. The following parameters are suggested.

- Keep APTT and prothrombin time (PT) ratio within 1.5 times normal with FFP.
- Keep platelets above 50×10^9/L with platelets.
- Keep fibrinogen above 2 g/L with cryoprecipitate.

Tranexamic acid reduces death due to bleeding in women with postpartum haemorrhage with no adverse effects. When used as a treatment for postpartum haemorrhage, it should be given as soon as possible after bleeding onset [4].

Standard coagulopathy monitoring includes platelet count, APTT, PT and fibrinogen every 30–60 min. In a massive haemorrhage setting, any delay in obtaining test results can mean they do not accurately reflect the clinical situation. Therefore, many centres are using near-patient testing such as thromboelastography or ROTEM. These measure the global viscoelastic properties of whole blood clot formation and reflect the interaction of platelets with the coagulation cascade. Common defects in coagulopathic patients, such as thrombocytopenia and increased fibrinolysis, can be easily identified and used to guide blood product replacement. They more accurately reflect the current clinical situation but are not currently recommended in guidelines due to the lack of trial data supporting their use.

Summary box 12.7

- Major obstetric haemorrhage remains a leading cause of direct maternal death.
- All centres should have an obstetric major haemorrhage protocol.
- Blood product replacement is similar to that for non-pregnant patients, except that fibrinogen replacement should be given at a higher level.

Thrombosis and thromboembolism

The leading cause of direct maternal death is venous thromboembolism (VTE), causing death in 1 in 100 000 pregnancies in 2011–2013 [5]. Half occured antenatally (50% first trimester, 25% second, 25% third) and half postnatally. Failings were shown in identifying those at risk, considering the diagnosis and implementing appropriate treatment.

Virchow's triad states that there are three components to thrombus formation: blood stasis, hypercoagulability and blood vessel wall damage. In pregnancy, blood flow in the lower limbs slows by up to 50% by 29 weeks and this persists for 6 weeks post partum. There is an increase in factor VIII and fibrinogen, reduction in protein S and impaired fibrinolysis, producing a hypercoagulable state and vessel wall damage during delivery by any means. The rate of VTE is increased fourfold to sixfold antenatally and 20-fold postnatally, although the absolute risk remains low at 1 in 1000 pregnancies.

Deep vein thrombosis (DVT) in pregnancy affects the left leg in 90% of cases (compared with 55% in non-pregnant women), due to compression of the left iliac vein by the right iliac and ovarian arteries; 70% are ileo-femoral, as opposed to 10% in non-pregnant patients, and they carry a much higher chance of pulmonary embolism (PE).

The diagnosis of VTE in pregnancy is difficult as many of the symptoms and signs, such as leg swelling, dyspnoea and chest pain, occur in normal pregnancy. Less

than 10% of pregnant women clinically suspected of having DVT and less than 5% suspected of having PE are confirmed on objective testing. However, as mortality of untreated PE is high, it is important that patients are treated with LMWH as soon as the diagnosis is suspected unless there are significant contraindications.

Compression duplex ultrasound of the entire proximal venous system should be undertaken when there is clinical suspicion of DVT. If negative but the diagnosis is likely, patients should remain anticoagulated and the scan repeated in a week. If iliac vein thrombosis is suspected, Doppler ultrasound of the iliac vein, magnetic resonance venography or conventional contrast venography should be performed.

In a haemodynamically stable patient, first-line investigations for suspected PE should be chest X-ray and ECG. Chest X-ray confers negligible radiation to the fetus, at any stage of pregnancy, and may reveal an alternative cause for the symptoms, such as pneumonia or pneumothorax. A *V*/*Q* scan can only be interpreted if the chest X-ray is normal. ECGs are more frequently abnormal in pregnant than non-pregnant women, with the most common abnormalities being T-wave inversion, S1Q3T3 and right bundle branch block.

Women with suspected DVT as well as PE should have compression duplex ultrasound of the lower limbs initially. If DVT is confirmed no further investigations are needed, as treatment for PE and DVT is the same. There is also an argument that women with suspected PE in the absence of leg symptoms should have leg scanning initially, as a positive diagnosis of DVT will negate the need for a radiation dose to the mother and fetus. However, the detection rate of this approach is very small and many centres have discontinued this practice.

In women with suspected PE and no DVT, either CT pulmonary angiography (CTPA) or *V*/*Q* scan should be performed. The choice will depend on a number of factors, including availability, local guidelines and patient preference. A *V*/*Q* scan cannot be used if the chest X-ray is abnormal.

Advantages of CTPA are that it is quick, readily available and conclusive and will identify alternative pathologies. CTPA delivers less radiation to the fetus than *V*/*Q* scanning in all stages of pregnancy. Its major disadvantage is the high radiation dose to the mother's breast tissue, which is associated with an increased lifetime risk of breast cancer of 13% above their background risk. Therefore, particularly in young women and those with a family history of breast cancer, lung perfusion scan may be the better choice. Ventilation–perfusion scans or perfusion scans alone are associated with a higher radiation dose to the fetus but this is still small (the risk of fatal cancer to the age of 15 is less than 1 in 280 000). They scans cannot evaluate other pathologies except PE but deliver a much smaller radiation dose to the breast tissue.

In non-pregnant patients, a normal D-dimer, in combination with pretest probability testing, has a high negative predictive value for VTE. However, because D-dimers rise in normal pregnancy, there are no clinically validated pretest probability scores in pregnancy and false negatives have been described in pregnant patients with VTE, D-dimer levels are not currently recommended in the pregnancy setting.

Treatment of haemodynamically stable VTE

On clinical suspicion of VTE, treatment should be instigated with LMWH unless strongly contraindicated. Bloods tests should be performed to check coagulation screen, platelet count and any evidence of renal or hepatic disease. Although half of patients who have a VTE in pregnancy will have an underlying inherited or acquired thrombophilia, thrombophilia testing is not recommended in the acute setting, as results are difficult to interpret and do not change immediate management.

LMWH is the treatment of choice in pregnancy as it is effective, easy to give, does not routinely require monitoring and has lower rates of haemorrhage, osteoporosis and heparin-induced thrombocytopenia than unfractionated heparin. Intravenous unfractionated heparin is useful in patients who might require their anticoagulation to be stopped quickly, for example those at high risk of bleeding or those in severe renal failure. Vitamin K antagonists should not be used as they cross the placenta and are associated with pregnancy loss, embryopathy and fetal haemorrhagic complications. Treatment of VTE with the new direct oral anticoagulants is becoming commonplace outside of pregnancy. However, the trials excluded pregnant patients and the teratogenicity in humans is unknown so currently they should be avoided.

LMWH should be dosed according to early pregnancy weight. Previously, dalteparin and enoxaparin were given twice daily in pregnancy due to altered renal glomerular filtration and volume of distribution but newer evidence suggests that once-daily dosing is adequate and this should be decided on a local level. Routine monitoring of LMWH with anti-Xa levels is only recommended for those at extremes of body weight (<50 or >90 kg) or with other complicating factors such as renal impairment. As the rate of heparin-induced thrombocytopenia is negligible with LMWH, platelet monitoring is not necessary.

Women on therapeutic anticoagulation require an individualized plan for delivery and the postpartum period. Women should not inject further LMWH if they think they are in labour or have any bleeding. Regional anaesthetics should not be used until 24 hours after the last therapeutic dose of LMWH or 12 hours after the last prophylactic dose. Induction of labour allows LMWH to be reduced to a prophylactic dose the day before induction and therefore facilitates the use of regional anaesthetics

with minimal interruption of anticoagulation. Epidural catheters should not be removed within 12 hours of a dose of LMWH, and LMWH should not be given until at least 4 hours post removal. Post partum, LMWH should be restarted as soon as possible. This is often a prophylactic dose 4–6 hours after delivery (assuming no bleeding concerns) and then treatment dose from 12 hours.

Women should remain on LMWH for the remainder of their pregnancy and for at least 6 weeks post partum and until at least 3 months of treatment has been given. Post partum, once-daily dosing is adequate and women may be switched to warfarin if they prefer. Before discontinuing treatment a review assessing an individual's ongoing risk of thrombosis should be performed.

Management of acute life-threatening PE

Massive PE may present with shock, refractory hypoxia and/or right ventricular dysfunction. It is a medical emergency and should be managed by a multidisciplinary team including senior medics, obstetricians and radiologists who decide on an individual basis whether a woman receives intravenous unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy.

Intravenous unfractionated heparin is preferred to LMWH due to its quicker effect and easier dose adjustments but it does not reduce the size of the clot in the pulmonary circulation. Therefore, in massive life-threatening PE with cardiovascular compromise (or in limb-threatening DVT) thrombolysis should be considered. Ideally, portable echocardiography or urgent CTPA should be performed first, but in extreme circumstances immediate thrombolysis may be appropriate.

The most common agent used is streptokinase and this is followed with an intravenous heparin infusion, minus the loading dose. There are now several cases of thrombolysis in pregnancy with no maternal deaths and with rates of bleeding (which is usually minor) similar to those in non-pregnant patients (6%).

Summary box 12.8

- VTE is the leading cause of direct maternal deaths in the UK.
- Treatment-dose LMWH (unless contraindicated) should be started on suspicion of VTE and the diagnosis confirmed by objective testing.
- CTPA and *V/Q* scans can both be used to confirm the diagnosis of PE in pregnancy.
- CTPA confers an increased risk to the mother of solid tissue tumours.
- Consider thrombolysis in suspected PE with haemodynamic compromise.

Prevention of VTE in pregnancy and the puerperium

In two-thirds of women suffering a PE there are identifiable risk factors (Tables 12.9 and 12.10).

Despite very limited data from randomized controlled trials, thromboprophylaxis in at-risk pregnancies has been recommended practice for a number of years and is known to be efficacious, cost-effective and safe [3]. Women should be risk assessed for VTE in early pregnancy and this should be repeated on admission, during and after birth, and if an additional problem develops. Hospitals should have patient information sheets on VTE and prescriptions for the entire course should be issued by secondary care to avoid breaks in treatment and enable dose checking by pharmacists [2].

High-risk women, prior to pregnancy, should be counselled and given a prescription for LMWH to start as soon as the pregnancy test is positive to ensure cover for the first trimester. Women on long-term warfarin for recurrent VTE or cerebrovascular accident are at high risk of VTE during pregnancy. Their care should be individualized, with input from an obstetric haematologist, but will likely be treated with high prophylactic or full-dose LMWH.

Tables 12.9 and 12.10 outline the recommended thromboprophylaxis. Women should be educated about the reasons behind thromboprophylaxis and the risk of bleeding and taught how to inject themselves. A plan for thromboprophylaxis around delivery should be made, as detailed in the previous section. Thromboprophylaxis should be started as soon as possible after delivery, assuming no haemorrhagic concerns arise.

Summary box 12.9

- All women should be risk assessed for VTE in early pregnancy or pre-pregnancy. This should be repeated if admitted or another problem develops and during or immediately after birth.
- Thromboprophylaxis should be given depending on the level of risk.

Inherited bleeding disorders

During pregnancy, inherited bleeding disorders can increase the risk of maternal bleeding and, depending on inheritance, confer a neonatal bleeding risk [7]. The commonest disorders in the obstetric population are von Willebrand disease and haemophilia A and B.

Von Willebrand disease (vWD) is caused by either a qualitative or quantitative deficiency of vWF, required for platelet adhesion. Severity varies, depending on type.

Table 12.9 Antenatal risk factors for venous thromboembolism (VTE).

Risk factors	Management
High risk	
Any previous VTE except a single event post surgery	Antenatal prophylaxis with LMWH
Intermediate risk	
Hospital admission	Consider antenatal prophylaxis with LMWH
VTE post surgery	
High-risk thrombophilia	
Medical comorbidities, e.g. cancer, nephrotic syndrome, sickle cell disease, SLE, IVDU	
Any surgical procedure	
Ovarian hyperstimulation syndrome (first trimester)	
Lower risk	
BMI >30 kg/m^2	Four or more risk factors: prophylaxis from first trimester
Age >35	Three or more risk factors: prophylaxis from 28 weeks
Parity ≥3	Less than three risk factors: mobilize and avoid dehydration; no pharmacological thromboprophylaxis
Smoker	
Gross varicose veins	
Current pre-eclampsia	
Immobility	
Family history of unprovoked or oestrogen-provoked VTE in first-degree relative	
Low-risk thrombophilia	
Multiple pregnancy	
In vitro fertilization/assisted reproductive technology	
Current systemic infection/hyperemesis/dehydration	
Long haul flight	

BMI, body mass index; IVDU, intravenous drug user; LMWH, low-molecular-weight heparin; SLE, systemic lupus erythematosus.
Source: adapted from Royal College of Obstetricians and Gynaecologists [6].

Table 12.10 Postnatal risk factors for VTE.

Risk factors	Management
High risk	
Any previous VTE	At least 6 weeks postnatal prophylactic LMWH
Anyone on antenatal LMWH	
High-risk thrombophilia	
Low-risk thrombophilia and family history of VTE	
Intermediate risk	
Caesarean section in labour	At least 10 days postnatal prophylactic LMWH
BMI >40 kg/m^2	If persisting or more than three risk factors, consider 6 weeks prophylactic LMWH
Readmission or ≥3 day admission in puerperium	
Any surgical procedure in the puerperium except immediate perineal repair	
Medical comorbidities	
Lower risk	
BMI >30 kg/m^2	Two or more risk factors: 10 days of postnatal prophylactic LMWH
Age >35	Less than two risk factors: early mobilization and avoidance of dehydration; no pharmacological thromboprophylaxis
Parity ≥3	
Smoker	
Gross varicose veins	
Immobility	
Family history of VTE	
Low-risk thrombophilia	
Multiple pregnancy	
Current systemic infection	
Elective caesarean section	
Current pre-eclampsia	
Preterm delivery in this pregnancy (<37 weeks)	
Stillbirth in this pregnancy	
Mid-cavity rotational or operational delivery	
Prolonged labour (>24 hours)	
Postpartum bleeding >1 L or blood transfusion	

vWF levels rise during pregnancy, so many women at the milder end of the spectrum do not require intervention. However, those with an abnormal or completely absent vWF can have severe bleeding complications without treatment. Levels decrease rapidly in the postpartum period, putting women at risk of postpartum haemorrhage.

Management should be multidisciplinary and begin before conception. Principles include educating the mother on her risk of bleeding and the inheritance of her particular type of vWD, potentially offering prenatal diagnosis, monitoring vWF levels and activity, and ensuring a detailed plan for delivery and the postpartum period. Women with bleeding or inadequate factor levels who are undergoing invasive procedures or delivery require treatment. This should be directed by a haemophilia centre but usually involves desmopressin or vWF concentrate. Mode of delivery should be obstetrically determined; epidural anaesthesia requires vWF activity to be greater than 0.5 IU/mL, although should not be undertaken likely due to the risk of spinal haematoma. For neonates at risk of moderate to severe disease, fetal scalp monitoring and sampling, ventouse and rotational forceps should be avoided. Active management of the third stage is suggested and tranexamic acid for 1–2 weeks during the postpartum period reduces vaginal bleeding.

The haemophilias are X-linked and therefore male fetuses have a 50% chance of being affected and female fetuses a 50% chance of being carriers. Most affected mothers are asymptomatic but due to unequal lyonization may have low factor levels requiring haemostatic support during invasive procedures, delivery and the postpartum period. This should be directed by a haemophilia centre and tends to be greater in haemophilia B carriers as factor IX levels do not increase in pregnancy.

Women should be offered prenatal diagnosis of haemophilia. If a couple are likely to consider terminating an affected fetus, this should be in early pregnancy. Maternal blood sampling is usually used to determine fetal sex by means of free fetal DNA between 9 and 11 weeks. If female, no further testing is required, but for males chorionic villous sampling is offered between 11 and 13 weeks. Women who do not wish to have invasive early testing should be encouraged to have their fetus sexed at the 20-week scan and in some centres third-trimester amniocentesis is offered for male fetuses to determine if they are affected and plan for delivery. For male babies at risk, traumatic procedures (as for vWD) should be avoided and they should receive vitamin K orally. Women should have active management of the third stage of labour.

Summary box 12.10

- Inherited bleeding disorders confer a bleeding risk to the mother and possibly the fetus.
- Care should be multidisciplinary starting before conception and continuing through the postpartum period.
- Mothers may need haemostatic support to cover invasive procedures, delivery and the postpartum period and should be encouraged to have an active third stage.
- Traumatic procedures should be avoided during delivery for potentially affected fetuses and vitamin K should be given orally.

Myeloproliferative disorders in pregnancy

The myeloproliferative disorders are a group of conditions characterized by the clonal proliferation of one or more haemopoietic bone marrow components. The commonest conditions are polycythaemia vera, chronic myelogenous leukaemia, primary or essential thrombocythaemia and primary myelofibrosis. Thrombosis and haemorrhage are major causes of morbidity in these conditions and pregnancy outcomes have historically been poor.

An awareness of these conditions is important for obstetricians as they occasionally present in pregnancy and if the diagnosis is made and treatment implemented, pregnancy outcomes are improved. Pregnancies in patients with a known myeloproliferative disorder are also becoming more commonplace. These should be managed in a multidisciplinary setting with the input of a haematologist and obstetrician specializing in high-risk patients. Management should include pre-conception optimization of the condition, including withdrawal of potentially teratogenic medications (hydroxycarbamide and anagrelide), thrombotic risk assessment and plan to control haematocrit and platelet count during pregnancy. Venesection and/or interferon alfa are safe for haematocrit and platelet count control and aspirin with or without LMWH for the thrombotic risk.

Haematological malignancy during pregnancy

Haematological malignancies, namely acute leukaemias and lymphomas, may be diagnosed during pregnancy. Optimal treatment for the woman may result in fetal malformations or death and therefore can present a

difficult dilemma for the patient, family and medical team. Patients should be managed in a multidisciplinary setting including haematologists, obstetricians and neonatologists and given plenty of support as they make their decision. Consideration should be given to gestation, risks to the mother of waiting to treat the condition, and the risks to the fetus of maternal treatment needed. In general, chemotherapy and radiotherapy in the first trimester are associated with significant risks of congenital malformations and miscarriage and this risk lessens with advancing pregnancy. It is often recommended to terminate pregnancies in women presenting with a malignancy in the first trimester. For those presenting after 32 weeks it is often possible to deliver the baby before starting chemotherapy; for those between 24 and 32 weeks, the risk of fetal exposure to chemotherapy drugs should be balanced against the risks of premature delivery at that stage of gestation.

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13

Maternal Infection During Pregnancy

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Perinatal infections continue to affect pregnancies in the UK and worldwide. Most perinatal infections are asymptomatic in the mother, but may have serious consequences for the fetus. Pregnant women are exposed to infections prevalent in the community but they are also likely to reside with young children and this represents a significant additional factor in exposure to infectious agents. Most infections in pregnancy resolve spontaneously without therapy or are readily treated with antimicrobial agents. Such infections usually have no effect on the developing fetus. However, the infecting organism may invade the bloodstream and subsequently infect the placenta and fetus. Transplacental spread and invasion of the bloodstream after maternal infection is the usual route by which the fetus is infected. Uncommonly, the fetus may be infected by extension of infection into adjacent maternal tissues and organs, including the peritoneum and the genitalia, during delivery, or as a result of invasive procedures, such as the use of monitors, chorionic villous biopsy, sampling of fetal blood and intrauterine transfusion. Before rupture of fetal membranes, organisms in the genital tract may invade the amniotic fluid and infect the fetus. These organisms can invade the placenta through microscopic defects in the membranes, particularly in devitalized areas overlying the cervical os.

Microorganisms of concern include those identified in the acronym TORCH: toxoplasmosis, rubella, cytomegalovirus, and herpesvirus; the 'O' in TORCH originally stood for 'other infections'. A new acronym should include other well-described causes of *in utero* infection: syphilis, hepatitis B, HIV and parvovirus. The UK screening programme for infectious disease in pregnancy advocates routine screening for HIV, hepatitis B, rubella and syphilis. The policy and standards are agreed by the National Screening Committee and published in the National Institute for Health and Care Excellence (NICE) antenatal care guidelines [1]. The prevalence of all four of these infections is still significant in the UK and particularly in inner cities such as London [2] (Table 13.1) and therefore routine antenatal screening is essential to prevent mother-to-child transmission of hepatitis B, HIV and syphilis. The screening programme also identifies women for whom postnatal MMR (measles, mumps, rubella) vaccination could protect future pregnancies. The programme stipulates the following.

1) All pregnant women are offered screening at the booking visit for rubella antibody, syphilis, HIV and hepatitis B as an integral part of their antenatal care during their first and all subsequent pregnancies regardless of immunization history.
2) Although every woman has the right to decline screening, if screening has been declined at booking, it should be re-offered at 28 weeks' gestation.
3) Pregnant women arriving in labour who have not received antenatal care elsewhere are offered screening for infectious diseases. Priority is given to hepatitis B and HIV screening and presumptive action is taken on a preliminary positive result until the result is confirmed. If an HIV test result is not available, appropriate preventive measures should be offered. In cases where consent for screening is withheld during labour, screening is offered again after delivery.
4) If there is a screen-positive result, the current national standards state a second sample should be taken for syphilis, hepatitis B and HIV to confirm the screening result. Following this result the women should be referred for specialist counselling and appropriate follow-up and management [3].

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 13.1 Prevalence of infections in London (data based on annual reports).

Infection	Prevalence (%) 2011–2012	Prevalence (%) 2012–2013	Prevalence (%) 2013–2014
Syphilis	0.3	0.3	0.3
Hepatitis B	1.1	1.5	0.9
HIV	0.4	0.7	0.3
Susceptibility to rubella	5.1	5.9	6.5

Human immunodeficiency virus

The human immunodeficiency virus type 1 (HIV-1) pandemic remains one of the greatest public health challenges in the 21st century. The care of HIV-infected women is more effective than ever and the rates of mother-to-child transmission of HIV are lower than ever in communities with access to therapy. Because of widespread implementation of routine antenatal screening for HIV, antiretroviral therapy (ART) during pregnancy, elective caesarean section and avoidance of breastfeeding, transmission of HIV-1 from mother to child is now a rare occurrence in the UK. However, mother-to-child transmission of HIV still represents the most common source of HIV infection among infants and children. In 2014, there were an estimated 103 700 people living with HIV in the UK. The prevalence of HIV in the UK among those aged 15–44 years in 2014 was estimated to be 1.7 per 1000 women. The HIV epidemic remains largely concentrated among gay, bisexual men and men and women of black African ethnicity [4,5].

Pathogenesis and transmission

HIV is a retrovirus that infects and damages T lymphocytes, resulting in immunosuppression and eventually leading to AIDS. Two types of HIV viruses, HIV-1 and HIV-2, can cause AIDS in humans. HIV-1 and HIV-2 are lentiviruses belonging to the *Retroviridae* family and have a complex genomic structure [6]. The commonest and most virulent form is HIV-1, with HIV-2 being relatively uncommon in Western countries.

HIV can be transmitted through sexual contact or via contaminated blood, for example needle sharing. Mother-to-child transmission of HIV can occur *in utero*, during labour and delivery, or postnatally through breastfeeding. *In utero* transmission may occur through HIV infection in the placenta or fetal exposure to cell-free or cell-associated HIV in the amniotic fluid. Intrauterine transmission occurs in about 20–25% of infections and mostly occurs during the last few weeks before delivery when the vascular integrity of the placenta is disrupted. Intrapartum transmission may occur because of direct exposure of the fetus to infected maternal secretions during birth. Although numerous maternal, obstetric, infant, host genetic, and viral factors may modify perinatal HIV transmission risk, maternal plasma HIV RNA level is the strongest predictor of intrauterine and intrapartum transmission. Other maternal risk factors associated with higher rates of perinatal HIV infection include women with advanced clinical disease, acute HIV infection during pregnancy, and low $CD4^+$ counts. Obstetric risk factors associated with increased risk of transmission include vaginal delivery, prolonged rupture of membranes, chorioamnionitis and invasive obstetric procedures.

In the absence of interventions, postnatal transmission of HIV through breastfeeding can account for one-third to half of all HIV infections globally and carries an estimated transmission risk of about 15% when breastfeeding is prolonged. Risk factors for breast-milk HIV transmission include women seroconverting during lactation, high HIV DNA or RNA level in maternal plasma and breast milk, low maternal $CD4^+$ cell count, maternal symptomatic disease or AIDS, prolonged duration of breastfeeding, mixed infant feeding, oral lesions in the infant, abrupt weaning and maternal breast problems.

Diagnosis

In England, the routine offer and recommendation policy was implemented in 2000, and similar policies were subsequently adopted elsewhere in the UK. National uptake of antenatal HIV screening was reported to be 95% in 2008. Between 2000 and 2004 the majority of HIV-infected women diagnosed before delivery were identified through antenatal screening. However, by 2011, over 80% of women diagnosed before delivery were already aware of their infection before they conceived, many of them diagnosed in a previous pregnancy. Pregnant women should be offered screening for HIV infection at their booking appointment because appropriate antenatal interventions can reduce mother-to-child transmission of HIV infection. If screening has been declined at booking, it should be offered again at 28 weeks' gestation. Pregnant women arriving in labour who have not received antenatal care elsewhere should be offered screening for HIV. If an HIV test result is not available, appropriate preventive measures should be offered. In cases where consent is withheld for screening during labour, screening is offered again after delivery [5].

Management

If there is a primary laboratory screen-positive result (positive ELISA), the samples are referred for testing by a specialist laboratory to confirm the reactivity is specific

for HIV (by Western blot) involving at least two further independent assays. Obtaining a CD4 count and a viral load provides the clinician with a useful snapshot of the patient's status and medication needs when she is first encountered. All women who have confirmed positive test results should be counselled in person and offered specialist counselling and support, which is also available for their partners and family if requested. Women found to be positive are referred for specialist HIV treatment within a multidisciplinary framework. This would involve advice about management of their infection and interventions to reduce the risk of vertical and sexual transmission, including discussions on the use of antiretrovirals and caesarean section, early treatment and care for the child, and decisions about breastfeeding. It also provides an opportunity to reinforce health promotion advice and to discuss arrangements for partner notification and testing of previous children. HIV-positive results also need to be accessible to members of staff at all times to inform appropriate clinical care, particularly in the delivery suite when the woman arrives in labour. It is also important to ensure that a paediatric care plan is determined prior to the birth to ensure the mother understands and has consented for testing and potential treatment regimens after delivery.

ART has been shown to significantly reduce the rate of vertical transmission. Zidovudine chemoprophylaxis given in the prenatal and intrapartum period and to the newborn reduces vertical transmission from 27.7 to 7.9% [7]. However, zidovudine monotherapy is considered inappropriate in mothers with high viral load or low CD4 counts because it fails to suppress viral replication and increases the risk of development of viral resistance. The British HIV Association [5] recommend the use of combination ART in order to achieve prolonged viral suppression when treatment is indicated, with the aim of reducing the viral load to below detectable levels, and recommend that HIV infection in pregnant women should be treated as infection in non-pregnant patients. It is therefore recommended that advanced HIV infection in pregnant women should be treated with combination ART, which through more complete suppression of viral replication allows greater and prolonged recovery of immune function. Women requiring ART for their own health should commence treatment as soon as possible, while all pregnant women should have commenced ART by week 24 of pregnancy. Zidovudine monotherapy can be used in women planning a caesarean section who have a baseline viral load of less than 10 000 HIV RNA copies/mL and a CD4 count above 350 cells/μL.

For women with a plasma viral load of less than 50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, a planned vaginal delivery is recommended. Where the viral load is 400 HIV RNA copies/mL or more at 36 weeks, elective caesarean delivery is recommended. Where the indication for caesarean section is the prevention of vertical transmission, delivery should be planned at 38–39 weeks' gestation. Intrapartum intravenous zidovudine infusion is recommended for women with a viral load above 1000 HIV RNA copies/mL presenting in labour, or with ruptured membranes or who are admitted for planned caesarean section; for untreated women presenting in labour or with ruptured membranes in whom the current viral load is not known; and in women on zidovudine monotherapy undergoing elective caesarean section.

Neonatal post-exposure prophylaxis (usually oral zidovudine) should be commenced very soon after birth, certainly within 4 hours and should be given for 4 weeks. All mothers known to be HIV positive, regardless of ART and infant prophylaxis, should be advised to exclusively formula feed from birth.

Summary box 13.1

- All HIV-positive women should have commenced ART by week 24 of pregnancy.
- With viral load <50 HIV RNA copies/mL at 36 weeks, a planned vaginal delivery is recommended.
- With viral load ≥400 HIV RNA copies/mL at 36 weeks, elective caesarean delivery is recommended.

Hepatitis B

Hepatitis B is an infection of the liver caused by the hepatitis B virus (HBV). Many new infections with hepatitis B are subclinical or may manifest as a flu-like illness. Jaundice only occurs in about 30–50% of adults. The UK is a very low prevalence country, but prevalence of HBsAg varies across the country. The prevalence rates found in antenatal women vary from 0.05 to 0.08% in some rural areas but rise to 1% or more in certain inner city areas. Overall, the prevalence in antenatal women in the UK is around 0.14%. The incidence of acute infection is high among those with certain lifestyle or occupational risk factors. Most reports of acute infection in the UK occur as a result of injecting drug use or sexual exposure [8].

Pathogenesis and transmission

HBV is a well-characterized, partially double-stranded DNA virus. The virus is transmitted by parenteral exposure to infected blood or body fluids. Transmission mostly occurs through vaginal or anal intercourse, as a result of blood-to-blood contact (e.g. sharing of needles

and 'needlestick' injuries) or through perinatal transmission from mother to child.

The incubation period ranges from 40 to 160 days (average 60–90 days). Current infection can be detected by the presence of HBsAg in the serum. Blood and body fluids from HBsAg-positive individuals should be considered to be infectious. In most cases, infection will resolve and HBsAg disappears from the serum, but the virus persists in some patients who become chronically infected. Chronic hepatitis B infection is defined as persistence of HBsAg in the serum for 6 months or more. Individuals with chronic infection are referred to as chronic carriers. Among those who are HBsAg positive, those in whom hepatitis B e-antigen (HBeAg) is also detected in the serum are the most infectious. Those who are HBsAg positive and HBeAg negative (usually anti-HBe positive) are infectious but generally of lower infectivity. A proportion of chronically infected people who are HBeAg negative will have high HBV DNA levels, and may be more infectious. Around 20–25% of individuals with chronic HBV infection worldwide have progressive liver disease, leading to cirrhosis in some patients. The risk of progression is related to the level of active viral replication in the liver. Individuals with chronic infection, particularly those with active inflammation and/or cirrhosis, are at increased risk of developing hepatocellular carcinoma.

Perinatal transmission occurs at or near the time of birth because of exposure to cervical secretions and maternal blood. To a minor degree, transplacental transmission might be responsible for perinatal infections, depending on risk factors that include maternal HBeAg positivity, HBsAg titre, and HBV DNA level [6]. Mothers positive for HBeAg and mothers with very high serum DNA levels (e.g. 10^9 copies/mL) have the greatest risk of transmitting HBV to their offspring. Approximately 70–90% of mothers who are HBeAg positive will transmit the infection to the baby. The rate of transmission is approximately 10% in women with antibody to e antigen (anti-HBe). Mode of delivery does not influence the likelihood of HBV transmission. Another possible route of HBV transmission is amniocentesis in HBsAg-positive mothers. Although HBsAg can be detected in the breast milk of HBV-infected mothers, several studies have shown that there is no additional risk of transmission of HBV to breastfed infants of infected mothers, provided that proper active and passive immunoprophylaxis is carried out.

Clinical manifestations

The clinical manifestations of HBV infection depend on the age of acquisition. The risk of chronic infection is greater than 90% in neonates, and observed in only 5% of adults exposed to HBV. Approximately 6% of infants born to mothers who are positive for anti-hepatitis B early antibody develop acute hepatitis at 2 months of age. Infants are ill with fever, jaundice and hepatic tenderness. Serum aminotransferases are elevated, and there is active inflammation in the liver biopsy specimen. About one-third of older children and adolescents with acute HBV develop these classic symptoms. Most infants, children and adolescents have chronic infection (lasting longer than 6 months) of the asymptomatic immunotolerant type. Inactive carriers are characterized by HBsAg positivity, seroconversion of HBeAg to anti-hepatitis B early antibody, undetectable HBV DNA, and normal serum aminotransferases. Individuals with active hepatitis are at greatest risk for developing cirrhosis and hepatocellular carcinoma.

Diagnosis

The diagnosis of HBV is most commonly made by the presence of HBsAg in the serum. UK guidelines recommend that all pregnant women should be offered screening for hepatitis B infection during each pregnancy. Confirmatory testing and testing for HBeAg of those mothers shown to be infected should follow. Where an unbooked mother presents in labour, an urgent HBsAg test should be performed to ensure that vaccine can be given to babies born to positive mothers within 24 hours of birth. Management of the infant should be based on the results of these markers and, if available, HBV viral load testing of the mother.

Management

If a woman is screen-positive for HBV, she should be referred to an appropriate specialist (hepatologist, gastroenterologist or infectious disease specialist) within 6 weeks of a positive result. There, she should be fully evaluated in terms of any acute management and arrangements made for appropriate postnatal vaccination of the baby. All babies born to these mothers should receive a complete course of vaccine on time. Babies born to highly infectious mothers (e.g. mother HBeAg positive; mother HBeAg positive and anti-HBeAg negative; HBeAg unknown; acute hepatitis B during pregnancy; HBV DNA level $\geq 1 \times 10^6$ IU/mL) should receive hepatitis B immunoglobulin (HBIG) as well as active immunization. HBIG should preferably be given within 24 hours of delivery, and should be ordered well in advance of the birth. HBIG may be given simultaneously with vaccine but at a different site. There should also be discussion about testing of other family members. Notification of hepatitis B is a legal requirement.

Summary box 13.2

- Women who are HBV surface-antigen positive but e-antigen negative should be offered postnatal vaccination of the baby to prevent vertical transmission.
- Women who are e-antigen positive are offered both vaccination and HBIG.

Rubella

Rubella, although usually causing a minor maternal illness, is one of the most teratogenic infections known. Fortunately, since the introduction of the rubella vaccine, the incidence of rubella and congenital rubella syndrome has decreased substantially. Universal immunization against rubella, using the measles, mumps and rubella (MMR) vaccine, was introduced in the UK in the October 1988. The aim of this policy was to interrupt circulation of rubella among young children, thereby protecting susceptible adult women from exposure. This led to a considerable decline in rubella in young children following the introduction of MMR, with a concomitant fall in rubella infections in pregnant women, from 167 in 1987 to one in 2003 [8]. However, recent data from Health Protection Agency national surveillance systems in the UK have reported a national increase in the number of women susceptible to rubella [3].

Pathogenesis and transmission

Rubella is caused by a togavirus and spread by droplet transmission. Following exposure to the virus via nasopharyngeal secretions, almost 80% of susceptible individuals become infected. Replication occurs in the nasopharynx and regional lymph nodes, and viraemia develops 5–7 days after exposure. Viraemia usually results in placental and fetal infection. The incubation period is 14–21 days, and in most cases a rash develops 14–17 days after exposure. Individuals with rubella are infectious from 1 week before symptoms appear to 4 days after the onset of the rash.

Clinical manifestations

Rubella is a mild disease. There may be a mild prodromal illness involving a low-grade fever, malaise, coryza and mild conjunctivitis. Lymphadenopathy may precede the rash and usually involves post-auricular and suboccipital glands. The rash is usually transitory, erythematous and mostly located behind the ears and on the face and neck. Clinical diagnosis is unreliable as the rash may be fleeting and is not specific to rubella. Complications include thrombocytopenia and post-infectious encephalitis. In adults, arthritis and arthralgia may occasionally be seen after rubella infection.

Maternal rubella infection in pregnancy may result in fetal loss or in congenital rubella syndrome (CRS). CRS presents with one or more of the following:

- cataracts and other eye defects;
- deafness;
- cardiac abnormalities;
- microcephaly;
- retardation of intrauterine growth;
- inflammatory lesions of brain, liver, lungs and bone marrow.

Deafness is the most common and sometimes the only manifestation, especially when infection occurs after 16 weeks' gestation. Cardiac defects include patent ductus arteriosus, pulmonary stenosis, septal defects and coarctation of the aorta. Eye defects include cataracts, microphthalmia, pigmentary retinopathy and glaucoma. Neurological problems include encephalitis, microcephaly, mental handicap and behavioural problems. Other abnormalities include hepatitis, splenomegaly, thrombocytopoenia and growth retardation. Diabetes mellitus occurs frequently in later childhood in those with CRS.

Infection from 8 to 10 weeks of pregnancy results in damage in up to 90% of surviving infants. The risk of damage declines to about 10–20% when infection develops between 11 and 16 weeks' gestation [9]. The risk of fetal damage is small when infection happens after 16 weeks of pregnancy: only deafness has been reported following infections up to 20 weeks of pregnancy. Some infected infants may appear normal at birth but perceptive deafness may be detected later.

Diagnosis

The diagnosis of rubella infection is usually based on serological analysis. Detection of rubella IgM indicates recent infection, although re-exposure to rubella may induce a reappearance of low-titre IgM. Following a primary rubella infection, IgM can be detected within 5–7 days and may persist up to 2 months. Specific IgG develops by 2 weeks and persists for life; re-exposure may increase IgG titres temporarily. A history of exposure to, or possible recent infection with, rubella in early pregnancy is actively sought, particularly in recent immigrants, and the laboratory is informed of a suspicious history so that the appropriate tests for primary rubella infection (IgM and IgG avidity) are performed [10]. If the first specimen has detectable antibody and was obtained within 7–10 days of exposure, there is no risk of infection and further evaluation is unnecessary. Diagnosis of subclinical infection is straightforward if the woman is known to be susceptible, the exposure is recognized, and a serum sample is obtained

approximately 28 days after exposure. The diagnosis of subclinical infection is more difficult if the immune status of the woman is unknown. It can be facilitated, however, if the acute-phase serum specimen is obtained as soon as possible after a recognized exposure that did not occur more than 5 weeks earlier. Testing is considered unnecessary if there is documented evidence of two tests on different blood samples both confirming the presence of rubella-specific IgG. Rubella immune status should be assessed at first prenatal care visit. Susceptible women should be counselled regarding prevention strategies and be vaccinated post partum.

Management

The management of the pregnant woman exposed to rubella needs to be individualized and depends on when during gestation she was exposed and on her state of immunity. Confirming the diagnosis, counselling about the risks of infection of and damage to the fetus, and discussing all the available options, including the use of immunoglobulin and consideration of termination of pregnancy, require an understanding of the natural history and consequences of rubella in pregnancy. In the case of congenital infection, emphasis is on diagnosis and acute and long-term management. Isolation may also be important to reduce spread of infection. There is no treatment for rubella and supportive care should be offered. Droplet precautions are recommended for 7 days after the onset of the rash. Human immunoglobulin is not routinely used for post-protection from rubella since there is no evidence that it is effective. It is not recommended for the protection of pregnant women exposed to rubella, and should only be considered when termination of pregnancy is unacceptable.

There is no evidence that rubella-containing vaccines are teratogenic. However, as a precaution, MMR vaccine should not be given to pregnant women. If MMR vaccine is given to adult women, they should be advised to guard against pregnancy for 1 month. Termination of pregnancy following inadvertent immunization should not be recommended. Pregnant women who are found to be susceptible to rubella should be immunized with MMR after delivery. Breastfeeding is not a contraindication to MMR immunization, and MMR vaccine can be given to breastfeeding mothers without any risk to their baby [8].

Summary box 13.3

- Pregnant women who are found to be susceptible to rubella should be immunized with MMR after delivery.
- Rubella antibody testing should be offered at least in a first pregnancy irrespective of a single previous report of rubella-specific IgG and immunization history.

Syphilis

Despite the description of syphilitic infection for more than 500 years and availability of adequate therapy for more than 50 years, syphilis in the adult and neonate still represents a relevant issue for public health providers. The elimination of congenital syphilis from the UK was considered within the framework of the 2013 WHO guidelines for validating the elimination of mother-to-child transmission of syphilis. Diagnoses of infectious syphilis in reproductive-age women fell from 268 in 2010 to 206 in 2013. The uptake of antenatal screening in England rose from 96.6% in 2010 to 97.9% in 2013. Despite the high antenatal screening coverage, concerns have been raised about the effectiveness of case management and control strategies [11].

Pathogenesis and transmission

Treponema pallidum, the causative agent of syphilis, is a Gram-negative bacterium. Syphilis can be passed horizontally from person to person through direct contact, such as during sexual activity, resulting in acquired syphilis, or vertically from mother to baby, resulting in congenital syphilis. Because sexual contact is the most common mode of transmission for acquired disease, the sites of inoculation are usually the genital organs, but lips, tongue and abraded areas of the skin have been described as well. Such an entry point is identified as the site of the initial ulcerating sore, or chancre. The cervical changes associated with pregnancy, including ectropion, hyperaemia and friability, increase the risk of spirochaete entry. Local replication then occurs and lymphatic dissemination leads to the systemic findings of secondary syphilis. The incubation period averages 3 weeks (3–90 days) depending on inoculum load and host factors. Although transmission of syphilis to the fetus can occur throughout pregnancy, the likelihood of vertical transmission increases with advancing gestation. A newborn occasionally may be infected perinatally, by contact at delivery with an infectious lesion present in the birth canal or perineum. Postnatal transmission from mother to child is rare. The likelihood of vertical transmission is directly related to the maternal stage of syphilis, with early primary syphilis resulting in significantly higher transmission rates than late latent infection. Among pregnant women with untreated primary or secondary early syphilis, the rate of transmission is 60–100% but decreases with later stages of maternal infection to approximately 40% with early latent infection and 8% with late latent infection.

Clinical manifestations

Maternal syphilis infection is staged according to duration and clinical features. Primary syphilis is the initial stage and its characteristic lesion is an erosion called a chancre. It is a typical, indolent, well-circumscribed, flat ulcer with a yellow-coated base and an indurated non-undermined wall. As it causes no symptoms and because of its location on the labia minora, within the vagina or on the cervix or perineum, it is often unrecognized. Two to ten weeks after the primary lesions, an infected woman may experience secondary disease: the time of systemic dissemination with involvement of many major organ systems. Of women with secondary syphilis, 90% have dermatological manifestations. The rash of secondary syphilis appears as rough, red or reddish-brown spots mostly occurring on the palms, soles and trunk, where they tend to follow skin lines. Plantar and palmar maculopapular target-like lesions are commonly seen. Patchy alopecia may result when hair follicles are involved. Mucosal lesions called mucous patches will develop in 35% of women. Systemic symptoms are commonly seen in secondary syphilis (70%), with generalized lymphadenopathy, fever, fatigue, weight loss, anorexia, pharyngitis, splenomegaly, sore throat, headache, myalgia and arthralgia (with a noticeable nocturnal pattern). The signs and symptoms of secondary syphilis usually resolve with or without treatment. However, without treatment the infection will progress to the latent stages of disease.

Latent syphilis is defined as the period after infection when patients are seroreactive but demonstrate no clinical manifestations of disease. Early latent syphilis is latent syphilis of less than 12 months' duration. During this stage, 20–25% of women will relapse. Late latent syphilis is diagnosed after being asymptomatic for more than 12 months. The woman is still infectious during latent stages. Of untreated women, 20–30% will progress to tertiary syphilis. After 15 years, three-quarters of infected subjects show evidence of tertiary syphilis, 50–80% of whom have cardiovascular complications. In 9% of untreated subjects the gummata of tertiary disease can be found: localized nodules that can have central necrosis. Approximately 15% of untreated infected subjects develop neurosyphilis in the tertiary stage. Mortality from untreated syphilis has been described to be about 8–14% [12].

Clinicians caring for pregnant women should be aware that any ulcer, regardless of location, that is painless, indurated and indolent and which fails to heal within 2 weeks needs exclusion of syphilis. Similarly, any generalized skin eruption, regardless of its morphology, should be viewed as secondary (disseminated) syphilis until proven otherwise.

The extent of damage to a fetus affected by congenital syphilis depends on the stage of development when infection occurs and the elapsed time before treatment. With infection early in pregnancy and in the absence of therapy, fetal demise or late-term stillbirth occurs, but premature delivery or neonatal death may also occur. In liveborn infants, infection can be clinically recognizable or silent. When symptoms are present, congenital syphilis is characterized by the presence of hepatosplenomegaly, lymphadenopathy, rash, mucocutaneous lesions, haemolytic anaemia or thrombocytopenia, osteochondritis and pseudoparalysis, periostitis, rhinitis and central nervous system (CNS) involvement, all of which usually appear within the first 2–8 weeks of life.

Late congenital syphilis lesions represent the scars induced by initial lesions of early congenital syphilis or reactions to persistent and ongoing inflammation. They usually present after 2 years of life and often in early adolescence, and include Hutchinson teeth, mulberry molars, interstitial keratitis, healed chorioretinitis, secondary glaucoma (uveitis), corneal scarring, eighth nerve deafness, 'saddle nose', protuberant mandible, rhagades, mental retardation, arrested hydrocephalus, convulsive disorders, optic nerve atrophy, juvenile general paresis, cranial nerve palsies and sabre shins. Congenital syphilis can be prevented or treated *in utero*.

Diagnosis

All pregnant women should have serological screening for syphilis at their first antenatal assessment. Tests should be repeated later in pregnancy if a woman has been at risk of infection after a negative initial screen. Diagnosis of syphilis in pregnant women is usually performed by a non-treponemal serological screening test, with a treponemal serological test for confirmation. Non-treponemal antibody tests consist of the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) assay. Treponemal antibody tests are represented by treponemal enzyme immunoassay (EIA), treponemal chemiluminescent assay (CLIA), *T. pallidum* haemagglutination assay (TPHA) and fluorescent treponemal antibody absorption test (FTA-abs).

An EIA/CLIA, preferably detecting both IgM and IgG, is the screening test of choice. Positive screening tests should be confirmed with a different treponemal test (not the FTA-abs) and a second specimen for confirmatory testing obtained. A quantitative RPR or VDRL should be performed when screening tests are positive as it is recommended for monitoring the serological response to treatment. An initial RPR/VDRL titre above 16 usually indicates active disease and the need for treatment.

The diagnosis of congenital syphilis prenatally is difficult. Sonographic findings may include hydrops fetalis, hepatomegaly, placental thickening and hydramnios, but often the infected fetus will have a normal sonogram. Polymerase chain reaction (PCR) can be performed on amniotic fluid.

Management

Treatment of pregnant women with congenitally transmissible syphilis can significantly reduce the risk of congenital syphilis, stillbirths, premature births, neonatal deaths and severe illness in infancy and beyond. The pregnant woman can also be treated to prevent progression of disease, as well as giving the opportunity of treatment for their sexual partners. Once a screen-positive result is confirmed, the woman and her family should be referred to a specialist in genitourinary medicine for assessment, counselling and possible treatment.

Where syphilis is treated in the current pregnancy, particularly when this is early infection, maternal referral to fetal medicine is recommended when 26 weeks' gestation has been reached prior to treatment. Fetal syphilis infection may be suggested by ultrasound detection of non-immune hydrops or hepatosplenomegaly. Fetal assessment will help planning of antepartum care as well as neonatal treatment.

A single dose of benzathine penicillin G 2.4 million units is effective in most cases. Physiological changes in pregnancy alter drug pharmacokinetics and may cause reduced plasma penicillin concentrations. For this reason, when treatment is initiated in the third trimester, a second dose of benzathine penicillin is recommended 1 week after the first, with careful assessment of the neonate at birth. Up to 50% of women treated for early-stage syphilis will have a systemic reaction called the Jarisch–Herxheimer reaction. Although transient with only mild constitutional symptoms, preterm labour and fetal distress may complicate treatment. The uterine contractions appear to occur secondary to the development of fever. Fetal heart rate decelerations are also reported, occurring in about 40%, concomitant with maternal fever, and resolve within 24 hours of maternal penicillin treatment.

After treatment, it may take several months to observe a fourfold drop in RPR/VDRL titre and in many pregnancies labour will occur before this period has elapsed. Hence, serological cure may not be demonstrable before birth of the neonate [13].

Summary box 13.4

- All pregnant women should have syphilis serology at their first antenatal clinic visit, and if risk of syphilis is recognized, re-screening later in pregnancy should be offered.
- Retreatment in pregnancy is indicated where there is uncertainty of treatment or serological cure is in doubt.
- When treatment of early syphilis is initiated in the third trimester, a second dose of benzathine penicillin 1 week after the first is recommended.

Toxoplasmosis

Toxoplasma gondii is an intracellular parasite that can infect humans and almost all warm-blooded animals. The infection is transmitted through infected cat faeces, undercooked raw meat, and transplacentally. It is common worldwide, including in the UK, but it is rarely reported because there are often no symptoms. Around 350 cases are reported in England and Wales each year, but it is thought the actual number of infections could be as high as 350 000. Congenital toxoplasmosis is rare in the UK, with estimates suggesting that only around 1 in 10 000–30 000 babies are born with this condition. Routine antenatal serological screening for toxoplasmosis should not be offered because the risks of screening may outweigh the potential benefits.

Pathogenesis and transmission

Toxoplasma gondii has a complex life cycle with asexual reproduction taking place in mammals and birds (secondary hosts) and sexual reproduction taking place in the digestive epithelium of cats (primary host). Cats mainly become contaminated by ingesting animal flesh encysted with *T. gondii*. Infected cats excrete millions oocytes a day; these oocytes then sporulate and become infectious. The three main routes of transmission are ingestion of raw or undercooked meats, exposure to oocyst-infected cat faeces, and vertical transmission. In pregnancy, the most common mechanisms of infection are through consuming raw or very undercooked meats or contaminated water, or exposure to soil (gardening without gloves) or cat litter [14]. Transplacental passage of toxoplasmosis occurs when a woman becomes infected during pregnancy. The risk of developing congenital toxoplasmosis increases with advancing gestational age. The incidence of transmission is 3–9% if infection occurs in the first trimester and highest (60–81%) if it occurs in the third trimester. Conversely, the severity of disease is worse if infection occurs in the first trimester, with a risk of development of clinical signs in the infected fetus of 60%. Infection prior to pregnancy confers immunity with minimal risk of vertical transmission [15].

Clinical manifestations

Toxoplasmosis is asymptomatic in more than 90% of cases. Only a small proportion of women will develop clinical signs of the disease, which often occurs as a flu-like illness, with lymphadenopathy and fatigue being the most common manifestations. The incubation period is 5–18 days following exposure. The symptoms are usually self-limiting, resolving within a few weeks or months.

Immunocompromised pregnant women are at higher risk of developing serious complications like severe encephalitis, myocarditis, pneumonitis or hepatitis.

Congenital toxoplasmosis is characterized by the tetrad of chorioretinitis, hydrocephalus, intracranial calcification and convulsion. Ultrasound evidence of intracranial calcification, microcephaly, hydrocephalus and intrauterine growth restriction suggests *in utero* infection when maternal infection is documented.

Diagnosis

Serological tests for the detection of specific anti-*Toxoplasma* IgG and IgM antibodies are the most widely used. Anti-*Toxoplasma* IgG can be identified 2–4 weeks after infection, reaches a peak after 2 or 3 months, and then stabilizes at a plateau for several months before decreasing to very low levels persisting throughout life. A positive IgG test before pregnancy means that the fetus is not at risk. Anti-*Toxoplasma* IgM is traditionally tested in parallel with IgG. IgM antibodies are the first to appear after an acute infection (1 or 2 weeks before IgG). Therefore, in a susceptible patient, IgM alerts to a possible acute infection before IgG antibodies are detected. After increasing for 1 month, IgM antibodies persist for a variable period. Absence of IgM when IgG antibodies are detected helps to exclude a recent infection. However, IgM can remain positive for months and even years, and interpretation of a positive result requires great caution. For this reason the measurement of IgG avidity is often useful in pregnant women who present with antibodies in their first sample. IgG avidity measures the strength of antigen–antibody binding, which increases with the time elapsed since infection. In the first month after primary infection IgG antibodies are of low avidity, while the ones produced months or years after infection show high avidity. High avidity allows the exclusion of an infection acquired in the last 12–20 weeks, and if a test was performed in the first trimester, a high-avidity index will exclude that infection took place during pregnancy.

The prenatal diagnosis of fetal infection is based on ultrasound scanning and PCR testing of amniotic fluid or blood. Ultrasound evidence of hydrocephaly, intracranial calcifications in the parenchyma or in a periventricular position, placental thickening, liver calcifications, hyperechoic bowel, ascites and growth restriction have been reported in fetuses affected by *T. gondii* infection *in utero*.

Management

Routine antenatal serological screening for toxoplasmosis should not be offered because the risks of screening may outweigh the potential benefits. Prevention of toxoplasmosis in pregnant women is paramount. Pregnant women should be informed of primary prevention measures to avoid toxoplasmosis infection, such as washing hands before handling food, thoroughly washing all fruit and vegetables, thoroughly cooking raw meats and ready-made meals, wearing gloves and washing hands after handling soil/gardening, and avoiding cat faeces in cat litter or in soil.

Treatment of toxoplasmosis in the infected pregnant women is variable, depending on maternal immune status, gestational age and presence of fetal infection. Primary maternal infection is usually a mild disease and is self-limiting, with symptoms disappearing within a few weeks or months without any treatment. However, treatment is thought to decrease the rate of congenital infection and reduce the severity of the disease in the neonate and therefore it is usually started in pregnant women. Drug regimens most commonly used rely primarily on spiramycin and a pyrimethamine/sulfadiazine combination. In countries with a monthly prenatal serological testing programme, such as France and Italy, the first-line drug for prevention of fetal infection is spiramycin, which is started as soon as maternal infection is suspected. When analysis of amniotic fluid confirms the presence of fetal infection, spiramycin is stopped and treatment switched to the combination of pyrimethamine and sulfadiazine.

Women should be counselled on the option of termination of pregnancy in the case of severe morphological lesions. Over 90% of neonates with congenital infection show no clinical signs of infection at birth. In the absence of any treatment neonates are at risk of developing long-term sequelae: chorioretinal disease (up to 85% of infected children), major neurological abnormalities, and psychomotor and mental impairments.

Summary box 13.5

- Routine antenatal serological screening for toxoplasmosis should not be offered because the risks of screening may outweigh the potential benefits.
- *Toxoplasma gondii* infection should be suspected and screening should be offered to pregnant women with suspicious ultrasound findings, including intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly or intrauterine growth restriction.

Cytomegalovirus

Cytomegalovirus (CMV) is the most common congenital infection in the UK, affecting around 3 per 1000 births, and can cause neurological impairment such as hearing loss. CMV seroprevalence is generally around 40–50%

among white populations but is as high as 80–100% in some non-white populations [16]. In the UK, it is estimated that one to two babies in every 200 will be born with congenital CMV. Of these, about 13% will have problems at birth, such as hearing loss and learning difficulties, with a similar number developing problems later.

Pathogenesis and transmission

CMV is a ubiquitous, double-stranded DNA herpesvirus that is transmitted by sexual contact or direct contact with infected blood, urine, nasopharyngeal secretions or saliva. The incubation period is 28–60 days and viraemia can be detected for 2–3 weeks after primary infection. After the primary infection, CMV remains latent in host cells and recurrent, or secondary, infection can occur. Vertical transmission of CMV mostly occurs by transplacental infection after primary or secondary infection, but can also follow exposure to contaminated genital tract secretions at delivery, or breastfeeding. The evidence of intrauterine transmission in the presence of maternal immunity has been attributed to reactivation of endogenous virus in some cases and to reinfection with different strains of CMV in others. With primary maternal CMV infection, the overall risk of transmission to the fetus is approximately 30–40%. In contrast, only 0.15–1% of women with recurrent infection will transmit the virus to the fetus. Among fetuses infected after a primary infection, 12–18% will have signs and symptoms of CMV at birth and up to 25% will develop sequelae. Fetuses infected after maternal CMV reactivation are usually asymptomatic at birth. As with other congenital infections, the risk of transmission is greatest in the third trimester (40–72%), compared with a lower risk in the first trimester (30%). However, fetal damage is more serious the earlier in gestation transmission occurs.

Clinical manifestations

The majority of adults infected with CMV experience few or no symptoms and no long-term sequelae. Some experience a mononucleosis-like syndrome with symptoms including malaise, headache, fever, myalgia, cervical lymphadenopathy and, less commonly, pneumonia and hepatitis. Secondary infections are usually asymptomatic.

Of congenitally infected infants, 10–15% will have symptoms at birth due to the involvement of multiple organs, in particular the reticuloendothelial system and the CNS, with or without ocular and auditory damage. The abnormalities most frequently present in infants with symptomatic congenital infection are hepatomegaly, splenomegaly, microcephaly, jaundice and petechiae. Hydrocephalus, haemolytic anaemia and pneumonitis can occasionally be present. Among the most severely affected infants 10–30% will die, mostly of disseminated intravascular coagulation, hepatic dysfunction or bacterial superinfection.

Nearly 90% of infants with congenital CMV infection have no signs or symptoms at birth, but at least 10–15% of them are at risk of developing a number of developmental abnormalities, including sensorineural hearing loss, microcephaly, motor defects, mental retardation, chorioretinitis, dental defects and others that were once thought to be limited to infants with symptomatic congenital infections. These abnormalities usually become apparent within the first 2 years of life.

Diagnosis

Primary maternal CMV infection in pregnancy is diagnosed on the basis of *de novo* appearance of specific IgG in the serum of a woman who was previously seronegative, or on identification of specific IgM associated with low IgG avidity. CMV IgM is detected within a few days of infection and may remain positive for 4–8 months and re-emerge with recurrent infection. A secondary infection should be diagnosed when a significant rise of IgG antibody titre is documented independently of the presence of IgM and high IgG avidity. In cases of proven secondary infection, amniocentesis may be considered.

Congenital CMV may be suspected prenatally on the basis of ultrasound findings suggestive of infection. The most frequently reported include abdominal and liver calcifications, hepatosplenomegaly, echogenic bowel or kidneys, ascites, cerebral ventriculomegaly, intracranial calcifications, microcephaly, hydrops fetalis, pleural effusion, oligohydramnios and growth restriction. The severity of the detected abnormalities can help in defining the prognosis of the fetus, but the absence of sonographic findings does not guarantee a normal outcome.

The prenatal diagnosis of CMV is possible by testing amniotic fluid obtained by amniocentesis, where sensitivity of PCR can reach 100% if the test is performed after 21 weeks of gestation and at least 7 weeks after presumed time of maternal infection. Unfortunately, a positive PCR result does not discriminate between infants who will have symptoms and those who will not. It has been suggested that when the viral load in the amniotic fluid is greater than or equal to 10^5 genome equivalents of CMV DNA, the risk of symptomatic congenital CMV infection is significantly high.

Management

Currently, no therapies are available for the treatment of maternal or fetal CMV infection. Use of antiviral medications in routine clinical care of pregnant women is not recommended. Similarly, passive immunization with CMV-specific hyperimmune globulin is not recommended outside of a research protocol [17]. The

principal source of CMV infection among women of childbearing age is exposure to children excreting CMV. Education of susceptible pregnant women has been shown to significantly reduce the incidence of infection. Preventive measures, like hand washing and minimizing exposure from high-risk areas such as nurseries, must be recommended.

Screening in pregnancy is not recommended because there is uncertainty regarding the natural history of primary and recurrent CMV as it relates to the risk to the fetus. Furthermore, the screening test for susceptibility lacks sufficient sensitivity and there is uncertainty regarding the further investigations needed to refine the risk to the fetus in women with primary infection. Finally, interventions have not been shown to be effective in preventing maternal infection or reducing the risk of transmission to the fetus.

When a recent primary infection is diagnosed, invasive testing can be offered to identify infected fetuses. In the counselling process it is important to consider the stage of infection and gestational age, and to stress that the majority (90–95%) of children with congenital CMV infection will not suffer significant CNS sequelae, and that only about 10% will experience some degree of hearing loss. When a primary maternal infection is documented, parents should be informed of a 30–40% risk for fetal infection, and a 20–25% risk for development of sequelae postnatally in infected fetuses.

As no specific antiviral treatment for prenatal therapy is available, the only options following a prenatal diagnosis of CMV infection are termination of pregnancy or observation. The presence or absence of fetal abnormalities diagnosed at ultrasound represent an important factor in the decision-making process. Fetal MRI may improve the prognostic evaluation, especially when brain abnormalities are seen on ultrasound.

Summary box 13.6

- Congenital CMV infection is the leading infection causing mental retardation and sensorineural deafness.
- Routine serological screening in pregnancy is not recommended, and testing should be reserved for pregnant women who develop flu-like illness or following detection of ultrasound evidence suggestive of CMV infection.

Parvovirus B19

Human parvovirus B19 is a single-stranded DNA virus with a predilection for infecting rapidly dividing cell lines, such as bone marrow erythroid progenitor cells, leading to severe anaemia in the fetus. Approximately 50–70% of women of reproductive age have immunity to parvovirus B19. About 1–3% of susceptible pregnant women will develop serological evidence of infection in pregnancy. Women at increased risk of infection include mothers of preschool and school-age children and school teachers. The reported number of infections in the UK is 1 in 512 pregnancies per year, while seroconversion occurs in 1–13% of susceptible pregnant women [18].

Pathogenesis and transmission

Transmission of parvovirus B19 from person to person is probably by droplets from oral or nasal secretions. Viral DNA is present in saliva at levels similar to those in blood. As the main mode of transmission is respiratory, epidemics of parvovirus B19 infection can occur. The virus can also be transmitted parenterally through blood or blood product transfusion, or vertically from mother to fetus. The incubation period is 4–20 days. Patients are infectious 10 days before the onset of the rash and remain contagious for only 1–2 days after the rash appears. Risk of intrauterine infection rise with increasing gestational age, ranging from 15% when infection occurs before 16 weeks of gestation, to 25–70% thereafter.

Clinical manifestations

The clinical expression of parvovirus infection is variable. Infection can be asymptomatic in up to 50% of cases, and in up to 70% of infected pregnant women. Children with parvovirus infection most commonly develop erythema infectiosum, characterized by the presence of flu-like symptoms, fever and headache, followed by a 'slapped cheek' rash (fifth disease) that usually spreads to the trunk and limbs after about 1 week. Adults with parvovirus B19 infection usually do not have an extensive rash, but may suffer from symmetrical polyarthralgias and arthritis.

Parvovirus has been associated with hydrops fetalis, with an overall incidence of 2.9%. Spontaneous miscarriage and stillbirth have also been reported. Possible mechanisms for hydrops include fetal anaemia following transplacental infection which, combined with the shorter half-life of fetal red blood cells, leads to severe anaemia, hypoxia and high-output cardiac failure. Another mechanism can be the development of a viral myocarditis leading to cardiac failure. Parvovirus infection is the most common infectious cause of non-immune hydrops.

Diagnosis

A pregnant woman suspected of having parvovirus because of symptoms or, more commonly, secondary to exposure to an infected child should have serological testing. In patients with a rash, recent parvovirus

infection should be confirmed or excluded by testing for parvovirus B19-specific IgM on the first serum obtained. Women who are IgM negative and IgG positive have evidence of previous exposure and immunity and are not at risk. Absence of parvovirus B19-specific IgM excludes infection in the 4 weeks prior to collection of the serum. Therefore infection cannot be excluded if testing is carried out more than 4 weeks after onset of rash illness. If parvovirus B19-specific IgM is detected in the first 20 weeks of pregnancy, confirmation is required. If IgM and IgG are both present, they indicate recent infection 1 week to 6 months previously. Infection can also be investigated by testing the antenatal booking sample in parallel with the sample at presentation to show seroconversion. Fetal parvovirus infection should be considered if non-immune hydrops is detected on ultrasound. Fetal infection can be diagnosed using PCR to detect parvovirus B19 DNA in amniotic fluid or fetal blood samples [19].

Management

Women with acute parvovirus B19 infection should be monitored for the development of fetal anaemia using serial ultrasonography every 1–2 weeks, up to 12 weeks after infection. Ultrasound monitoring for the features of fetal anaemia should include assessment for ascites, placentomegaly, cardiomegaly, hydrops and intrauterine growth restriction. Above all, Doppler assessment of peak systolic velocity of the fetal middle cerebral artery should be performed as an accurate predictor of fetal anaemia. If hydrops fetalis is present or severe fetal anaemia is suspected, fetal blood sampling should be performed to determine the need for a fetal transfusion. If a transfusion is performed and the fetus survives, 94% will recover within 6–12 weeks. Most fetuses require only one transfusion as fetal haematopoiesis resumes as the parvovirus infection resolves. No significant delay was noted on standard neurodevelopmental testing in the assessment of long-term neurodevelopmental outcomes of children treated with intrauterine transfusion for parvovirus infection.

Summary box 13.7

- In pregnant women exposed to, or who develop symptoms of, parvovirus B19, recent parvovirus infection should be confirmed or excluded by determining parvovirus B19 IgG and IgM.
- If a recent parvovirus B19 infection has been diagnosed in the woman, she should be referred to a fetal medicine specialist and serial ultrasound should be performed every 2 weeks, up to 12 weeks after infection, to allow timely detection of fetal anaemia and arrangements for *in utero* fetal transfusion.

Herpesvirus

Genital herpesvirus infection has been rising in prevalence in the developed world and in the UK, and neonatal infection still represents a tremendous consequence of genital herpes. Neonatal herpes is rare in the UK. Active surveillance by the British Paediatric Surveillance Unit (BPSU) between 1986 and 1991 found an annual incidence of 1.65 per 100 000 live births. Subsequent surveillance from 2004 to 2006 showed an approximate doubling of incidence over the 3-year surveillance period. This might be mostly due to the rise in the prevalence of sexually transmitted infections, demographic and social changes within the general population and improvements in diagnostic techniques [20].

Pathogenesis and transmission

Herpes simplex virus (HSV) types 1 and 2 are members of the large family of herpesviruses. A common characteristic of all members of the herpesvirus family is the ability to establish latency, to persist in this latent state in cranial nerves or dorsal spinal ganglia for various intervals of time, and to reactivate and cause active infection (with or without disease) and viral transmission. Transmission of HSV most often occurs by person-to-person contact. Virus must come in contact with mucosal surfaces or abraded skin for infection to be initiated. The incubation period is 3–6 days. Genital herpes and neonatal herpes may be caused by HSV-1 or HSV-2. HSV-1 was originally localized to orolabial areas, but recent data show that approximately 50% of neonatal herpes is due to HSV-1 and 50% to HSV-2. Recurrent genital herpes is mostly secondary to HSV-2 (>90%).

The risk of neonatal HSV depends on multiple factors: the type of maternal infection (primary or recurrent), the presence of maternal antibodies, the duration of rupture of membranes before delivery, the use of fetal scalp electrodes and the mode of delivery. The risks are greatest for a primary infection occurring in the third trimester, particularly within 6 weeks of delivery, as viral shedding may persist and the baby is likely to be born before the development of protective maternal antibodies. Rarely, congenital herpes may occur as a result of transplacental intrauterine infection. Neonates born from mothers suffering recurrent herpes at the time of delivery, which is commonly asymptomatic or unrecognized, have a modest risk of developing the localized forms of neonatal herpes, both local CNS disease and skin, eye and mouth infection. Most infants who develop neonatal disease are born to women who are completely asymptomatic for genital HSV infection during the pregnancy and at the time of delivery.

Clinical manifestations

Maternal HSV infection can be described by either stage of infection (first clinical episode of infection or recurrence) or prior immune status (primary or non-primary). Typical clinical manifestations include vesicular lesions, with an erythematous base, located on the genital skin or adjacent areas. They often evolve into pustules, then ulcerations and finally, if on keratinized skin, crusted lesions. Atypical presentations are common, including minor erythema, fissures, pruritus, and pain with minimal detectable signs.

Recurrent infection has a variable clinical presentation, from completely asymptomatic viral shedding to overt clinical recurrences. Of pregnant women with a history of HSV, 5–10% will present with a symptomatic recurrence. Finally, asymptomatic viral shedding may occur in the absence of any signs and symptoms.

The manifestations of neonatal or congenital HSV infection have been classified into three levels of disease: (i) skin, eye and mouth infection; (ii) CNS disease (manifested as encephalitis); and (iii) disseminated disease (the most serious form of infection, with a 90% mortality rate if untreated). A typical clinical presentation and/or the presence of a positive culture from the neonate more than 48 hours after delivery allow a diagnosis of neonatal HSV infection.

Diagnosis

Patient history and clinical examination can help in the diagnosis of HSV infection. However, it can be difficult to distinguish clinically between primary and recurrent genital HSV infections, as in up to 15% of cases reported as a first episode of clinical HSV infection it will actually be a recurrent infection. All the lesions identified should be unroofed and the fluid cultured. For women presenting with first episode of genital herpes in the third trimester, particularly within 6 weeks of expected delivery, specific HSV antibody testing (IgG to HSV-1 and HSV-2) is advisable. The presence of antibodies of the same type as the HSV isolated from genital swabs would confirm this episode to be a recurrence rather than a primary infection. For these women, characterizing the infection will influence the management and the counselling regarding mode of delivery and risk of neonatal HSV infection.

Management

Women with suspected genital herpes should be referred to a genitourinary medicine physician, who will confirm or refute the diagnosis, advise on management of genital herpes and arrange a screen for other sexually transmitted infections. Management of the woman usually involves the use of oral aciclovir in standard doses (400 mg three times daily, usually for 5 days) as it reduces the duration and severity of symptoms and decreases the duration of viral shedding. Aciclovir is not licensed for use in pregnancy but has not been associated with increased incidence of birth defects. Following primary first- or second-trimester acquisition, providing that delivery does not ensue within the following 6 weeks, the pregnancy should be managed expectantly and vaginal delivery anticipated. Daily suppressive aciclovir 400 mg three times daily from 36 weeks of gestation reduces HSV lesions at term and hence the need for delivery by caesarean section. In the third trimester, treatment will usually continue with daily suppressive aciclovir 400 mg three times daily until delivery. Caesarean section should be the recommended mode of delivery for all women developing first-episode genital herpes in the third trimester, particularly those developing symptoms within 6 weeks of expected delivery, as the risk of neonatal transmission of HSV is very high at 41%. In the case of a recurrent infection, women should be informed that the risk of neonatal herpes is low, even if lesions are present at the time of delivery (up to 3% for vaginal delivery).

Summary box 13.8

- Following primary HSV infection, providing that delivery does not ensue within the following 6 weeks, the pregnancy should be managed expectantly and vaginal delivery anticipated. Daily suppressive aciclovir 400 mg three times daily from 36 weeks of gestation should be given.
- Women with primary genital herpes in the third trimester of pregnancy have a high risk of transmitting HSV to their neonates and should be offered a caesarean section to decrease this risk.
- In the case of a recurrent infection, women should be informed that the risk of neonatal herpes is low.

At the time of admission to the labour ward, a woman with a history of HSV infection should be questioned about prodromal symptoms (vulvar itching, burning) and recent HSV lesions. A careful examination of the vulva, vagina and cervix should be performed. Suspicious lesions should be cultured. Women with any evidence of prodromal or active HSV infection should be offered a caesarean delivery. Caesarean section should be recommended to all women presenting with primary-episode genital herpes lesions at the time of delivery, or within 6 weeks of the expected date of delivery. Counselling should stress a decreased risk of HSV transmission with a caesarean delivery but not a negated risk, as 10–15% of

infants with HSV are born to women undergoing a caesarean delivery.

Varicella-zoster virus

Varicella-zoster virus (VZV) is the causative agent of one of the most communicable of human diseases: chickenpox (or primary VZV infection), a common childhood disease. Over 90% of individuals over 15 years of age in England and Wales are seropositive for VZV IgG antibody. For this reason, although contact with chickenpox is common in pregnancy, especially in women with young children, primary VZV infection in pregnancy is uncommon, estimated to complicate only 3 in 1000 pregnancies.

Pathogenesis and transmission

VZV is a double-stranded DNA virus of the *Herpesviridae* family. It is transmitted by respiratory droplets and by direct personal contact with vesicular fluid. The incubation period lasts 10–21 days, with a mean of 15 days, and an infected person is contagious 24–48 hours before the rash appears and continues to be infectious until the vesicles crust over. Following the primary infection (e.g. chickenpox) the virus remains latent in sensory ganglia and can be reactivated causing a vesicular rash known as herpes zoster, or shingles.

Transplacental passage of the virus may occur, causing fetal varicella syndrome (FVS) or congenital varicella. FVS has been reported to complicate maternal chickenpox, occurring as early as 3 weeks and as late as 28 weeks of gestation. The incidence has been reported to be 0.91% before 20 weeks, while the risk appears to be lower in the first trimester (0.55%). Neonatal infection can occur after exposure of the fetus or newborn a week before to a week after delivery before protective maternal antibodies develop.

Clinical manifestations

The primary infection (chickenpox) is characterized by fever, malaise and a pruritic rash that develops into crops of maculopapules, which become vesicular and crust over before healing. The head and trunk are affected first, then spreading sporadically to the lower abdomen and extremities. The vesicles are intensely pruritic. Although varicella infection is much less common in adults than in children, it is associated with a higher risk of complications such as pneumonia, hepatitis, encephalitis and even death. The incidence of pneumonia complicating varicella in pregnancy has been quoted at 10–14%. The reported mortality rate in pregnancy is 0–14%.

FVS is characterized by one or more of the following: skin scarring in a dermatomal distribution; eye defects (microphthalmia, chorioretinitis or cataracts); hypoplasia of the limbs; and neurological abnormalities (microcephaly, cortical atrophy, mental retardation or dysfunction of bowel and bladder sphincters). Neonatal varicella that occurs following exposure near or around delivery carries a mortality rate approaching 25%. Clinical manifestations include pneumonia, disseminated mucocutaneous lesions and visceral infection.

Diagnosis

The diagnosis of varicella is usually made on the basis of clinical signs. When the diagnosis is not readily evident, VZV can be isolated from an unroofed skin lesion or vesicular fluid can be tested using a qualitative varicella PCR assay. Seroconversion can be documented by antibody assay with the use of varicella IgG serology.

Prenatal diagnosis of FVS is possible using ultrasound by identification of the following findings: limb deformity, microcephaly, hydrocephalus, soft tissue calcification and fetal growth restriction. Fetal MRI may provide additional information in cases where ultrasound has identified morphological abnormalities. VZV DNA can be detected in amniotic fluid by PCR. However, the presence of VZV DNA has a high sensitivity but low specificity for the development of FVS and women should be counselled about this limitation.

Management

Symptomatic treatment and hygiene are advised to prevent secondary bacterial infection of the lesions. Oral aciclovir should be prescribed for pregnant women with chickenpox if they present within 24 hours of the onset of the rash. Women should avoid contact with potentially susceptible individuals. A hospital assessment should be considered in a woman at high risk of severe or complicated chickenpox. The timing and mode of delivery of the pregnant woman with chickenpox must be individualized.

Prophylaxis using VZV immunoglobulin (VZIG) is an important objective for susceptible, exposed pregnant women. VZIG is recommended for VZV antibody-negative pregnant contacts exposed at any stage of pregnancy, within 10 days of contact. When supplies of VZIG are short, clinicians are advised to check availability of VZIG before offering it to pregnant women. Pregnant contacts with a positive history of chickenpox do not require VZIG. Those with a negative history must be tested for VZV antibody before VZIG is given.

Women who develop chickenpox in pregnancy should be referred to a fetal medicine specialist, at 16–20 weeks

or 5 weeks after infection, for discussion and detailed ultrasound examination. If varicella or serological conversion develops in the first 28 weeks of pregnancy, the woman has a small risk of FVS and should be informed of the implications.

If maternal infection occurs in the last 4 weeks of pregnancy, there is a significant risk of varicella infection of the newborn. A planned delivery should normally be avoided for at least 7 days after the onset of the maternal rash to allow for the passive transfer of antibodies from mother to child.

Breastfeeding is not contraindicated in women with chickenpox. An attenuated live-virus vaccine is available, and varicella vaccination before pregnancy or post partum is an option that should be considered for women who are found to be seronegative for VZV IgG [21].

Summary box 13.9

- Pregnant women with an uncertain or no previous history of chickenpox who have been exposed to infection should have a blood test to determine VZV immunity.
- If the pregnant woman is not immune to VZV and has had a significant exposure, she should be offered VZIG as soon as possible. VZIG is effective when given up to 10 days after contact.

Zika virus

Zika virus (ZIKV) infection is rapidly emerging on a global scale. The last epidemic began in Brazil in 2015 and has now spread rapidly to more than 30 countries in the Americas and the Caribbean, infecting more than 2 million inhabitants. Recent outbreaks and concerning links to Guillain–Barrè syndrome and microcephaly are incompletely understood. The limited understanding of ZIKV presents an enormous challenge for responses to this rapidly emerging threat to human health.

Pathogenesis and transmission

ZIKV is a flavivirus, a single serotype has been described, and infection is thought to lead to lifelong immunity. The incubation period ranges between approximately 3 and 12 days. It is spread through the bite of mosquitoes, and multiple mosquito species are capable vectors. Sexual transmission of ZIKV is possible, with virus detectable in semen for at least 2 months after infection. The association of ZIKV with birth defects suggests transplacental transmission. The risk window for fetal exposure to ZIKV, the rate of vertical transmission and the incidence of birth defects with maternal infection are unknown.

Clinical manifestations

Up to 80% of ZIKV infections may be subclinical [22]. The remainder are typically mild, self-limited illnesses lasting 5–7 days. A pruritic maculopapular rash, conjunctival injection, headache and fever are dominant features, although none are universally present. Arthralgia, particularly of the hands, wrists and ankles, is common and is frequently associated with periarticular swelling. ZIKV infection has been associated with development of Guillain–Barré syndrome, typically a self-limiting neurological disease that may be severe if associated with respiratory failure, profound or persistent paralysis or autonomic instability.

Maternal infection with ZIKV at any stage of pregnancy may be associated with a range of serious and adverse fetal outcomes: fetal death, placental insufficiency, intrauterine growth restriction and CNS abnormalities, including microcephaly and cerebral calcifications (Fig. 13.1). Microcephaly is manifested as incomplete brain development in the setting of an abnormally small head circumference. Recent studies report fetal abnormalities detected by ultrasonography in 30% of ZIKV-positive women.

Diagnosis

Several diagnostic RT-PCR-based assays have been used to identify ZIKV from the body fluids and tissues of infected individuals. The virus may be detectable in serum for only 2–3 days after the onset of illness and this would challenge the identification of suspected cases and confirmation of infection by serum PCR. ZIKV is detectable by PCR in urine samples for longer than in serum samples. From 5 days after the onset of disease, serological investigations can be performed to detect ZIKV-specific IgM antibodies. ZIKV serological testing will be most informative when ZIKV occurs as a primary flavivirus infection and less helpful, even misleading, in the common setting of prior flavivirus exposure or vaccination.

Management

Treatment of ZIKV infection is supportive: rest, oral hydration and treatment of symptoms with acetaminophen-based products are appropriate. No specific antiviral or vaccine is available for ZIKV, although vaccines are in development. Providers should maintain a high level of suspicion for ZIKV infection in any patient

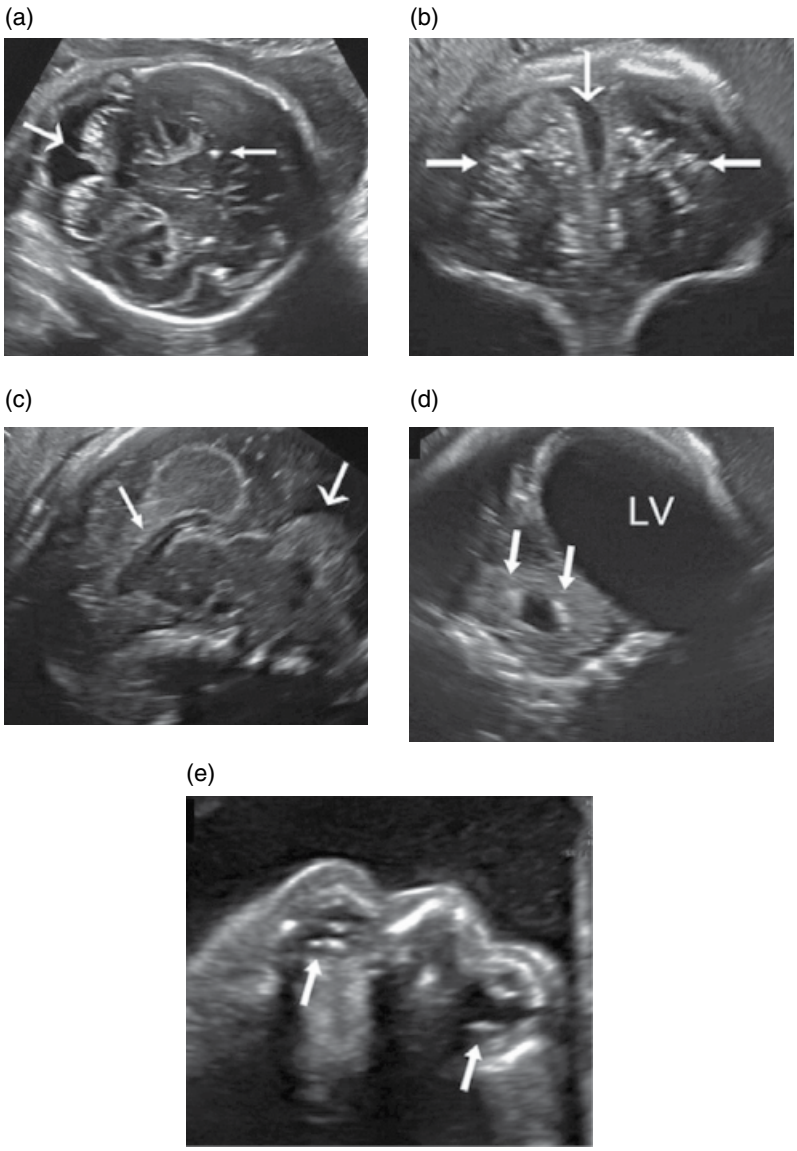

Fig. 13.1 Ultrasound images showing fetal brain malformations seen in common for toxoplasmosis, CMV and ZIKV infections. (a) Transabdominal axial ultrasound image shows cerebral calcifications with failure of visualization of a normal cerebellar vermis (large arrow). Calcifications are also present in the brain parenchyma. (b) Coronal plane shows a wide interhemispheric fissure (large arrow) due to brain atrophy and bilateral parenchymal coarse calcifications (small arrows). (c) Transvaginal sagittal image shows dysgenesis of the corpus callosum (small arrow) and cerebellar vermis (large arrow). (d) Evidence of ventriculomegaly (LV) and calcifications in the fourth ventricle (arrows). (e) Axial view shows calcifications in both eyes (arrows). Note that the proximal eye is very small and lacks normal anatomic landmarks. *Source:* Oliveira Melo *et al*. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 2016;47:6–7. Reproduced with permission of Wiley Publishers.

presenting with rash and either a personal history of recent travel to an area with active ZIKV transmission or a similar travel history for a sexual partner. Women with suspected or confirmed ZIKV infection should be monitored closely with serial ultrasonography to evaluate for signs of placental insufficiency, given the risks of fetal death and intrauterine growth restriction.

The Centers for Disease Control and Prevention has recommended the use of condoms for at least 1 month after returning for men who reside in or have travelled to an area of active ZIKV transmission to prevent transmission of ZIKV via sexual activity with pregnant or non-pregnant partners. Pregnant women in unaffected areas are currently advised to postpone travel to ZIKV-endemic regions if possible, to practice strict measures for mosquito bite avoidance if travel cannot be postponed, and to avoid sex with male partners who have visited endemic regions.

Summary box 13.10

- Despite mild clinical symptoms, ZIKV infection during pregnancy appears to be associated with adverse outcomes, including fetal death, placental insufficiency, fetal growth restriction and CNS abnormalities.
- Pregnant women are advised to postpone travel to areas with ZIKV transmission and to avoid sex with male partners who have visited endemic regions.
- Men who reside in or have travelled to an area of active ZIKV transmission are advised to practise safer sex for at least 1 month after returning in order to reduce the potential risk of onward sexual transmission.

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14

Psychiatric Problems in Pregnancy and Post Partum

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Effects of untreated prenatal depression, anxiety and stress

It is important to identify prenatal mood and anxiety disorders in the mother since untreated disorders can have negative effects on fetal development, birth outcome and child development. As such, it is important for clinicians to have an understanding of identification and treatment options for the most common disorders. It is difficult to distinguish the effects of untreated prenatal depression, anxiety and stress since so many studies examine them together. Depression, anxiety and stress during pregnancy can lead to poor health behaviours including inadequate prenatal care, poor nutrition, lack of exercise, poor compliance with prenatal vitamins and prescribed medications, and increased alcohol, smoking and drug abuse. A recent systematic review and meta-analysis reported that untreated depression was associated with a 1.56 odds ratio (OR) of preterm birth (PTB) and a 1.96 OR of low birthweight (LBW) [1]. Given the high infant morbidity and mortality associated with PTB and LBW, these increased risks with untreated prenatal depression have large public significance. Untreated prenatal depression, anxiety and stress have also been linked to increased maternal cortisol levels, spontaneous miscarriage, pre-eclampsia, caesarean section, lower Apgar scores and placental abruption. Studies have reported associations between untreated depression and anxiety and adverse outcomes on child development, such as decreased grey matter density, disrupted sleep, developmental delay and autism, cognitive impairment, internalizing and externalizing behaviours (such as attention deficit disorder, conduct disorders, antisocial behaviour), depression, anxiety and psychotic disorders, as well as obesity and metabolic dysfunction [2]. It is difficult to separate the prenatal exposure from the postnatal exposure to maternal depression, as well as other postnatal environmental factors.

Proposed mechanisms underlying maternal prenatal stress and child outcomes include the direct and indirect effect on health behaviours, maternal physiology, placenta and the postnatal environment [2]. Psychosocial stress in pregnancy can negatively impact maternal behaviours, such as smoking, substance use, unhealthy eating, sleep disturbances and physical activity, which may increase adverse pregnancy and child outcomes. Maternal exposure to stress activates the hypothalamic–pituitary–adrenal (HPA) axis and subsequent release of cortisol. Cortisol may enter the fetal circulation through direct transport across the placenta. It can also increase production of placental corticotrophin releasing hormone (CRH), which stimulates the fetal HPA axis. High cortisol concentration *in utero* influences fetal behavioural, immunological and brain development, and placental CRH concentration has been associated with decreased fetal growth and size at birth. The role of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is to convert cortisol to inactive cortisone, a built-in protection against heightened maternal cortisol concentrations. However, maternal prenatal anxiety may downregulate the 11β-HSD2 enzyme and allow more cortisol to cross into fetal blood.

Catecholamines may also play a role in maternal stress, influencing infant outcomes. For example, catecholamines in maternal blood result in constriction of placental blood vessels, which can decrease the supply of nutrients and oxygen to the fetus and increase fetal catecholamine release. Chronic prenatal stress may negatively impact maternal immunity, resulting in increased risk of infections, increased proinflammatory cytokines (which may affect the developing fetal brain) or immune alterations in the offspring. The postnatal environment

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

also plays a central role in child development and can be difficult to control for when assessing the impact of prenatal stress. Often, prenatal psychosocial stress is a predictor for the postnatal environment. It has been suggested that the fetal programming that occurs as a result of prenatal stress may be protective, equipping the child for the postnatal environment, and it is only when there is a mismatch between the prenatal and postnatal environments that problems in health and behaviour may be anticipated [2].

Summary box 14.1

- Antenatal mood and anxiety disorders in the mother can have negative effects on fetal development, birth outcome and child development.
- Proposed mechanisms include the direct and indirect effects on health behaviours, maternal physiology, placenta and the postnatal environment.

Depression during pregnancy

Depression has been reported in up to 10–15% of pregnant women. This prevalence reflects major depressive disorder (MDD) and less severe depression. MDD is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by at least 2 weeks of low mood, or loss of interest or pleasure, associated with at least five other symptoms such as change in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, decreased energy or fatigue, sense of worthlessness or guilt, difficulty concentrating or making decisions, and recurrent thoughts of death, dying or suicide [3]. The prevalence of MDD in perinatal women is similar to that in women of reproductive age outside the perinatal period, but some women may be at risk during pregnancy. Risk factors for having MDD during pregnancy include being adolescent, poor socioeconomic status, having a prior MDD, current anxiety, comorbid medical problems, life stress, intimate partner violence, poor social support and unintended pregnancy.

Screening guidelines for depression in adults were updated in early 2016, which included screening recommendations for pregnant and postpartum women [4]. Screening pregnant and postpartum women was reported to have 'small to none' harms, and the process of screening could reduce depressive symptoms. It is recommended that screening takes place in healthcare settings with 'adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up'. The most widely used screening measure utilized in perinatal women is the Edinburgh Postnatal Depression Scale (EPDS), where a score greater than 10 suggests a possible depression. The Patient Health Questionnaire (PHQ-9) is a widely used screening measure for depression that can be applied to perinatal women [4].

Postpartum blues

Postpartum 'blues' occur in up to 80% of newly postpartum women. Common symptoms include mood lability, low mood, tearfulness, irritability, interpersonal sensitivity, anxiety, fatigue and confusion. The incidence of symptoms peaks in the first 3–5 days after delivery, and symptoms generally resolve spontaneously by 2 weeks. Support and reassurance are generally helpful. Although the expression of the symptoms is presumed to be related to the rapid decrease in hormone levels after delivery, this association has not been unequivocally demonstrated. The clinical significance of postpartum blues is that in up to 25% of women the symptoms do not resolve spontaneously and a full depressive episode may develop.

Postpartum depression

Postpartum depression (PPD) occurs in 10–15% of new mothers. As mentioned in the section about depression during pregnancy, the prevalence of PPD is similar to that in women of reproductive age outside the perinatal period, but some women may be at particular risk during the postpartum period. Risk factors for PPD are similar to the risk factors for developing MDD during pregnancy, and include prior MDD, current depression or anxiety, poor partner and other social support, preterm infant or complicated delivery, being adolescent, poor socioeconomic status, psychosocial stressors and marital conflict. The EPDS and other depression rating scales can screen for the presence of PPD. Ruling out thyroid dysfunction and anaemia is indicated.

As with postpartum blues, studies have failed to unequivocally find an association between hormone concentrations and PPD. It has been postulated that there may be multiple PPD phenotypes. Within the 'hormone-sensitive' phenotype, the normal perinatal fluctuations of reproductive hormones potentially lead to abnormal responses in neurotransmitters (serotonin, monoamine oxidase), HPA axis function, allopregnanolone responsivity, thyroid function, immune function, oxytocin function and genetic expression [5]. In this group of sensitive women, hormonal fluctuations trigger affective dysregulation with the expression of depressive and anxiety symptoms.

The DSM-5 definition of PPD is MDD that has onset within 1 month of childbirth [3]. In reality, many women who are depressed in the postpartum period had

depression during pregnancy, or develop it beyond the first postpartum month. A large-scale study administered the EPDS to 10 000 postpartum women 4–6 weeks following delivery and identified that 14% of them had an EPDS score above 10. Of these women, the onset of the MDD was prior to pregnancy in 27%, during pregnancy in 33%, and developed after delivery in 40% [6]. This study also demonstrated the high psychiatric comorbidity with PPD. Approximately two-thirds of the women who had an EPDS score above 10 had a comorbid anxiety disorder, 23% had bipolar disorder, and 19% endorsed self-harm ideation [6]. Maternal suicide is a leading cause of death in postpartum women in some countries and is often by violent means. Severe PPD can also be a risk factor for infanticide. Suicidal and infanticidal ideation should be inquired about at postnatal visits.

It is important to treat PPD due to the well-established negative effects on infant and child development, in addition to negative effects on the mother and family. PPD can lead to decreased mother–infant attachment and decreased initiation and maintenance of breastfeeding. Children of depressed mothers have been reported to have temperament difficulties, sleep problems and poor self-regulation. Young children may have delayed motor development, behavioural inhibition, externalizing disorders (such as conduct problems), poor emotion regulation and altered cognitive function. Older children and adolescents exposed to PPD have increased prevalence of depressive disorders, anxiety disorders, attention deficit disorder, conduct disorders and medical illnesses.

Eight randomized controlled trials have been published involving antidepressant medications for PPD, including a total of 715 postpartum women. In a pooled analysis of three of these studies, sertraline and paroxetine were found to be more effective than placebo for reducing depressive symptoms in women with PPD [7]. More studies are needed to compare the efficacy of antidepressant medications with psychotherapy, to examine the efficacy of combined antidepressants and psychotherapy, and to confirm that improvement of symptoms after treatment with antidepressant medications also leads to improvement in maternal functioning and infant and child development.

Summary box 14.2

- Postpartum blues occur in up to 80% of newly postpartum women, with symptoms including mood lability, low mood, tearfulness, irritability, interpersonal sensitivity, anxiety, fatigue and confusion.
- PPD has been reported in up to 10–15% of pregnant women and is defined by at least 2 weeks of low mood, or loss of interest or pleasure, associated with at least five other symptoms such as change in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, decreased energy or fatigue, sense of worthlessness or guilt, difficulty concentrating or making decisions, and recurrent thoughts of death, dying or suicide.
- Maternal suicide is a leading cause of death in postpartum women in some countries and is often by violent means, and PPD can also be a risk factor for infanticide.
- It is important to treat PPD due to the well-established negative effects on infant and child development, the mother and the family.

Anxiety disorders

Anxiety disorders are defined in DSM-5 as disorders of excessive fear, which is an emotional response to a perceived or real threat, and anxiety, which is anticipation of future threat [3]. While anxiety disorders are often comorbid with one another, they differ with regard to the stimulus or scenario that induces the fear or anxiety, as well as the associated belief. With all the disorders, a defining feature is that the fear or anxiety is excessive, out of proportion or persisting beyond the appropriate periods, taking cultural contextual factors into consideration. The symptoms may not be attributable to the physiological effects of a substance, medication, another medical condition or mental disorder. Approximately 30% of women experience an anxiety disorder during their lifetime. As anxiety disorders often have a relatively early and chronic course, many women will experience symptoms during the peripartum period, with prevalence estimates for any anxiety disorder ranging from 4.4 to 39% [8].

Generalized anxiety disorder

Generalized anxiety disorder (GAD) is the most common perinatal anxiety disorder, diagnosed by having excessive anxiety and worry that occurs more days than not and can cause functional impairment. DSM-5 criteria for GAD requires symptoms for at least 6 months, so if the onset occurs during pregnancy it may exclude those with excessive worries for less than 6 months and may be difficult to differentiate new-onset GAD from an adjustment disorder with anxious mood. The worries include a number of events or activities, and feel difficult to control. Associated symptoms include restlessness, easy fatiguability, difficulty concentrating, irritability, muscle tension and sleep disturbance, often symptoms that may be considered normal in pregnancy and post

partum. In the general population, prevalence ranges from 1.2 to 6.4%, with higher rates in pregnancy ranging from 8.5 to 10.5% [9]. The worries often involve pregnancy complications and fetal well-being, maternal wellness and partner illness. A previous history of GAD is the strongest predictor of GAD in pregnancy, with additional risk factors including personal or family history of anxiety disorder, lower social support, childhood abuse and lower education. Postpartum, the anxious thoughts often involve mothering skills and the transition to motherhood, breastfeeding, finances, and change in partner relationship, with prevalence rates between 4.4 and 10.8% [9]. GAD is highly comorbid with MDD, often resulting in a more severe and protracted course of illness. GAD can also predict an increase in the development of PPD. In one study, pregnancy anxiety was the strongest predictor of alcohol consumption in the prenatal period.

Maternal anxiety during pregnancy has been associated with an increased risk of PTB and LBW. Research has suggested that GAD and recurrent negative thinking has resulted in less responsive and engaged maternal interactions with their infants. These infants were withdrawn with lowered emotional tone. As a result of excessive maternal worry, mothers may be less able to identify happy infant faces. Maternal GAD during pregnancy was found to result in lower levels of fetal brain-derived neurotrophic factor in cord blood of newborns, suggesting a potential negative impact on the neurodevelopment of the fetus [9].

The mainstays of treatment are individual psychotherapy and selective serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs). Cognitive behavioural therapies (CBT) are the first-line choice for mild to moderate perinatal GAD, with the goal of reducing worries to a more reasonable level, lessen the mothers concern over her worries, and reducing autonomic arousal. Additional therapeutic techniques include mindfulness training, relaxation techniques and psychoeducation. SSRIs/SNRIs should be considered in moderate to severe cases, weighing the risk of untreated maternal anxiety and its consequences for the developing infant against the potential risks of medication treatment [9].

Panic disorder

Panic disorder is diagnosed when an individual experiences recurrent unexpected panic attacks, and persistent worry about additional panic attacks or their consequences. A panic attack is defined by an abrupt surge of intense fear or discomfort, along with at least four other symptoms such as accelerated heart rate, sweating, sensation of shortness of breath, chest pain, nausea, feeling dizzy or light-headed, paraesthesias, fear of dying or losing control, and derealization or depersonalization. Agoraphobia, defined as excessive fear or anxiety about being in a situation where escape may be difficult or help not available in the event of developing panic-like or embarrassing symptoms, is often comorbid with panic disorder [3]. In the general population, the 1-year prevalence rate for panic disorder is 2–3%, with a 0.2–5.7% prevalence during pregnancy, decreasing to 0.5–2.9% prevalence at 6–10 weeks post partum. The onset of panic disorder during pregnancy ranges between zero and 54%, with unpredictable courses (worsening, improving or staying the same) that vary widely among studies. There is a risk of onset of panic disorder post partum and after weaning, which is hypothesized to occur due to fall in progesterone levels. Panic disorder in pregnancy may have 4.2 times greater risk of PPD (during the first year postpartum) than those without [8]. Medical conditions that should be considered in the differential for new-onset perinatal panic attacks include thyroid dysfunction, anaemia, pre-eclampsia and phaeochromocytoma.

Case–control studies have reported that untreated panic disorder during pregnancy has been associated with PTB, LBW, shorter gestational age, small for gestational age, anaemia, isolated cleft lip with or without cleft palate and other congenital abnormalities [10].

CBT is the treatment of choice for panic disorder, and has been demonstrated to decrease panic symptoms. Antidepressant medications are considered the first-line pharmacotherapy option, with the goal of reducing panic symptoms and number of attacks. Benzodiazepines are also effective, but have an increased risk of abuse and dependence.

Obsessive compulsive disorder

Obsessions are recurrent persistent thoughts, urges or images that are experienced as unwanted and intrusive, causing marked anxiety or distress. Compulsions are repetitive behaviours or mental acts that one feels driven to complete. The behaviours or acts are clearly excessive, and are not connected in a realistic way to their goal of preventing a dreaded event or situation. The obsessions or compulsions must be time-consuming or cause clinically significant distress or impairment, which helps differentiate the disorder from occasional intrusive thoughts or behaviours that may be common during the perinatal period [3]. In pregnancy, the prevalence of obsessive compulsive disorder (OCD) ranges from zero to 5.2%, and studies show that the course of illness is variable. One meta-analysis showed that prevalence increases as women progress from pregnancy to the postpartum period, and that pregnant or postpartum women are approximately 1.5–2 times more likely to experience OCD compared with the general population [11]. Up to 47% of women retrospectively date their first onset of

OCD in the peripartum period. During pregnancy, the obsessions or compulsions often involve contamination fears and cleaning rituals. During the postpartum period there are often intrusive ego-dystonic obsessional thoughts of intentionally or accidentally harming the infant, fears of contaminating the infant resulting in repetitive washing, fears of infant death, compulsive checking, compulsive ordering and avoidance of being alone with the infant. Postpartum OCD appears to be characterized by the rapid onset of obsessional symptoms after the birth, with onset as early as the second postpartum day [12]. It is important to recognize that most postpartum women, greater than 65%, experience intrusive thoughts of harm coming to their infants, but it is unlikely they will act on those thoughts or develop OCD. Aggressive thoughts related to the child are perceived as distressing to mothers, and women with OCD are not at increased risk of harming their infants [11]. This is important to differentiate from postpartum psychosis, in which the thoughts are not distressing to the mother and the risk of actual harm is increased.

OCD in pregnancy has been associated with lower quality of life in pregnant women, and increased likelihood of PPD [8]. Maternal OCD may have negative impacts on the infant's development. A mother's fear of harming her infant and subsequent avoidance may hinder a secure mother–child relationship, and may also cause the infant to receive inadequate care. Increasing data show that a poor early interaction between the mother and infant can have long-term detrimental effects on the child, such as increased vulnerability to stress and increasing risk for later development of psychiatric disorders [12].

Non-pharmacological options that are effective for treating OCD include CBT and the specific behavioural therapy technique, exposure and response prevention. SSRIs and the tricyclic antidepressant (TCA) clomipramine are the first-line pharmacological treatments, often requiring dosages higher than those used for MDD.

Fear of childbirth

As many as 78% of women experience some fear of childbirth, such as pain, health complications, death of fetus or loss of control. In a subset of women (5–6%), this fear is persistent and causes significant distress, often associated with previous traumatic delivery, anxiety and depressive symptoms during pregnancy, lack of support, dissatisfaction with partners, advanced maternal age and previous caesarean section. The fear may result in less tolerance of pain during childbirth, increased elective and emergency caesarean section rates and increased intrusive memories of childbirth [13].

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) follows exposure to actual or threat of death, serious injury or sexual violence, accompanied by recurrent intrusive symptoms for over a month that include avoidance of stimuli associated with the event, negative alterations in cognitions and mood associated with the event, and marked alterations in arousal and reactivity. There is high comorbidity with MDD, GAD and substance misuse [3]. Prevalence rates among women are around 5% for current PTSD and range from 10 to 20% for lifetime PTSD. During pregnancy, the prevalence may be as high as 24% for women at high risk (racial minorities, teens, less educated, or poor) [14]. Women who have experienced a previous trauma, especially childhood or reproductive trauma, may be at increased risk for exacerbation of symptoms during the peripartum period. Prevalence rates of PTSD during the first year post partum range from 0.9 to 4.6%, with PTSD symptoms found in up to 24% [15]. Risk factors associated with postpartum PTSD include previous traumatic life events, sexual abuse, previous depression or psychiatric treatment, previous traumatic births, pregnancy complications, labour anxiety and traumatic experiences during the birth process [15]. Preventive strategies may include providing psychoeducation, extra support, improving coping strategies and increasing the woman's sense of control. One example could include establishing a care plan for delivery, which is shared with the care team, and includes her desires for pain control and medications and immediate post-birth wishes.

Perinatal PTSD increases adverse pregnancy and birthing outcomes, including poor prenatal care, high-risk health behaviours, miscarriage, ectopic pregnancy, PTB and LBW [14]. Perinatal PTSD has been associated with postpartum depression and bonding impairment with the infant, impaired relationship with partner, sexual dysfunction, as well as negatively impacting future reproductive choices [14].

Psychotherapeutic treatment options for PTSD include CBT, exposure therapy and eye movement desensitization.

Summary box 14.3

- Anxiety disorders involve excessive fear out of proportion or persisting beyond the appropriate periods.
- They may not be attributable to the physiological effects of a substance, medication, another medical condition or mental disorder.
- They occur almost twice as often in women than men, with approximately 30% of women experiencing an anxiety disorder during their lifetime.
- Prenatal maternal stress and anxiety have been linked to adverse obstetric, fetal and neonatal outcomes.

SSRIs are considered first-line pharmacotherapy. Prazosin has an off-label role in treating nightmares.

Antidepressant medications during pregnancy

Up to 10% of women take antidepressants at some point during pregnancy. SSRIs are the most widely used; there are fewer data with SNRIs and TCAs. Studies suggest that discontinuation of an antidepressant after conception, in a woman who is doing well, may be associated with an increased risk of relapse. This may be particularly true in women with a multiple past recurrent episodes of MDD or a recent episode. Given the potential adverse effects of untreated prenatal depression, it is important to treat depression to remission, if possible. Adverse effects from SSRIs have been reported, so the minimum effective dose should be used. The recent screening guidelines reported that the harms to the fetus from maternal use of SSRIs/SNRIs are considered 'small to moderate' and the likelihood of serious harms is rated 'low' [4].

The prevalence of most of the adverse effects discussed in this section is low. When there is a potential increased risk from exposure to antidepressant medications during pregnancy, the absolute value of the increased risk is also generally low. Most of the hazard ratios of increased risk range from 1.5 to 2. For many of the adverse effects, underlying disease in the mother (treated or not) may itself be associated with the adverse effect. It is difficult to interpret studies of antidepressant exposure during pregnancy: 'because these are observational studies, causality cannot be determined; it is not possible to control for all possible confounders related to depression, particularly the fact that women with more severe depression may be more likely to take antidepressants during pregnancy' [4].

Miscarriage and birth outcome

Studies of the risk of miscarriage with antidepressant use in the first half of pregnancy have reported mixed results. An increased spontaneous abortion rate may exist in women with depression who do not take an antidepressant. Thus, in studies that do report an increased risk of spontaneous abortion with SSRI use, the increased risk may be due to the underlying depression. Several meta-analyses have reported that antidepressant use during pregnancy is associated with an increased risk of PTB; however, a recent systematic review of studies reported that antidepressant use during pregnancy was not significantly associated with PTB [16]. Studies are also mixed on the association of antidepressants and LBW. It is important to note that the risks of PTB and LBW with antidepressants is similar in magnitude to risks of PTB and LBW with untreated prenatal depression [1].

Congenital malformations

Most recent studies report that prenatal exposure to antidepressants does not increase the risk of major congenital malformations. Although paroxetine has been associated with cardiac malformations, the data have been mixed [16]. A recent study reported that the small increased risk of cardiac malformations with SSRIs became non-significant when the data were adjusted for underlying depression [17]. If there is a small increased risk of cardiac anomalies with an SSRI, it is presumed to be due to serotonergic influence on cardiac development.

Persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn (PPHN) occurs in one to two infants per 1000 live births with a 10–20% mortality risk that can vary with aetiology. A meta-analysis reported that exposure to SSRIs in late pregnancy was associated with a 2.5 times increased risk ratio of PPHN while exposure to SSRIs in early pregnancy was not associated with PPHN [18]. The absolute risk difference for development of PPHN after SSRI exposure in late pregnancy was 2.9–3.5 per 1000 live births. A more recent cohort study suggested that the odds ratio for SSRI use and PPHN was 1.51, which decreased, but remained significant, with adjustment for potential confounders [19]. SSRIs may increase circulating levels of serotonin in the fetus which might increase vasoconstriction and smooth muscle cell proliferation [19]. PPHN may represent the severe end of a spectrum of respiratory difficulties with SSRI exposure.

Neonatal symptoms

One of the most consistent findings with prenatal use of antidepressants is an increased risk of neonatal symptoms that include respiratory distress [16], temperature instability, jitteriness, poor feeding, hypotonia and hypertonia, tremors, cyanosis and seizures. There is no evidence that tapering the antidepressant prior to expected delivery lessens the neonatal symptoms, which can occur in 30% of neonates. The neonatal symptoms are generally mild, require minimal treatment and resolve within the first month. The symptoms may be discontinuation symptoms from abrupt withdrawal of the antidepressant or serotonergic toxicity due to accumulation of the antidepressant in the neonate. Neonatal symptoms, sometime termed poor neonatal adaptation syndrome, have particularly been reported with paroxetine, fluoxetine, venlafaxine and TCAs.

Long-term effects

A recent systematic review of prenatal exposure to antidepressants and developmental outcomes reported inconsistent findings [20]. Some studies suggest delayed motor development and motor control, and possibly delayed language, but no studies have reported a significant association with cognitive problems [21]. When adverse effects are noted, they appear to be within normal limits and resolve with age. It is difficult to separate the effects of prenatal exposure to antidepressants from exposure to the underlying prenatal illness and the influence of postpartum factors such as untreated maternal depression. Studies in older children report some behavioural or emotional problems with prenatal exposure to antidepressants, but the literature is mixed.

A potential long-term consequence of exposure to antidepressant medication during pregnancy is autism or autism spectrum disorders (ASD). Several studies have been published in the past decade, and the results have been contradictory. Untreated maternal depression may be a risk factor for the development of ASD, and many of the studies examining the risk of ASD with SSRI exposure have not taken into account maternal psychiatric diagnosis during pregnancy. Studies that do report an association between SSRI use and ASD generally report a 2–3% increased risk, with the absolute value of the increased risk remaining small. Causality cannot be concluded from these studies. A recent study comparing SSRI exposure during pregnancy to prenatal depression without SSRI exposure did not report an increased risk of ASD, attention deficit disorder or anxiety disorders in offspring [22]. However, this study did report a significant adjusted hazard ratio of 1.78 of depression in adolescence with SSRI exposure during pregnancy compared with exposure to maternal psychiatric disorder without medication [22].

Other effects

Recent studies have reported an increased risk of hypertension and pre-eclampsia with prenatal exposure to antidepressants. The risk of gestational hypertension and pre-eclampsia may be higher with SNRIs compared to SSRIs. Recent reports have suggested a small increased risk of postpartum haemorrhage with SSRIs. Case reports have identified prolonged QTc interval in neonates that resolve after a few days. Positive effects with SSRI exposure has included accelerated infant speech perception and enhanced attention measures. Adverse effects reported with TCAs are similar to those reported with the SSRIs, including increased risks of PTB, LBW and neonatal symptoms. Clomipramine, in particular, has been associated with a possible increased risk of cardiovascular malformations and more severe and prolonged neonatal symptoms.

Summary box 14.4

Antenatal exposure to antidepressants

- Studies often do not control for underlying illness, comorbidities and associated behaviours.
- Untreated antenatal depression is associated with PTB and LBW.
- Although some studies suggest statistically significant increased risks with exposure to SSRIs, SNRIs and TCAs, the increase in absolute risks are small and may not be of clinical significance.
- Possible increased risk of spontaneous miscarriage.
- Possible increased risk of PTB and LBW.
- Possible increase in congenital malformations, but no consistent organ system implicated.
- Possible increased risk of cardiac malformations with paroxetine.
- Increased risk of PPHN with SSRI exposure after week 20.
- Increased risk of neonatal adaptation symptoms.
- Possible increased risk of autism or ASD.
- Long-term effects on child development may be transient, difficult to disentangle from continued maternal depression and other childhood environmental factors.

Breastfeeding and antidepressants

The antidepressant exposure risk with breastfeeding is considerably lower than the exposure risk during pregnancy. A relative infant dose of 10% or less of the maternal dose of psychotropic medications is generally considered low risk, and most studies of antidepressant levels report a relative infant dose of 10% or less [23]. Sertraline, paroxetine and nortriptyline have been reported to have low-to-undetectable infant serum levels in breastfeeding infants, and sertraline is generally considered the first-line choice during breastfeeding. Fluoxetine and citalopram are more likely to have relative infant doses above 10% and have been associated with negative effects in case reports. Adverse effects that may occur include poor feeding, irritability, colic, sedation and sleeping difficulties [24]. Premature infants may be more vulnerable to adverse effects due to decreased capacity to metabolize the antidepressants.

Summary box 14.5

Breastfeeding and antidepressants

- Compatible with most antidepressants.
- Sertraline, paroxetine and nortriptyline are the preferred choices due to very low infant levels.
- Case reports of elevated infant levels with fluoxetine and citalopram.

Benzodiazepines

Many women with mood and anxiety symptoms during pregnancy take benzodiazepines as sole agents or in addition to antidepressants. Cohort studies of prevalence rates of major malformations with benzodiazepine exposure do not suggest an increased risk, but case–control studies have suggested an increased risk of oral cleft with benzodiazepines as a class, and anal atresia with lorazepam. Benzodiazepines have been associated with an increased risk of PTB and LBW. Third-trimester exposure has been associated with the 'floppy infant' syndrome, which includes low APGAR scores, muscle hypotonia and hypothermia. Lorazepam is often utilized during pregnancy due to lower accumulation in fetal tissue [9]. The concurrent use of SSRIs with a benzodiazepine particularly increases the risk of neonatal discontinuation symptoms. The concern with maternal benzodiazepine use and breastfeeding is sedation in infants; this is not commonly reported as an issue.

Non-pharmacological treatments

Non-pharmacological strategies may be the treatment of choice for depression and anxiety disorders in peripartum women who want to minimize fetal exposure to psychotropic medications, and can also be adjunctive treatments. However, systematic studies of whether non-pharmacological therapies for prenatal depression and anxiety disorders reduce the risks from untreated disorders have not been done [1]. Meta-analyses of psychotherapy modalities in pregnant and postpartum women have suggested that psychotherapy is moderately effective compared with usual care [25]. The recently published screening guidelines recommended CBT as effective treatment with 'small to none' harms, noting that most studies have been conducted in postpartum versus pregnant samples [4]. Interpersonal psychotherapy is particularly applicable to pregnancy, with its attention to role transition, interpersonal issues and building social support [25]. Less well studied but promising treatments include exercise, yoga, massage and repetitive transcranial magnetic stimulation. Results with omega-3-fatty acids, folate, St John's Wort, light therapy and acupuncture have been mixed. Pregnant women with severe symptoms who are not responsive to medications or non-pharmacological treatments may need electroconvulsive therapy (ECT). Although ECT has been used safely in pregnancy, there are specific maternal precautions. Reduction in fetal heart rate, uterine contractions, premature labour and fetal demise have been reported [26].

Bipolar disorder

Bipolar I disorder is defined by experiencing at least one lifetime manic episode, which is a distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy. The symptoms must last at least 1 week or any duration of time if hospitalization is necessary. The presence of three or more additional symptoms, such as grandiosity, decreased need for sleep, pressured or increased speech, racing thoughts, distractibility or high-risk behaviour must be present, and cause marked impairment in functioning [3]. A diagnosis of bipolar II disorder requires meeting criteria for at least one hypomanic episode (similar symptoms as a manic episode, but only required to be present for four consecutive days with change in functioning, without marked impairment in functioning or necessitating hospitalization) and at least one major depressive episode [3]. The risk of having a recurrence of a bipolar disorder is increased during pregnancy, and particularly during the postpartum period. The risk of relapse is further increased both during pregnancy and after delivery if mood stabilizers are discontinued. Untreated bipolar illness carries many of the risks evident with depressive episodes: poor prenatal care, poor nutrition and health behaviours, substance abuse and suicidal ideation. In addition, impulsive and poor judgement behaviours can complicate the pregnancy. Untreated bipolar disorder has been associated with PTB, microcephaly and neonatal hypoglycaemia.

In the postpartum period, a recent meta-analysis concluded that the risk of relapse in women with bipolar disorders was 37% [27]. Postpartum relapse rates were lower in patients using pharmacotherapy, particularly lithium, during pregnancy (23%) compared with women who discontinued pharmacotherapy (66%) [27]. Risk factors for relapse are medication discontinuation, a previous postpartum mood episode or psychosis, unstable mood in pregnancy, younger age at onset of bipolar disorder and primiparity.

Psychotic disorders and postpartum psychosis

Schizophrenia spectrum and other psychotic disorders are defined by abnormalities in one or more of five domains, which include delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behaviour and negative symptoms [3]. Almost 50% of women with schizophrenia become pregnant, and active psychotic symptoms in pregnancy and

the postpartum period have been associated with adverse outcomes, such as maternal self-harm and physical harm to the infant, negative impact on attachment and poorer developmental trajectories for the child. There are limited data on the course of schizophrenia in pregnancy. According to a recent population study, women with schizophrenia are at lower risk of hospitalization during pregnancy and the first year post partum when compared with the year prior to pregnancy, with the exception being an increased risk in the first 9 days post partum [28]. While psychotic disorders were previously treated with typical or first-generation antipsychotics (FGAs), in recent years atypical or second-generation antipsychotics (SGAs) have become first-line treatments, mainly due to lower rates of extrapyramidal side effects. SGAs have minimal impact on prolactin levels, which is thought to be contributing to the increased fertility rates among women with schizophrenia.

In DSM-5, postpartum psychosis is not recognized as a distinct disorder, but as with mood and anxiety disorders, the specifier 'with peripartum onset' is used if onset of symptoms occurs during pregnancy or within 4 weeks from delivery. Postpartum psychosis has a prevalence of 1–2 per 1000 births in the general population. It can occur as a relapse of a chronic disorder such as schizophrenia or bipolar disorder, or as an initial onset of symptoms postpartum, most commonly taking the form of mania, mixed episodes (with features of both high and low mood) or severe psychotic depression. Patients with bipolar disorder have the highest risk of experiencing a postpartum psychosis. There is a proportion of women with first-onset postpartum psychosis who do not go on to experience a bipolar illness, but have symptoms isolated to the postpartum period. Postpartum psychosis is considered a psychiatric emergency as a result of the rapid onset of severe symptoms and the high potential for devastating outcomes, such as infanticide or suicide. Approximately 4% of women with postpartum psychosis commit infanticide and approximately 5% commit suicide. A recent study reported a greatly elevated 1-year risk of suicide (mortality rate ratio of 289) in mothers with the onset of severe psychiatric illness within 90 days post partum relative to healthy mothers [29].

In the majority of cases, postpartum psychosis has an acute onset within 2 weeks after delivery, with clinical features including mood lability, confusion, insomnia, bizarre behaviour, agitation and disorganization. The content of psychotic symptoms is frequently related to the infant, and delusions are ego-syntonic, or experienced as reasonable or appropriate. There is a loss of reality testing, with a compulsion to act on beliefs and an inability to recognize the consequences of their action, resulting in the increased risk of harm. This is important to differentiate from the ego-dystonic intrusive thoughts that are often present in postpartum depression and anxiety disorders. Treatment often includes inpatient hospitalization and medication management similar to that for psychosis or mood disorders outside of the peripartum period, such as antipsychotics, mood stabilizers, benzodiazepines, sleep regulation, supportive psychotherapy and ECT. It is crucial to rule out other cerebral or systemic conditions, such as delirium, infection, thyroid disorders, drug toxicity or withdrawal, among others.

In the postpartum period, a recent meta-analysis concluded that the risk of relapse in women with a previous postpartum psychosis was 31% [27]. Severe postpartum episodes were more likely in women with previous postpartum psychosis compared to women with bipolar disorder (17%). Additional risk factors for postpartum relapse include relapse during pregnancy, family history of bipolar disorder or postpartum psychosis, primiparity and obstetric complications. In those with isolated postpartum psychosis, initiation of medication immediately after delivery, rather than maintenance during pregnancy, may effectively prevent recurrence of postpartum psychosis [27].

Mood stabilizers

Lithium

An association between lithium exposure and Ebstein's cardiac malformation was reported in the 1970s, but more recent studies have not found lithium to be teratogenic. However, due to the possible increased risk of cardiac malformations, fetal echocardiography and high-resolution ultrasound are recommended at 16–18 weeks. Lithium levels and renal function need to be monitored throughout pregnancy due to increased fluid volume and lithium excretion in the second and third trimesters. Lithium levels generally need to be increased over the course of pregnancy [30]. Thyroid function tests and fetal growth also need to be monitored through pregnancy [31].

Lithium dose can be reduced 24–48 hours prior to delivery or at delivery, but the dose can be maintained if a recent level is normal [30]. Adequate hydration through labour and delivery is important. Following delivery, lithium dosing should be resumed at pre-conception levels and serum levels measured often to rule out toxicity. Neonatal complications have included 'floppy baby' syndrome, nephrogenic diabetes insipidus, hypothyroidism, low muscle tone, lethargy, tachycardia, cyanosis and respiratory difficulties. Few studies have examined the long-term effects of lithium on neurodevelopment, but to date no significant adverse effects have been reported [30].

Valproate

Valproate should be avoided in pregnancy, if possible, due to several adverse effects. Exposure to valproate is

associated with up to 10% increased rates of congenital malformations, including neural tube defects, craniofacial anomalies, cardiac defects, hypospadias and oral clefts [31]. The risks of malformations increase with higher doses and the use of multiple antiepileptic medications. Neonatal symptoms include hypertonia, irritability, poor feeding, hepatic toxicity and hypoglycaemia. The neurodevelopmental teratogenicity is of concern. Neurocognitive impairment has been documented in children through age 6 exposed to valproate *in utero*. There has also been an increased risk of the development of autism and ASD with valproate exposure [30].

Complete blood count, thyroid function tests, liver function tests and antiepileptic serum level should be regular monitored when using valproate (and carbamazepine) during pregnancy [31]. Folic acid supplementation before and during pregnancy is recommended for women on any antiepileptic medication to possibly reduce the risk of a neural tube defect. An α-fetoprotein test can assess a neural tube defect, and high-resolution ultrasound of the face, heart and neuraxis during the beginning of the second trimester is recommended. A careful morphological examination of the neonate and monitoring for withdrawal symptoms, sedation, abnormal clotting, hypoglycaemia or hyperglycaemia are recommended [31].

Lamotrigine

Recent studies do not demonstrate an increased rate of congenital malformations with prenatal lamotrigine exposure, although early studies suggested an increased risk of oral clefts. The increasing oestrogen levels as pregnancy progresses leads to increased glucuronidation, which results in increasing lamotrigine clearance. Lamotrigine doses can be prophylactically increased through pregnancy, or increased when mood symptoms worsen [30]. After delivery, lamotrigine levels increase and the dose should be decreased to the pre-conception dose over the first 2–3 weeks [30]. Neonatal symptoms with maternal lamotrigine use are not common. As yet, there have been no reports of neurodevelopmental impairment after prenatal exposure.

Other antiepileptics

Carbamazepine exposure has been associated with an increased risk of PTB, LBW, spina bifida, other neural tube defects, renal tract abnormalities and other malformations. Studies examining the effect of carbamazepine on cognitive and motor development have reported mixed results. Exposure to topiramate is associated with an increased risk of oral clefts and possibly LBW. Gabapentin has been associated with an increased risk of PTB and LBW. Most of the literature about effects of exposure to antiepileptics comes from studies of women with epilepsy, not with psychiatric disorders.

Antipsychotics

Most of the literature about the effects of prenatal exposure to antipsychotics has not adjusted for underlying psychosis or bipolar illness, both of which can be major confounds. A recent meta-analysis reported a 2.12 OR of increased risk of major malformations with FGAs and SGAs, most commonly cardiac malformations compared to no exposure [32]. There was a 1.86 OR of increased risk of PTB and a lower mean birthweight. There was no increased rate of spontaneous abortions or stillbirths [32]. Third-trimester exposure to both FGAs and SGAs has been associated with abnormal muscle movements and withdrawal symptoms after delivery. There are few studies examining neuromotor development in children, but lower neuromotor performance has been reported in 6-month-old infants with prenatal exposure to both FGAs and SGAs. International registries are available for pregnant women on antipsychotics [30].

Summary box 14.6

Antenatal exposure to mood stabilizers and antipsychotics

- Lithium has a possible increased risk of Ebstein's anomaly or other cardiac anomaly.
- Monitor lithium level and thyroid and renal function through pregnancy.
- Lithium dose needs to be increased during pregnancy, but decreased after delivery.
- Carbamazepine is associated with spina bifida and renal tract anomalies.
- Valproate is contraindicated during pregnancy due to high teratogenicity and neonatal symptoms.
- Valproate is associated with lower IQ and delayed neurocognitive development in children.
- Monitor valproate and carbamazepine levels, hepatic function, complete blood count and thyroid function through pregnancy and supplement with folate before and during pregnancy.
- Lamotrigine does not have an increased rate of congenital malformations.
- Lamotrigine dose often needs to be increased during pregnancy, but should be decreased after delivery.
- Antipsychotics have possible increased risk of congenital malformations, particularly cardiac, possible increased risk of PTB and LBW, possible extrapyramidal symptoms and withdrawal symptoms after delivery, and possible delayed neuromotor development in infants at 6 months.

Breastfeeding and mood stabilizers and antipsychotics

Both valproate and carbamazepine are considered compatible with lactation [23]. Breastfeeding requires close infant observation since serum lithium levels in the infant have been reported to be as high as 50% of the maternal serum level. The infant should be monitored for hypotonia, poor feeding, sustained behavioural change and slow growth. Lithium level, renal function and thyroid status in the infant should be monitored [23]. Lamotrigine levels in breast milk have also been reported to be up to 50% of maternal level, but adverse effects are few, and lamotrigine is considered compatible with breastfeeding. Transient rashes in infants have been reported with maternal lamotrigine use [30]. Lamotrigine could lead to apnoea, sedation and weakness in premature infants [23]. Infant serum levels of topiramate above 10% of maternal level have been reported, but topiramate is considered compatible with breastfeeding. There have been few published reports about maternal antipsychotic use and adverse effects on breastfed infants. To date, there are only a few case reports without consistent patterns. Clozapine is contraindicated during breastfeeding.

Summary box 14.7

Breastfeeding and mood stabilizers and antipsychotics

- Lithium levels in infants may be up to 50% of maternal levels: watch for hypotonia, slow growth and poor feeding. Monitor lithium level, blood urea nitrogen, creatinine and thyroid stimulating hormone in infant.
- Compatible with valproate and carbamazepine.
- Lamotrigine levels in infants may be up to 50% of maternal levels, but minimal adverse effects reported to date.
- Minimal data on topiramate, gabapentin and levetiracetam.
- Compatible with antipsychotics, but minimal data.
- Clozapine not recommended.

Conclusion

There are no risk-free decisions for the pregnant woman with psychiatric illness. It is important for obstetricians to have an understanding of the diagnosis, course and treatment options for the most common mental disorders, as perinatal illness has been associated with adverse obstetric, fetal and neonatal outcomes. There is also potential for adverse effects on the fetus, neonate and child from exposure to psychotropic medication during pregnancy and while nursing. The management of women during the perinatal period needs to be individualized, with a thorough risk–benefit analysis that takes into account the woman's psychiatric course and response to treatments, potential adverse effects of untreated illness, exposure to psychotropic medications and availability of non-pharmacological treatment options. The National Institute for Health and Care Excellence (NICE) has created an antenatal and postnatal mental health clinical management and service guidance that covers recognition, assessment and treatment of mental health problems in women who are planning to have a baby, are pregnant, or have had a baby or been pregnant in the past year (Table 14.1), with recommendations relevant to all healthcare professionals who recognize, assess and refer for or provide interventions for mental health problems in pregnancy and the postnatal period.

Table 14.1 Key recommendations from the National Institute for Health and Care Excellence Clinical Guideline CG192: *Antenatal and postnatal mental health: clinical management and service guidance*.

- Discuss with all women of childbearing potential and a past or current mental health problem use of contraception, how pregnancy and childbirth might affect the mental health problem, and how the mental health problem or treatment might affect the woman, fetus or baby as well as parenting
- Avoid valproate in women of childbearing potential
- Coordinate care by establishing an integrated care plan with all healthcare professionals treating the woman
- Provide detailed information around treatment decisions, advice and monitoring for women, as well as guidance around starting, using and stopping treatment taking into account the risk–benefit ratio for psychotropic medication
- Recognize mental health problems in pregnancy and the postnatal period through screening for depression and anxiety and referring to providers with appropriate knowledge base
- Be aware of considerations for women and their babies in the postnatal period, particularly traumatic birth, stillbirth and miscarriage with interventions facilitated by experienced practitioners
- Establish clinical networks for perinatal mental health services, managed by a coordinating board of healthcare professionals, commissioners, managers, and service users and carers

*The complete list of recommendations can be viewed at https://www.nice.org.uk/guidance/cg192/chapter/1-Recommendations

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15

Autoimmune Rheumatic Diseases and Other Medical Disorders in Pregnancy

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Background

The 2009–2012 MBRRACE (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report has shown a 48% decrease in direct maternal deaths, yet there has not been a significant decrease in indirect maternal deaths [1]. The rate of indirect maternal deaths is now twice that of death from direct causes (6.87 per 100 000 vs. 3.25 per 100 000). Two-thirds of women died from medical or mental health problems in pregnancy, of whom 74% had pre-existing medical (or mental health) problems prior to pregnancy.

With more successsful artificial reproductive therapies, a woman's childbearing years have been greatly extended; some women are facing motherhood at a much older age, thereby increasing the risk of the pregnancy being complicated by coincidental medical conditions. In the UK the latest figures collected through 2009–2012 reveals there were 3 182 873 deliveries of which 3.9% were to women aged 40 years and older; 27% of women who died were obese (body mass index ≥30 kg/m^2) and one-quarter of them smoked. This reflects a major shift, thereby increasing risk of morbidity from medical disorders, and possibly introducing a contributory factor towards indirect deaths in the maternal mortality enquiry.

While many medical conditions in this age group do not result in serious morbidity, others have the potential to do so (e.g. epilepsy, asthma, autoimmune rheumatic diseases and infections). It is important that women receive good advice prior to pregnancy about the potential implications of their medical condition, and enter pregnancy with appropriate confidence about their medication or have specific management plans to alter treatment in early pregnancy. This necessitates that they have ready access to specialist advice once they become pregnant. With more data emerging on the safety of drugs in pregnancy, clinicians no longer have to compromise the effectiveness of medical treatment for long-term conditions. However, changing the mindset of women and other clinicians who are less familiar with pregnancy remains a challenge. It would be ideal if these issues were addressed prior to pregnancy; examples include the continuation of pregnancy-friendly immunosuppressants or biologics in pregnancy and the safety profile of most antiepileptic drugs in pregnancy. This is so that women will be appropriately reassured and will not abruptly discontinue their medications in early pregnancy. Hence the importance of pre-conception counselling cannot be sufficiently emphasized, and was further highlighted in the 2014 report on Saving Lives, Improving Mothers' Care [1].

Management of women with medical disorders is often best coordinated within clinics, with obstetric, medical and midwifery input available. Such clinics make outpatient management much more convenient for the woman, and facilitate good communication between the relevant medical teams. They also serve as a focal point with which the woman may make contact in early pregnancy when treatment changes may need to take place without delay or in later pregnancy if there are problems. Integrated care plans for women with medical disorders should be made. Within units, consideration needs to be given to how such cross-specialty communication occurs if there is no formal multidisciplinary meeting where high-risk cases are discussed. The role of the midwife and support workers cannot be emphasized enough in ensuring that there is a more holistic approach to the care provided.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the commonest multisystem autoimmune rheumatic disorder affecting women of childbearing age. Prevalence depends on ethnicity, with more severe phenotypes seen in people of African, Far East (Chinese, Korean) and Hispanic extraction. Approximately 30% will have overlap with antiphospholipid syndrome (APS) and are classified as secondary APS.

Fertility is unimpaired in women with SLE unless they have had prior significant cyclophosphamide exposure, secondary APS or have current severe flare. Pregnancy outcomes are worse if conception occurs within 4–6 months of a flare, so planning pregnancy is of paramount importance. Contraception should be discussed with these women. The combined oral contraceptive pill is not associated with an increased risk of flares or SLE disease activity, but is contraindicated in those with secondary APS.

Pre-conception counselling enables any potentially teratogenic drugs (e.g. cyclophosphamide and mycophenolate mofetil) to be switched to more pregnancy-compatible substitutes while the woman's disease is in remission. Folic acid 5 mg should be commenced at least 3 months prior, vitamin D sufficiency confirmed, and hydroxychloroquine (HCQ) must be continued as observational studies have shown improved obstetric outcomes with reduction of flares when there is uninterrupted HCQ use in pregnancy. Aspirin 75 mg and calcium carbonate 2.5 g daily could be considered in women with SLE as their risk of pre-eclampsia is significantly higher than the normal population.

Effect of SLE on pregnancy

Good obstetric outcomes are associated with disease that is in sustained remission for at least 4–6 months prior to conception, ongoing HCQ use in pregnancy and lack of major organ involvement (e.g. lupus nephritis, neuropsychiatric lupus) [2].

Flares of SLE are not more common in pregnancy. The flares that occur in pregnancy generally follow a similar pattern to previously: those with predominantly mucocutaneous disease before pregnancy will flare in a similar fashion, whereas those with lupus nephritis will experience renal involvement. *De novo* presentation with lupus nephritis can occur and may be mistaken for pre-eclampsia if it occurs after 20 weeks' gestation.

Women with SLE have an increased risk of adverse pregnancy outcomes from placental insufficiency. Up to one-quarter of women with SLE develop pre-eclampsia or eclampsia, and 20–31% have preterm delivery. Rates of fetal growth restriction (FGR) range from 5 to 23% in women with SLE.

The risk of deterioration of renal function in pregnancy from a flare of lupus nephritis or pre-eclampsia is higher if the patient is hypertensive or has pre-existing heavy proteinuria or an elevated serum creatinine at baseline. A meta-analysis reported that the incidence of renal lupus flares during pregnancy was 11–69% and renal impairment occurred in 3–27%, which was permanent in up to 10% [3]. One case–control study showed that 28% of patients with class III or IV lupus nephritis developed pre-eclampsia, of whom 35% had a preterm delivery and a significantly lower birthweight compared to the women with SLE without nephritis [4].

Early studies in pregnant women with SLE have demonstrated high circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1). Similar to the general population, higher circulating levels of sFlt-1 and soluble endoglin (sEng), lower placental growth factor (PGF) and a high sFlt-1/PGF ratio assist in the prediction of pre-eclampsia in SLE pregnancies. In the multicentre Predictors of Pregnancy Outcome: Biomarkers in Anti-phospholipid Syndrome and SLE (PROMISSE) study, low sFlt levels (<1872 pg/mL) and elevated PGF (>70.3 pg/mL) have a negative predictive value in women with SLE, with less than 5% of the cohort developing adverse pregnancy outcomes [5].

Differentiating a flare of SLE from pre-eclampsia

Markers for SLE disease activity are less useful in pregnancy as levels of complement C3 and C4 and erythrocyte sedimentation rate (ESR) all rise in a normal pregnancy; therefore, a relative drop of C3 and C4 from the baseline established in early pregnancy could be a useful marker if previously quantified. Table 15.1 includes helpful tips to differentiate a flare of SLE (especially lupus nephritis) from pre-eclampsia.

Managing a flare of SLE in pregnancy

The management of a flare of SLE depends on the organ systems involved. Prevention is best, and therefore HCQ should be continued in pregnancy. Steroids remain the mainstay of treatment of a flare, but should never be empirically started for the prevention of a flare. Infusions of immunoglobulins which 'mop up' circulating antibodies can be useful for the treatment of a moderate to severe flare; their use must be accompanied by thromboprophylaxis as they increase the risk of thrombosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are safe and non-teratogenic but should only be used up to 32 weeks' gestation (and not within 48 hours of imminent delivery) due to a reversible effect on the neonate's patent ductus arteriosus, resulting in neonatal pulmonary hypertension.

Table 15.1 Useful features for differentiating pre-eclampsia from a flare of SLE or lupus nephritis.

	SLE flare/lupus nephritis	Pre-eclampsia
Hypertension	+	++
Other manifestations of SLE (e.g. rash or oral ulcers)	+	–
Complement (C3, C4)	↓ from baseline (in early pregnancy)	Unchanged
ESR	↑	Unchanged
Double-stranded DNA titres	↑	Unchanged
Proteinuria ≥0.3 g per 24 hours	++	+
Casts	May be present	–
Serum urate	May be ↑	↑↑
Liver function tests	Unchanged	ALT may be ↑
sFlt-1/PGF* ratio	↑	↑

*PGF can be raised in a flare of SLE.
+, present; –, absent; ↑, raised; ↓, decreased; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; PGF, placental growth factor.

Azathioprine has a good safety record in pregnancy. There is increasing evidence for the efficacy of tacrolimus for the treatment of lupus nephritis in pregnancy. On the other hand, mycophenolate mofetil and cyclophosphamide are teratogenic and should never be used in the first 12 weeks of pregnancy. However, if the maternal flare is severe enough to necessitate the use of cytotoxics, cyclophosphamide has been used after the initial period of organogenesis. Long-term follow-up studies of the offspring exposed to cyclophosphamide have shown normal growth and neurodevelopment when followed up until their adolescent years [6]. Rituximab (a B-cell-depleting agent) is not teratogenic but it has a very long half-life and will suppress the neonate's B-cell production for 6–8 months after exposure. Nevertheless, there have not been any adverse effects seen in the exposed offspring, who were able to mount a normal immunological response to vaccination, nor did they have an increased rate of infections. Nevertheless, the number of children exposed to rituximab *in utero* remains small, and there are more cumulative long-term data on cyclophosphamide in pregnancy compared with rituximab.

Congenital heart block and neonatal lupus syndromes

Up to 30% of patients with SLE have Ro antibodies. Ro and La antibodies are part of the extractable nuclear antigens that cross the placenta and potentially damage the neonate's cardiac conduction system resulting in irreversible fibrosis. Ro antibodies are present in 90–100% of mothers of affected offspring, and 68–91% have La antibodies. The risk of congenital heart block is approximately 2% in Ro-positive mothers and is strongly correlated to the titre of Ro antibodies present in the mother. If affected, the overall mortality is around 20%, with deaths usually occurring *in utero* (after developing hydrops and pleural and pericardial effusions). Most infants who survive the neonatal period do well, although two-thirds require pacemakers. The risk of congenital heart block increases exponentially to 15–50% in subsequent pregnancies if there have been previously affected offspring.

Detection of heart block can occur from 18 weeks onwards. However, once in second-degree heart block, the process is almost invariably irreversible, and the treatment would be delivery – if viable – with the implantation of a permanent pacemaker in the neonate. Heart block rarely develops after 28 weeks' gestation, though there are rare instances of heart block developing up to 3 years post partum. Hence most screening programmes for mothers who are Ro or La antibody positive start at 18 weeks and if the second echocardiogram (to determine the PR interval of the neonate) is normal at 28–32 weeks, then no further screening is needed until an ECG at delivery.

The treatment of heart block remains controversial, since none of the therapies previously tried have been effective in reversing second-degree heart block. HCQ has been shown to reduce the incidence of heart block and could be considered even in asymptomatic women who have Ro or La antibodies [7]. High-dose dexamethasone and repeated infusions of immunoglobulins have not been efficacious in reversing established second-degree heart block.

Neonatal cutaneous lupus is an erythematous annular rash, and develops soon after exposure to sun or ultraviolet light. It affects approximately 5% of offspring born to mothers who are Ro or La positive. The rash typically resolves within 6–8 months, with clearance of maternal Ro and La antibodies. Treatment with topical corticosteroids is reserved for severe cases as the rash usually clears spontaneously with only residual hypopigmentation or telangiectasias persisting for up to 2 years.

Summary box 15.1

Women on SLE should remain on HCQ as it affects pregnancy outcomes positively and reduces the risk of fetal congenital heart block in mothers who are Ro and La antibody positive.

Secondary antiphospholipid syndrome

In the normal population, antiphospholipid antibodies are often transient and can be induced by a variety of factors. Medium-to-high titres of antiphospholipid antibodies do not correlate with adverse obstetric outcomes in the absence of accompanying clinical features of recurrent (and consecutive) spontaneous miscarriages under 10 weeks, unexplained mid-trimester losses, preterm delivery before 34 weeks as a result of placental insufficiency or previous thrombotic phenomena [8]. Up to 50% of women with SLE will have circulating antiphospholipid antibodies. Lupus anticoagulant is a much stronger predictor of poor outcomes than anticardiolipin antibodies.

Women with secondary APS who have experienced thrombosis, late losses and features of placental insufficiency should be offered prophylactic low-molecular-weight heparin (LMWH), which should be continued for at least 6 weeks post partum. The use of LMWH to prevent recurrent early pregnancy losses remains controversial; a meta-analysis concluded that LMWH has not demonstrated additional benefit compared with low-dose aspirin [9].

Long-term maternal health and cardiovascular disease

Women with SLE have a much higher risk of premature cardiovascular disease and death compared with the normal population, even in the relative absence of any cardiovascular risk factors. Women with SLE who have had their pregnancies complicated by placental insufficiency are at greater risk of death from cardiovascular causes and accelerated development of cardiovascular disease. Preterm delivery before 34 weeks, which could be a surrogate marker for active SLE in pregnancy, has also been associated with accelerated cardiovascular events in this cohort [10].

Rheumatoid arthritis and other inflammatory arthritides

The adage that rheumatoid arthritis (RA) improves in pregnancy no longer holds true since prospective population-based studies have indicated active disease in at least 40% of women. Those with more severe disease (erosive disease or joint deformities) and anti-cyclic citrullinated peptide (anti-CCP) antibodies often flare more severely than those with seronegative RA.

Seronegative spondyloarthropathies, such as psoriatic arthritis, enteropathic arthritis and ankylosing spondylitis, are less responsive to conventional disease-modifying antirheumatic drugs (DMARDs, e.g. HCQ, methotrexate and sulfasalazine) or prednisolone to treat flares.

Precautions and special considerations in women with inflammatory arthritides

Though women with RA are less fertile, they have similar obstetric outcomes to the normal population, unless they experience active disease in pregnancy. A nationwide prospective study in the Netherlands has shown that active disease in pregnancy is associated with a lower gestational age at delivery and a lower birthweight. Studies from the USA indicate that women with RA have an increased risk of FGR, particularly if they have severe erosive disease. There was also a trend towards an increased risk of developing pre-eclampsia, though the absolute risk remains small when compared to women with SLE.

There is a higher rate of elective caesarean section in women with RA compared to the normal population, which is most likely iatrogenic. Limitation in hip abduction is rarely severe enough to impede vaginal delivery. Additional care is necessary in women with juvenile idiopathic arthritis who may have had hip joint replacements.

Women with inflammatory arthritides should be reviewed by an obstetric anaesthetist to assess cervical spine involvement and degree of jaw excursion in order to anticipate any problems should they require a general anaesthetic in labour. Atlantoaxial subluxation and subsequent paralysis is a rare complication that can occur if a general anaesthetic is administered without due precautions in a woman with erosive disease affecting her cervical spine.

DMARDs and other drugs in pregnancy and breastfeeding

DMARDs are likely to have contributed to the reduced fecundity seen in women with inflammatory arthritides. Methotrexate, previously used as first-line therapy in all patients with RA, is a well-known teratogen. It must be discontinued at least 3 months prior to any attempt at conception and high-dose (5 mg) folic acid should be prescribed. Leflunomide, a pyrimidine synthesis inhibitor, is another commonly used DMARD that has teratogenic potential. Cholestyramine 8 mg for at least 11 days 'washout' should be given prior to pregnancy, but this can also be commenced in very early pregnancy if necessary. There should be confirmation of successful cholestyramine washout with undetectable drug levels (<0.03 μg/mL) taken 2 weeks apart. However, if this is not possible, then ongoing washout with cholestyramine should continue until organogenesis is completed.

Table 15.2 lists a number of DMARDs and other drugs and their suitability in pregnancy and lactation.

Use of anti-TNF and other biologics

'Biologics' are modified part murine and human monoclonal antibodies that act on targeted receptors to reduce the production of various inflammatory molecules. They are increasingly used in women with RA, seronegative spondyloarthropathies and inflammatory bowel disease. At present, they are reserved for patients who have had refractory disease and 'failed' conventional therapy. Therefore, by default, these women have more severe disease. The most commonly used drugs at present are the anti-tumour necrosis factor (TNF) agents, usually infliximab, etanercept, adalimumab, golimumab and certolizumab, and the B-cell depleting agents rituximab and belimumab.

Multiple registries dedicated to studying the effects of these drugs in pregnancy have not demonstrated an increased teratogenic risk. The cases of fetal malformations are sporadic and not part of a syndrome that would suggest interference with organogenesis. Therefore, it is no longer recommended that anti-TNF agents be discontinued prior to pregnancy.

As monoclonal antibodies, these drugs do not cross the placenta (except by slow diffusion in early pregnancy) until after 16 weeks' gestation when syncytiotrophoblasts develop receptors that will bind with the Fc portion of these modified monoclonal antibodies. Transplacental transfer of these drugs increases exponentially from around 22 weeks to its maximal efficiency around 28 weeks' gestation. The efficiency of transfer depends on the half-life of the drug and its Fc portion. Cord blood levels of biologics with a long half-life and an Fc receptor that is conducive to transplacental transfer (e.g. adalimumab and infliximab) are often higher than maternal serum levels if the drug is administered towards the end of pregnancy [11].

There is significant debate surrounding the timing of drug cessation to avoid transplacental transfer, with the European League Against Rheumatisim (EULAR) [12] suggesting that infliximab and adalimumab be discontinued at 20 weeks, whereas etanercept (with its modified Fc portion and short half-life) be discontinued at 30–32 weeks; on the other hand, the British Society of Rheumatology [13] recommends that adalimumab and etanercept can be continued until the end of the second trimester and infliximab stopped at 16 weeks' gestation. However, experts are unanimous that certolizumab, with its large pegylated molecule, only crosses the placenta via slow diffusion and therefore can be continued throughout pregnancy.

The predominant concern with anti-TNF use in pregnancy beyond the recommended gestation is the risk of significant immunosuppression in the newborn. The immature reticuloendothelial system may take 6–8 months to clear the drug, and is dependent on the gestation at which the anti-TNF was discontinued. Therefore, neonates who are exposed *in utero* beyond the recommended gestation should be promptly assessed if there is a suspicion of infection. Live vaccinations (usually rotavirus and BCG) should be avoided for the first 6–7 months of life. The woman, her primary caregiver and paediatric teams should be informed prior to delivery so that the necessary precautions can be undertaken.

Rituximab has an exceedingly long half-life but is not associated with any teratogenesis. However, it is associated with a high rate of miscarriage that is most likely due to underlying maternal disease for which this drug (and likely other drugs as well) is prescribed. EULAR guidelines suggest that, if clinically indicated, it could be continued throughout pregnancy. Transient cytopenias (from B-cell depletion) may occur in the offspring exposed *in utero*; however, neonatal infections or inability to mount a response to vaccination has not been a problem.

The decision to continue any biologic needs to be individualized to the woman, bearing in mind the refractory nature of the underlying disease that has not been amenable to other therapies. If there is a significant risk of flares, with associated maternal (and fetal) morbidity from a flare, then the option to continue these drugs can be discussed, given the caveats that suspected infections in the newborn are promptly assessed and the avoidance of live vaccinations for the first 6–7 months of life.

The obstetrician should be aware that women on biologics are significantly immunosuppressed and they should also be carefully screened for infections at each visit.

Table 15.2 Commonly used drugs used for the treatment of rheumatic diseases and their effect on pregnancy and breastfeeding.

Drug	Effects on organogenesis	Effects on fetus/neonate	Breastfeeding	Authors' recommendations on use in pregnancy
NSAIDs	None	Reversible constriction of ductus arteriosus after 27/40; oligohydramnios; transient anuria and renal failure if used <48hours prior to delivery	✓	Likely a class effect for all NSAIDs. Use if indicated at lowest dose possible till 32 weeks' gestation and stop if delivery is imminent (within 48 hours)
Cyclooxygenase (COX)-2 inhibitors	Likely no increase in anomalies in humans	Oligohydramnios is less profound and preterm closure of the ductus arteriosus is delayed compared with NSAID use	✓ for celecoxib	As more data are available on NSAIDs, it would be safer to change to an NSAID in early pregnancy. However, there could be a role for selective COX-2 inhibitor use in women requiring NSAIDs >32 weeks
Prednisone/prednisolone	None	More than 80% metabolized by placenta and fetus inactivates steroids by hepatic conjugation, and therefore receives <10% of non-fluorinated steroid dose. Theoretical effects in doses in excess of 80 mg: possible cataracts, adrenal insufficiency and infection	✓	The effects are predominantly maternal with immunosuppression with ascending infections, preterm rupture of membranes, increasing risk of gestational diabetes and hypertension. Use lowest dose possible; ensure there is a plan to taper the dose. If disease persistently active, then consider addition of DMARD/biologic to ensure woman does not remain on prolonged courses of high-dose steroids
Hydroxychloroquine	None	None	✓	Continue in pregnancy and breastfeeding
Sulfasalazine (and other 5-aminosalicylic acid compounds)	None	None	✓ except in very preterm jaundiced neonates	Commence folic acid supplementation 5 mg/day 3 months prior to pregnancy. In men with fertility problems, it may need to be swapped with another agent as it affects spermatogenesis and motility
Methotrexate (MTX)	Aminopterin syndrome; high rate of pregnancy loss; 15% rate of congenital anomalies	If no congenital anomalies, long-term follow-up of children exposed to MTX did not reveal any problems	×	Reliable contraception advised. Discontinue ≥3 months prior to pregnancy with daily 5-mg folic acid supplementation. Exposed fetuses should be scanned at 16/40 to determine if there are any congenital anomalies to facilitate elective termination if the mother wishes. No effect if paternal MTX use
Leflunomide	In animal studies, malformations of the head, rump, vertebral column and limb defects. Increased rate of miscarriage	If pregnancy continues, no major structural anomalies noted especialy after cholestyramine washout in very early pregnancy	×	Reliable contraception advised. Wash out with cholestyramine 8 g t.d.s. for 11 days; repeat until drug levels <0.03 μg/mL taken 2 weeks apart (or continue until 12 weeks' gestation). If exposed in early pregnancy, offer washout and reassure woman that, to date, birth outcomes of exposed women no different from disease-matched controls

Azathioprine*	None	None	✓	Continue in pregnancy and lactation
Cyclosporin	None	Transient immune alterations in the neonate	✓	Continue in pregnancy; probably safe in breastfeeding though wide range of concentrations excreted in breast milk
Tacrolimus	None	None	✓	Continue in pregnancy and safe in breastfeeding
Intravenous immunoglobulin	None	None	✓	Concurrent thromboprophylaxis is advised
Cyclophosphamide	Cyclophosphamide embryopathy with high rate of miscarriage	Transient cytopenias. No long-term effect on the neonate if survives pregnancy	×	Use only if there is life-threatening maternal disease after the first trimester. If maternal disease necessitates cyclophosphamide in first trimester, discuss termination
Mycophenolate mofetil	OMENS† and congenital cardiac defects. Phenotype is not dose dependent	Neonates described in the literature, had also been exposed in the period of organogenesis	×	Discontinue for at least 3 months prior to pregnancy

*OMENS: O, orbital distortion; M, mandibular hypoplasia; E, ear anomalies; N, seventh cranial nerve root involvement; S, soft tissue deficiency.
†Azathioprine is converted to the active metabolite 6-thioguanine nucleotides in 15 min but the half-life of the active metabolite in erythrocytes is weeks to months.
✓, safe for breastfeeding; ×, unsafe or not recommended for breastfeeding.
Source: adapted from Soh & Nelson-Piercy [13].

Infections may present atypically (i.e. absence of fever or tachycardia) as these women are unable to mount an adequate immunological response to pathogens. Atypical infections should also be considered. In the longer term, patients on biologics have an increased risk of malignancy, a differential that should be considered if a woman presents unwell [11].

Summary Box 15.2

Anti-TNF agents and rituximab do not appear to be teratogenic but have potent immunosuppressive effects on both the mother and exposed fetus. Fetuses exposed beyond the late second trimester should not receive live vaccinations (rotavirus and BCG) for the first 6–7 months of life.

Scleroderma and other connective tissue diseases

Scleroderma, or systemic sclerosis, is less common than SLE and other inflammatory arthritides, and its inclusion in this chapter is due to its potentially devastating effects in pregnancy. The peak incidence is between 30 and 50 years of age, with a female preponderance of 3 : 1.

Ideally, pregnancy should be planned and the extent of cutaneous disease and systemic involvement carefully quantified. Those with early diffuse disease (<5 years from onset), significant renal impairment, severe restrictive lung disease, pulmonary hypertension or severe cardiomyopathy should be strongly advised against pregnancy. Pulmonary hypertension occurs in 8–12% of patients with scleroderma and is now the main cause of disease-related mortality.

Risk factors associated with poor obstetric outcomes in scleroderma

Women with early (<5 years) or diffuse cutaneous disease, systemic involvement (particularly lung, cardiac or renal) or anti-topoisomerase (anti-Scl-70) antibodies are at greater risk of having more active aggressive disease than those with long-standing disease and anti-centromere antibodies. Up to 40% will have Ro or La antibodies and these should be screened for at booking.

Diffuse cutaneous involvement is associated with twice the risk of miscarriage (24% vs. 12%) and preterm delivery occurs in about 9%. The live birth rate is 77% in those with diffuse disease compared to 84% in women with limited disease.

Pregnancy should be deferred for at least 5 years after diagnosis to ensure that early disease can be aggressively treated with potent and sometimes teratogenic immunosuppressants. Moreover, most renal crises occur in early disease [14].

Scleroderma renal crisis

Scleroderma renal crisis has an almost identical clinical picture to accelerated pre-eclampsia or HELLP (haemolysis, elevated liver function tests, and low platelets) syndrome. Renal histological changes may aid in differentiating the two pathologies. However, as scleroderma renal crisis tends to occur in the third trimester, its management is prompt delivery, prior to initiation of an angiotensin-converting enzyme (ACE) inhibitor. Pregnancy following scleroderma renal crisis is not advised as the risks of recurrence following the cessation of ACE inhibitors (which are contraindicated in pregnancy) cannot be quantified.

Historically, observational studies have linked high doses of corticosteroids (prednisone >30 mg/day or equivalent) with a risk of precipitating a renal crisis. While these data remain contentious, many experts advocate avoidance of high doses of steroids (note that 4 mg betamethasone or dexamethasone for fetal lung maturation is approximately equivalent to 30 mg prednisolone). Presence of anti-RNA polymerase III antibody may be useful in prognosticating the risk of renal crisis, but the strongest predictor remains new-onset diffuse disease (<5 years) with rapidly progressive cutaneous involvement [15]. Therefore, the benefits of antenatal steroids for fetal lung maturation should be very carefully weighed against the risk of precipitating a maternal renal crisis, and they may have to be withheld at gestations for which they are normally prescribed.

Other considerations in pregnant women with scleroderma

Venepuncture, venous access, oxygen saturation and blood pressure measurements may be complicated by the cutaneous involvement. Endotracheal intubation is often difficult as a result of microstomia. There is an increased risk of aspiration and trauma to telangiectatic areas in the nasopharynx. Regional anaesthesia (especially epidural) is usually the preferred option.

Calcium channel antagonists are often used for the treatment of Raynaud's phenomenon. Gastro-oesophageal reflux worsens in pregnancy and proton-pump inhibitors may be added to histamine H_2-receptor antagonists.

Close observation must continue in the immediate postnatal period, particularly in those with cardiac, pulmonary or renal involvement. They are also more vulnerable to pressure sores.

Summary box 15.3

Scleroderma is a multisystem connective tissue disease that has potentially catastrophic effects on the woman's lungs (pulmonary hypertension), heart (cardiomyopathy and arrhythmias) and kidneys (scleroderma renal crisis). These complications are more common with early disease, so women with recently diagnosed (<5 years) scleroderma should be advised to avoid pregnancy.

Ehlers–Danlos syndrome types III and IV

Ehlers–Danlos syndrome (EDS) is a group of disorders characterized by a spectrum of clinical presentations ranging from skin fragility, easy bruising, hypermobility and large joint subluxation to vascular and visceral rupture as a result of (usually) an autosomally dominant inherited defect in collagen metabolism.

EDS type III or benign hypermobility syndrome is the commonest type in young women, presenting typically with generalized hypermobility, recurrent (often spontaneous) joint dislocations and early-onset osteoarthritis with resultant chronic pain and fibromyalgia. There is often an overlap with functional bowel disorders and autonomic dysfunction, such as orthostatic intolerance and postural orthostatic tachycardia syndrome. Aortic root dilatation is typically of a mild degree with no increased risk of dissection in the absence of significant dilation. In labour, precautions are needed to avoid hip dislocations.

EDS type IV (vascular form) is characterized by hypermobility of the small joints, tendon and muscle rupture, arteriovenous fistulae, acrogeria and combined vascular (arterial), visceral and uterine fragility or rupture due to a defect in type III procollagen. In pregnancy, there is an increased risk of preterm rupture of membranes, malpresentation of the fetus, FGR, uterine rupture and postpartum haemorrhage [16]. Because of the high rate of preterm rupture of membranes, prophylactic administration of steroids for fetal lung maturation should be considered, though timing may be difficult. Hence, those with EDS IV require the involvement of the multidisciplinary team for careful monitoring of the aorta for any dilatation. Experts recommend planned lower segment caesarean section before 36 weeks (often at 34 weeks' gestation) to avoid the risk of labour and uterine rupture. Postpartum deaths from aortic rupture can occur.

Summary box 15.4

Women with EDS type IV (vascular) need close multidisciplinary follow-up due to the high risk of complications incuding visceral and vascular rupture, which can extend into the postpartum interval.

Vasculitides in pregnancy

Most vasculitides are more common in elderly males, with the exception of Takayasu's arteritis and Behçet's disease.

Takayasu's arteritis

Takayasu's arteritis is the 'pulseless disease' that occurs in women of the Far East (Japan and Korea). Pregnancy tends to have a positive effect, with lower C-reactive protein levels and improved digital plethysmography up to a year following delivery. However, if there is pre-existing hypertension and involvement of the aortic valve and abdominal aorta, then superimposed pre-eclampsia and FGR are common, with up to 62% and 11–52% of pregnancies affected, respectively. Pulmonary hypertension should be excluded before pregnancy.

Obstetric outcomes are likely dependent on the extent of vessel involvement. FGR is likely due to a combination of impaired placental perfusion as a result of both hypertension and vascular compromise of the abdominal aorta and its branches. There is a correlation between disease severity and poor obstetric outcomes [17].

Behçet's disease

Behçet's disease does not adversely affect maternal and fetal outcomes. Pregnancy results in a threefold reduction in flares; flares were more common in those off their medications, usually mucocutaneous and in the third trimester. However, previous thromboses and vascular complications were associated with poorer outcomes. Thrombotic complications are more likely to recur in pregnancy. Colchicine, the mainstay of treatment, is not teratogenic. However, thalidomide is still used for Behçet's disease and women of childbearing age on this teratogen should be using reliable contraception.

Respiratory disorders

Respiratory disorders in pregnancy constitute a frequent cause of morbidity and occasional mortality. Given the potential difficulties in defining the roles of respiratory

sepsis, bronchospasm and underlying cardiovascular morbidity, it is recommended that women presenting with acute respiratory compromise require prompt assessment by a physician and an anaesthetist or intensive care specialist [1].

Women with respiratory disorders require careful and multidisciplinary assessment when they present for antenatal care. All women with known severe lung disease should be screened for pulmonary hypertension prior to conception [1]. An anaesthetic opinion prior to the third trimester is valuable for those with possible respiratory compromise.

Breathlessness can arise during the course of a normal pregnancy. However, the same complaint can be a manifestation of life-threatening complications such as thromboembolism, cardiac disease or deterioration of background respiratory disease. Patients should have a careful clinical assessment; oxygen saturation, arterial blood gases and chest X-ray (CXR) may assist in differentiating physiological breathlessness from true pathology. In pregnancy there is elevation of the diaphragm and increased tidal volume, although measures of airway flow such as forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) are unchanged and still valuable in the assessment of respiratory compromise. Women with recurrent admissions have been identified in the maternal mortality enquiry as a high-risk group, and should be assessed by experienced clinicians.

Management of acute respiratory compromise may require delivery. While the physiological adaptation to pregnancy is not critically dependent on any respiratory change, in the presence of pathology the negative impact of pregnancy, including splinting of the diaphragm, may mean that delivery is an important part of the treatment plan for recovery. This may mandate caesarean delivery in difficult circumstances and experienced obstetric, medical and anaesthetic input is required. These women may require general anaesthesia and intensive care after delivery.

Asthma

Asthma is the most common respiratory disorder, with a prevalence of approximately 4% in pregnancy, but was disproportionately represented (prevalence 15%) in those who died. Asthma remains the most common respiratory cause of maternal death [1]. Most women with asthma do not suffer adverse obstetric outcomes, though 'brittle' asthma is always challenging and associated with greater perinatal complications, with a need for fetal monitoring. It is important that women with asthma are given the reassurance that all medications commonly used to control and treat an exacerbation of asthma are safe in pregnancy, and that optimal control is paramount for good obstetric outcomes (see British guideline on the management of asthma at https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/). Patient education early in pregnancy should include advice on smoking cessation and flu vaccination.

Generally, a short course of oral steroid therapy (prednisolone 0.5 mg/kg daily for 5 days) will achieve control of symptoms where conventional inhalers are failing. As these women may present directly to delivery suites, treatment protocols for an acute exacerbation of asthma and medical back-up should be available. National guidelines emphasize that there should be a lower threshold to refer and admit pregnant women with an acute severe exacerbation of asthma to critical care units [1]. Ideally, women should have optimal control of their asthma prior to childbirth. Those with brittle asthma may require serial visits for stepwise escalation in treatment. Acute exacerbations in labour are rare and are treated in the normal way, with the added precaution of anaesthetic support, supplemental oxygen, intravenous steroids and fetal monitoring.

Summary box 15.5

With the exception of lower thresholds for admission and the involvement of intensive care specialists, asthma should be managed in the same way during pregnancy as when the woman is not pregnant.

Pneumonia

The incidence of pneumonia in pregnancy is similar that in the non-pregnant state. Productive cough and pleuritic chest pain are the most common complaints in addition to breathlessness. Acute pneumonia should be managed by experienced clinicians, and clinically appropriate imaging should not be withheld. Threshold for admission to critical care should be lower in pregnancy, and the focus should be on oxygenation, antimicrobial treatment (including antiviral agents) and thromboprophylaxis. Many will have background respiratory disease, and in one series 24% of patients also had asthma. Infections should be treated vigorously. Most antibiotics (with the exception of tetracyclines) can be used to treat pneumonia in pregnant women; aminoglycosides could be added in severe cases. Preventing progression of underlying infection to sepsis syndrome with associated haemodynamic instability is paramount. Adverse outcomes include a high risk of preterm delivery and abruption. Urgent anaesthetic input is required as delivery may be required.

Varicella pneumonia is a particular cause for concern and can occur in 5% of pregnant women with varicella. It typically arises some days after onset of the rash and is most likely to occur in the third trimester. Women with respiratory symptoms, concurrent encephalitis and hepatitis in the presence of primary varicella infection should be managed with intravenous aciclovir and supportive care. There do not appear to be adverse sequelae for the fetus from aciclovir. Case fatality rates have reduced markedly with aciclovir treatment.

Viral influenzas in pregnancy

The impact of an influenza outbreak on maternal mortality is clear from the 2014 maternal mortality report, and caution regarding influenza vulnerability should be extended into the postpartum period [1]. H1N1 influenza A was the predominant circulating strain then and remains the most widely studied form of all viral influenzas in pregnant women. Antiviral agents (e.g. oseltamivir 75 mg twice daily for 5 days and zanamivir two puffs of 5-mg inhalations twice daily for 5 days) are safe in pregnancy. If the index of suspicion for a viral influenza is high, treatment should be started immediately pending confirmation with nasopharyngeal swabs or aspirates. Poor prognostic factors are presentation in the third trimester with evidence of respiratory compromise at presentation, infiltrates on CXR, obesity and lymphopenia.

Two highly contagious coronavirus respiratory infections are severe acute respiratory syndrome (SARS) from Hong Kong in 2003, and Middle East respiratory syndrome coronavirus (MERS-CoV), which was first described in 2012 in Saudi Arabia. They resulted in severe hypoxaemia necessitating intubation, particularly in women in late gestation, and were associated with a high mortality rate. Fortunately, the number of pregnant women affected remains small, with limited case reports or small case series in the literature. Treatment regimens include ribavirin, interferon alfa 2a, glucocorticoids and antibiotic cover for superimposed bacterial infections. Treatment should not be modified for pregnant women. To date, vertical transmission has not been reported for these coronaviruses in pregnancy.

There appears to be a high rate of spontaneous miscarriage in women with influenza in early pregnancy, but problems with respiratory embarrassment tend to occur in the third trimester. If close to term, delivery should be considered to improve maternal ventilation and markedly reduce oxygen requirements by removal of the fetoplacental unit.

Overarching principles of care are the need for careful isolation of these women to prevent the spread among other vulnerable pregnant women. Women suspected of highly contagious coronaviruses should be placed in a negative pressure isolation room on arrival in triage/hospital. Staff caring for these women should be appropriately protected from airborne infections with N95 (or higher standard) masks in addition to standard isolation gear.

As pregnant women are particularly vulnerable to influenzas, and these vaccinations are safe in pregnancy, women must be strongly encouraged to seek seasonal influenza vaccinations, preferably before 30 weeks' gestation to ensure adequate transplacental transfer of maternal antibodies to the fetus.

Tuberculosis

Tuberculosis can present *de novo* during pregnancy. Symptoms of cough, malaise or weight loss in high-risk groups should be treated with a high index of suspicion. Pregnancy poses a diagnostic difficulty as it is more difficult to interpret non-specific symptoms such as malaise. In the UK, the immigrant population, particularly those who have recently relocated (<5 years), are most at risk, with Somali and Asian women representing nearly all cases [18]. It is associated with a high risk of preterm delivery and intrauterine growth retardation. Delay in diagnosis is greatest for those with extrapulmonary disease. Most treatment options – ethambutol, rifampicin, isoniazid (co-prescribed with pyridoxine) and pyrazinamide – are safe in pregnancy. Streptomycin carries risks of eighth nerve damage and should be avoided. Extrapulmonary disease is as common as pulmonary disease in the UK, and co-infection with HIV significantly increases the risk [18].

Cystic fibrosis

While men with cystic fibrosis are often infertile, fertility is preserved in women. Prenatal diagnosis of this autosomal recessive condition should be discussed before pregnancy. Pregnancy is inadvisable when there is hypoxaemia, poor nutritional status and pulmonary hypertension. Added concerns include liver disease, cystic fibrosis-related diabetes, and the ability of the woman to cope with the demands of a newborn baby, especially in the context of limited life expectancy (late thirties). Pulmonary function tests, echocardiography to exclude pulmonary hypertension, and arterial gases may all guide the decision as to whether pregnancy is advisable. Chest infections require prompt and expert treatment. Early involvement of the anaesthetic staff is advisable, and regional analgesia in labour is preferable. Most women with cystic fibrosis will have a good outcome to their pregnancy, though the most recent confidential enquiry emphasizes that maternal death may occur despite optimal care [1]. There are now an increasing

number of reports of successful outcome to pregnancy following lung transplantation for cystic fibrosis, though there remains a high risk of subsequent rejection, progressive decline in pulmonary function and eventual demise from infection.

Respiratory failure post partum

Respiratory failure is a medical emergency and can arise for the first time in the postpartum period. The differential diagnosis includes adult respiratory distress syndrome, amniotic fluid embolism, pulmonary embolism, infection, side effect of tocolysis and pulmonary oedema secondary to pre-eclampsia, peripartum cardiomyopathy, other undiagnosed cardiac disease or nephrotic syndrome. In the first instance, care is supportive prior to reaching a definitive diagnosis.

Neurological conditions

Epilepsy

Deaths from neurological causes including epilepsy are the third most frequent cause of indirect maternal death. In the 2014 maternal mortality report, there were seven deaths from epilepsy and 17 from other neurological causes. Most women with epilepsy who died did not have pre-conception counselling, and often had poorly controlled epilepsy even prior to pregnancy. Unsurprisingly, the report concluded that many could have had improvements to care which would have influenced outcome. It was also recommended that an identified epilepsy nurse should be part of the care team.

Deaths from epilepsy arise directly from seizures, or SUDEP (sudden unexpected death in epilepsy). The latter category is ill-defined, usually unwitnessed, and may or may not occur during a seizure.

Women of childbearing age who suffer from epilepsy must have their treatment designed to maximize safety and compliance in pregnancy. Ideally, these women are jointly managed by a neurologist (or an epilepsy nurse specialist) with a special interest in pregnancy and an obstetrician specializing in maternal medicine. Pre-conception counselling should discuss the woman's past history (including drug history), the choice of antiepileptic drug (AED) and its effects on organogenesis, the importance of seizure control and SUDEP [1]. Folic acid 5 mg should be started at least 3 months prior to conception due to the relative folate deficiency in this cohort and its beneficial effects on fetal neurocognitive development.

Seizures not only represent a direct threat to maternal health (e.g. drowning, physical injury), but recurrent seizures also put the fetus at risk from hypoxia. Approximately one-fifth of women may experience a deterioration in seizure control during pregnancy [19]. Its causes include poor adherence to medications and falling drug levels (especially with the newer AEDs such as lamotrigine and levetiracetam) with the alteration in protein binding, expansion of intravascular volume and increased renal clearance in pregnancy. The negative effect on seizure control is further compounded by lack of sleep and anxiety.

Some AEDs increase the risk of congenital malformations and women may stop treatment in view of this unless counselled otherwise. The risk of major congenital malformations varies with AEDs, with the lowest rates being found with monotherapy: 2.2% with carbamazepine, 3.2% with lamotrigine, 3.7% with phenytoin and 6.2% with valproate. A higher risk of congenital malformation is associated with higher doses and polytherapy, especially if this includes valproate.

Sodium valproate not only causes congenital malformation (10%) but affects subsequent neurocognitive development (30–40%) [20]. Hence, lamotrigine and levetiracetam are now first-line choices for women of childbearing age. A careful anomaly scan at 20 weeks can exclude specific abnormalities in women on AEDs, but will not achieve 100% detection.

In pregnancy, women must be followed up to ensure doses are titrated, and that they are maintained on as few drugs as possible. Approximately 3% have a seizure during labour, and women should be strongly advised against pool deliveries.

If lamotrigine and levetiracetam doses have been increased in pregnancy, they should be appropriately decreased within 2 weeks of delivery due to the return of maternal physiology to pre-pregnancy levels. Specific advice on childcare, such as not bathing the baby on their own and changing the baby on the floor (not on an elevated changing table), should be provided to the new mother. Patient organizations often have useful information on their websites (see https://www.epilepsy.org.uk/info/caring-children).

Summary box 15.6

Epilepsy in pregnancy has to be well controlled due to the high risk of SUDEP, but control should be maintained on a minimum of AEDs to avoid fetal toxicity.

Headache and migraine

Pregnant women may suffer from headaches that may resolve spontaneously in the second trimester. Migraine is also common in pregnancy. The natural history of migraine in pregnancy suggests a reduction in incidence

throughout the trimesters. Focal migraine can arise in pregnancy and requires an experienced opinion to exclude serious underlying causes. Treatment strategies include low-dose aspirin as prophylaxis, paracetamol, NSAIDs (used intermittently up to 32 weeks) and codeine as pain relief during an acute attack. Propranolol can be added if attacks are persistent. Triptans are safe in pregnancy and a reasonable option for those with troublesome migraine.

Focal transient neurological symptoms can arise in pregnancy and usually have a benign course. One study which assessed women presenting with first occurrence of dysphasia or hemisensory and hemimotor syndromes found a very low incidence of cerebral ischaemia on cerebral imaging [21]. In most cases, it was concluded that these were migrainous attacks, despite the lack of prior history. Subsequently, only 29% demonstrated recurrent migraine on follow-up, suggesting that pregnancy can lower the threshold for a migraine. It is very important that patients presenting with headache are assessed by fundoscopy, and have neck stiffness excluded [1].

Cerebral vascular disease

Strokes in pregnant women are often the result of haemorrhage [1], the main risk factor being poor blood pressure control. Investigation of neurological signs, including cerebral imaging, in pregnancy are the same as in the non-pregnant state.

The incidence of maternal mortality from a cerebral haemorrhage was 0.75 per 100 000 deaths in the 2014 MBRRACE report; 13 of 26 cases were due to subarachnoid haemorrhage and the rest were due to intracerebral bleeds. Risk factors for cerebral haemorrhage include advanced maternal age, African American race, hypertensive disorders with poor blood pressure control, coagulopathy and drug abuse. The period of greatest risk is during the postpartum interval, and this risk is heightened by increasing maternal age. Blood pressure can often be most difficult to control postnatally.

Several UK maternal deaths from cerebral haemorrhages occurred during labour, raising the spectre that labour is a potential risk factor. Defining any increased risk of vascular rupture during labour is not possible from the literature. Decisions on mode of delivery for those with a previous cerebral haemorrhage must be individualized and reflect the patient's wishes, parity and recommendations from the neurosurgeon.

When cerebral aneurysms are detected in pregnancy, management decisions regarding embolization (and the degree of radiation exposure) should be jointly made by obstetricians and neurosurgeons. Pregnancy should not alter the management of an acute stroke; pregnant women should be referred to stroke units and thrombolysis considered as with a non-pregnant patient [1].

Any woman presenting with a severe incapacitating headache should have a full neurological examination and neuroimaging considered.

Summary box 15.7

Strokes in pregnancy are usually haemorrhagic; risk factors include advancing maternal age, hypertension, coagulopathy and drug abuse. An acute stroke should be managed in exactly the same way in a pregnant woman as in a non-pregnant patient.

Cerebral vein thrombosis

Cerebral vein thromboses are more common in pregnancy. Presenting features include a very severe headache, seizures, photophobia and signs of raised intracranial pressure. An experienced opinion should be sought to determine if magnetic resonance angiography is warranted. The treatment involves anticoagulation that should be continued until the postpartum period. Thrombophilias are common in this group. Anticoagulation with LMWH is also needed in subsequent pregnancies.

Summary box 15.8

Cerebral vein thromboses are more common in pregnancy and the woman is likely to have an underlying thrombophilia that will necessitate anticoagulation in the cuurent pregnancy and future pregnancies.

Acute abdominal complications

Up to 2% of all pregnant women will require general surgery, with appendectomy and cholecystectomy being the most common procedures. These problems must be managed aggressively to minimize any risk of associated peritonitis, which can result in premature labour and associated sepsis. The estimated risk of fetal loss is 20% with a perforated appendix as opposed to 5% if uncomplicated. Diagnosis of such complications can be difficult and requires an experienced opinion. The data on route of surgery for appendectomy and cholecystectomy is quite limited, with conflicting data on miscarriage and preterm birth rates. There is a suggestion of a higher rate of fetal loss with laparoscopic approaches, though timing of surgery – with implications for the level of inflammatory insult – is more important than the route of surgery [22]. Caution is

required during the procedure and afterwards, given the risks of preterm delivery and the risk that contractions may be masked by perioperative analgesia.

Half of all cases of newly diagnosed inflammatory bowel disease (IBD) are under 35 years of age. Women with IBD are at increased risk of spontaneous miscarriage, preterm birth and FGR, particularly if active disease is present. Quiescent disease at conception is always a good prognostic sign, with up to 80% remaining in remission. Relapse is often related to discontinuation of medications.

Women with IBD need multidisciplinary care in pregnancy and to deliver at a unit with supportive care for the neonate in the event of prematurity. IBD is treated in the same way in pregnancy as in the non-pregnant state; steroids and 5-aminosalicylic acid compounds (e.g. sulfasalazine, mesalazine, olsalazine) are the mainstays of treatment. Supplementation with haematinics and vitamin D may be required. Anti-TNF drugs may be used in more severe cases (see section on biologics).

Mode of delivery will need to be discussed if there are intra-abdominal adhesions or active disease in the perineal and perianal regions. The 2015 European consensus group lists ileorectal anastomosis or ileoanal pouch as a relative indication for caesarean section; nevertheless the decision still has to be individualized to each woman [23].

Malignant disease

The overall incidence of malignant disease in pregnancy is between 1 in 1000 and 1 in 5000. In the past decade there has been an increasing preparedness to investigate and treat malignant disease in much the same way as in the non-pregnant state. This reflects increasing evidence of safety of chemotherapy in different contexts beyond the first trimester [24]. Not all chemotherapeutic agents are safe, examples including selective oestrogen receptor modulators, tamoxifen and angiogenesis inhibitors. A judgement needs to be made in relation to each agent, the gestation at which it is used, and the underlying malignancy and staging. Antiemetic treatment, steroids and thromboprophylaxis will all need to be considered as part of the treatment profile in view of the nausea associated with chemotherapy and the increased risk of thrombosis in this group.

The MBRRACE 2015 report [25] included a total of 180 maternal deaths between 2009 and 2013, and showed that the range of organ involvement (major categories were breast, brain, haematological, melanoma, lung and gastrointestinal) was similar to that in the non-pregnant group. Older mothers were at greater risk of malignancy and also of dying as a result of it. The report emphasized the need for full investigation of possible malignancy, treatment in the same manner as in the non-pregnant state unless there was specific evidence that this would do harm, and multidisciplinary input but with a named person to coordinate care.

Delayed diagnosis can be a problem in pregnancy as symptoms may be attributed to pregnancy, or signs masked by the abdominal and breast changes of pregnancy. Treatment options may be more limited in view of greater vascularity with pregnancy, more difficult surgical access and greater thromboembolic risk. Chemotherapy and radiotherapy can be considered in pregnancy, based on the increasing volume of reassuring evidence for chemotherapy. There is a modest but generally reassuring level of data looking at development of children exposed to maternal malignancy and chemotherapy *in utero* [26]. The most significant predictor of impairment of neonatal development is prematurity. Therefore, the 2015 maternal mortality report recommends avoiding preterm delivery whenever possible.

Pregnancy may exacerbate the growth of hormone-dependent tumours such as breast cancers. The incidence of pregnancy-related breast cancer is approximately 1 in 1000, and is likely to increase with advancing maternal age. Breast cancer is more likely to present late in pregnancy and prognosis is similar to that of the non-pregnant state when allowance is made for staging. Termination of pregnancy is most likely to be considered if breast cancer is diagnosed in the first trimester, but treatment strategies that allow continuation of the pregnancy may be considered. Treatment can involve surgery, as in the non-pregnant patient. Radiotherapy has been used, but requires careful counselling dependent on the gestational age, the dose required and the potential to shield the fetus. Chemotherapeutic protocols can be used that do not pose a significant risk to the fetus, but are generally avoided in the weeks preceding delivery to minimize the risk of coincident neutropenia or thrombocytopenia [27].

Current advice is that women should defer pregnancy for at least 2 years after a diagnosis of breast cancer, and longer with advanced stages of disease. Similar principles will apply to other tumours. A pragmatic approach has to be taken following a diagnosis of cancer in pregnancy that allows for the individual's wishes, the gestational age, and the feasibility of most forms of cancer treatment in pregnancy with reasonable success rates.

In rare instances, tumours may metastasize to the placenta and fetus. Histological examination of the placenta should be carried out if there is suspected metastatic disease or when maternal death from malignancy occurs. If placental metastatic disease is identified, neonatal follow-up needs to be arranged.

Table 15.3 Ionizing radiation for clinical imaging in pregnancy: doses to mother and baby.

Procedure	Typical effective dose (mSv)*	Average dose absorbed by breast tissue (mGy)	Average dose absorbed by uterus/fetus (mGy)
Chest X-ray	0.02		
CT pulmonary angiogram	2.2–7.0 (max. 21.0)	44.35	0.46
Ventilation–perfusion (*V*/*Q*) scan	1.3–4.4	0.37	0.40
Q-scan	1.0–2.4	0.28	0.25
CT chest	7.0		
CT head	2.0		
CT abdomen	8.0–10.0		

*A range of values are provided because doses will depend on the machine, older machines having higher doses of radiation.
Source: Astani SA, Davis LC, Harkness BA, Supanich MP, Dalal I. Detection of pulmonary embolism during pregnancy: comparing radiation doses of CTPA and pulmonary scintigraphy. *Nucl Med Commun* 2014;35:704–711.

Summary box 15.9

Maligancy can occur in pregnancy and should be investigated in the same way as in the non-pregnant state. Chemotherapy is possible in pregnancy; deliveries should be planned to avoid extreme prematurity.

Imaging in pregnancy

Pregnancy must not preclude effective imaging where clinically indicated. Irradiation from a CXR is minimal and should constitute first-line imaging for any breathless woman. A normal CXR is essential before further ventilation–perfusion (*V*/*Q*) scans are considered. On the other hand, a CT abdomen delivers a substantial dose of irradiation to the abdomen and fetus (8–10 mSv) and alternative forms of imaging should be preferentially considered (Table 15.3).

There have been long-standing concerns about the risks of imaging on the fetus. The International Commission for Radiological Protection has issued some guidance regarding such risks [28]. The risks are low and there is no increased risk of congenital malformations at doses below 100 mGy (equivalent to 100 CT abdomens). These levels could be achieved during fluoroscopically guided interventional procedures or if the woman is undergoing radiotherapy. The risk of childhood leukaemia is trivial, with 10 mGy resulting in one additional case in 1700 exposed individuals. If there has been early exposure (<16 weeks) to doses of radiation exceeding 100 mGy, then there is a risk of reduction in IQ. At doses more than 1000 mGy, there is a risk of microcephaly and severe learning difficulties. However, most of the imaging performed (non-interventional radiological procedures) will not result in such high levels of irradiation to the fetus.

Of greater concern is the exposure of active maternal breast tissue to ionizing radiation in the form of CT pulmonary angiograms when investigating a woman for breathlessness. Hence, the imaging of choice for a pregnant or postpartum woman with a suspected pulmonary embolus is a half-dose *V*/*Q* or *Q*-scan, which has sufficient negative predictive value if the preceding CXR is normal.

Summary box 15.10

Extremely high doses of radiation – beyond the doses for conventional non-interventional imaging – are necessary before there are any deleterious effects on the fetus. On the other hand, maternal breast tissue is vulnerable. Imaging should not be withheld due to an unfounded fear of ionizing radiation in pregnancy.

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16

Obesity and Pregnancy

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Rates of women with a body mass index (BMI) greater than 30 of reproductive age are rising, with recent estimates of over 25% common in many countries. Therefore obesity in pregnancy is a significant health issue. Obstetricians, when meeting an obese woman in early pregnancy, often focus on the short-term complications of obesity in pregnancy, such as the risk of gestational diabetes mellitus (GDM), pre-eclampsia and thromboembolism, the difficulty of fetal assessment, using ultrasound and fetal heart rate (FHR) monitoring, and the risks of labour. These complications often increase with increasing BMI in a dose–response fashion. Complications need to be considered seriously, as the potential problems may not be minor: obesity has been shown to increase the risk of morbidity and mortality [1].

While the immediate risks may be evident to any clinician in practice, what may not be appreciated are the subtle risks of obesity in pregnancy, how even mild obesity may affect progress in labour, the relative malnutrition of vitamins and minerals, maternal malabsorption and consequent malnutrition as a result of bariatric surgery, as well as the effects of maternal obesity on both fetal programming and long-term risk of cardiovascular disease and the increased risk of childhood obesity. In addition, though many appreciate the risks of morbid obesity (BMI >40, class 3 obesity; Table 16.1) on pregnancy, the clinical team may not fully appreciate the risks of even 'mild' obesity on pregnancy and the effect of pregnancy on the associated complications of obesity. Adipose tissue is an endocrine organ, synthesizing and secreting a variety of hormones and inflammatory markers, including cytokines, leptin and adiponectin. These adipocytokines can have profound effects on pregnancy.

It is well recognized that obesity is increasing in prevalence in both the developed and developing world. Increased sedentary lifestyles, changes in diet and nutrition and a reluctance to implement large-scale public health policies to challenge obesity [2] have resulted in a population very different to that of the 1950s when Friedman first described the 'normal' progress of labour, now known as the Friedman curve [3]. Then, as now, the average BMI of women in labour corresponded to the average BMI of those times, but in the 1950s the median BMI range was 20. Friedman's curve may not apply to the obese, or even overweight, woman.

While all obstetricians appreciate that routine antenatal care needs to be modified in order to provide optimal care to overweight, obese and morbidly obese women, this chapter aims to review the up-to-date evidence that will guide those adaptations.

Contraception, fertility and conception

In adolescence, several studies have shown that obese teenagers may have a higher number of sexual partners, older partners and less use of contraception [4]. This is a worrying pattern that does not continue into adulthood, but does lead to concerns regarding pregnancy risk in a vulnerable group.

For those not wishing to conceive, obesity may be a significant factor when considering contraceptive options. In contrast to adolescents, use of contraceptives does not differ in adult women based on BMI. The following points should be noted when discussing with obese women the most effective contraception. Safety of contraception should also be discussed at length, including the risk of thromboembolism with some forms of contraception.

- Contraceptive implants: no difference in efficacy. Weight gain may be a concern.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 16.1 Classification of maternal BMI (kg/m^2) and cut-off points for defining maternal obesity.

BMI	Class
<19.9	Underweight
20–24.9	Normal weight
25–29.9	Overweight
30–34.9	Obese class I ('mild')
35–39.9	Obese class II ('moderate')
40+	Obese class III ('morbid')

- Depot progesterone: no difference in efficacy. Concerns regarding weight gain are reassuring for adult women, with mean weight gain of less than 2 kg. In contrast, adolescents showed increased weight gain, with obese adolescents having more weight gain than normal-weight adolescents.
- Combined oral contraceptives: data are conflicting but overall there is no significant reduction in efficacy in obese women. Risks of thromboembolism need to be balanced against risk of pregnancy.
- Transdermal combined contraception: body weight over 90 kg is a significant risk factor for failure.
- Emergency contraception: both levonorgestrel and ulipristal acetate have reduced efficacy in obese women (efficacy same as placebo for levonorgestrel and BMI >26 kg/m^2, and for ulipristal and BMI >35 kg/m^2). The copper intrauterine device is considered the most effective form of emergency contraception in all women, irrespective of body weight.
- Tubal ligation: no difference in efficacy, though obesity confers additional risks of surgery (access, infection, risk with anaesthesia).
- Intrauterine device/system: overall, no difference in efficacy. Additional benefits may include improvement in menstrual irregularities and reduction in risk of endometrial carcinoma.

It is now well recognized that there is a reduction in fecundity in obese women. Median time to conception in obese women is 5 months, compared with 3 months for normal-weight women. Various theories suggesting a causative mechanism have been proposed, including the following [5].

- Derangements in hypothalamic–pituitary–ovarian axis.
- Decreased sex hormone-binding globulin (SHBG) with increased free estradiol and testosterone.
- Increased hyperinsulinaemia, resulting in stimulation of ovarian androgen production and hypersecretion of lutenizining hormone.
- Increased rate of polycystic ovarian syndrome (PCOS)/disease: obesity may promote the development of the PCOS phenotype in susceptible women.
- Differences in oocyte quality.
- Differences in endometrial receptivity.
- Menstrual irregularity.
- Inflammatory mechanism (e.g. insulin resistance, metabolic syndrome, increased levels of C-reactive protein, interleukin-6, tumour necrosis factor).
- Effect of adiopocytokines (hormones secreted by adipose tissue).

What is known is that the rate of pregnancy decreases by 5% for every unit of BMI over 29 kg/m^2, even when controlled for PCOS, so there is an indirect correlation between higher BMI and fertility.

Given the possible complications of obesity in pregnancy the ethics of providing subfertility treatment to obese women may be hotly debated, with some centres advocating that couples undergo weight loss prior to commencing any treatment. This is also an opportunity for pre-pregnancy consultation, which will be outlined in more detail in the next section. Weight loss has been shown to increase conceptions, pregnancy and live births; in contrast, women desiring fertility treatment may be concerned regarding non-modifiable factors such as age. Temporarily withholding fertility care may feel patriarchal, but may be an incentive to motivate women and their partners to achieve change. Even a weight loss of 10% of body weight can increase the rate of fertility, between 77 and 88%. The rate of spontaneous conception was doubled (to 35%), a figure comparable to the success rates of some *in vitro* fertilization (IVF) programmes; this suggests that weight reduction should be used as a primary tool prior to embarking on other forms of fertility treatment.

When undergoing fertility treatment, women who are obese face additional challenges, including:

- lower oocyte utilization rate;
- more embryos discarded;
- fewer embryos cryopreserved;
- poorer mean embryo grade;
- higher dose of gonadotrophins used;
- lower implantation rates.

Even in those where fertility treatment is successful, there are still increased risks to pregnancy, including increased risk of prematurity following IVF pregnancy in obese women. This risk of prematurity occurs at all ages of gestation, from viability to term. The risk of prematurity is also seen in twin deliveries following IVF; women with increased BMI are twice as likely to delivery twins prior to 28 weeks' gestation when compared with women with a normal BMI and a twin pregnancy.

Summary box 16.1

- Obesity should be considered when making contraceptive choices, though most have no difference in efficacy. Transdermal combined contraception is a notable exception, with a reduction in efficacy in obese women.
- The most effective form of emergency contraception is the copper coil.
- Obesity reduces fertility, and weight loss can improve fecundity.
- The success of fertility treatment is reduced in obese women when compared with normal-weight women.

Pre-pregnancy consultation

Women with pre-existing medical diseases (e.g. diabetes, cardiac disease, chronic autoimmune diseases) are advised that if they are considering a pregnancy to participate actively in multidisciplinary pre-pregnancy counselling. This aims not just to inform the woman and her partner of the possible risks of pregnancy but also to modify behaviour and medical care in order to best prepare her for a pregnancy. Obesity, given the significant risks of maternal and fetal morbidity, should be regarded similarly. Indeed, this may be a more productive consultation, as the risk factor is modifiable in a way that cardiac disease and autoimmune disease may not be. Women who present for pre-pregnancy consultations self-select to inform themselves and make decisions. Empowering women to make changes can influence not just their health but also the risks of obesity to their pregnancies and their children. Most of the studies reviewing the effects of lifestyle intervention focus on pregnancy itself, but expert opinion suggests that pre-pregnancy interventions hold considerable potential to improve maternal metabolic health.

When?

Opportunities for these consultations include general practice review visits, gynaecological reviews and fertility consultations as well as specialist obstetrics visits with multidisciplinary input. Unlike other long-term diseases, obesity is modifiable, with even small differences in weight significantly reducing the risks to both mother and child.

Bariatric surgery

In addition, women who have undergone bariatric surgery (even if their BMI has normalized) should be counselled regarding the requirement for supplementation after surgery, especially in the context of pregnancy. Nutritional support needs to be tailored both to the patient and the type of surgery she had; an appropriately trained dietitian should ideally provide this. As an example, women who have undergone bariatric surgery may require supplemental calcium, iron, vitamin B_{12}, vitamin A, folic acid, iodine and vitamin K [6].

It is advised that pregnancy should be avoided for 1 year after bariatric surgery because of the rapid weight loss and because malabsorption may increase the rate of intrauterine growth restriction, neural tube defects, neonatal hypoglycaemia and low birthweight. Weight loss following bariatric surgery is associated with a reduction in the rate of GDM, hypertension and pre-eclampsia and with reduced pregnancy-related weight gain.

Concerns have been raised regarding mechanical complications during pregnancy as a result of pregnancy-related vomiting, increased intra-abdominal pressure and repositioning of the abdominal organs to facilitate fetal and uterine growth. Band migration, band leakage, dehydration, herniation and rotation as well as electrolyte disturbances have been described [5]. Some women may choose to undergo tubal ligation concurrently to bariatric surgery.

Screening and general advice

Screening for obesity-related comorbidities (such as type 2 diabetes, chronic hypertension, sleep apnoea, proteinuria, non-alcoholic fatty liver disease and cardiac disease) would be valuable. Specific comorbidities such as ischaemic heart disease may be a relative contraindication to pregnancy. Women should be advised not to smoke cigarettes as this is an additional modifiable risk factor for morbidity and mortality. It has been suggested that those with a history of PCOS specifically should have a cardiovascular risk assessment due to the association with metabolic syndrome. Such an assessment could include family history, waist circumference, blood pressure, glycaemic control (e.g. oral glucose tolerance test) as well as a lipid profile [5]. Weight and height should be measured accurately in order to assess BMI and appropriately advise risks. Special bariatric equipment may be required, for example blood pressure should be measured with an appropriately sized cuff in order to most accurately measure a baseline and assess risk. Bariatric scales may be appropriate.

Because of the relative malnutrition associated with obesity – where the maternal diet may comprise mostly of carbohydrates and fat, high in calories, with minimal minerals and vitamins – it is generally recommended that obese and overweight women should take a higher dose of folic acid than normal-weight women. A dose of 4–5 mg, similar to that for women with diabetes,

epilepsy or a family history of neural tube defects, should be encouraged.

Women should be encouraged to enter pregnancy with a BMI below 30, ideally below 25. Weight is a very personal issue: being labelled 'obese' or 'morbidly obese' may upset women. They are much more than just their weight. At all times care and communication should be conducted sensitively and respectfully.

Summary box 16.2

- Obesity should be considered a medical disease on a par with any other chronic illness.
- Pre-pregnancy planning should be offered to all women with a BMI over 30 with a view to reduction of BMI.
- Pre-pregnancy consultation presents an opportunity to screen for obesity-related comorbidities such as diabetes, hypertension, cardiac disease and sleep apnoea.

Maternal complications: gestational diabetes, pre-eclampsia and pregnancy-induced hypertension

For many women, especially those with a BMI just over the obese range, the booking visit may be the first opportunity for education regarding the impact of obesity on pregnancy, delivery and their children. Because of sensitivities regarding the personal nature of weight and self-image, clinicians may shy away from the challenge of counselling women of the risks of obesity. Some may believe that little can be gained from it as the pregnancy has already started and significant weight loss will not be achievable. Advice regarding exercise, weight gain, nutritional choices and screening for complications such as GDM are appropriate, as pregnancy is a window of opportunity where women are motivated to adopt lifestyle changes.

It is important that this advice is repeated, and from multiple angles from different clinicians. An *honest* discussion means that all members of the team caring for a pregnant woman with obesity approach the pregnancy openly and give the woman information on what may happen in her pregnancy.

Similar to the pre-pregnancy consultation, the first booking visit can be an opportunity to screen for pre-existing disease in order to be able to accurately discuss prognosis. Weight and height should be measured to assess BMI. Self-reporting of weight is unreliable. Blood pressure should be measured with an appropriately sized cuff to establish pregnancy baseline.

Pregnant obese women have been shown to have a diet high in saturated fats and inadequate in carbohydrates, calcium, iron, folate and vitamin D [7]. These micronutrients are crucial for pregnancy. If not already started, consideration should be given to prescribing high-dose folic acid in order to reduce the risk of neural tube defects (it is obviously best to commence this before conception). Depending on the location, consideration can also be given to supplementation with vitamin D (e.g. 400 IU) as obesity predicts poor vitamin D status in both mother and neonate. This will depend on maternal exposure to sunlight of appropriate wavelength and clothing (e.g. those living in cooler climates as well as those with more restrictive clothing). It is also recommended that obese pregnant women lower their intake of processed high-fat foods and confectionary, with a concomitant increase in complex carbohydrates (wholegrain rice, pasta, bread and cereals) in order to be able to improve macronutrient intake by diet. A specific referral to a dietitian for individualized advice may be required, especially for women with a BMI over 40.

Women who have lost weight since a previous pregnancy or a pre-pregnancy consultation should be congratulated: even a small loss of weight can reduce the morbidity associated with a pregnancy affected by obesity. Advice regarding gestational weight gain can be gently but assertively given; the Institute of Medicine recommends a total weight gain in pregnancy of 5–8 kg in obese women [8] (Table 16.2). This is not just for the pregnancy but also for long-term health, since the strongest predictor of weight retention at 1 year post partum is weight gain in pregnancy.

Table 16.2 Institute of Medicine recommendations for total weight gain and rate of weight gain in pregnancy, based on pre-pregnancy BMI (kg/m^2)

Pre-pregnancy BMI	Total weight gain range (lbs)	Rate of weight gain in second and third trimester (mean range, pounds per week)
<19.9 (underweight)	28–40 *(12.7–18.2)**	1 (1–1.3) *0.45 (0.45–0.6)**
20–24.9 (normal weight)	25–35 *(11.4–15.9)*	1 (0.8–1) *0.45 (0.36–0.45)*
25–29.9 (overweight)	15–25 *(6.8–11.4)*	0.6 (0.5–0.7) *0.27 (0.23–0.32)*
30+ (obese, all classes)	11–20 *(5.0–9.1)*	0.5 (0.4–0.6) *0.23 (0.18–0.27)*

*Ranges in italic represent kilogram equivalents.
Source: Institute of Medicine and National Research Council. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academies Press, 2009.

Provided there are no obstetric or medical contraindications, obese women should be encouraged to exercise during and after pregnancy, just as with normal-weight women. Self-reporting shows that one-third of obese pregnant women are compliant with exercise in pregnancy guidelines; this may be reviewed with caution as a consistent finding is that obese women will over-report activity and under-report dietary intake [7].

Written comments in the medical notes should be factual and non-judgemental.

Dedicated clinics

There is no current evidence that one model of antenatal care is superior to any other for obese pregnant women. A dedicated obesity clinic may stigmatize women. Depending on the population demographics, the services may be overwhelmed if the 'bar' for admission is set too low. In contrast, however, a dedicated clinic may not only send a message that obesity is being taken seriously by all members of the multidisciplinary team, but also allow for a package of care to be provided that is consistent to all participants.

Pregnancy following bariatric treatment

Women who have undergone bariatric surgery prior to pregnancy have specific needs to maximize the health of the pregnancy. Those with gastric banding may need bands to be loosened during pregnancy. Dietetic input is essential in order to ensure adequate nutritional intake. This advice may also apply to women who have achieved a normal BMI after surgery, given the nature of the surgery to cause malabsorption.

There are several case reports of internal bowel rotation during pregnancy following gastric bariatric surgery. Women presenting with severe upper abdominal pain should have urgent surgical assessment as they may require emergency laparotomy and bowel excision. Some of these case reports have also described emergency caesarean delivery at the time of laparotomy; others have described preterm delivery or intrauterine demise in the postoperative period in pregnancies at gestations of very early viability.

Gestational diabetes

Although the association between obesity and GDM is well described, it is interesting that a universal theme amongst women with a new diagnosis of GDM is their shock at the diagnosis. This experience was independent of BMI: even those with morbid obesity were surprised and upset at a diagnosis of GDM. Whether the local guidelines suggest risk factor-based or universal screening, women should be screened between 24 and 28 weeks' gestation.

Consideration should be given to screening earlier in women with significant risk factors, such as morbid obesity, as discussed in the sections on booking visit and pre-pregnancy consultations. Where the screening test and diagnostic tests are positive for GDM in obese and morbidly obese women, strong consideration should be given to repeating the test in the postnatal period due to the heterogeneity of GDM, with some women having underlying undiagnosed type 2 diabetes.

It is equally important to gently inform women with GDM, especially those with obesity and morbid obesity, that pregnancy can be considered a 'treadmill test' for future health, and that a diagnosis of GDM is a prognostic indicator for increased risk of diabetes later in life. Modification of risk factors may affect the prognosis.

Hypertension and hypertensive disorders

Obesity is a risk factor for essential hypertension, pregnancy-induced hypertension and pre-eclampsia. This is why it is crucially important to accurately measure blood pressure at both booking visits (to establish baseline) and at subsequent visits in order to screen for both pregnancy-induced hypertension and pre-eclampsia. Nulliparous morbidly obese women (BMI >40) have a 30% chance of developing pre-eclampsia. The risk of both early and late-onset pre-eclampsia is increased in obesity.

Stages in the pathogenesis of pre-eclampsia (cytotrophoblast migration, placental ischaemia, release of placental factors into the maternal circulation, maternal endothelial and vascular dysfunction) are increased as a result of obesity-related metabolic factors [9].

Summary box 16.3

- The first antenatal visit can be an opportunity to inform and plan.
- Consider both calcium and high-dose folic acid supplementation.
- Antenatal anaesthetic consultation should be considered due to the potential difficulties with venous access and regional or general anaesthesia.
- Antenatal visits are opportunities for screening, especially for GDM, pregnancy-induced hypertension and pre-eclampsia.

Fetal complications: ultrasound, anomalies and intrauterine demise

Miscarriage

The risk of miscarriage is increased in obese women, irrespective of the form of conception. In addition, the risk of recurrent miscarriage and intrauterine death is also increased. Given the difficulty of adequate visualization in obesity, it is suggested that a transvaginal probe should be used to scan in early pregnancy in obese women, especially when making the diagnosis of miscarriage.

Fetal anomalies

Obesity confers an increased risk of fetal anomalies, in particular an increased rate of neural tube defects and congenital heart disease. This may be due to a difference in oocyte quality, increased need for artificial reproductive technologies, relative malnutrition or other yet unidentified factors.

Ultrasound assessment

Balanced against the increased risks of congenital abnormalities is the difficulty in obtaining high-quality ultrasound assessment in obese women, with a substantial number of incomplete anatomical assessments. Many centres offer a first anatomy ultrasound at 20 weeks' gestation, allowing both a second attempt at 22 weeks should the assessment be incomplete and the option of termination of pregnancy before 24 weeks should the couple so choose. A recent study analysing the addition of an earlier second-trimester transvaginal ultrasound in obese women (BMI >30) showed an increase in the percentage of 'complete' anatomy scans, from 42 to 51%. Adding a second-trimester transvaginal ultrasound at 14–16 weeks' gestation to the routine anatomy ultrasound at 18–20 weeks' gestation also improved visualization of the head, thorax and abdomen, but not the spine. It is disappointing that the rate of complete anatomy ultrasound was not higher, but this reflects the difficulty of assessing fetal anatomy in obese pregnant women [10].

Growth assessment

Because of the difficulty of assessing fetal growth trajectories by measuring symphysis–fundal height in the obese woman, and the risk of either macrosomia or intrauterine growth restriction, a formal ultrasound assessment of fetal growth in the third trimester is recommended.

Preterm delivery

The rate of premature labour is increased with increasing BMI. This may be iatrogenic (e.g. with a diagnosis of pre-eclampsia, GDM or fetal anomaly) or spontaneous. Spontaneous labour may be the result of polyhydramnios in association with fetal macrosomia, increased maternal inflammation or infection resulting in preterm rupture of the membranes, endometrial factors or increased requirement for IVF (discussed previously) but may also be a result of some other as yet unidentified factors.

Intrauterine death

Obese and morbidly obese women are at increased risk of intrauterine death compared with normal-weight women. Similar to other fetal complications, this may be a result of confounders such as GDM, pre-eclampsia or fetal anomalies, or as a result of a yet unidentified factor. The threshold for investigation should be reduced in obese and morbidly obese women, for example women presenting with reduced fetal movements or with complications in labour.

Summary box 16.4

- Infants of obese women have an increased rate of fetal anomalies, in particular neural tube defects and congenital heart disease.
- Obese women of childbearing age should be advised to take high-dose folic acid.
- There is an increased risk of prematurity and stillbirth in women with BMI over 30.

Delivery issues

Place of delivery

Obese women have a higher incidence of comorbidities and, as such, women with a BMI above 35 may not be suitable for a home birth.

Induction of labour

Obese women have a higher rate of induction of labour. This is due in some to development of complications of pregnancy such as GDM and in others to a postdates pregnancy, which is also increased in pregnancies affected by maternal obesity. The rate of failure of induction increases with increasing BMI, with over half of all inductions of women with a BMI above 40 being unsuccessful. In a nulliparous woman with a BMI over 60, the rate of success of induction may be as low as 20% [11].

So should women with a BMI greater than 40 have an elective caesarean section if the success of induction is not reassuring, and the risks of an emergency caesarean section are high? In a retrospective study of 661 mother–infant pairs with maternal BMI over 40, women having an elective caesarean section had the same morbidity as those with induction of labour. This was despite the fact that 40% of women undergoing induction of labour required an intrapartum caesarean section. Similarly, the risks of neonatal morbidity were equally distributed between the groups [12]. On closer reading, the risks of maternal and neonatal morbidity were highest in those with unsuccessful induction of labour and emergency caesarean section. A composite maternal morbidity score showed a 45% morbidity rate in women with an emergency caesarean birth, compared with 24% in those undergoing elective caesarean birth and 18% in those having a vaginal delivery following induction of labour. Neonatal morbidity followed a similar pattern: 21% with emergency caesarean section, 10% with planned caesarean and 8% following a vaginal delivery after induction. What can be taken from this? That vaginal delivery is an appropriate aim, which means correct selection of women and careful management of labour induction.

Regarding options for induction and augmentation of labour, there are few published studies comparing efficacy of methods in obese women [11]. Those that are available suggest the following.

- Mechanical induction: no data specific to obesity.
- Dinoprostone tampon: obese women are twice as likely to require a second cervical ripening agent compared with non-obese women, and had labour lasting 5 hours longer.
- Misoprostol: obese women receiving misoprostol may have a longer labour than non-obese women (up to 4 hours longer in morbidly obese women) and had a higher rate of caesarean section.
- Dinoprostone tampon compared with misoprostol (oral or vaginal): women receiving dinoprostone had a higher rate of caesarean section after adjusting for confounders.
- Oxytocin: in management of induction and augmentation, obese women require higher doses and longer duration of oxytocin use than non-obese women.

Management of labour

Equipment

There are multiple challenges to managing labour in obese women, not least the logistics of providing the appropriate equipment. Increasingly units are dedicating 'bariatric rooms', where morbidly obese women can labour in a dedicated bed with access to dedicated bariatric equipment, including patient hoists, wheelchairs and seats. Even for obese women who are not morbidly obese, equipment such as longer spinal needles, longer speculums, large blood pressure cuffs and specialized surgical equipment are required to provide safe care [12].

Communication

High-quality communication is a key part of the working of any multidisciplinary team caring for patients, and no less so on the labour ward. BMI can be discreetly noted so that this can be included at staff handover as part of the risk assessment of each woman. Both the consultant obstetrician and anaesthetist should be informed when obese women, at least class 3, present in labour. The remainder of the anaesthetic and obstetric teams, as well as the clinical midwife manager, also need to be aware of obese women in labour due to the increased risk of morbidity, and so early intravenous access and epidural/spinal/combined analgesia should be sited.

Analgesia in labour

Obese and morbidly obese women should undergo a pre-labour anaesthetic review in order to plan options for analgesia in labour and allow more fully informed consent. The BMI at which this should occur would differ between units depending on patient demographics; some suggest all women with a BMI over 40, others a BMI over 50. As well as a focused history and examination, a tactful discussion would include discussion of risks, potential for failure and the mutual goals of both comfort and safety.

It may be difficult for both the staff and the woman for her to be placed adequately to allow safe siting of an epidural catheter or administration of spinal anaesthesia. Appropriate equipment (such as long needles) is very helpful. Consideration should be given to obtaining neuraxial analgesia early in labour, with the most senior anaesthetist performing, or at the very least supervising, placement. Poorly palpable landmarks are associated with placement difficulty, so ultrasound may be useful [13]. Obese women may have a reduced volume of epidural space, so smaller doses of anaesthesia and analgesia may be required. Even if successfully placed, the rates of failure and resiting are higher than in normal-weight women [14].

Difficult regional techniques increase the risk of epidural haematomas, abscesses (1 in 1000) and meningitis (1 in 50 000); however, overall, regional anaesthesia would be considered safer than general anaesthesia. General anaesthesia holds risk of a difficult intubation and the risk of failed intubation (which occurs in 1 in 250 in the general pregnant population but is increased with maternal BMI >30 due to laryngeal oedema and poor airway access) [15].

Fetal monitoring in labour

There are three methods by which fetal heart rate may be monitored in labour: intermittent monitoring, continuous transabdominal and continuous transvaginal with fetal scalp electrode. Because of comorbidities and practicalities, obese women are often unsuitable for intermittent FHR monitoring. External transabdominal monitoring reduces the concerns of introducing infection in an already high-risk group, but is often not practical, especially in women with morbid obesity. Internal monitoring by means of a fetal scalp electrode is sometimes the only method of continuously monitoring FHR patterns in obese and morbidly obese women.

An intriguing recent study has proposed FHR monitoring using transabdominal monitoring of fetal ECG patterns, showing that fetal ECG was more reliable than traditional transabdominal FHR monitoring. The mean BMI in this study was 32 kg/m^2 [16].

Progress in labour

Women who are obese and overweight have statistically significantly longer labours: the average length of labour in normal-weight women is 6.2 hours, in overweight women 7.5 hours and in obese women 7.9 hours. The main 'delay' point in overweight women is between 4 and 6 cm of cervical dilatation, and in obese women prior to 7 cm dilatation; after this there is no difference in progression of labour.

As maternal BMI increases there is a poorer response to oxytocin and an increased need for intrapartum caesarean section. A recent review of labour progress which reported on a study of 5204 labours that ended in vaginal deliveries aimed to develop a more modern partogram to reflect changing demographics. More than half of the participants (53%, $N = 2791$) had a BMI greater than 30, reflecting the increased BMI in parturiants. There was an increased length of the first stage in women with a BMI greater than 30, with the time it took to progress from 4 to 6 cm ranging from 0.5 to 10 hours. Therefore the labour of obese pregnancies may have to be modified to reflect the longer time to progress to the active stage of labour, especially important in the context of the risks of emergency caesarean section [17].

Mode of delivery

Obese women have a higher rate of delivery by caesarean section. This may be due to multiple factors, including increased comorbidity (e.g. GDM, pre-eclampsia), increased fetal weight and macrosomia, increased dystocia as well as clinician concerns of risk of shoulder dystocia and morbidity associated with emergency caesarean section. As discussed previously, the rate of successful induction is decreased in obese women compared with normal-weight women; the overall risk of delivery by caesarean (whether elective or emergency following spontaneous or induced labour) is up to 50% in women with morbid obesity. The odds ratio of caesarean delivery has been reported as 1.46 among overweight women, 2.05 among obese women and 2.89 among severely obese women [18], although this increase is significant only for emergency caesarean deliveries. The success rate of vaginal delivery after caesarean section is also decreased in women with a higher BMI.

Obese and morbidly obese women have the same rights as normal-weight women to request a caesarean section, but a greater emphasis should be placed on fully informing the woman of the significant risks of maternal and fetal morbidity as a result of the caesarean delivery, including the issue of reduced access and increased risk of infection.

As discussed previously, it may take the anaesthetic team longer to establish effective regional analgesia. Conversion to general anaesthesia is not an easier option, as risk of failure of intubation is increased with both pregnancy and obesity. If a caesarean delivery is being performed as an emergency, the anaesthetic team may need to decide quickly the safest method of anaesthesia for the mother and fetus. Good communication with all members of the multidisciplinary team means that provisional plans should be in place for this eventuality, as well as having immediate senior back-up. Early establishment of a good working epidural anaesthesia and intravenous access in labour can also allow for quicker caesarean delivery in the event of an emergency in labour. If there are any delays in establishing effective anaesthesia, then it is prudent to continue fetal and maternal monitoring, continuously feeding back to the anaesthesia team regarding current maternal and fetal well-being.

Modifications of standard caesarean delivery procedures have been suggested for obese women. These include consideration of vertical or transverse subumbilical or supraumbilical incisions [19], as well as propylactic use of subcutaneous drains or negative pressure wound dressings. The evidence for these procedures is currently limited and, as with any procedure, the potential benefits (reduced wound infection, though some suggest an increased risk of infection with use of drains) need to be balanced against potential risks (increased analgesia use, increased bleeding, aesthetics of scar, increased operative time).

In women with 2 cm or more of subcutaneous fat, suturing the subcutaneous space may reduce risk of wound infection, wound separation and haematoma or seroma formation. There is no clear evidence for the best method of skin closure in obese women undergoing caesarean section.

Macrosomia and shoulder dystocia

Infants of obese and morbidly obese women have a higher birthweight and increased risk of shoulder dystocia. Concerns for these in turn leads to a higher rate of induction that is in turn associated with a higher rate of dystocia in labour and caesarean delivery.

Postpartum haemorrhage

Obese and morbidly obese women have an increased risk of postpartum haemorrhage. This highlights again the continuing theme of early intravenous access, early effective epidural and high-quality multidisciplinary team discussion in the management and care of the obese woman in labour. Obese and morbidly obese women should have active management of the third stage of labour.

Summary box 16.5

- The rate of induction of labour failure is higher in obese women.
- Epidural analgesia may be compromised by difficult access; early siting of epidural may be appropriate.
- Risks of caesarean and instrumental delivery may be higher.
- There are increased rates of postpartum haemorrhage.

Postnatal care

Infection and sepsis

Obese women have a higher susceptibility to infections, both bacterial and viral. In pregnancy there is a shift of T helper cells from type 1 to type 2, suppressing antibody-mediated immune responses and activating the innate immune system. The alterations in the maternal immune system allow the genetically foreign fetus to develop without rejection but a side effect is increased susceptibility to infection, including certain pathogens such as *Listeria*, *Toxoplasma*, malaria, influenza, varicella and measles. In obesity there is suppression of function of CD4 and CD8 cells, impairment of natural killer (NK) cells and decreased production of cytokines. In combination the differences in immune response in both pregnancy and obesity have been shown clinically, with increased susceptibility of obese pregnant women to infection compared with normal-weight controls. Other comorbidities, such as anaemia, diabetes, preterm delivery and instrumental or operative delivery, may further increase the risk.

Postnatal infections such as chorioamnionitis, wound infections, mastitis, breast abscess and urinary tract infections are increased in postnatal obese and morbidly obese women. It has been reported that the rate of endometriosis or surgical site infection in women with a BMI above 45 may be as high as 26%. Obesity and pregnancy are major risk factors for respiratory complications of H1N1 influenza infection, with higher rates of admission and mortality in the pregnant obese population. The association with respiratory compromise may be due to restricted lung volume in association with the additive effects of pregnancy- and obesity-mediated immunological changes.

A high requirement for analgesia after an otherwise routine caesarean section may be an indicator of underlying pathology such as a subclinical surgical site infection or necrotizing fasciitis. Obese and morbidly obese women are at increased risk of hospital-acquired infections, partly due to increased risk and partly due to reduced mobility and longer hospital length of stay. Screening for methicillin-resistant *Staphylococcus aureus* (MRSA) may not be routine for obstetric patients but may become so; in one study in the USA, 1 in 50 postnatal women screened positive for MRSA.

It is now nearly universally recommended that all women undergoing elective or emergency caesarean section should receive prophylactic antibiotics; some also suggest repeating the antibiotics following delivery or even dose adjusting to weight. These suggestions are based on altered pharmacokinetics, poorer vascular perfusion of wounds and decreased local immunological response in obese and morbidly obese women [14]. The physical presence of a pannus (or apron) of fat can physically reduce access to the wound, forming a moist, warm and dark environment that promotes bacterial growth and infection.

Use of a pressure dressing (such as PICO) may reduce the incidence of infection. A high vertical incision or transverse subumbilical or supraumbilical incision as an alternative skin incision in morbidly obese women undergoing caesarean delivery has been suggested to reduce not only wound infection but also the physical pressure of retracting a pannus near to the patient's thorax [19].

Thromboembolic disease

It is also nearly universally recommended that all women undergoing elective or emergency caesarean section, instrumental delivery or other operations during the postnatal period should receive prophylactic thromboprophylaxis. This may take the form of appropriately sized thromboembolic deterrent stockings, positive-pressure leg garments or low-molecular-weight heparin (LMWH). Consideration should always be given to individualization of risk assessment and updating this risk assessment based on recent events

(e.g. unexpected caesarean delivery, postpartum haemorrhage); these decisions should be made at a senior level. It has been suggested that independent of other risk factors that all women with morbid obesity should receive thromboprophylaxis to prevent venous thromboembolism (VTE), with LMWH for at least 10 days following even normal delivery and consideration for a full 6 weeks of the postnatal period if other risk factors are present [20].

With regard to LMWH, dose adjusting for maternal weight is critically important [20]. When using a 'standard' dose (e.g. LMWH 75 IU/kg, depending on the formulation) the dose for a 60-kg woman may be a routine 4500 IU, but for a woman weighing 100 kg would be 7500 IU, and for a woman weighing 120 kg would be 9000 IU (nearly twice the 'routine' dose). For some morbidly obese women the propylactic dose may be similar to the therapeutic dose for other women; some women may require two subcutaneous injections to obtain an adequate prophylactic dose and, as such, may have to be given as divided daily doses.

If women present with symptoms suggestive of VTE, full assessment and investigations should be carried out. Wells' score has not been validated in pregnancy and should not be currently used to decide management.

Neonatal issues

Infants of obese mothers have a higher rate of birth injury, respiratory distress, bacterial sepsis, neonatal hypoglycaemia and admission to the neonatal intensive care unit.

Breastfeeding

Obese and morbidly obese women are less likely to initiate and continue breastfeeding. Given the long-term effects in childhood of maternal obesity and the protective effects of breastfeeding, obese and morbidly obese women should be encouraged to breastfeed and may need extra services to help them to do so successfully. Women who have undergone bariatric surgery may need to continue their dietary supplementation while breastfeeding, following the advice of a trained dietitian.

Postnatal anxiety and depression

There is a positive association between obesity and anxiety disorders, and pregnancy is considered to be a special risk group for this given the baseline level of anxiety during or after pregnancy [21]. Many women undergo transient physiological anxiety due to transition to parenting, but for some this may become pathological and continue for some time after delivery. It is well recognized that anxiety and depression during pregnancy increase the risk of anxiety and depression in the postnatal period. Obese and morbidly obese women have higher anxiety trait levels even before 20 weeks' gestation compared with normal-weight women. The rate of anxiety is significantly increased further in morbidly obese women compared with obese women. This is concerning for a number of reasons. Anxiety is considered a barrier to both the treatment and prevention of obesity. The risk of postnatal depression is also increased. Maternal obesity and consumption of a high-fat diet during pregnancy can increase offspring vulnerability for mental or behavioural disturbances.

So why are obese and morbidly obese women more anxious? The perinatal risks of obesity in pregnancy are well described, and we have already mentioned the importance of a full discussion with the pregnant woman at the start of her pregnancy (ideally prior to considering pregnancy) in order to fully inform her of potential risks. Stigmatization of pregnancy obesity may be a factor. Socioeconomic disadvantage and behavioural and neurophysiological changes may all be associated with obesity and anxiety disorders.

Long-term effects

Fetal growth and development is a complex process under the influence of multiple conditions including genetics, maternal environment, uterine environment and hormonal status. Obstetricians are familiar with the Barker hypothesis, which states that the influence of the fetal environment persists into later life. While the most common example of this is the effect of intrauterine growth restriction, there is increasing evidence that maternal obesity alters glucose metabolism and maternal factors that in turn induce changes in developmental trajectories. The effects are numerous, including increased risk in humans of offspring obesity, diabetes, cardiovascular disease, schizophrenia and asthma. In comparison, infants of mothers who have successfully undergone bariatric surgery have

Summary box 16.6

- Increased risk of infection and venous thromboembolism.
- Increased risk of postnatal depression.
- Infants have higher neonatal morbidity compared with infants of normal-weight women.
- Children of obese women have higher rates of childhood obesity and cardiac disease; these effects may be transgenerational.

sustained improvements in cardiovascular markers. This 'diabesity' phenotype has been described as a chronic self-perpetuating cycle [22].

Interventions

There have been calls for educational, environmental and commercial changes to influence people's dietary and lifestyle habits, but without clear leadership and changes in regulations these may not be effective. For the local unit, unable to effectively change national policies with ease, lifestyle advice for obese and morbidly obese women has been proposed with the aim of reducing the morbidity associated with obesity in pregnancy. A number of antenatal interventions in pregnancy have produced differing impacts on pregnancy outcome. The ROLO study (randomized controlled trial of a low glycaemic index diet to reduce macrosomia) resulted in less gestational weight gain and improved maternal glucose tolerance [23]. The LIMIT trial (randomized controlled trial of lifestyle advice with standard care for BMI >25) resulted in less large-for-gestational-age infants with no impact on gestational diabetes [24] and the UPBEAT trial (randomized controlled trial of lifestyle intervention in obese pregnancy) showed less gestational weight gain but no impact on birthweight nor gestational diabetes [25]. While some success has been achieved with pregnancy interventions in terms of improved diet quality and less gestational weight gain, additional focus is required for periods before and after pregnancy as opportunities to improve maternal metabolic health in preparation for subsequent pregnancy.

Summary

Obesity has a significant risk for both maternal and fetal morbidity and mortality in pregnancy. These effects can persist in the children of obese and morbidly obese women, and perhaps even across generations to the children of these children. Interventions in pregnancy have been hindered by lack of interest and compliance and to date have failed to show any real difference. The main challenge reverts back to the reduction in population levels of obesity, so that women enter their pregnancies at a healthier BMI.

One thought of interest on obesity guidelines: while the increased rate of obesity and its corresponding risks in obstetrics and gynaecology is well recognized, it is interesting to note that in a review of national guidelines, only 13 of 31 countries studies had a guideline specific to obesity. In addition, no one guideline reviewed all the aspects that the reviewers had considered relevant to management of obesity in pregnancy. Many discussed screening for GDM or risk of fetal macrosomia. In contrast, the least commonly mentioned components included referral to a local initiative to manage obesity, review by a specialized midwife, monitoring of blood pressure (with an appropriate cuff), utilization of a fetal scalp electrode for monitoring in labour, providing thromboprophylaxis (weight adjusted) and providing prophylactic antibiotics for caesarean section [26].

If women wish to maximize their chances of a healthy pregnancy, and healthy children, then a healthy normal weight should be given as a target prior to their next pregnancy. If their family is complete, aiming for a healthy BMI can act as a target for future health and well-being.

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Part 4

Fetal Medicine

17

Fetal Growth Restriction

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Fetal growth restriction remains a major cause of perinatal mortality and morbidity, with over 30% of stillbirths having suboptimal growth as a contributory factor. The aetiology of growth restriction is multifactorial and there remains no robust means of predicting fetuses at high risk. This is, in part, due to the fact that the underlying causes are diverse. There also remains no single definition and it is becoming increasingly evident that fetal growth trajectory is as important (and in many case more important) than a single measurement. The balance between iatrogenic prematurity and consequent developmental problems and increased maternal interventions must be weighed against the increased risk of stillbirth. At preterm gestations, management protocols using fetal Doppler and computerized cardiotocography (CTG) improve outcomes, whilst at term gestations delivery does not increase poor outcomes; between 32 and 37 weeks' gestation the evidence for optimal management remains to be established. In order to reduce stillbirth rates further, there remains a need to improve detection of growth restriction and further refine current management protocols.

Definition

There is no single definition of a small or growth-restricted fetus. Variably, some have considered the fetus with an abdominal circumference or estimated fetal weight (EFW) below the 10th centile as small for gestational age (SGA), whilst others have used the 5th or 3rd centile or required Doppler abnormalities to also be present. It is clear that not only a single measurement is important, but fetuses that have significant reductions in growth velocity are at increased risk even if the biometry is still within normal limits [1].

A recent multinational expert consensus statement defining placental fetal growth has set out definitions of early (<32 weeks) and late (>32 weeks' gestation) growth restriction [2] (Table 17.1).

Consequences of growth restriction

The most evident consequence of growth restriction in a fetus is stillbirth. Suboptimal fetal growth is thought to be a significant contributor in 30–50% of antepartum stillbirths, of which placental dysfunction is likely the primary cause. SGA fetuses are at risk of premature delivery, both spontaneous and iatrogenic. Prematurity itself carries gestation-dependent risks, particularly below 30 weeks' gestation, and at this point SGA fetuses are at increased risk of these complications, estimated to be equivalent to being born about 2 weeks prematurely to actual birth gestation. Complications of prematurity include neonatal death, intraventricular haemorrhage, necrotizing enterocolitis and lung disease, which may be chronic.

Low birthweight, particularly when associated with prematurity, has long-term consequences for health and effects are seen particularly in neurodevelopmental outcomes and cardiovascular and metabolic changes. The Barker hypothesis was developed from the historical cohort related to the Dutch famine of 1944. It proposes that the *in utero* environment, particularly with low birthweight babies, causes 'fetal programming' to optimize fetal well-being, but has long-term deleterious effects on cardiovascular and metabolic well-being. Whilst compelling, it should be noted that further factors including genetics and postnatal environment are also important in contributing to long-term health outcomes.

Although the phenomenon of shunting blood to the brain in a compromised fetus is sometimes termed

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 17.1 Definition of fetal growth restriction.

Early-onset growth restriction
AC or EFW <3rd centile or absent EDF in the umbilical artery
or
1) AC/EFW <10th centile **combined with**
2) Uterine artery PI >95th centile **and/or**
3) Umbilical artery PI >95th centile
Late-onset growth restriction
AC or EFW <3rd centile
or
At least two of three of the following:
1) AC/EFW <10th centile
2) Crossing centiles of more than two quartiles on growth centiles
3) CPR <5th centile

AC, abdominal circumference; CPR, cerebroplacental ratio; EDF, end-diastolic flow; EFW, estimated fetal weight; PI, pulsatility index. *Source:* adapted from Gordijn *et al.* [2].

'brain-sparing', it might best be considered as cerebral redistribution as abnormal brain development can be found in these children. Paediatric follow-up of growth-restricted fetuses shows poorer motor and cognitive function and lower IQ in these children. This is particularly the case when there has been fetal Doppler evidence of cerebral redistribution or evidence of significant placental dysfunction such as absent or reversed umbilical artery end-diastolic flow (EDF) [1,3]. There is also evidence of reduced grey matter, reduced myelination, thinner cortex, reduced number of neurones and smaller head circumference in children born with growth restriction. However, other studies have not replicated these findings and the final determination on whether cerebral redistribution is independent of birthweight and gestation and related to abnormal neurodevelopment remains unclear [2,4].

Impaired angiogenesis results in reduced arteriole and capillary formation. As a consequence there is increased vascular resistance and hypertension. Endothelial dysfunction is evident with increased intimal thickness and vascular stiffness. Consequently, as well as hypertension, there is increased risk of earlier onset cardiovascular morbidity in adulthood [2,5]. Low birthweight is associated with an increase in adult type 2 diabetes and increased insulin resistance and dyslipidaemia has been shown in animal models of growth restriction.

Regulation of fetal growth

The regulation of fetal growth is complex. A fetus has genetically predetermined optimal growth, but the actual fetal growth is determined by the influence of maternal health, placental function and environmental factors. Embryonic growth in the first trimester is remarkably constant. As uteroplacental circulation becomes the major determinant of fetal growth, from the early second trimester discrepancies in fetal growth may become apparent. This is even more so the case in the third trimester.

The function of the placenta is to facilitate oxygen and nutrient transfer to the fetus, whilst removing waste products. Early adaptation of the spiral arteries and trophoblast invasion is essential. This process is not fully understood, but involves complex interactions between genetic and epigenetic programming as well as an appropriate maternal immune response. Failure of this process may result in suboptimal fetal growth, though this is not invariable. Abnormal spiral artery transformation may be associated with completely normal outcomes and vice versa.

Unlike children and adults, glucose is the main source of energy to the fetus and over 95% in the fetus is derived from maternal plasma glucose. Placental glucose transfer is primarily mediated by the glucose carrier GLUT-1 via a mechanism of facilitated diffusion [6]. The transfer of cholesterol, fatty acids and amino acids across the placenta is also closely regulated. There is evidence of increased glucose and fatty acid transfer in cases of increased growth, as seen in gestational diabetes. Conversely, in placentas of growth-restricted fetuses there is evidence of deranged amino acid transfer.

Insulin-like growth factor (IGF)-2 plays an important role in the regulation of fetal growth and amino acid transport. Postnatally, IGF-2 is produced by the liver in response to growth hormone (GH). *In utero*, however, IGF-2 is primarily synthesized within the cytotrophoblast layer of the placenta. IGF-2 binds the IGF receptor (IGF-R), of which there are two types, IGF-1R and IGR-2R. Binding of IGF-2 to IGF-1R results in promotion of growth, whilst binding to IGF-2R results in degradation of IGF-2. Notably, whilst the *IGF2* gene is paternally expressed, the *IGF2R* gene is maternally expressed, demonstrating the opposing parental effects of growth promotion and growth restriction [7]. Regulation of growth by IGF-2 is highlighted by two conditions: Beckwith–Wiedemann syndrome (BWS), an overgrowth syndrome, and Russell–Silver syndrome (RSS), a syndrome of growth restriction. In BWS there is gain of methylation resulting in biallelic *IGF2* gene expression and subsequent overgrowth. Conversely, in RSS the loss of methylation results in biallelic loss of *IGF2* gene expression and subsequent reduced growth. In some cases of BWS and RSS, there may be biallelic gain or loss, due to the relevant part of the chromosome carrying these genes being inherited from the same parent; this is referred to as uniparental disomy.

BWS and RSS are examples of genomic imprinting and epigenetics. Epigenetics is the presence of modifications to the genome that affect gene regulation and which are heritable but potentially reversible. DNA methylation is the commonest form of modification, although more complex histone modification may occur. Over 100 genes have been found to be affected by imprinting; many are involved in fetal and placental growth or thyroid, insulin and glycogen metabolism, with variation between those maternally and those paternally expressed. The recognition of epigenetic influences supports the parental conflict hypothesis: maternally expressed genes are involved in resource conservation (i.e. less flow to the fetus) and paternally expressed genes in resource extraction (i.e. more energy to fetus) [8]. This provides a mechanism for the increasingly recognized paternal contribution to fetal growth disorders.

The association between pre-eclampsia and hypertensive disorders of pregnancy is well known. There is increasing evidence for the association of maternal haemodynamic changes, which may be subclinical, and fetal growth restriction. Reduced maternal cardiac output, lower heart rate and increased peripheral vascular resistance is seen in growth restriction and quite possibly predate its development. There is also evidence of increased vascular stiffness and endothelial dysfunction. Whether these effects are a consequence of growth restriction or cause the condition remains to be elucidated.

Assessment and investigation

Symphysis–fundal height

Routinely, symphysis–fundal height (SFH), the distance from the symphysis pubis to the uterine fundus, is measured at each midwife or antenatal attendance from 24 weeks' gestation. As a guide, the SFH in centimetres is equal to the number of weeks of gestation plus or minus 2 cm. After 36 weeks, the acceptable difference increases to 3 cm. However, SFH has poor intra- and inter-observer reproducibility. SFH is also prone to error due to factors unrelated to fetal biometry, such as maternal obesity, fibroids, polyhydramnios and fetal lie.

There has been recent interest in standardizing SFH measurement by introducing training packages, and plotting the measurement on SFH charts that are generated at booking and adjusted for maternal characteristics. The validity and usefulness of this approach remains to be proven.

Ultrasound biometry

Ultrasound is the current gold standard for fetal growth assessment. Measurements are made of the head circumference, abdominal circumference and femur length. In some cases, biparietal diameter may also be measured. These measurements are inputted into an algorithm, the most common being that developed by Hadlock, to calculate EFW, particularly the four-parameter model. This can then be plotted against gestation-specific centiles.

Customized charts

There remains controversy as to whether fetal growth is the same in all healthy populations, or whether specific differences exist. Two recent studies, INTERGROWTH and WHO, both carried out in different centres throughout the world, have reached different conclusions on this matter. INTERGROWTH suggests that fetal growth is no different in optimally healthy women throughout the world, whereas the WHO study has shown small but significant differences in growth. The controversy is sure to continue, and with it the question of whether customizing birthweight percentiles based on maternal characteristics is appropriate.

Causes

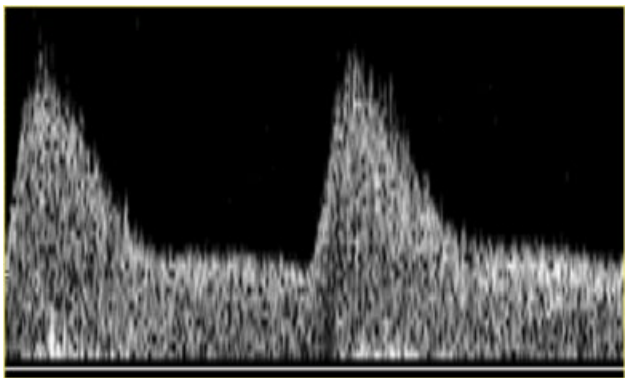
The assessment of the cause of an SGA fetus has important implications for the antenatal management and long-term prognosis. At initial presentation, accuracy of dating of the pregnancy should be assessed and expected date of delivery confirmed. Gestation should be assigned by crown–rump length between 45 and 84 mm (11^{+2} to 13^{+6} weeks' gestation); beyond this gestation, head circumference should be used, although in cases of *in vitro* fertilization (IVF), embryo transfer dates can be used with a correction for day 2 or 5 transfer.

Evidence of poor placentation, failure of adaptation of the spiral arteries and adaptation of the maternal vasculature can be assessed by increased impedance and/or 'notching' in the uterine arteries (Fig. 17.1). Abnormal fetal Doppler indices or oligohydramnios are also suggestive of placental dysfunction as the cause of a small fetus.

A small fetus may have an underlying chromosomal abnormality, particularly when presenting in the second trimester, and invasive testing should be discussed. A detailed anomaly scan should be performed, as any further anomaly would increase this risk further. Serological testing for cytomegalovirus and toxoplasmosis should be performed in severely growth-restricted fetuses. It should be borne in mind, though, that features of placental dysfunction (see above) may also be seen in a poorly functioning placenta secondary to a chromosomal abnormality or infection.

After exclusion of these causes, it should be considered whether a small fetus is constitutionally small. In such cases surveillance is warranted, although these fetuses

(a)



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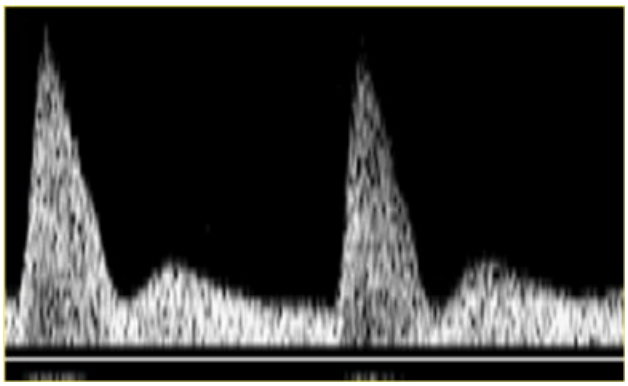

Fig. 17.1 (a) Normal and (b) abnormal uterine artery Doppler waveforms. The waveform in (b) has reduced diastolic flow velocities and an early diastolic notch.

will often follow a normal growth trajectory and have a good prognosis.

Prediction

Because of its heterogeneous aetiology, prediction of growth restriction is complex particularly in first pregnancies. At booking, which usually takes place at 10–13 weeks' gestation, women can be assessed for risk factors. From history alone, these can be subdivided into maternal risk factors, maternal medical conditions and previous pregnancy history (Table 17.2). Paternal SGA should also be noted as this has an odds ratio (OR) of 3.7 for an SGA fetus.

As pregnancy progresses, further risk factors may become evident. In women undergoing combined screening for common trisomies, pregnancy-associated plasma protein A (PAPP-A) is routinely measured. PAPP-A is a placentally derived protease whose main substrate is insulin-like growth factor binding proteins and its serum levels are related to both the function and size of the placenta. There is an association between low PAPP-A levels and low birthweight. Multiple other serum markers have been studied. These include those related to placental mass and function (e.g. ADAM-12, PP-13, IGFBP-1 and IGFBP-3), those related to angiogenesis (e.g. VEGF, endoglin, PGFa and sFlt-1) and those related to endothelial function (e.g. asymmetrical dimethylarginine and homocysteine). None of these has been found to have predictive value that is of clinical use [9].

Ultrasound parameters have been shown to have some utility. The impedance to flow within the uterine arteries can be readily measured. In healthy pregnancy there is normally low resistance and high flow. Abnormalities of uterine artery Doppler waveform include increased impedance and 'notching' (Fig. 17.1). Uterine artery Doppler performed at 24 weeks' gestation has 80% sensitivity for a 5% screen-positive rate for the prediction of a fetus that will require delivery prior to 34 weeks due to growth restriction. The predictive value of uterine artery

Table 17.2 Pre-existing and maternal factors associated with fetal growth restriction.

Risk	OR (95% CI)
Pre-existing maternal factors	
Age >40 years	3.2 (1.9–5.4)
Smoker >11/day	3.21 (2.03–2.4)
Cocaine use	3.23 (2.43–4.3)
Vigorous exercise	3.3 (1.5–72)
Maternal obstetric history	
Previous SGA	3.9 (2.14–7.12)
Previous stillbirth	6.4 (0.78–52.56)
Maternal SGA	2.64 (2.28–3.05)
Maternal disease	
Chronic hypertension	2.5 (2.1–2.9)
Diabetes with vascular disease	6 (1.5–2.3)
Renal impairment	5.3 (2.8–10)
Antiphospholipid syndrome	6.2 (3.47–10.27)
Paternal factors	
Paternal SGA	3.47 (1.17–5.6)
Pregnancy complications	
Heavy bleeding	2.6 (1.2–5.6)
Pregnancy-induced hypertension	2.5 (2.3–2.8)
Pre-eclampsia	2.26 (1.22–4.18)
Echogenic bowel	2.1 (1.5–2.9)
Unexplained APH	5.6 (2.5–12.2)
PAPP-A <0.4 MoM	2.6
Low weight gain	4.9 (1.9–12.6)

APH, antepartum haemorrhage; MoM, multiple of median; SGA, small for gestational age.

Doppler on its own in the first trimester has low sensitivity.

Various algorithms have been developed for the prediction of fetal growth restriction. These commonly use a combination of maternal history, maternal physiological measurements, serum markers and ultrasound parameters. To date, none has had sufficient sensitivity at an acceptable false-positive rate to warrant introduction into routine clinical practice.

Monitoring SGA

There is a clear association between growth restriction and hypertensive disorders of pregnancy, particularly pre-eclampsia. Up to 70% of women with a growth-restricted fetus will develop pre-eclampsia. As such, blood pressure and urine dipstick for proteinuria should be performed at each visit.

Umbilical artery Doppler

The umbilical artery Doppler waveform is the primary Doppler assessment in fetuses with growth restriction. Management protocols based on measurement of the umbilical artery waveform in high-risk pregnancies has been shown to reduce perinatal deaths by up to 29%, though it is not clear on what basis decision-making is improved.

As placental dysfunction increases, there is increasing impedance in placental vessels. This initially presents as raised umbilical artery impedance, detected by increased values in either the resistance index (RI) or pulsatility index (PI). As the uteroplacental circulation is increasingly impaired, absent EDF in the umbilical artery is noted, indicative of loss of normal function in about 60–70% of villi, with progression to reversed EDF as remaining normal placental function is lost (Fig. 17.2). The progression of changes in umbilical artery Doppler waveforms can be rapid and unpredictable, particularly in early-onset fetal growth restriction (FGR). Absent or reversed EDF after 26 weeks of gestation has been shown to have an independent impact on neurodevelopment.

A recent Cochrane systematic review and meta-analysis, including 18 studies and over 10 000 women, demonstrated that women who had Doppler assessment had a significantly lower perinatal mortality (1.2%) compared with those who had not been assessed by Doppler (1.7%; relative risk or RR 0.67; 95% CI 0.46–0.96). Although the data for secondary outcomes showed that there were fewer adverse outcomes in the Doppler group, this did not reach statistical significance [10]. Interestingly, there was a reduction in interventions including induction of labour and lower segment caesarean section in the Doppler group. There was no difference in operative vaginal delivery rates or Apgar scores at 5 min. Notably, though, there is a lack of data on long-term neurological development in the babies in either group.

Middle cerebral artery Doppler

Unlike umbilical artery Doppler, middle cerebral artery (MCA) Doppler can be a proxy for hypoxia and may be abnormal for many weeks in early-onset FGR. The role of the cerebral arteries and the changes that occur in the vessels are important in relation to the concept of 'brain-sparing' in the chronically, or indeed acutely, hypoxic fetus. Although now debated, the concept of 'brain-sparing' involves redistribution of blood by dilatation of the cerebral vessels, thus increasing substrate and oxygen supply to the brain, in response to fetal chemoreceptor or baroreceptor stimulation.

The value of MCA Doppler in the prediction of adverse fetal outcome and assessment of the at-risk fetus has been reported variably. Some studies have suggested that assessment of MCA Doppler is a useful tool, whereas others have found poor predictive value [11–14]. Recently, a meta-analysis of eligible studies (35 in total) including 4025 fetuses has been performed [15]. This found that low MCA PI appears to be associated with fetal well-being assessed by acidosis (pH <7.20) at birth (although this finding is largely biased by a single study in a high-risk population [16]), Apgar score below 7 at 5 min or admission to neonatal intensive care.

It is important to recognize that while these findings do suggest that there is an association between abnormal MCA and adverse outcomes, the association is weak. Overall, this meta-analysis suggests that in clinical practice MCA alone has limited predictive value for compromise of fetal or neonatal well-being.

Cerebroplacental ratio

As discussed in the previous section, the normal physiological response of MCA dilatation in fetuses exposed to acute or chronic hypoxic conditions results in a reduction in fetal MCA PI. Commonly, though not universally, this is associated with increasing impedance in the umbilical artery. Whilst the values obtained on measuring these Doppler parameters individually may be within normal limits, it is possible that the fetus is compensating. By using the ratio of MCA to umbilical artery Doppler PI – the cerebroplacental ratio (CPR, also called the cerebro-umbilical ratio) – it may possible to determine which fetuses may be at risk of compromise, as those with abnormal (i.e. low) CPR may be considered to have failed to reach their growth potential [17,18].

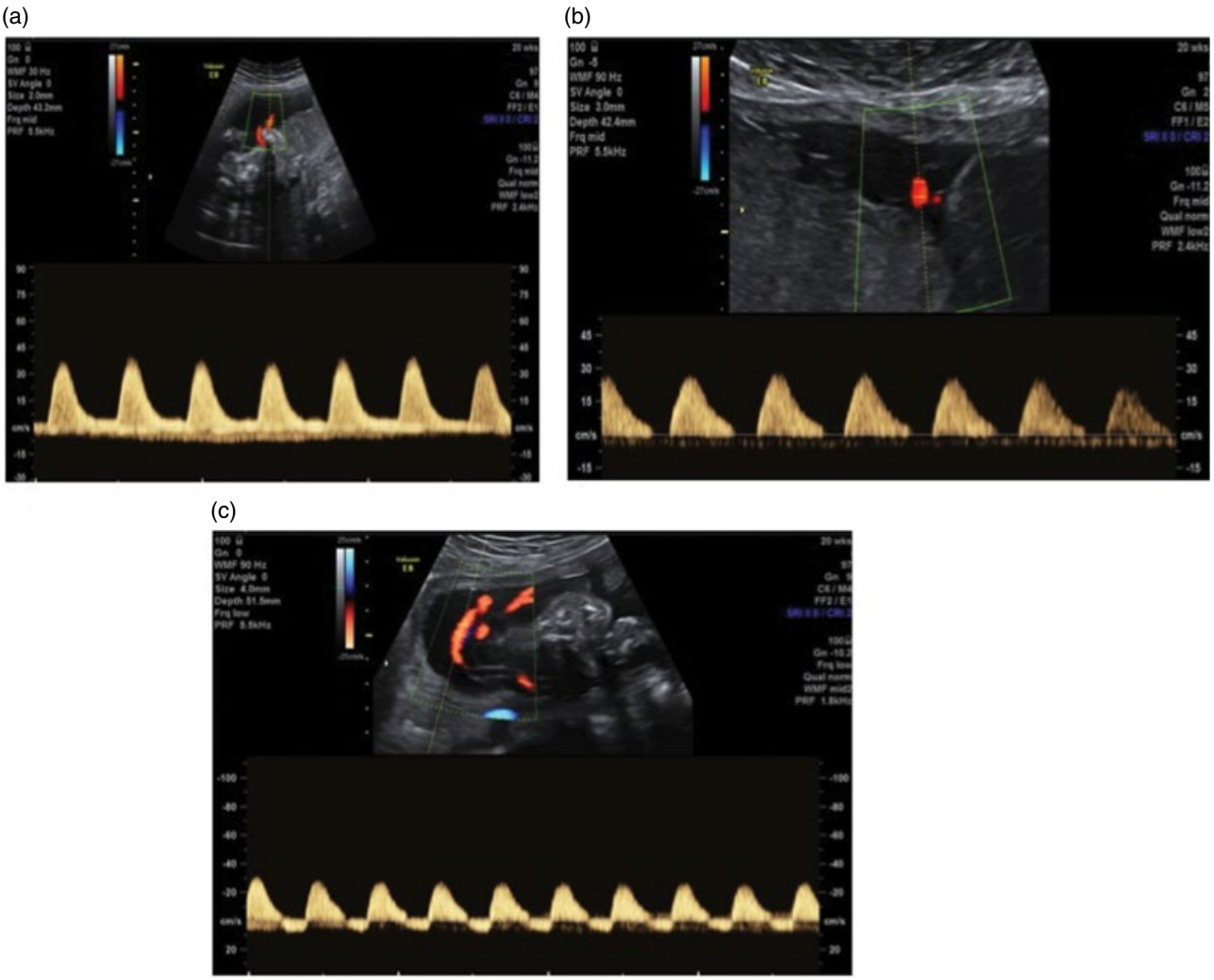

Fig. 17.2 Umbilical artery Doppler waveforms: (a) normal; (b) absent end-diastolic flow; (c) reversed end-diastolic flow. (*See also colour plate 17.2*)

A low CPR [17,19] may be associated with delivery by lower segment caesarean section due to fetal compromise, determined by either abnormal CTG or fetal blood sample below pH 7.20, although no differences in Apgar scores and arterial pH (taken at time of delivery) were found nor is there evidence of adverse neonatal outcomes in the groups with low CPR in either study. However, others [20] have also associated low CPR (PI <1) with adverse perinatal outcome in intrauterine growth restriction (IUGR) and impaired neurodevelopment at 2 years of age.

CPR may be of most use when umbilical artery PI is greater than the 95th centile with a normal waveform, in which situation a low CPR gives an OR for adverse perinatal outcome of 11.7 (95% CI 6.0–22.9). This provides similar predictive value to an abnormal umbilical artery waveform (OR 10.8, 95% CI 3.8–30.5) compared with raised umbilical artery PI alone (OR 6.9, 95% CI 2.9–16.5). It should be remembered that gestation and birthweight remain the most important predictors of morbidity and long-term outcome.

Ductus venosus Doppler

The ductus venosus (DV) is a fetal vessel connecting the intra-abdominal portion of the umbilical vein to the left portion of the inferior vena cava just below the diaphragm [21]. The function of the DV is to shunt the oxygen and substrate-rich blood coming from the placenta via the umbilical vein to the heart. The DV diverts 25% of the blood to the heart, with the remainder being distributed to the liver and joining the circulation via the hepatic portal system. Although entering the heart via the right atrium, this substrate- and oxygen-rich blood is

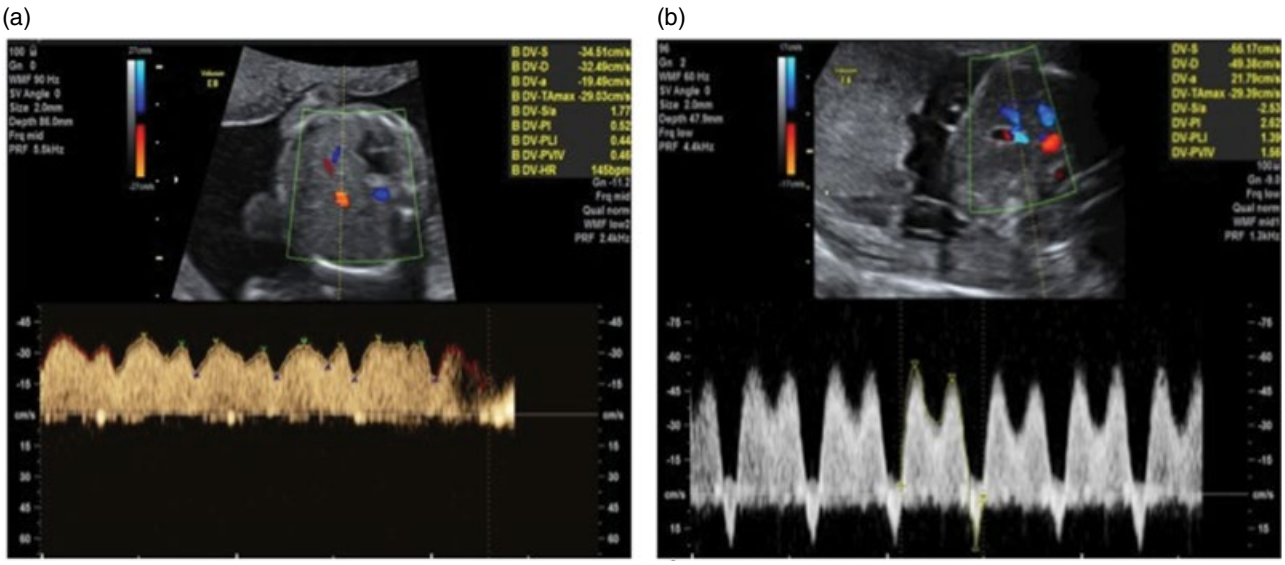

Fig. 17.3 Ductus venosus waveforms: (a) normal; (b) reversed a-wave. (*See also colour plate 17.3*)

preferentially directed to the left atrium and then, via the left ventricle and aorta, to the fetal heart and brain [22,23].

The utility of the DV waveform is primarily in the very premature fetus with IUGR, or the preterm fetus with abnormal umbilical artery waveforms (Fig. 17.3). Reversal or absence of the DV a-wave, particularly in combination with umbilical vein pulsations, has been shown to be closely associated with a pH below 7.20 [24] and perinatal mortality irrespective of gestational age, with a risk of up to 100% in early-onset FGR. It has been shown that DV abnormalities precede changes in computerized CTG in 50% of cases, although it is safe to wait DV PI or waveform changes in cases where computerized CTG remains normal [25].

The TRUFFLE study and the application of its results to the timing of delivery in early-onset IUGR is discussed later.

Cardiotocogram and biophysical profile

CTG monitoring as an assessment of fetal well-being has become a routine part of antenatal care. There is, however, no evidence of benefit in high-risk cases and may in fact result in unnecessary intervention [26].

However, computerized CTG monitoring can provide assessment of short-term variability (STV), which cannot be performed by visual assessment alone. Reduced STV (<3 ms) has been shown to correlate with the fetal metabolic state and significantly reduced STV is closely associated with fetal acidaemia [27–29]. This has been shown to reduce perinatal mortality compared with traditional CTG in the high-risk population (RR 0.20, 95% CI 0.04–0.88) [26], although this effect was not evident once deaths due to congenital anomalies were excluded (OR 0.23, 95% CI 0.04–1.29).

As such, CTG monitoring should not be used as the only form of surveillance in SGA fetuses. If CTG monitoring is used, interpretation should be based on analysis of STV on computerized CTG [30].

The biophysical profile combines the use of CTG with the ultrasound assessment of fetal movement, fetal tone, fetal breathing movements and amniotic fluid. Each parameter is scored 0–2 points, with a maximum total score of 10. A normal score (8 or greater) is reassuring. Biophysical profile has a high false-negative rate and is not a good predictor of fetal acidaemia. It has also been shown to increase caesarean section rates, but not improve perinatal outcome. The use of biophysical profile is not recommended for surveillance of the SGA fetus.

Timing of delivery

Timing of delivery of the small or growth-restricted fetus can be challenging. This is particularly so at very preterm gestations, which are associated with high rates of perinatal complications. Neonatal morbidity and mortality have improved significantly in the past decade, with survival rates of 13% at 24 weeks, 43% at 25 weeks, up to 76% at 26 weeks and up to 90% at 30 weeks' gestation [31]. Timing of delivery must take into account not only survival but also associated significant morbidities such as bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis and cerebral palsy.

Similarly, neonatal survival without significant morbidity progressively increases with increasing gestational age.

However, both birthweight centile and gestational age are important factors at very preterm gestations and must be considered in combination when considering neonatal outcomes. The PREM scoring system has also been recently validated [32] and it has been suggested that it might be used in combination with the Clinical Risk Index for Babies (CRIB) scoring system for neonatal mortality risk adjustment. Outcomes for growth-restricted neonates below 29 weeks are similar to those of appropriately grown neonates delivering at a gestation 2 weeks earlier [31].

Below 32 weeks, timing of delivery can be based on DV waveforms or computerized CTG analysis of the STV. The TRUFFLE study randomly assigned growth-restricted fetuses between 26 and 32 weeks' gestation to delivery based on one of DV PI above the 95th centile, absent DV a-wave or abnormal STV [33]. The results showed that neonatal survival without neuroimpairment was similar across all groups. However, among survivors at 2 years there were better functional outcomes in those delivered based on waiting for late DV changes rather than CTG abnormality. The earlier GRIT study had shown no difference in outcomes at 2 years between immediate delivery and delayed delivery in compromised fetuses between 24 and 36 weeks' gestation. Based on the fact that these survival rates are good, with low morbidity rates beyond 32 weeks [34,35] and, in light of TRUFFLE data, appear to be improving, delivery of an SGA fetus with absent or reversed EDF in the umbilical artery should be recommended at 32 weeks' gestation.

Beyond 36 weeks, delivery may be informed by the findings of the Disproportionate Intrauterine Growth Intervention Study at Term (DIGITAT) study. This study randomized women between 36^{+0} and 41^{+0} weeks' gestation with fetuses less than the 10th centile to either delivery within 48 hours or expectant management. There were no significant differences in long-term outcomes between the two management strategies [36]. An increased incidence of admission to neonatal care was found in the delivery group [37]. Importantly, there was a higher perinatal mortality in women who did not consent to take part in the study and who in the main opted for conservative management, i.e. waiting, without a clear protocol for monitoring.

In the absence of harm, SGA fetuses beyond 37 weeks can be considered for delivery and delivery should be recommended if there are Doppler abnormalities, including increased umbilical artery PI or decreased MCA PI. However, a pragmatic approach to delay delivery beyond 38^{+0}, if clinically possible, may reduce neonatal admissions.

There remains an absence of high-quality data to guide the timing of delivery between 32 and 36 weeks' gestation. A multicentre European study (TRUFFLE 2) is currently in development to address this. An approach of conservative management with increased surveillance with Doppler and CTG can be adopted in these cases. At 37 weeks, delivery should be considered, as outlined above. Prior to this, if there are any clinical concerns, Doppler waveform abnormalities or reduction in growth velocity, earlier delivery should be advised.

Summary box 17.1

- Fetal growth restriction is a major cause of perinatal morbidity and stillbirth.
- Fetal growth restriction is best defined by both fetal smallness and abnormal Doppler (usually umbilical artery) findings.
- Accurate prediction of growth restriction remains difficult.
- Fetal growth trajectory, as well as absolute fetal size, is important.
- Before 32 weeks, neonatal outcomes can be improved by timing delivery by changes in the ductus venosus Doppler in conjunction with computerized CTG.

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18

Third Trimester Fetal Assessment

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If the first and second trimesters of pregnancy are defined by embryonic and fetal development, the third trimester is defined by consolidation of these processes through maturation, growth and preparation for delivery. Traditional, the term 'third trimester' is used to describe the antenatal period between 28 and 42 weeks' gestation, but it may be more appropriate to subdivide this into parts, based on the potential complications of pregnancy that may occur. Fetal viability now descends to 24 weeks (or earlier) and many of the physiological and pathological processes that impact the 28-week fetus are equally relevant at this earlier gestational point. Phenotypes and underlying aetiologies of intrauterine growth restriction (IUGR) differ before and after 32–34 weeks' gestation and different approaches are needed to recognize complicated pregnancies. Delivery issues at 24–34 weeks focus on prediction, prevention and improvement of outcome of prematurity. In contrast, assessment for delivery at gestations of 37 weeks or more should focus around prediction and prevention of complications of term intrapartum care. Whilst this chapter describes tools and approaches to third-trimester fetal assessment, it is important to recognize that these need to be placed in clinical context, first defining potential risks to an individual pregnancy and then tailoring assessment accordingly.

Stillbirth, broadly defined as death *in utero* during the third trimester of pregnancy (with varied gestational end-points described internationally), continues to present a major problem in obstetric management and should, by necessity, be a focal point of third-trimester fetal assessment. Rates of stillbirth have not changed significantly in the last 30 years, whilst deaths due to congenital abnormality have been significantly reduced through first- and second-trimester screening and rates of neonatal death have fallen through improvements in neonatal care. As a consequence this adverse outcome, which was typically the 'Cinderella' of obstetric complications, is now the subject of major public health and research initiatives. If congenital abnormalities are excluded, the leading causes of stillbirth are very early preterm birth, IUGR, antepartum haemorrhage and infection. A number of tools can be used to assess risks for these complications and their application may help improve fetal outcomes.

Predicting preterm birth

Preterm birth, which affects approximately 10% of pregnancies, is most commonly iatrogenic, following recognition of maternal, placental and/or fetal complications that are likely to result in worse obstetric outcomes through expectant management rather than through delivery [1,2]. Some interventions that may reduce the prevalence of these complications, such as first-trimester prediction and prevention of severe early-onset pre-eclampsia, are making their way in to clinical practice [3,4]. The other major causes of preterm birth are spontaneous onset of preterm labour and delivery after preterm pre-labour rupture of membranes [2]. Less progress has been made in preventing these conditions, but several investigative tools are of value for stratifying risk in the third trimester.

Spontaneous preterm birth can be predicted through transvaginal assessment of cervical length [5,6]. This can be applied as a screening tool in the second trimester, as a component of the 20-week scan. Asymptomatic women who have a short cervix may benefit from progesterone therapy, which has been reported to effect a 45% reduction in rates of preterm birth below 34 weeks' gestation [7–9]. In the third trimester, cervical length is typically used as an assessment tool for women who attend with symptoms (abdominal pain and/or vaginal bleeding) of

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

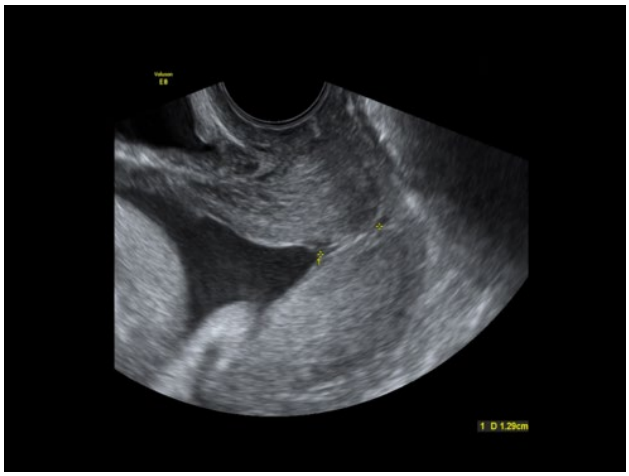

Fig. 18.1 A transvaginal ultrasound image evaluating cervical length. There is partial effacement of the cervix from the internal os (left side of the image) so the cervix appears to be 'funnelled'. The absolute length of the cervix (13 mm) is short, increasing the risk of preterm delivery.

preterm labour (Fig. 18.1). A short cervix, defined by various researchers as closed cervical length less than 15 or 25 mm, is associated with a higher risk of preterm delivery [10,11]. The cervix is measured using a standardized approach [12]. The transvaginal probe is introduced into the vagina and advanced in the midline into the posterior fornix so that the boundaries of the internal and external os can be clearly seen. The probe should be withdrawn a little, taking care to maintain a high-quality image, so that pressure is not put on the cervix that will falsely increase its length. Measurements should be made with good image magnification to improve accuracy and are made in a straight line between the internal and external os. As the cervix is dynamic, three measurements should be made over the course of a 3–5 min period and the shortest of these measures is typically used in most formulas that define risk on the basis of cervical length.

This examination is easy to perform after appropriate training and demonstrates effacement of the lower segment/internal cervical os that is not visible during speculum examination. Many would therefore advocate that women with threatened preterm labour are better served through assessment with a transvaginal scan rather than speculum or digital examination [13]. The sensitivity and specificity of cervical length for prediction of risk of delivery within 7 days have been reported to be 100% and 42%, respectively [10]. This is very similar to the efficacy of vaginal biochemical screening tools such as the vaginal fetal fibronectin test [14]. An ultrasound-based approach is advantageous in so far as the examination is quick, gives an immediate result, is easily repeated (to assess change) and is cheap, but requires the presence of a trained operator. The biochemical tools are less subjective but may not be accurate in some circumstances (e.g. after intercourse/with significant vaginal bleeding) and are more expensive, particularly for use on repeated occasions. Different clinical groups tend to favour one or the other approach to assessment of threatened preterm labour – typically due to local strengths and weaknesses of service provision – but there is also some evidence that a combined approach (using cervical length as a primary screening tool and fetal fibronectin as a second tier screen) is effective in reducing rates of hospital admission and prescription of corticosteroids in circumstances where delivery is not imminent [14].

Identifying placenta praevia, placenta accreta, vasa praevia and uterine scar

Ultrasound, and specifically transvaginal assessment of the cervix, is also useful for third-trimester assessment of placental position and vasa praevia. Up to 20% of placentas may be identified as being low-lying during a transabdominal 18–20 week morphology scan [15]. This cohort are recognized as being at risk of having placenta praevia, with implications for risk of antepartum haemorrhage and mode of delivery. Women who have a low placenta at 20 weeks are typically offered another scan at 34–36 weeks' gestation to confirm placental position [16]. The timing of this assessment is a compromise between allowance of adequate time for development of the lower uterine segment and of performance of the scan before the onset of spontaneous labour. The leading edge of the placenta is often best assessed using a transvaginal approach, particularly if the placenta is posterior, as the leading edge may be masked by the sonographic signal returned from the presenting part, particularly if the fetus is cephalic [17].

Whilst the third-trimester transvaginal scan is being performed, colour Doppler can be used to interrogate the area within the chorionic membrane overlying the internal cervical os. This is a very sensitive means of identifying vasa praevia, with the potential to prevent fetal mortality and morbidity following spontaneous rupture of membranes and rapid exsanguination [18]. There is some debate as to whether all women should be routinely screened for vasa praevia, which has a prevalence of 1 in 1500 to 1 in 2000 pregnancies; whilst routine screening may identify most cases, there is the potential for false positives that may be harmed through a policy of preterm abdominal delivery [19]. The positive predictive value of screening will be low (due to the low disease prevalence), so the prospect of the risk of harm needs careful prospective assessment. An alternative strategy

would involve routine transvaginal assessment for vasa praevia in women deemed to be at high risk; this can be defined through maternal characteristics such as advanced maternal age, *in vitro* fertilization (IVF) pregnancy, known placenta praevia or velamentous cord insertion [20]. Screening for vasa praevia may be performed at 20 weeks rather than in the third trimester but there are few prospective data comparing the efficacy of this screening tool at these two time points.

Cervical length can also be used to predict the potential for success of induction of labour. Induction is commonly offered to some cohorts, for example diabetic women, due to recognized increased risks of perinatal mortality. A transvaginal scan may be used to predict the likely success of induction and could potentially be used to guide the style of induction, although there are currently no prospective data demonstrating that this improves outcomes [21]. The findings of a transvaginal/transperineal assessment can be combined with measures of fetal biometry and other maternal characteristics to predict the likelihood of emergency caesarean section [22]. Some researchers have suggested that this could be used to define a cohort of women that should be offered an elective caesarean section, but others believe that the predictive value of the test is not sufficient to merit such significant intervention.

Women who have had a previous caesarean section, or other uterine surgery, have an increased risk of placenta accreta. The risk of placenta accreta is associated with the number of previous caesarean sections [23]. Transabdominal ultrasound can be used to predict placenta accreta and percreta, and may be used in conjunction with MRI to define the level of risk and extent of extrauterine invasion [24]. Thinning and disruption of the hypoechoic interface between the placenta and myometrium can often be seen using conventional two-dimensional grey-scale imaging. The placenta may include large lacunae and these, together with other aspects of increased and chaotic myometrial/placental blood flow, may be identified using colour Doppler.

There are also some data describing the value of measuring myometrial thickness for the prediction of risk of scar dehiscence in women who have had a previous caesarean section [26,27]. This is a difficult measure to make reliably as there are limitations to approach using both transabdominal and transvaginal methodologies. Various cut-offs for defining a high-risk cohort have been described and there are no data to demonstrate improved perinatal outcomes by screening all women who have had a previous caesarean section during the later part of the third trimester [27]. Although there is continued research interest in screening this cohort of women, it is probably premature to suggest this should be routine clinical practice.

Predicting intrauterine growth restriction and intrapartum fetal hypoxia

The second commonest cause of stillbirth (excluding congenital abnormalities) is IUGR [28]. There appear to be two different phenotypes of IUGR in the third trimester [29]. In the absence of an underlying chromosomal, genetic or structural anomaly or of fetal infection, early-onset IUGR (leading to delivery before 32 weeks) is typically an expression of placental insufficiency and is defined by demonstrating poor growth, with measures of the abdominal circumference and estimated fetal weight lying below an established (3rd, 5th or 10th) centile [30]. The process of fetal compensation then decompensation can be assessed using a number of clinical tools and this process and subsequent management is described in more detail in Chapter 17 [31]. In contrast to this, late-onset IUGR (>34 weeks' gestation) is associated with placental failure rather than insufficiency [32]. Consequently, the fetus may have initially maintained normal growth, and a single measure of biometry may not be sufficient to identify reduced growth velocity. Similarly, tests that are traditionally used to define and manage placental insufficiency (umbilical artery and ductus venosus Doppler) may not be of value, or may have to be used in a different way to be useful in detecting fetal compromise due to placental failure [29].

Stillbirth is a clearly defined, catastrophic but uncommon (in developed societies) end-point. IUGR may have other more insidious impacts. Fetuses that have limited reserve are more likely to be adversely affected by uterine contraction during labour and are at higher risk of hypoxic ischaemic encephalopathy. IUGR is the most significant antenatal risk factor for the development of neonatal encephalopathy and term cerebral palsy [33]. IUGR is also strongly associated with non-communicative cardiovascular and metabolic diseases that affect infants, adolescents and adults and therefore potentially has a lifelong impact on an individual's health and well-being [34,35]. Appropriate identification of IUGR fetuses, through third-trimester fetal assessment, provides the means to intervene to improve outcomes for a significant proportion of pregnancies.

There are conflicting opinions about the most appropriate strategies and methodologies that should be used to define normal fetal growth. Fetuses cannot be repeatedly removed and measured and replaced in the uterus to develop charts based on longitudinal measures and most charts for parameters such as birthweight include populations of fetuses that delivered because of some inherent abnormality. Charts based on data derived from such populations have centiles that are too low, particularly at early gestations, where there is also increased

inaccuracy due to smaller numbers of cases [36]. Other researchers have focused on the issues of population diversity and have suggested that all charts should be customized according to a mother's own characteristics [37]. A third approach, based on the observation that 'perfect' subgroups of women from a range of ethnic groups have similar patterns of growth, suggests that we should use international standardized charts to reduce heterogeneity [38]. There are no data to show whether use of customized or standardized charts improves perinatal mortality, and it is important to recognize that intervention in fetal growth (through premature delivery) may cause harm [39,40].

The simplest approach to identifying babies that are small for gestational age (SGA), and at increased risk of IUGR and its sequelae, involves clinical assessment through abdominal palpation and measurement of symphysis–fundal height. The effectiveness of this assessment has been variously reported but in one large trial involving more than 6000 women had a low sensitivity (28%) at 95% specificity [41]. Whilst single measures have poor predictive value (7% in this trial), this improves with serial measurement and through the use of customized charts, although there are no prospective studies that have proven improvement in perinatal mortality and morbidity [42].

Ultrasound can be used to assess fetal biometry, and measures of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) are typically used to estimate fetal weight (Fig. 18.2) [38,43]. Imaging and measuring these structures becomes more difficult as the third trimester advances and the sensitivity, specificity and positive and negative predictive values have been described as 53% (95% CI 49–58%), 81% (95% CI 80–83%), 26% (95% CI 23–29%) and 93% (95% CI 93–94%), respectively [44]. In addition, assessment of single measures of biometry will not identify previously well-grown fetuses that have been exposed to a later insult and are now crossing centiles. In a study involving 4000 pregnancies, Sovio *et al.* [45] showed that the routine application of ultrasound for serial growth assessment improved detection of SGA nearly threefold when compared with routine clinical management (57% vs. 20% in those that had a 'selected' ultrasound). Further improvements might be seen though computerized analysis of growth velocity and a number of groups have developed different methodologies for this process of risk assessment [46,47]. Implementation of a programme of serial ultrasound assessment to monitor fetal growth has not been tested to establish whether it leads to an improvement in perinatal mortality and morbidity. Given the potential for harm through preterm delivery and the significant expense of adding serial scans to routine care, it would be important to demonstrate the added value prior to implementation.

Improvement of the outcomes of fetuses with late-onset IUGR first requires better detection of affected fetuses. Given the difficulties of assessing fetal biometry, other measures that show functional changes in growth-restricted fetuses may be of value in improving screening efficiency. The simplest of these tools involves the mother, by asking her to monitor fetal movement and to report reduced fetal movement in a timely fashion.

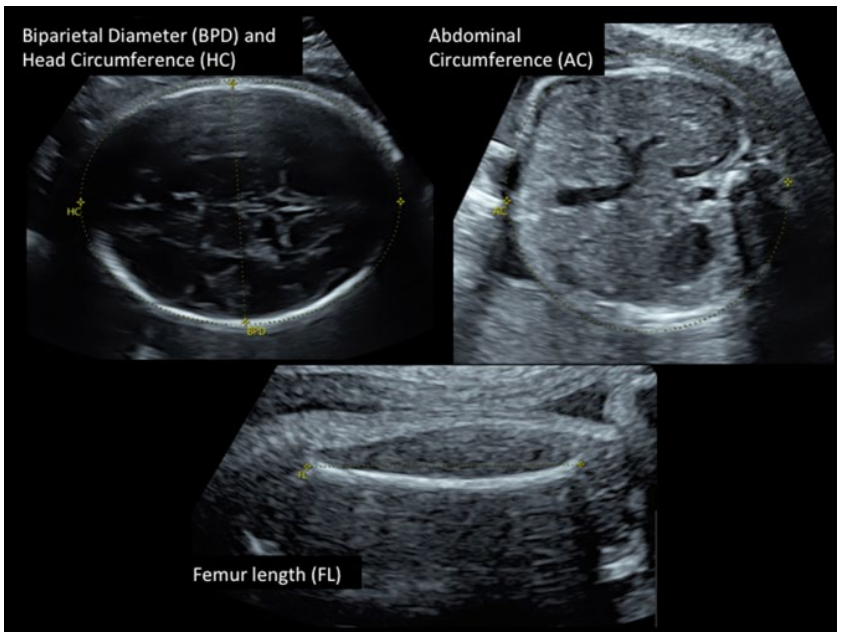

Fig. 18.2 A composite image showing measurement of the biparietal diameter, head circumference and femur length, measures used in most formulas to estimate fetal weight. Measurement accuracy is affected by the plane of assessment: the head should be imaged in an axial section at the level of the cavum septum pellucidum and posterior horn of the lateral ventricle; the abdomen should be imaged in an axial section at the level of the intrahepatic portion of the umbilical vein. Measurement accuracy is also affected by caliper placement; the biparietal diameter measures inner to outer parts of the cranium.

A large randomized controlled trial conducted in the 1980s failed to demonstrate any value in self-reporting of reduced fetal movement, but the quality of these data is disputed as there was (amongst other issues) a significant improvement in outcomes in the non-treatment arm as well as in women randomized to assessment of fetal movement [48]. More recent work has suggested that maternal assessment of fetal movement is important and that perinatal mortality is lower amongst groups that are counselled about self-monitoring [49]. Outcomes may also be improved through protocol-driven management of women who attend with reduced fetal movements, often through inclusion of investigational tools such as cardiotocography (CTG) or targeted ultrasound assessment [50].

The Perinatal Society of Australia and New Zealand (PSANZ) guideline for management of reduced fetal movement recommends that CTG should be performed for all women who present with reduced fetal movements during the third trimester of pregnancy [51]. CTG provides continuous graphical representation of the fetal heart rate together with information about uterine activity. CTG can be used in a variety of circumstances including intrapartum monitoring as well as for antenatal fetal assessment. The interpretation of a CTG depends on clinical circumstance, specifically whether a woman is defined as being in labour. Consequently, it is extremely important that an appropriate history and examination is performed before CTG can be interpreted; our anecdotal experience has shown that inappropriate interpretation of antenatal CTG in women who present with reduced fetal movements and some uterine activity, but who are not in active labour, can lead to false reassurance of clinicians and poor pregnancy outcomes.

There is limited evidence demonstrating that antenatal CTG improves perinatal outcome but the tool is commonly used and is generally freely available within the antenatal assessment environment, so traces are easy to procure [52]. Difficulties in application lie in interpretation. Some aspects, such as measures of baseline heart rate, acceleration, deceleration and short- and long-term variability, can be defined through computer analysis and algorithms for further management can be defined on the basis of these findings [53]. In a series of 305 women presenting with reduced fetal movement during the third trimester, Dutton *et al.* [54] found that an abnormal CTG was the most significant finding associated with adverse pregnancy outcome, reporting an odds ratio (OR) of 7.08 (95% CI 1.31–38.18); the impacts of other clinical findings, such as diastolic blood pressure and a low estimated fetal weight centile, were much less significant.

Whilst an abnormal antenatal CTG is strongly associated with adverse fetal outcome in a woman presenting with reduced fetal movements, this may not prove the best investigation for defining fetal well-being and making decisions about timing of delivery. The antenatal CTG that shows reduced variability, no accelerations and, on some occasions, shallow decelerations may be indicative of a fetus that is compromised by hypoxia, but these findings may be indicative of an irreversible neurological impact so delivery at this stage would be too late to effect the best outcome for this fetus. Alternatively, in some acute situations, the cardiovascular response to a hypoxic insult may be incomplete; the changes seen in baseline heart rate, variability and decelerations may only occur a few hours before death and could be missed through monitoring prior to this time.

CTG monitors fetal heart rate and uterine activity. This information may be valuable and may help define the need for delivery. CTG does not report other maternal parameters (e.g. heart rate, temperature and blood pressure) nor does it provide information about fetal size. It is therefore important to recognize the potential limitations of the technology and to interpret the findings with a good understanding of the clinical circumstances and risks. In a trial of postdates women being randomized to induction or ongoing expectant management, a reassuring CTG was associated with higher perinatal mortality; clinicians need to be aware of the risk of false reassurance that individual tests can provide [55].

In addition to assessing fetal biometry, ultrasound can be used to assess functional parameters that may be impacted by poor fetal growth. The growth-restricted fetus may compensate by reducing renal perfusion, with consequent reduction in urine production that can be assessed through measurement of amniotic fluid levels [56]. The amniotic fluid index (measurement of the liquor in the four quadrants) is used as a surrogate measure of amniotic fluid volume and should be measured in a standardized manner, holding the ultrasound probe perpendicular to the abdomen (an oblique measure will be falsely increased) and measuring the maximal clear (no fetal parts) pool in each quadrant (Fig. 18.3). Normal amniotic fluid indices vary widely across the third trimester, with wide standard deviation [56]. The amniotic fluid index peaks at about 34 weeks' gestation and levels typically reduce towards term. Cut-offs of less than 5 cm and more than 25 cm are typically used to define oligohydramnios and polyhydramnios, respectively. A recent meta-analysis that examined the association between anomalous amniotic fluid indices and adverse perinatal outcome reported that oligohydramios was associated with birthweight below the 10th centile (OR 6.31; 95% CI 4.15–9.58) as well as with perinatal mortality (OR 8.72; 95% CI 2.43–31.26), although the association did not have a strong predictive value for these outcomes [57].

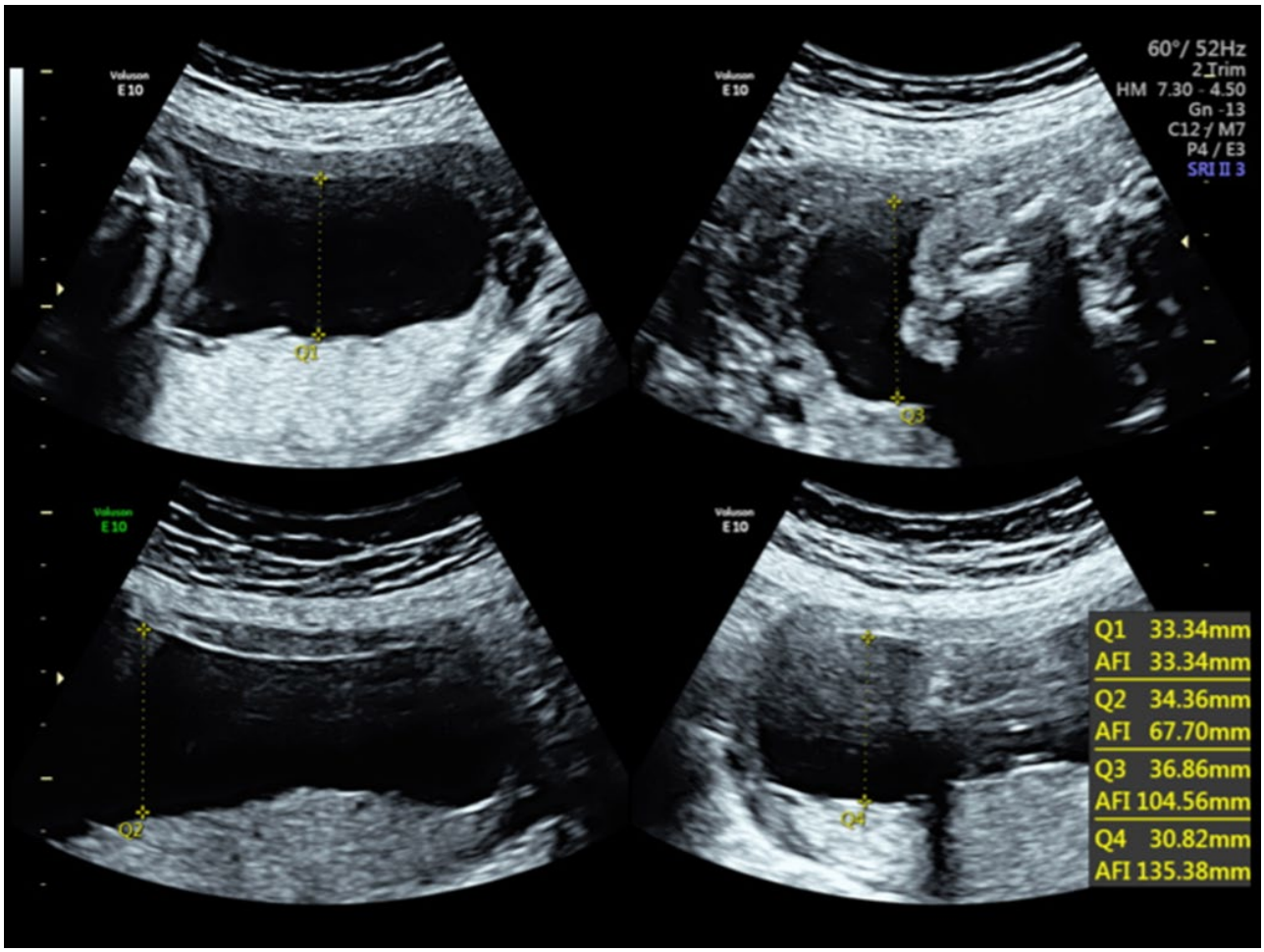

Fig. 18.3 The maximum vertical pool of amniotic fluid is measured in each uterine quadrant to calculate the amniotic fluid index.

A variety of different uteroplacental Doppler measures can also be assessed by ultrasound and may be of value in assessing fetal growth and well-being. The vessel most commonly assessed in the third trimester is the umbilical artery (Fig. 18.4). In early-onset IUGR, associated with placental insufficiency, the umbilical artery Doppler waveform typically changes with reduced forward flow in diastole and an increase in the vessel's pulsatility index (PI). A meta-analysis of studies that reported umbilical artery Doppler parameters in pregnancies defined as having a high risk of fetal growth restriction during the third trimester found that absent or reversed end-diastolic flow was associated with a significant increase in risk of perinatal mortality [58]. In many centres, umbilical artery Doppler parameters are now reported as a matter of routine during a third-trimester scan, but it is important to interpret the findings in the context of the literature, as other studies have shown that this is not a useful marker for fetal well-being in low-risk patient cohorts late in the third trimester [59]. Management of IUGR, placental insufficiency and the finding of an abnormal

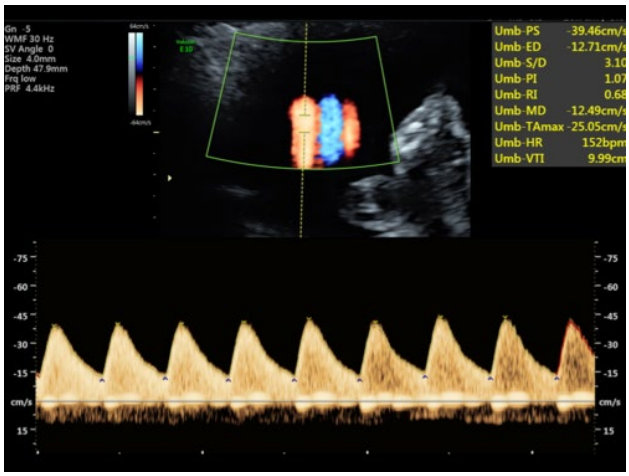

Fig. 18.4 The umbilical artery is typically assessed in a free loop. The vein and arteries can be identified with colour Doppler and pulse wave is used to illustrate the waveform characteristics, which can be measured and compared with standardized charts. In this example there is forward flow in diastole, a normal finding in the third trimester of pregnancy. (*See also colour plate 18.4*)

umbilical artery Doppler is addressed in more detail in Chapter 17.

Later in the third trimester, where the pathology underlying growth failure and ultimately stillbirth is more likely to be due to placental failure rather than placental insufficiency, other Doppler indices become more important in defining fetal welfare. Recent research has shown that, later in the third trimester (i.e. above 32 or 34 weeks) the best marker of fetal compensation for hypoxia is diversion of blood flow, and therefore more oxygen, to the brain. The middle cerebral artery (MCA) can be examined as a marker for this, with demonstration of reduced vascular resistance and a low PI in the fetus that is compromised but compensating effectively (Fig. 18.5) [60,61]. A number of groups have reported that a low MCA PI is associated with low fetal birthweight as well as with fetal distress and the need for emergency caesarean section in labour [62–64]. It has been suggested that presentation of Doppler data as a ratio of middle cerebral and umbilical artery PIs (the cerebroplacental ratio) improves the sensitivity and specificity of this tool in defining high-risk pregnancies [65]. As yet, there are few data that have demonstrated that either routine screening with a cerebroplacental ratio or application to specific high-risk groups (e.g. those with decreased fetal movements) improves pregnancy outcome but there is a lot of interest in the potential value of this tool and further trials of Doppler monitoring late in the third trimester are ongoing [66].

The ultrasound assessment of fetal growth, amniotic fluid index and haemodynamics has, to a large extent, replaced the more formal process of assessing fetal well-being by scoring the biophysical profile. A formal biophysical profile includes four ultrasound-based assessments – fetal breathing, movement and tone and the amniotic fluid index – which are then combined with a CTG 'non-stress' test [67]. Each component of the test is scored two points (if normal) or zero points (if abnormal). Scores below 10 lead to further intensive surveillance or induction of labour depending on the level of the score and the gestation of the pregnancy. Whilst the biophysical profile provides a clear structured method of assessing fetal well-being, it fails to include all parameters that may be of importance (biometry and Doppler) and does not adequately weight the various components of the test in relation to their likely association with pathology. The score has, on occasion, been modified and applied in various high- or low-risk circumstances with various ongoing management strategies [68,69]. Despite this, there is no clear evidence of benefit compared with interpreting ultrasound and/or CTG findings through a less structured approach [70].

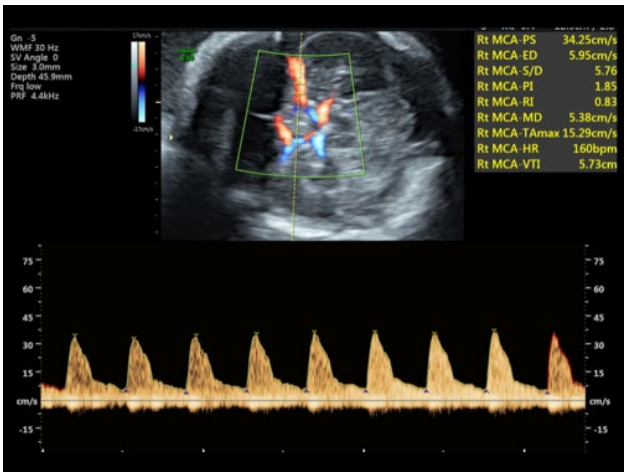

Fig. 18.5 The middle cerebral artery waveform can also be assessed by first identifying the vessels running away from the circle of Willis, then using pulse wave to demonstrate the waveform (sampling approximately 5–10 mm away from midline structures). In this example there is low flow in diastole, a feature of normal perfusion. (*See also colour plate 18.5*)

Predicting fetal macrosomia, risk of failure to progress and shoulder dystocia in labour

Fetal macrosomia also poses a significant risk of adverse pregnancy outcome in the third trimester of pregnancy. Macrosomia is associated with stillbirth and birth injury (shoulder dystocia, brachial plexus injury and limb fracture) as well as increased rates of operative delivery and perineal trauma [71]. Postnatally, macrosomic infants have higher rates of admission to the neonatal unit and are more likely to develop hypoglycaemia and hyperbilirubinaemia [72]. Macrosomic infants have increased rates of diabetes, metabolic syndrome and cardiovascular disease later in childhood and in adult life [73]. Across the world, changes in lifestyle and diet are contributing to increasing rates of gestational diabetes and hyperglycaemia in pregnancy and we face a global epidemic of macrosomia and its sequelae [74].

Despite this, and in comparison with IUGR, macrosomia is poorly defined and under-researched. Macrosomia has traditionally been defined using a fixed birthweight cut-off (commonly 4000 or 4500 g) independent of gestational age of delivery. These thresholds are based on the finding of increased rates of morbidity above these limits, although the reality is that these are continuous variables and it would likely be better to describe risks based on algorithms that define centiles in relation to, rather than being independent of, gestational age, although this adds complexity to categorization [75]. The association with stillbirth, and the underlying mechanism

of death, is also poorly understood, which makes functional assessment of risk to the macrosomic fetus challenging. Many macrosomic infants are born to women who have diabetes in pregnancy and it has been suggested that stillbirth results from metabolic acidosis in these cases [76]. Interestingly, others have suggested that death might occur if the fetal cell mass exceeds placental ability for tissue oxygenation, and it has been proposed that maternal cardiac failure may contribute to fetal death in this circumstance [77].

Clinicians have a poor history for accurate estimation of fetal weight in the later part of the third trimester. In 1992, Chauhan *et al.* [78] reported that women predicted fetal weight more accurately than either clinical or ultrasound examination. The heterogeneity of the literature, using different charts and cut-offs to define macrosomia, make it difficult to determine absolute sensitivity of ultrasound and studies have reported detection rates of 15–79% [79]. Researchers have compared different algorithms for estimation of fetal weight and prediction of macrosomia which have shown significant variation in findings. Predicting risk purely through ultrasound assessment using standard biometric parameters appears unlikely to be useful in defining a macrosomic cohort in routine practice [80]. There is also evidence that different algorithms should be applied to diabetic and non-diabetic populations [81].

Risk assessment may be improved by acknowledging differing maternal characteristics and using a Bayesian multivariate approach to screening [82]. It is not clear whether screening should then be limited to high-risk cohorts (perhaps defined through maternal characteristics and/or medical history), through a contingent process based on findings of screening tests performed at an early stage of pregnancy, or to the whole population [83].

Opinion regarding the management of macrosomic fetuses at term has typically been divided, with few prospective data to inform clinical practice. Some have argued that induction of labour may prevent maternal and neonatal morbidity associated with delivery of an overgrown infant whilst others have maintained that the process of induction carries its own inherent risks. There are now four randomized controlled trials that, in meta-analysis, appear to show that induction of labour may be beneficial and result in reduction in rates of neonatal birth injury (brachial plexus injury and limb fracture) [84]. Some of the trials in this meta-analysis are relatively small and did not report all outcome measures. These are also relatively uncommon outcomes, so 60 inductions need to be performed to prevent one adverse outcome. When this is coupled to the fact that we do not yet have a validated and strongly predictive screening test, it is difficult to advocate a process of routine screening and intervention without further research in this field [85].

In addition to developing algorithms that identify the macrosomic fetus, some groups have focused on the development of algorithms that will predict the likely success of induction of labour or the spontaneous onset of labour. These algorithms variously include maternal demographic factors with ultrasound estimates of fetal size and/or fetal Doppler, cervical length and/or mobility of the pelvic floor [86–89]. There is currently no consensus on the factors that should be included in such a predictive model and no prospective validation or demonstration of improved maternal and perinatal outcomes through application of such a test [90].

Conclusion

Ultrasound is a diverse tool that has many applications in the third trimester. In many settings, a third-trimester scan is not currently part of a routine antenatal screening strategy and there are limited data to support routine population-based screening. It is important, however, to recognize that many contemporary obstetric issues are centred around the third trimester and ultrasound is likely to play a significant role in defining an individual's risk and ensuring that appropriate strategies for maintaining pregnancy and expediting delivery are developed. Ultrasound is often best applied as one component of multivariate risk assessment and this is the subject of much ongoing research, with applications as diverse as the prevention of stillbirth, shoulder dystocia or maternal perineal trauma. Given the current medicolegal environment, it is likely that these methods of risk assessment will become an integral part of management of the third trimester as they will allow clinicians to have better informed conversations about risk with their patients.

Summary box 18.1

- The fetus faces a number of risks that vary through the third trimester and tests for fetal welfare need to be tailored to the issue of surveillance.
- Predictive tools (ultrasound and biochemical testing) for preterm birth improve the chances of preventing or ameliorating outcomes of early birth.
- Ultrasound assessment allows early recognition of invasive placentation and appropriate management at delivery improves maternal outcomes.
- The pathophysiology of IUGR differs before and after 32 weeks and different tests are needed to recognize fetal compromise. Further research is needed to determine whether routine third-trimester ultrasound surveillance reduces the prevalence of stillbirth.

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19

Fetal Medical Conditions

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Fetal thyroid function

The advent of fetal blood sampling has allowed direct and accurate quantification of fetal thyroid function. Fetal thyroid hormone synthesis commences at 10–12 weeks' gestation. Prior to this the fetus relies on placental transfer of maternal thyroid hormones. Fetal serum thyroid-stimulating hormone (TSH), thyroxine-binding globulin (TBG), free and total thyroxine (T4) and triiodothyronine (T3) increase with advancing gestation, from 14–16 weeks onwards [1,2]. The concentrations of total and free T4 (FT4) reach adult levels by 36 weeks' gestation. In contrast, T3 concentrations are lower than adult levels throughout pregnancy. There is no relationship between maternal and fetal thyroid hormone levels, confirming that development of the fetal pituitary–thyroid axis is independent of the mother. Fetal TSH concentrations are low until 15–18 weeks' gestation, and the lack of correlation between it and thyroid hormone concentrations indicates that thyroid maturation is independent of TSH. Fetal TSH receptors become responsive to TSH at 20 weeks' gestation.

Thyroid hormones promote normal growth, development and neurological function. Disruption of normal thyroid function, if unrecognized and untreated, can therefore have significant long-term sequelae. Thyroid dysfunction in the fetus can result from a primary problem affecting the fetus. More commonly it occurs secondary to maternal thyroid disease and/or its treatment.

The presence of fetal goitre indicates thyroid dysfunction, provided other differential diagnoses of a fetal neck mass, such as cystic hygroma, cervical teratoma and haemangioma, have been excluded. The goitre may represent fetal hyperthyroidism or hypothyroidism. The serious adverse consequences of fetal hyperthyroidism are miscarriage and intrauterine death, and of hypothyroidism neonatal cretinism.

Fetal hyperthyroidism

Fetal hyperthyroidism is most likely to occur secondary to maternal Graves' disease as a result of placental transfer of autoantibodies. TSH receptor-stimulating antibodies (TRAbs) are of the IgG class and therefore readily able to cross the placenta and stimulate the fetal thyroid gland. TRAbs can stimulate the fetal thyroid from 20 weeks' gestation. TRAbs are increased in at least 80% of women with Graves' disease. It has been estimated that neonatal thyrotoxicosis occurs in 2–10% of babies born to women with Graves' disease [3]. The risk of fetal hyperthyroidism is related to TRAb concentrations. The placenta is more permeable to IgG in the second half of pregnancy and fetal concentrations of TRAbs reach maternal levels at around 30 weeks' gestation. As a result, fetal hyperthyroidism usually develops in the second half of pregnancy

Pregnancies at risk

A pregnant woman with Graves' disease can be categorized as follows [3].

1) Euthyroid, not on medication, but who has previously received antithyroid drugs: the risk of fetal/neonatal hyperthyroidism is negligible and measurement of TRAbs is not necessary.
2) Euthyroid, previously treated with radioactive iodine or surgery: TRAbs should be measured in early pregnancy to detect presence and, if present, their concentration. High concentrations of antibodies identify a pregnancy at risk of fetal hyperthyroidism. TRAbs should be measured again in the third trimester to identify risk of neonatal hyperthyroidism.
3) Requiring antithyroid drugs to achieve normal thyroid function: TRAbs should be measured in the last trimester.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Features

Fetal tachycardia (>160 bpm) is the most common feature of fetal hyperthyroidism, although it is not always present. Other findings include intrauterine growth restriction (IUGR), accelerated bone maturation, cardiomegaly, cardiac failure and hydrops. A large fetal goitre can cause hyperextension of the fetal neck resulting in malpresentation. Oesophageal compression may result in polyhydramnios with its associated risk of preterm labour.

Management

Ultrasound can detect fetal goitre, which is the earliest ultrasound feature of fetal thyroid dysfunction and appears before fetal tachycardia. Fetal goitre is defined as a thyroid circumference equal to or greater than the 95th centile for gestational age and normative fetal thyroid measurements have been defined [4]. Colour flow Doppler may help differentiate between a hyperthyroid and a hypothyroid goitre. Hyperthyroidism is associated with a signal throughout the gland, whereas a signal confined to the periphery of the gland is suggestive of hypothyroidism [5,6]. In at-risk pregnancies monthly ultrasound should be carried out from around 20 weeks' gestation to assess thyroid size.

Cordocentesis is the only direct method of assessing fetal thyroid function. This is an invasive procedure, with a risk of miscarriage, and should be reserved for cases in which it is impossible to distinguish fetal hyperthyroidism from fetal hypothyroidism on clinical grounds, or for cases where the response to fetal therapy is not as anticipated (i.e. deterioration despite treatment).

Treatment

Treatment by maternal administration of antithyroid drugs is both safe and effective in the management of fetal hyperthyroidism. Propylthiouracil is the drug of choice because of the reduced risk of side effects. If the mother is euthyroid she may require thyroxine supplementation. This may also be necessary for women already on antithyroid medication who need to increase the dose.

Fetal hypothyroidism

Worldwide, iodine deficiency is the leading cause of fetal hypothyroidism. Other causes include thyroid dysgenesis, thyroid dyshormonogenesis, TSH receptor mutations and TSH receptor blocking IgG, antithyroid drugs and radioactive iodine after 10–12 weeks' gestation [7]. Maternal thyroid disease associated with thyroid autoantibodies can cause fetal hypothyroidism. Anti-thyroperoxidase antibodies cross the placenta in the third trimester but have little effect on fetal thyroid function. However, although generally stimulatory TRAbs can be inhibitory, resulting in fetal hypothyroidism.

Features

Ultrasound features include IUGR, goitre and decreased fetal movements. There may be tachycardia or bradycardia and in severe cases complete heart block. Cardiomegaly and delayed skeletal maturation may occur. Fetal hypothyroidism is often unrecognized and should be considered in all women with a history of thyroid disease and/or antithyroid medication.

Management

If fetal hypothyroidism is secondary to maternal antithyroid therapy, the dose of the drug should be reduced with the aim of keeping maternal FT4 levels at the upper end of the normal range for gestational age. Ultrasound of the fetal thyroid should be carried out at no greater than fortnightly intervals to ensure reduction in size, which is usually noted within 2 weeks of reducing therapy [8].

Transplacental transfer of T4 is inadequate to treat fetal hypothyroid goitre. The intra-amniotic route is used and 250–500 µg of T4 at 7–10 day intervals is a proposed regimen [9]. The success of treatment can be monitored by ultrasound assessment. If the fetal condition deteriorates despite treatment, cordocentesis is needed to measure fetal TSH and FT4 levels.

Summary box 19.1

- There is a risk of fetal thyroid dysfunction in women who are thyroid receptor antibody positive or who are taking antithyroid medication.
- Fetal goitre, present on ultrasound, indicates fetal thyroid dysfunction if other differential diagnoses have been excluded.
- It should be possible to distinguish fetal hyperthyroidism from hypothyroidism on clinical grounds in most cases.
- Cordocentesis is reserved for those cases in which this distinction on clinical grounds is not possible.
- Fetal thyroid dysfunction can be treated successfully *in utero*.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) occurs when abnormal adrenal steroidogenesis results in androgen excess. Five enzymes are responsible for the conversion of cholesterol to cortisol, and a defect in any one of these will cause precursors to be diverted to the production of androgens. CAH is an autosomal recessive condition and

in 90–95% of cases is due to a deficiency of 21-hydroxylase. Androgen excess *in utero* leads to virilization of a female fetus and in the severe form is associated with salt loss secondary to aldosterone deficiency. Androgen excess does not affect development of fetal male genitalia. Virilized females may be assigned the wrong gender at birth and are likely to require corrective genital surgery.

The aim of therapy is to prevent virilization of a female fetus. The fetal adrenal gland can be suppressed by maternal administration of dexamethasone. A minimum dose of 20 μg per kilogram pre-pregnancy weight in two divided doses is the recommended regimen and therapy must be commenced at 6–7 weeks' gestation when the external genitalia begin to differentiate [10].

Approach to management

- A family with an index case should be offered pre-pregnancy counselling and identification of the genetic mutation.
- The risk of an affected fetus in a subsequent pregnancy is 1 in 4, and of a virilized female fetus 1 in 8.
- Commence dexamethasone treatment at 6–7 weeks' gestation.
- Perform chorionic villous sampling (CVS) at 11–12 weeks' gestation to identify an affected fetus.
- Discontinue dexamethasone in all male fetuses and all unaffected female fetuses.
- If the fetus is an affected female, continue treatment for the remainder of the pregnancy.

This regimen means that seven of eight pregnancies are exposed to unnecessary steroid therapy early in the first trimester. Non-invasive analysis of cell-free fetal DNA from maternal blood can identify the Y chromosome from 7 weeks' gestation and therapy could be discontinued in the pregnancies with a male fetus without waiting for CVS results. If the fetus is female, treatment will have to continue until genetic results from CVS are available, still exposing three of eight fetuses to potentially unnecessary treatment. Future detection of the genetic defect by non-invasive means will be the only way to eliminate this blind approach to early therapy. There are no reported teratogenic effects of antenatal dexamethasone treatment. Information regarding longer-term effects is limited and parents must be made aware of this when discussing the pros and cons of therapy.

Fetal dysrhythmias

These comprise irregular fetal heart rhythm, fetal tachycardias and fetal bradycardias. Rhythm disturbances are encountered in approximately 2% of pregnancies during routine ultrasound. M-mode and pulsed-wave Doppler echocardiography are the main diagnostic techniques. The common dysrhythmias are discussed here. The reader is referred to other literature for a more comprehensive discussion of all dysrhythmias and their diagnosis [11–13].

Irregular fetal heart rate

This is typically described as a 'missed beat' and is usually due to atrial extrasystoles. These extrasystoles are more common in the third trimester and are detected in 1.7% of fetuses after 36 weeks' gestation. Ventricular extrasytoles are much rarer. The extrasystoles are benign and usually resolve prior to delivery. Occasionally (2–3% of cases) a sustained tachycardia develops and it is wise to auscultate the heart regularly to ensure this does not occur.

Tachycardia

A fetal tachycardia is defined as a sustained heart rate above 180 bpm. Fetal tachycardia occurs in 0.5% of pregnancies and is therefore relatively common. Supraventricular tachycardia (SVT) is the most common type (66–90% of cases), followed by atrial flutter (10–30%). Atrial fibrillation and chaotic atrial tachycardia are much less common and ventricular tachycardia is extremely rare during fetal life.

Supraventricular tachycardia

The most common type of SVT is a re-entry phenomenon where an accessory conducting pathway allows rapid retrograde passage of the electrical impulse from ventricle to atrium, establishing a re-entry circuit. This is defined as atrioventricular (AV) re-entrant tachycardia. In this type of SVT the time interval between ventricular and atrial contraction (VA interval) is short. In SVT caused by atrial ectopic tachycardia or permanent junctional reciprocating tachycardia, the VA interval is long. Establishing the length of the VA interval is important when deciding on therapy. In SVT the fetal heart rate is often in the region of 240 bpm with reduced variability. The ratio of atrial to ventricular contractions (AV ratio) is 1 : 1.

Atrial flutter

The atrial rate is very fast at 350–500 bpm. At such a fast rate 1 : 1 AV conduction is not possible. More commonly there is a degree of AV block, usually 2 : 1, but it can be greater.

Management options

The fetus with a sustained tachycardia is at risk of developing cardiac failure, hydrops and ultimately death. Conservative management is an option provided the

fetus is monitored closely to detect early signs of cardiac failure. Delivery, followed by postnatal therapy, is an option if close to term, but it is recognized that pharmacological control of the heart rate in the neonatal period is not always straightforward. *In utero* therapy is effective in restoring sinus rhythm and is the preferred option for treating preterm infants, reserving delivery for those cases that fail to respond to indirect or direct fetal therapy.

The transplacental route is the route of choice for fetal therapy. A number of drugs can be used in the management of fetal tachyardia. Digoxin, flecainide and sotalol are considered first-line treatments for SVT and atrial flutter (AF). Digoxin and flecainide are the best agents for treating SVT, and sotalol is best for AF. Better control is seen for SVT than AF. The presence of fetal hydrops or incessant SVT/AF are independently associated with slower rates of cardioversion. Digoxin can be given as a loading dose, 0.5–1 mg i.v., followed by maintenance therapy, 0.25–0.5 mg t.d.s. Maternal administration is ineffective if fetal hydrops is present. Flecainide is a proarrhythmic drug, given at a dose of 100 mg t.d.s. An effect is generally seen within 72 hours. Sotalol, also proarrhythmic, is given at a dose of 80–160 mg b.d. Owing to their good placental transfer, sotalol and flecainide are the drugs of choice if fetal hydrops is present. Maternal administration of drugs should take place in a hospital setting because of potential proarrhythmic effects (flecainide, sotalol, amiodarone). Baseline ECG and urea and electrolytes should be performed prior to starting medication; these tests should be repeated after starting therapy or increasing drug dosage, looking for prolongation of the QT interval on ECG. Serum drug levels should be monitored if facilities permit.

If there is no response to maternal drug administration or there is severe hydrops, direct fetal therapy is required. This can be intravascularly via cordocentesis, intraperitoneally or intramuscularly. The risks associated with cordocentesis are greater in the presence of hydrops. Digoxin and amiodarone are the preferred drugs for direct fetal therapy.

In the absence of hydrops, success rates of transplacental therapy can be up to 100%. Fetal mortality is 17% if hydrops is present.

Bradycardia

This is defined as a fetal heart rate persistently below 100 bpm.

Atrioventricular block

In AV block there is disturbance of electrical conduction between the atria and ventricles. Three types are described. In first-degree block there is a prolonged AV interval and this cannot be detected on routine ultrasound. Second-degree block is of two types. In type I there is progressive lengthening of AV conduction time until an impulse is blocked; this results in an irregular rhythm but the fetal heart rate may be normal. In type II second-degree block there is conduction of some beats and not others, without lengthening of the AV conduction time. On M-mode the atrial rate may be twice that of the ventricular rate (2 : 1 block) and occasionally 3 : 1 block is seen.

In complete AV block (CAVB) there is complete dissociation of atrial and ventricular contractions. This rare condition (1 in 15 000–22 000 live births) has two important causes: congenital heart disease (CHD) and immune-mediated disease. CHD accounts for 50% of cases of CAVB, the most common defects being left atrial isomerism and congenitally corrected transposition of the great vessels. Immune-mediated disease has been the subject of fetal therapy. Transplacental transfer of maternal anti-Ro and anti-La antibodies results in inflammation and damage to the fetal myocardium and conduction tissue. These antibodies may be present in women with a history of Sjögren's syndrome or systemic lupus erythematosus. The risk of CAVB in a woman with antibodies is approximately 2%, with a recurrence risk of 16%. The risk to the fetus is maximal between 16 and 26 weeks' gestation. Poor prognostic features for CAVB include hydrops, heart rate below 55 bpm and premature delivery. The mortality ranges from 18 to 43%.

There are no treatment options that are clearly effective. Steroids, either dexamethasone or betamethasone, have been administered with variable results. The same is true for beta-sympathomimetics, which are given with the aim of increasing the fetal heart rate. The current lack of evidence confirming efficacy of therapy, and the potential maternal and fetal side effects of medication, must be borne in mind in the evaluation of whether or not to treat.

Summary box 19.2

- Fetal cardiac arrhythmias are common, affecting 1–2% of pregnancies.
- Ectopic beats usually resolve spontaneously.
- Fetal therapy for tachycardias is preferred to premature delivery.
- Detailed fetal echocardiography and testing for maternal anti-Ro and anti-La antibodies should be performed in cases of complete heart block.
- There is currently no therapy of proven benefit for complete heart block.

Fetal and neonatal alloimmune thrombocytopenia

The incidence of fetal and neonatal alloimmune thrombocytopenia (FNAIT) ranges from 1 in 350 to 1 in 1000 pregnancies [14], although it is likely to be underdiagnosed. It occurs when maternal platelets lack antigens that are present on the fetal platelets. An alloimmune response develops whereby maternal antibodies (IgG) are produced that cross the placenta and cause fetal platelet destruction and thrombocytopenia. Fetal platelets express specific antigens from the first trimester. FNAIT is the platelet equivalent of red cell alloimmunization. However, in contrast to red cell alloimmunization, FNAIT can complicate at least 50% of first pregnancies.

To date, 24 human platelet antigens (HPAs) have been described, which are grouped into the following systems: HPA-1, HPA-2, HPA-3, HPA-4, HPA-5 and HPA-15. The distribution of HPA systems is affected by race, and 2% of Caucasian women are HPA-1a negative. HPA-1a antibodies account for 85% of cases of FNAIT. The other antibodies most frequently encountered in Caucasians are HPA-5b and HPA-3a. HPA-5b is associated with milder FNAIT than that induced by HPA-1a. In some cases a responsible antibody cannot be identified, despite a clear clinical diagnosis of FNAIT.

FNAIT is rare, but platelet incompatibility is not infrequent: 1 in 50 pregnancies will be incompatible for HPA-1a. The observed frequency of alloimmunization is much less than this. The development of HPA-1a alloantibodies is related to HLA phenotype. Alloimmunization is rare in the absence of HLA-DRB3*0101 phenotype. The rate of alloimmunization in HPA-1a-negative women exposed to HPA-1a-positive platelets is only 10%, and of these 30% of fetuses will be thrombocytopenic [15].

Most affected infants are asymptomatic or present with signs of minor haemorrhage such as petechiae. In more severe cases there will be internal haemorrhage, and intracranial haemorrhage (ICH) is most frequent. ICH occurs in 7–26% of untreated first pregnancies affected by FNAIT [14]. The sequelae of ICH can be severe, and include perinatal mortality, hydrocephalus and long-term neurological disability. There is at least a similar or increased risk of thrombocytopenia in a subsequent pregnancy when the father is homozygous for the responsible antigen. Obstetric history is relevant. If there was no ICH in the index pregnancy, the risk of ICH in a subsequent affected pregnancy is 7%. If a previous sibling was affected by ICH, the recurrence risk is 75% [16]. The international No IntraCranial Haemorrhage (NOICH) observational cohort study reported that 54% of cases of ICH occurred before 28 weeks' gestation; 63% of cases of ICH affected the first-born child. The catastrophe of ICH is reinforced by the data that 35% died within 4 days of delivery and 53% survived with severe neurological disability [17].

Management

The aim of treatment is to reduce the risk of *in utero* and perinatal ICH. The only method of assessing the fetal platelet count is cordocentesis, and early management strategies for this condition relied on this technique. However, if the fetus is thrombocytopenic, the risk of exsanguination as a result of cordocentesis is greater. Direct transfusion of platelets at the time of cordocentesis will increase the fetal platelet count, but the lifespan of platelets is only 4–5 days, necessitating repeat transfusions at 7–10 day intervals if a normal platelet count is to be maintained. The cumulative fetal loss rate per pregnancy can be up to 8% if cordocentesis and platelet transfusion is the chosen management strategy [18]. An alternative approach is to defer cordocentesis until prior to delivery at which point a single platelet transfusion can be given, if indicated, and the baby delivered a couple of days later. This obviously reduces the risks associated with multiple procedures. However, the fetus may have already been exposed to prolonged thrombocytopenia and suffered an ICH.

Invasive strategies are no longer viewed as primary management options and a non-invasive approach to the management of FNAIT has developed. The use of intravenous immunoglobulin (IVIG) in the management of FNAIT was first reported by Bussel *et al.* [19]. A dose of 1 g/kg per week resulted in a significant increase in fetal platelet count. The mechanism of action of IVIG remains unclear but a number of possible explanations are described [14]. Firstly, anti-HPA antibodies in the maternal circulation will be diluted by the presence of immunoglobulin and therefore less will be transferred across the placenta. Secondly, IVIG may block placental Fc receptors, thus preventing transmission of maternal antibodies. Finally, IVIG may block Fc receptors on fetal macrophages, preventing destruction of antigen–antibody complex-coated cells. IVIG reduces the risk of ICH even in those fetuses that do not show an increase in platelet count, implying some additional protective effect of this therapy.

Several hundred pregnancies have been treated with IVIG, with no occurrence of ICH. There is ongoing discussion about the dose (0.5 vs. 1.0 vs. 2.0 g/kg) and treatment schedules, the gestation at which to start treatment and the role of corticosteroids. Steroids have been efficacious in some cases that are unresponsive to IVIG, and prednisolone is the drug of choice. Antenatal management should be tailored according to disease

severity, recognizing that treatment may be started as early as 12 weeks' gestation for very high risk cases. One of the keys to improving outcomes in the future is to identify factors predictive of severe FNAIT.

Delivery is a time of high risk of ICH in the thrombocytopenic fetus. Elective caesarean section is frequently the chosen mode of delivery, although it must be acknowledged that it does not eliminate the risk of ICH. Vaginal delivery can be considered if the fetal platelet count is above $50–100 \times 10^9$/L prior to delivery. For lower-risk women, namely those whose previous pregnancy was not complicated by ICH, there is evidence from a small series that vaginal delivery is not associated with adverse neonatal outcome [14].

Summary box 19.3

- ICH is the devastating complication of FNAIT.
- ICH occurs in 7–26% of untreated first pregnancies affected by FNAIT.
- Bleeding occurs before 28 weeks' gestation in 50% of cases, and can occur as early as 18–20 weeks' gestation.
- Non-invasive therapy with IVIG is the recommended treatment, acknowledging that the optimal regimen has yet to be established.

Fetal anaemia

This can result from red cell alloimmunization or parvovirus infection. The mechanism of fetal anaemia, its management and treatment are discussed for both aetiologies.

Red cell alloimmunization

If a pregnant woman is exposed to fetal red cells that possess different antigens to her own red cells (i.e. the antigens have been inherited from the father), she will mount an immune response. The initial response is production of IgM antibodies, which do not cross the placenta and therefore the pregnancy in which antibodies are first detected is unlikely to be affected. However, on further exposure to the foreign red cell antigen, IgG antibodies are produced which do cross the placenta and can cause fetal haemolytic anaemia. The antibodies most commonly associated with haemolytic disease of the fetus and newborn (HDFN) are the rhesus system antibodies RhD, Rhc and RhE, and Kell.

Some aspects of the assessment and management of pregnancies at risk of HDFN are discussed in Chapter 12. Figure 19.1 outlines a proposed management strategy for rhesus-sensitized pregnancies. Important points to recognize include the following.

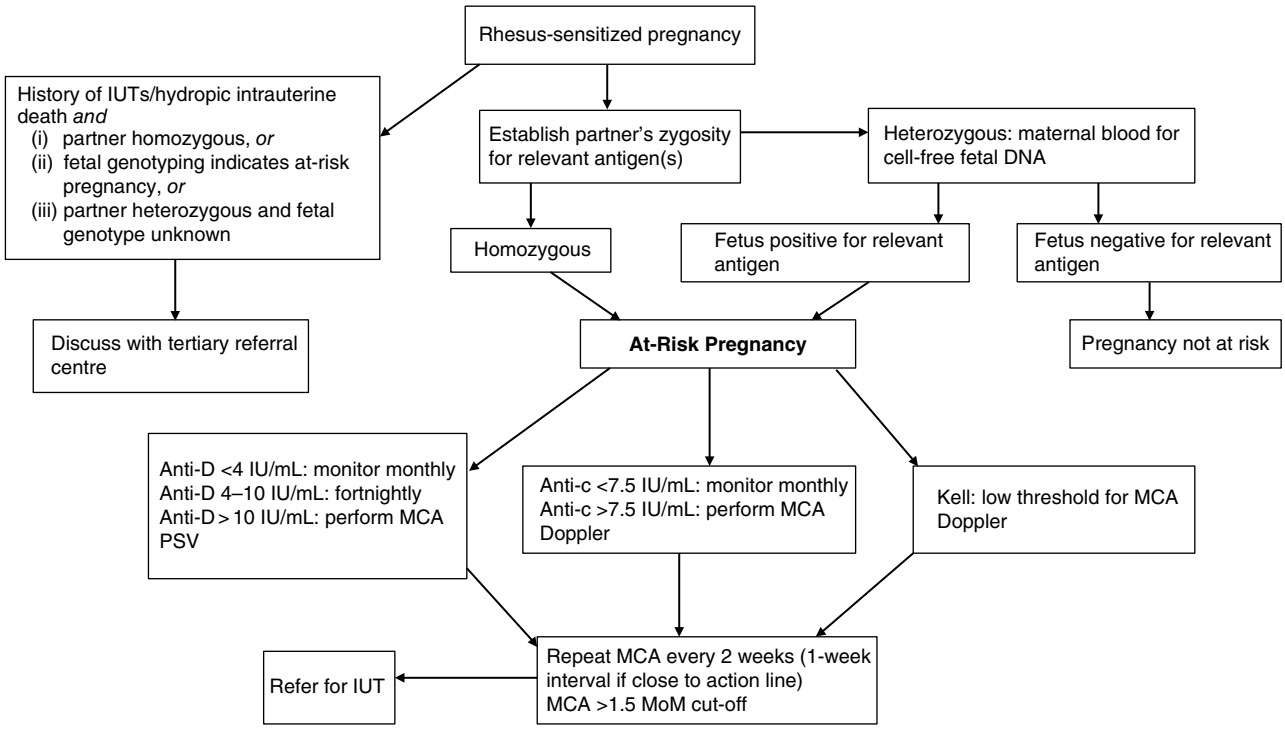

Fig. 19.1 Algorithm for the management of rhesus-sensitized pregnancies. IU, international units; MCA, middle cerebral artery; PSV, peak systolic velocity; IUT, intrauterine transfusion; MoM, multiples of the median. *Source:* Fisher DA. Fetal thyroid function: diagnosis and management of fetal thyroid disorders. *Clin Obstet Gynecol* 1997;40:16–31. Reproduced with permission of Elsevier.

- If the father is heterozygous for the relevant antigen, fetal blood group should be established using the non-invasive technique of assessing cell-free fetal DNA in maternal blood.
- Anti-D and anti-c concentrations can be quantified; this is not possible for anti-E or Kell antibodies.
- The trend of rise in antibody concentration is as important as a particular cut-off level.

Monitoring: middle cerebral artery Doppler

Having established that a pregnancy is at risk of fetal anaemia secondary to red cell alloimmunization, the aim of monitoring is to determine the point at which fetal therapy is indicated, before the fetus becomes severely anaemic. Fetal hydrops indicates the presence of severe anaemia. The early ultrasound features of hydrops are ascites and cardiomegaly, followed by progressive skin oedema, pericardial and pleural effusions and placental oedema. The entire purpose of the monitoring described here is to intervene before hydrops develops (Fig. 19.2).

Doppler is informative in fetal anaemia because of some basic principles of blood flow. If the cross-sectional area of a vessel remains constant, blood velocity is directly proportional to blood flow. In addition, decreased blood viscosity will increase blood flow [20]. The anaemic fetus has a reduced blood viscosity and a hyperdynamic circulation, both of which will increase blood flow and hence blood velocity. In the middle cerebral artery (MCA) this is reflected by an increase in peak systolic velocity (PSV). MCA PSV measurements that are above a cut-off of 1.5 multiples of the median for gestational age identify moderate to severely anaemic fetuses with a sensitivity of 100% and a false-positive rate of 12% [21]. MCA PSV is not a good predictor of mild anaemia, but this is not a concern since this group of fetuses does not require *in utero* therapy. MCA PSV measurement is shown in Fig. 19.3 and the technique is described by Mari *et al.* [21].

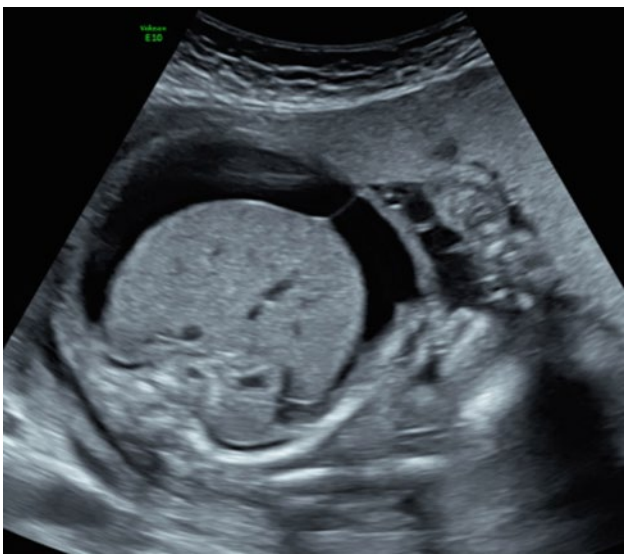

Fig. 19.2 Transverse section through fetal abdomen demonstrating ascites.

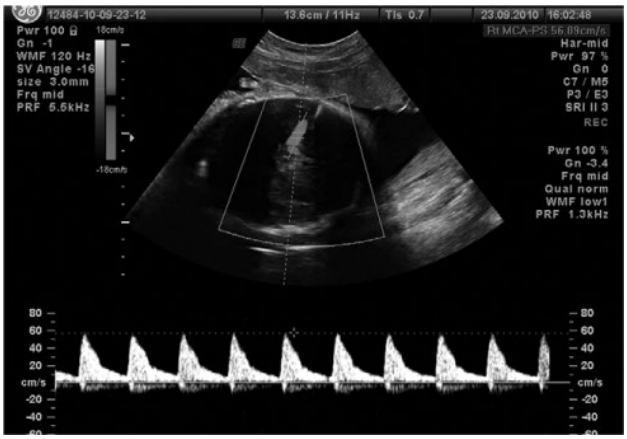

Fig. 19.3 Middle cerebral artery peak systolic velocity measurement.

Non-invasive monitoring using MCA Doppler has replaced serial amniocentesis in the management of at-risk pregnancies. Amniocentesis is an invasive procedure with a procedure-related loss rate of up to 1%. Repeated procedures are usually necessary in the same pregnancy and each procedure carries a risk of fetomaternal haemorrhage, thus exacerbating the degree of fetal anaemia. A multicentre study comparing MCA Doppler with amniocentesis for monitoring at-risk pregnancies has demonstrated that MCA Doppler has a significantly greater accuracy and sensitivity [22]. In addition, 51% of women would have avoided an invasive procedure if MCA Doppler had been solely relied on. It is therefore the monitoring modality of choice in the majority of centres.

Summary box 19.4

- The main antibodies causing fetal anaemia are anti-RhD, anti-Kell and anti-Rhc.
- Parvovirus infection is an important cause of fetal anaemia, and should be considered in all cases of non-immune hydrops.
- Non-invasive testing has replaced invasive testing for the management of fetal anaemia.
- Fetal blood group should be determined on cell-free fetal DNA in maternal blood.
- MCA Doppler has replaced amniocentesis for timing intrauterine transfusion in the majority of centres.
- The need for intrauterine transfusion should be predicted before hydrops develops.

Treatment: intrauterine transfusion

The first intrauterine transfusion (IUT) was performed by Liley in 1963 [23] via the intraperitoneal route. Donor red blood cells are absorbed into the circulation via the diaphragmatic lymphatics. This results in slower restoration of fetal haemoglobin than if blood is given directly into the circulation, and as a result is no longer the route of choice for fetal therapy. It does still have a place in those cases requiring transfusion before 18–20 weeks' gestation, when intravascular access may not be possible. Intraperitoneal transfusion from 16 weeks' gestation has been employed successfully in a small cohort of severe cases of rhesus alloimmunization, until a gestation at which intravascular access could be achieved [24].

The introduction of real-time ultrasound facilitated needle-guided intraperitoneal transfusion in 1977. The first intravascular transfusion was performed fetoscopically by Rodeck *et al.* in 1981 [25]. A variety of techniques for IUT have been employed. Direct intravascular transfusion is the preferred technique in which the additional volume is absorbed by the fetoplacental circulation, thus 'protecting' the fetus from fluid overload. The fetal circulation is accessed via the umbilical cord at its placental insertion (Fig. 19.4) or the intrahepatic portion of the umbilical vein. Intracardiac transfusion is also described. The choice of route will be influenced by placental site and fetal position. Access to the cord insertion is easiest if the placenta is anterior. When accessing the cord insertion the vein is targeted rather than an artery, as the latter is prone to spasm and there is an increased risk of complications.

Technical aspects of the procedure are:

- maternal sedation, antibiotics, single course of steroids at 26 weeks' gestation and above;
- aseptic technique;

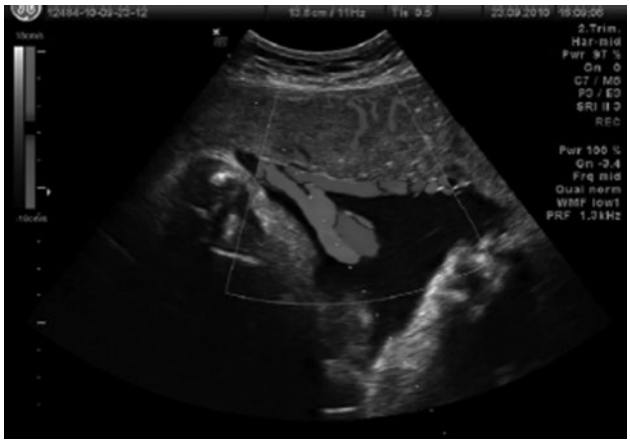

Fig. 19.4 Anterior placental cord insertion, with needle guideline.

- needle guide and free-hand approach, using 20 gauge needle;
- cord insertion/intrahepatic vein;
- cross-matched, O, Rh-negative, cytomegalovirus-negative, irradiated blood;
- repeat at 2-week intervals;
- aim for delivery at 34–35 weeks' gestation.

Once the chosen vessel is punctured, a sample of fetal blood is analysed immediately by on-site laboratory staff to obtain the fetal haematocrit. The volume of blood to be transfused is calculated by a formula incorporating fetal haematocrit, donor haematocrit and fetoplacental blood volume. It is important that the donor haematocrit is as high as possible (≥75%) to reduce the risk of volume overload. The aim is for a post-transfusion haematocrit of 40–45%. The estimated post-procedure decline in haematocrit is 1–2% per day, and in general a transfusion interval of 14 days is used, although cases vary individually, as will the policies of different centres. If the fetus is severely anaemic and/or hydropic, a stepwise transfusion is given, aiming for a haematocrit of 30%, with repeat transfusion 1 week later.

Complications of IUT

There are a number of procedure-related complications of IUT. The perinatal mortality rate is 1.6–2% [26]. Complications include vasospasm and fetal bradycardia, chorioamnionitis and preterm labour/delivery, emergency delivery and augmentation of the alloimmunization with implications for future pregnancies.

Outcomes

A review of 19 studies using IUT shows an overall survival rate of 84% [26]. The survival rate is higher for non-hydropic fetuses (94%) compared with hydropic fetuses (74%). There is evidence that infants severely affected by rhesus disease have lower birthweights than matched controls. Infants treated with IUT show evidence of catch-up growth *in utero* and birthweights comparable to controls. Existing data for short-term neurodevelopmental outcome following IUT suggest that this can be expected to be normal in more than 90% of cases, irrespective of a history of hydrops [27,28].

Kell alloimmunization

This can result in profound fetal anaemia, hydrops and intrauterine death. It differs from rhesus alloimmunization for a number of reasons. Past obstetric history is not reliable in predicting outcome in a subsequent pregnancy. Maternal antibody titres do not correlate well with the severity of fetal anaemia; poor outcomes have

been reported with low titres. The type of anaemia is not solely haemolytic, but is also due to erythroid suppression. For these reasons, management of a Kell immunized pregnancy is challenging. Fortunately, the incidence of HDFN due to Kell is low; only 9% of the white population is Kell positive and 0.2% are homozygous [29]. MCA PSV monitoring has been shown to be reliable in the management of Kell alloimmunization. Fortnightly MCA PSV measurements once the antibody titre is 1 : 32 is a reasonable approach to management. However, owing to the unpredictable nature of Kell immunization, earlier implementation of MCA measurements cannot be criticized.

Summary box 19.5

- Ultrasound-guided cordocentesis has revolutionized fetal investigation and therapy.
- Intrauterine transfusion can treat anaemia secondary to alloimmunization or parvovirus infection.
- Intravascular access is obtained at the placental cord insertion or the intrahepatic portion of the umbilical vein.
- The procedure-related loss rate of IUT is 1–2%.
- This risk is higher if fetal hydrops is present.

Parvovirus

Parvovirus infection should be considered in any fetus presenting with non-immune hydrops. Alternatively, a woman contracting parvovirus infection during pregnancy requires appropriate monitoring to detect developing fetal anaemia. The topic has been reviewed extensively by other authors [30–32].

Parvovirus B19 is thought to exclusively infect humans, and it binds to the blood group P-antigen cellular receptor that is present on haematopoietic precursors, endothelial cells, fetal myocytes and placental trophoblast. Its effect on the haematopoietic system results in profound anaemia and non-immune hydrops fetalis (NIHF). In addition, viral particles have been identified in fetal myocardial tissue, and cardiac dysfunction due to myocarditis may also contribute to the development of cardiac failure.

Approximately 50% of pregnant women are susceptible to infection, and outbreaks occur every 3–4 years, most commonly in late winter and spring. The peak incidence of hydrops occurs with infection between 17 and 24 weeks' gestation. The risk of developing hydrops if infection occurs between 13 and 20 weeks' gestation is 7.1%. The virus infects the fetal liver, which in the second trimester is the main source of haematopoietic activity. Haematopoiesis is augmented at this gestation to meet the demands of the growing fetus, and the lifespan of red blood cells is decreased, rendering the fetus particularly susceptible to any arrest in haematopoietic production. Levels of the P-antigen are negligible in the third trimester, and hence the risk of anaemia and hydrops appears to be low. The risk of vertical transmission during pregnancy is 30%, and the mean interval from maternal infection to development of NIHF is 2–6 weeks, although longer intervals have been reported.

Maternal serology will confirm recent infection. If IgM titres exceed IgG titres, the infection took place within the previous month and the fetus remains at risk of complications, even if none are present at initial presentation. Maternal serology can be misleading if checked earlier than 7 days after contact as IgG and IgM could both be negative at this stage. Similarly, by the time of clinically established hydrops, IgM levels may already be low or, rarely, undetectable. Fetal serology is of no help diagnostically as the fetal immune system is too immature to mount a detectable IgG/IgM immune response. Polymerase chain reaction techniques to detect viral DNA are required.

Management

MCA PSV is reliable in predicting fetal anaemia secondary to parvovirus infection. The anaemia can be successfully treated by IUT, which reduces the mortality rate of severe hydrops. Frequently a single transfusion is required. Cordocentesis and IUT are obviously not without risk, and the risks are higher when the fetus is hydropic. Thrombocytopenia is often a feature of parvovirus infection and this will potentially increase the procedure-related risk of exsanguination. In addition to red cell transfusion, consideration should be given to transfusion of platelets in those fetuses with severe thrombocytopenia.

Close fetal surveillance is required following maternal seroconversion prior to 24 weeks' gestation. Weekly MCA PSV should be carried out and IUT considered for results above the cut-off of 1.5 multiples of the median. Serial surveillance for 8–12 weeks after conversion is indicated. Anaemia due to parvovirus has the potential to resolve as the fetus mounts its own immune response. As a result, MCA Doppler monitoring may identify some fetuses that are anaemic at presentation but which are actually in the recovery phase of the infection. If other signs of fetal well-being are present, such as good fetal movements and normal liquor volume, it may be possible to continue conservative management and avoid IUT in these particular cases. A proposed management plan is summarized in Fig. 19.5.

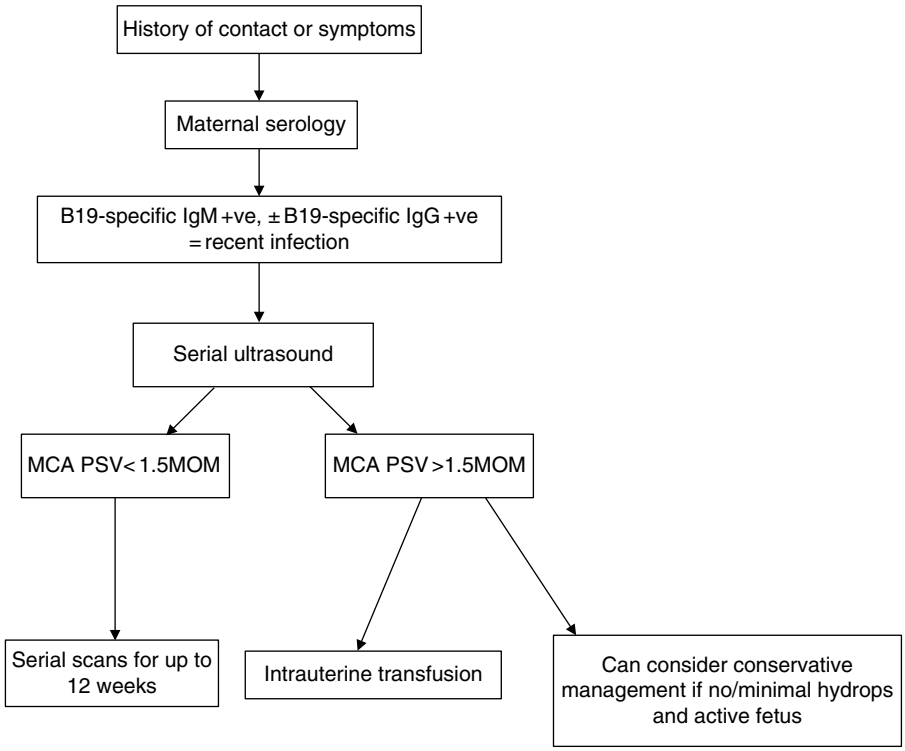

Fig. 19.5 Algorithm for the management of parvovirus infection. MoM, multiples of the median.

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20

Fetal Anomalies

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Almost 5% of newborns have a congenital malformation. In many cases these malformations are minor and do not impact on either the short- or long-term outcome for the individual. However, major congenital malformations are a significant contributor to both perinatal morbidity and mortality and indeed the detection of such anomalies has been the goal of antenatal screening programmes worldwide. In many countries the antenatal detection of fetal anomalies and the subsequent termination of these fetuses have been responsible for the decline in perinatal mortality rate seen over the last three decades. The detection of fetal structural abnormalities is generally made by ultrasound with additional more sophisticated techniques, such as three/four-dimensional ultrasound, fetal MRI and fetoscopy, reserved for complex cases where standard two-dimensional ultrasound fails to clarify the diagnosis.

The objectives of an antenatal screening programme should be (i) to provide appropriate information for women so that they are able to make an informed choice about their screening options and pregnancy management, (ii) to identify serious fetal abnormalities, either incompatible with life or associated with morbidity, allowing women to make timely decisions about pregnancy outcome, (iii) to identify abnormalities that may benefit from antenatal intervention and (iv) to identify abnormalities that may require early intervention following delivery. Clearly the successful implementation of an antenatal fetal anomaly screening programme depends on many factors including the provision of adequate patient information, the availability of trained sonographers and good ultrasound equipment and clear management pathways for patients once an anomaly has been detected.

The European Surveillance of Congenital Anomalies (EUROCAT) recorded a total prevalence of major congenital anomalies of 23.9 per 1000 births for 2003–2007. Congenital heart defects (CHDs) were the most common non-chromosomal anomalies (6.5 per 1000 births), followed by limb defects (3.8 per 1000), anomalies of the urinary system (3.1 per 1000) and nervous system malformations (2.3 per 1000). It has been estimated that the perinatal mortality rate associated with congenital anomalies is in the region of 0.9–1 per 1000 births.

Although first- and second-trimester aneuploidy screening is widely available in the UK, Europe, North America and many parts of Australasia, for many women the first antenatal ultrasound scan will be the mid-trimester fetal anomaly scan which is generally done at 18–22 weeks' gestation. The majority of fetal structural anomalies will be detected during this examination. With better high-resolution machines and trained sonographers, many structural anomalies are now diagnosed during the late first and early second trimester, which is clearly preferable for women.

Timing and development of fetal malformations

The crucial morphogenetic window during which the fetus is particularly susceptible is the period of blastogenesis, which extends throughout the first 4 weeks of development (from fertilization until the end of the gastrulation stage, days 27–28 post conception). Any insult during this period can result in structural malformations, including patterns of multiple congenital anomalies arising from developmental field defects. Severe damage may cause demise of the fetus or, because of the pluripotent nature of the embryo and early fetus in general, compensatory changes may occur allowing development to continue in a normal or near-normal fashion. Because the fetus is less susceptible to damage when the developmental process of the majority of organs has been

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completed, the most common anomalies associated with teratogenic exposures during the fetal period are fetal growth restriction (intrauterine growth retardation) and mild abnormalities of phenotype (epicanthic folds, clinodactyly, etc). However, teratogenic drugs can result in a wide variety of effects that range from infertility, prenatal-onset growth restriction, structural defects, and functional central nervous system (CNS) abnormalities to miscarriage or fetal death. Similarly, various perinatal infections (particularly viruses) can have significant teratogenic effects on the developing fetus with an extremely wide spectrum of resulting malformations.

Summary box 20.1

- The fetus is most vulnerable in the first 4 weeks of life.
- Many maternal conditions, drugs and infections can cause structural malformations in specific organ systems.
- Ultrasound is the usual modality of imaging in pregnancy and detects the vast majority of anomalies.

Selected fetal anomalies in specific organ systems

Cardiovascular system anomalies [1]

The fetal heart develops from the splanchnic mesoderm and in its earliest and most rudimentary form is represented by two tubes which subsequently fuse and then canalize. Repeated rotations and septations then occur which ultimately results in a four-chamber organ.

The structural and functional cardiac abnormalities are some of the commonest disorders seen in prenatal life, with the incidence of congenital heart disease estimated at 6–12 per 1000 live births, at least half of which should be detectable before birth. There are many risk factors for fetal cardiac abnormalities, some of which cause structural malformations whilst others perturb function or cause rate and rhythm abnormalities. Common maternal risk factors include pre-gestational diabetes mellitus, phenylketonuria, drug exposure, maternal autoimmune conditions such as systemic lupus erythromatosus (SLE) and infections such as rubella. Other risk factors are a history of maternal or paternal congenital heart disease, aneuploidy, genetic syndromes, twin–twin transfusion syndrome (particularly in the recipient) or in association with other structural malformations or tumours.

Fetal echocardiography should be considered for the following.

- First-degree relative with congenital heart disease: one previous sibling affected, 2–4% risk; two or more previous siblings affected, 10% risk; mother affected, 5–12% risk; father affected, 1–3% risk.
- Maternal insulin-dependent diabetes: 3–4% risk.
- Autoimmune antibodies (anti-Ro and anti-La).
- Drug therapy (lithium, 10% risk) or epilepsy (4–7% risk with monotherapy, 15% risk with polytherapy).
- Monochorionic twins: 4% risk.
- Increased nuchal translucency ≥3.5 mm: 3% risk, rising to 23% risk if >5.5 mm.
- High-risk structural anomalies: tracheo-oesophageal fistula, 15–40% risk; duodenal atresia, 17% risk; omphalocele, 20–30% risk; and diaphragmatic hernia, 10–20% risk.

Detection of any cardiac abnormality should prompt a detailed evaluation for extracardiac anomalies. Karyotyping should be offered (risk 1–50%) depending on the type of lesion. Fetuses with CHD are at increased risk of structural brain abnormalities. The prevalence of prenatal structural brain abnormalities in fetuses with CHD is approximately 28% (95% CI 18–40%). The more common abnormalities include ventriculomegaly, agenesis of the corpus callosum, ventricular bleeding, increased extra-axial space, vermian hypoplasia, white-matter abnormalities and delayed brain development. Fetuses with CHD are also more likely to have reduced brain volume, delay in brain maturation and altered brain circulation identified by Doppler sonography. These changes are usually evident in the third trimester, although have been reported as early as the second trimester. Concomitant 22q deletion testing should be performed for outflow tract abnormalities (1% risk overall but 10% with outflow tract lesions). Delivery should generally take place in a tertiary unit. The mode and timing of delivery is usually decided on standard obstetric criteria.

Aortic stenosis and hypoplastic left heart syndrome

Aortic stenosis accounts for 4–6% of all cardiovascular abnormalities and is four times more common in males. It has an incidence of 3–4 per 10 000 live births. It may be subvalvular, valvular or supravalvular. Stenosis secondary to valve abnormalities is usually due to cusp malformations seen in unicuspid or bicuspid aortic valves. The incidence of bicuspid aortic valves is approximately 1 in 100 newborns. Critical aortic stenosis causes reduced left ventricular output and increased diastolic filling pressure, which then causes hypertrophy followed by dilatation of the left ventricle.

Critical aortic stenosis can cause coronary hypoperfusion, subendocardial ischaemia and significant metabolic acidosis. The development of hydrops fetalis carries a very poor prognosis. Differential diagnoses include hypoplastic left heart syndrome (HLHS), coarctation of

the aorta and cardiomyopathy. HLHS is frequently associated with both aortic and mitral valve atresia.

HLHS is a major congenital heart anomaly and accounts for 1% of congenital cardiac abnormalities. HLHS involves a range of abnormalities, the cardinal feature of which is the inability of the left side of the heart to maintain the systemic circulation. The most severe form involves mitral and aortic valve atresia and an extremely hypoplastic left ventricle, with the degree of hypoplasia determining postnatal outcome. Other causes of HLHS are proximal aortic hypoplasia and left ventricular hypoplasia. Without treatment, newborn babies with HLHS usually die and it is responsible for 25% of all cardiac deaths in the first week of life. Important associated anomalies include pulmonary venous return abnormalities. CNS anomalies, including agenesis of the corpus callosum, microcephaly and holoprosencephaly, have also been reported. HLHS is associated with aneuploidy, genetic syndromes (Holt–Oram, Noonan's) and extracardiac abnormalities.

The majority of cases of HLHS occur too early in gestation for any intervention to be feasible; however, there is a subgroup of fetuses where the initiating insult occurs in mid-gestation or later, rendering some of these fetuses amenable to fetal cardiac intervention. The objective of *in utero* balloon dilatation of the aortic valve is to modify disease progression by opening the aortic valve and promoting prograde flow, thereby allowing growth of left-sided cardiac structures. The ultimate aim is to maintain a heart with two reasonably functioning ventricles and therefore make the fetus a candidate for postnatal biventricular repair. In many congenital heart centres, transcatheter balloon valvuloplasty is the initial procedure of choice in newborns with congenital aortic stenosis that are either duct dependent or have low cardiac output. After delivery, patency of the ductus arteriosus should be maintained with prostaglandin (PG)E_2 and any associated metabolic acidosis corrected. Early neonatal echocardiography should be performed to confirm the cardiac abnormality and treatment then planned.The pregnancy and birth should be managed in a tertiary centre by a multidisciplinary team including fetal medicine specialists, perinatal cardiologists, paediatric intensivists and cardiac surgeons. Karyotyping should be performed and termination of pregnancy should be discussed with parents as the outcome for the majority of cases is very poor.

Pulmonary stenosis and hypoplastic right heart syndrome

This is a fairly common abnormality, with the diagnosis often made after delivery. It has an incidence of approximately 1 in 1500 live births. Pulmonary stenosis may be isolated, occur in association with other abnormalities (Fallot's tetralogy), or occur in association with genetic syndromes (William's syndrome, Noonan's syndrome) or secondary to congenital rubella infection. Narrowing of the pulmonary valve can lead to hypertrophy of the right ventricle and, in severe cases, hypoplasia of the right ventricle. Pulmonary stenosis may progress *in utero*, resulting in tricuspid regurgitation, heart failure and hydrops.

Delivery of the baby should take place in a tertiary unit. The ductus arteriosus should be kept patent with a PGE_2 infusion. Early echocardiography to confirm the diagnosis and to exclude other cardiac malformations should be performed. Cardiac catheterization and balloon valvuloplasty is the treatment of choice, although some cases may require open heart surgery.

Hypoplastic right heart syndrome is ususally due to pulmonary valve atresia with an intact interventricular septum. Occasionally the tricuspid valve is also atretric. The left ventricle thus supplies both the systemic and the pulmonary circulation (by retrograde flow through the ductus arteriosus). The malformation is suspected if there is an obvious discrepancy in size between the two ventricles. Karyotyping may be indicated if additional anomalies are present, although the overall risk for aneuploidy is low. Termination of pregnancy should be discussed, particularly if hydrops is present.

Atrioventricular septal defect

This anomaly covers a spectrum of congenital heart malformations characterized by a common atrioventricular junction coexisting with deficient atrioventricular septation. In ostium primum atrial septal defect there are separate atrioventricular valvular orifices despite a common junction, while in complete atrioventricular septal defect there is a common valve. There is a strong association (30–50%) with Down's syndrome. Additional cardiac malformations are present in more than 70% of cases. The key diagnostic feature on the four-chamber view of the heart is the presence of a common atrioventricular valve. Once the abnormality is detected, referral to a tertiary centre and paediatric cardiologist is advisable. Karyotyping is essential and careful assessment of the fetus for additional anomalies is important. Termination of pregnancy should be offered for large lesions with fetal hydrops, if aneuploidy is detected or if there are other major associated anomalies.

Tetralogy of Fallot

Tetralogy of Fallot occurs in approximately 1 in 3600 live births and accounts for 3.5% of infants born with congenital heart disease. It comprises a ventricular septal defect, right ventricular outflow tract obstruction, the aorta overriding the interventricular septum and right ventricular hypertrophy. The spectrum of severity is wide, ranging from right outflow tract obstruction to

pulmonary atresia; 15% of cases may be associated with DiGeorge's syndrome caused by a deletion on the long arm of chromosome 22 (22q11.2). Once the diagnosis is suspected, referral to a paediatric cardiologist is essential. Karyotyping should be offered (including 22q deletion studies). The development of hydrops is a poor prognostic sign and termination of pregnancy should be discussed.

Central nervous system anomalies

Development of the human CNS involves several complex steps, including neural proliferation, neuroblast migration and neuronal differentiation. This is an extremely complex process influenced by both genetic and environmental factors and continues *ex utero* for several years. Some types of CNS anomalies are associated with an increased incidence of abnormal chromosomal microarray analyses. Pathogenic copy number variants are more common in fetuses with Dandy–Walker syndrome and holoprosencephaly. Chromosomal microarray analyses should be considered as part of the prenatal work-up in fetuses with CNS malformations.

Agenesis of the corpus callosum [2]

Agenesis of the corpus callosum (ACC) is a failure to develop the large bundle of fibres that connect the two cerebral hemispheres. It occurs in 1 in 4000 individuals and has been estimated to have a prevalence of 1.4 per 10 000 live births. ACC can be either complete or partial. It may occur in isolation, associated with aneuploidy, as part of a genetic syndrome (e.g. Aicardi's or Andermann's syndrome) or in association with other brain malformations. Various teratogens (alcohol, antiepileptic medication and cocaine), environmental factors and viral infections (rubella) have also been associated with ACC. If ACC is suspected, a careful search for both intracranial and extracranial anomalies is required. Karyotyping should be offered; the overall rate of aneuploidy is 17–18%. As the association of ACC with other cerebral malformations increases the likelihood of neurological impairment, fetal MRI should be performed in all suspected cases.

Counselling by a paediatric neurologist is essential as the spectrum of potential problems is wide. The prognosis in ACC is dependent on the coexistence of other abnormalities. For complete ACC, normal neurodevelopmental outcome can be expected in almost 84% of cases and severe disability in approximately 8% of affected individuals. There is some evidence to suggest that outcomes in partial ACC may be worse. The outcome for complete and partial ACC is conflicting, the majority of studies showing no difference in behavioural and medical outcomes between the two, with an overall rate of 25–30% of neurodevelopmental delay. Most children with isolated ACC will have mild behavioural problems.

Dandy–Walker malformation [3,4]

Dandy–Walker malformation is the most common congenital malformation of the cerebellum, with an incidence of 1 in 5000 births. Classic Dandy–Walker malformation is characterized by absence of the cerebellar vermis accompanied by dilatation of the fourth ventricle and a posterior fossa cyst. The cerebellum itself may be hypoplastic. In the Dandy–Walker variant, the posterior fossa is minimally enlarged, there is partial agenesis of the vermis, the fourth ventricle communicates with the arachnoid space, and no hydrocephalus is present. Other associated posterior fossa abnormalities include mega cisterna magna, Blake's pouch cyst or isolated vermian hypoplasia. There is an association with a variety of genetic syndromes, chromosomal abnormalities, infections and environmental teratogens. The prevalence of aneuploidy in fetuses with Dandy–Walker malformation and no associated CNS or extra-CNS anomalies is approximately 16%, with chromosomal deletions representing the most common abnormality. Ventriculomegaly is frequently seen. Aneuploidy or other CNS or extra-CNS anomalies are much less common in cases of mega cisterna magna, Blake's pouch cyst or isolated vermian hypoplasia. In contrast, associated CNS malformations are present in up to 68% of cases of Dandy–Walker malformation, the most common of which is agenesis or hypoplasia of the corpus callosum.

Karyotyping should be offered in all cases of Dandy–Walker malformation. Fetal MRI is extremely helpful in both confirming the diagnosis and determining the presence of other CNS malformations. Termination of pregnancy is an option regardless of gestation if classic Dandy–Walker malformation is detected because of the very poor long-term prognosis. The situation is more difficult with isolated Dandy–Walker variant as many of these children may have good long-term outcome. Counselling by a paediatric neurologist is essential.

Holoprosencephaly [5]

Holoprosencephaly (HPE) is a spectrum of congenital malformations involving the brain and face and is characterized by impaired or incomplete midline division of the embryonic forebrain (prosencephalon). Holoprosencephaly has an incidence of 1 in 16 000 live births. Only 3% of fetuses with HPE survive to birth. Facial anomalies associated with HPE include cyclopia, ethmocephaly, cebocephaly, median cleft lip, and less severe facial manifestations. Midline facial defects occur in the majority (>80%) of cases. Approximately 40% of live births with HPE have a chromosomal anomaly and trisomy 13 accounts for over half of these cases.

Alobar HPE is the most severe form. There is incomplete division of the cerebral hemispheres with a single midline forebrain ventricle (monoventricle), which often communicates with a dorsal cyst. The interhemispheric fissure and corpus callosum are completely absent. In semi-lobar HPE, there is failure of separation of the anterior hemispheres, with some separation of the posterior hemispheres. The frontal horns of the lateral ventricle are absent, but posterior horns are present. The corpus callosum is absent anteriorly. In lobar HPE (the mildest form), the cerebral hemispheres are fairly well divided, with fusion of only the most rostral/ventral aspects.

Karyotyping must be offered. Fetal MRI is often very helpful in confirming the diagnosis as well as grading the severity of the HPE. Termination of pregnancy should be discussed and offered. Alobar and most cases of semi-lobar HPE are not compatible with prolonged *ex utero* survival. Lobar HPE can be associated with long-term survival and will need evaluation for endocrine abnormalities and/or craniofacial surgery. Genetic counselling is essential and prenatal diagnosis may be an option in selected cases. HPE due to euploid non-syndromic causes have an empiric recurrence risk of 6%.

Ventriculomegaly [6]

Depending on the gestational age at ascertainment, the prevalence of ventriculomegaly varies between 0.3 and 1.5 per 1000 births. Ventriculomegaly is defined as a measurement of the atrium of the posterior or anterior horns of the lateral ventricles of more than 10 mm at any gestation. A measurement above 15 mm is considered severe. It may be unilateral or bilateral, symmetrical or asymmetrical. In fetuses with apparently isolated unilateral ventriculomegaly, increased dilatation of the ventricles occurs in 5% of cases. Once detected it is important to obtain a detailed history, especially of recent viral illness or significant maternal trauma, family genetic history, previous congenital abnormality or fetal/neonatal thrombocytopenia. Karyotyping should be discussed (7–15% overall risk of aneuploidy), although the risk of chromosome abnormalities for isolated unilateral ventriculomegaly is extremely low. Amniotic fluid should also be sent for viral polymerase chain reaction (PCR) analysis. Maternal blood for infection screening, particularly *Toxoplasma*/cytomegalovirus (CMV) and rubella, should be performed. If the ventriculomegaly is associated with intracerebral haemorrhage, evidence of fetal alloimmune thrombocytopenia should be sought (antiplatelet antibodies/HPA typing).

Fetal MRI should be arranged and further review with a paediatric neurologist is essential, particularly if the prognosis is in doubt. For isolated unilateral ventriculomegaly, additional brain abnormalities are detected by fetal MRI in 5% and 6% of the cases prenatally and postnatally, respectively. Neurodevelopmental outcome for mild isolated ventriculomegaly (<15 mm) appears to be not significantly different from the general population. In general, 6–7% of cases experience some neurodevelopmental delay of variable severity. However, asymmetric bilateral ventriculomegaly may carry a worse prognosis, with these children at significant risk for behavioural abnormalities. Poor prognostic factors include coexistent cerebral anomalies and progression of the ventriculomegaly. In severe ventriculomegaly, the outcome may still be variable but less than 30% of children will develop normally. Termination of pregnancy should be discussed for severe ventriculomegaly (>15 mm), aneuploidy, spina bifida or other associated major malformations. The mode of delivery is on standard obstetric criteria. In the presence of severe macrocephaly, caesarean section or cephalocentesis may be required. Cephalocentesis is associated with a high incidence of procedural/intrapartum demise.

Neural tube defects [7,8]

Most neural tube defects are multifactorial in origin, with a genetic component that interacts with a number of environmental risk factors. The ccommonest forms of neural tube defect are referred to as 'open', where the involved neural tissues are exposed to the body surface. These include anencephaly, craniorachischisis and myelomeningocele. Between 2 and 16% of isolated open neural tube defects occur in association with aneuploidy or a single gene defect. If additional structural anomalies are present, the risk may be as high as 24%. Most cases of neural tube defects are multifactorial in origin. Anticonvulsant use, mutations in the *MTHFR* (methylenetetrahydrofolate reductase) gene, maternal hyperthermia, obesity, diabetes mellitus and a previous family history are all risk factors. Recurrence in any subsequent pregnancy can be significantly reduced by taking high-dose folic acid (4–5 mg) periconceptually. Some neural tube defects are lethal (anencephaly, craniorachischisis) whereas others are compatible with long-term survival. However, there is risk of significant morbidity, including mobility issues and bladder and bowel dysfunction, and counselling by a neurologist is essential.

Prenatal surgical closure of selected cases of myelomeningocele is now an option, with evidence of significant reduction in the need for ventriculo-peritoneal shunting compared with standard postnatal closure. In addition, prenatal surgery improves reversal of hindbrain herniation as well as ambulation by 30 months. However, prenatal surgical intervention is associated with significantly higher rates of oligohydramnios and chorioamniotic separation, as well as spontaneous membrane rupture and preterm delivery.

Gastrointestinal tract anomalies

Duodenal atresia [9]

Duodenal atresia has an incidence of 1 in 5000–10 000 live births. The diagnosis is suspected on ultrasound when polyhydramnios and a double-bubble appearance (due to a dilated stomach and proximal duodenum) are present. Duodenal atresia results from failure of recanalization of the duodenum after the seventh week of gestation, possibly due to an ischaemic event; occasionally, genetic factors may also play a role. Although sometimes seen earlier in gestation, the diagnosis is usually made after 24 weeks. Approximately 50% of cases of duodenal atresia have associated structural anomalies. Almost 30% are associated with Down's syndrome and other anomalies are usually related to the VACTERL group (*V*ertebral, *A*norectal, *C*ardiac, *T*racheo*E*sohageal, *R*enal and *L*imb). If the diagnosis is suspected on antenatal ultrasound, karyotyping must be offered because of the high risk of Down's syndrome. Because of the significant risk of polyhydramnios (50%), regular scans are required and amnioreduction may be necessary if the amniotic fluid index increases substantially or if the patient is symptomatic. Preterm labour occurs in approximately 40% of cases. Delivery should take place in a tertiary centre with neonatal and paediatric surgical facilities. After birth, a nasogastric or orogastric tube is placed to decompress the stomach to minimize aspiration, and routine supportive management usually includes administration of intravenous fluids. Once clinically stable, surgical repair via laparotomy or laparoscopy is performed. Intraoperatively, it is important to exclude any associated malrotations, other small bowel atresia, or an annular pancreas. The long-term prognosis for duodenal atresia is very good, with survival rates of approximately 90%.

Meconium ileus/peritonitis [10,11]

Meconium ileus is impaction of abnormally thick meconium in the distal ileum. Meconium peritonitis occurs when there is perforation of bowel *in utero*, resulting in a sterile chemical peritonitis. Ultrasound features of meconium peritonitis include intra-abdominal calcifications, hyperechogenic bowel, ascites and bowel dilatation. Polyhydramnios may also be present. Serial ultrasound scans should be performed to assess progression of bowel dilatation, development of ascites or intra-abdominal cysts and polyhydramnios, which might indicate complicated meconium peritonitis with a 50% chance of requiring neonatal surgery. If these are present, consideration should be given to delivering the baby in a tertiary centre with neonatal surgical facilities.

Parental cystic fibrosis carrier testing and/or invasive fetal testing should be offered. If cystic fibrosis is diagnosed, appropriate genetic counselling should be offered and termination of pregnancy discussed if the diagnosis is made early in pregnancy. Long-term outcome depends on the underlying cause for the meconium peritonitis. In simple isolated meconium peritonitis the prognosis is usually excellent. In the simple form, thickened meconium begins to form *in utero*, and results in obstruction to the mid-ileum that causes proximal dilatation, bowel wall thickening, and congestion. In complicated cases, thickened meconium and obstruction lead to complications such as segmental volvulus, atresia, necrosis, perforation, meconium peritonitis (generalized) and giant meconium pseudocyst formation. In infants with cystic fibrosis the long-term outlook is guarded because of other extra-abdominal complications that can develop.

Abdominal wall defects

Omphalocele (exomphalos) [12,13]

This is a midline anterior abdominal wall defect of variable size characterized by the absence of abdominal muscles, fascia and skin. It can occur in the upper, mid or lower abdomen. A defect in cranial folding results in a high or epigastric omphalocele, classically seen in pentalogy of Cantrell (epigastric omphalocele, anterior diaphragmatic defect, sternal cleft and pericardial/cardiac defects). Lateral folding defects result in a mid-abdominal omphalocele and caudal defects cause a hypogastric omphalocele seen in bladder or cloacal exstrophy. The herniated viscera are covered by a membrane consisting of peritoneum on the inner surface, amnion on the outer surface and Wharton's jelly between the two layers. The umbilical cord inserts into the sac and not the body wall. It has an incidence of 1.5–3 per 10 000 births. Omphaloceles may be stratified into three groups: small, giant or ruptured. A giant omphalocele is often described as one with an abdominal wall defect of more than 5 cm or with more than 50–75% of the liver within the sac. The larger the defect, the higher the risk of postnatal complications, such as pulmonary hypoplasia and respiratory insufficiency and an increased prevalence of neurodevelopmental delay.

Most cases of omphalocele are sporadic and associated with advanced maternal age. It may occur in isolation or associated with aneuploidy (40%) or as part of a genetic syndrome. If aneuploidy is present, trisomy 18 is the most common chromosome abnormality. Smaller defects are more likely to be associated with chromosome abnormalities. Associated abnormalities are common (50–70%), with cardiac lesions predominating (30–40% of cases). Fetal mortality is strongly associated with the presence of additional structural malformations. The diagnosis can be made in the first trimester,

although most are detected at mid-trimester anomaly scan. Maternal serum α-fetoprotein is usually raised by an average of 4 multiples of the median.

Once the abnormality has been detected, the patient should be referred to a tertiary centre where there are facilities for detailed evaluation of the fetus. Karyotyping and fetal echocardiography should be performed. If macroglossia and other organomegaly are detected, Beckwith–Wiedemann syndrome should be suspected and the cytogenetics laboratory alerted to specifically look for abnormalities in the 11p15.5 region. Beckwith–Wiedemann syndrome is a growth disorder characterized by macroglossia, macrosomia, omphalocele, hypoglycaemia leading to seizures, visceromegaly, hemihyperplasia, renal abnormalities, ear creases and pits, nevus flammeus, and embryonic tumours (e.g. Wilms' tumour, hepatoblastoma, neuroblastoma and rhabdomyosarcoma). Omphalocele may also be part of the OEIS (omphalocele, bladder exstrophy, imperforate anus, spina bifida) complex.

Multidisciplinary counselling with paediatric surgeons, neonatologists, paediatric cardiologists and fetal medicine specialists should take place. The parents should be advised about increased incidence of fetal growth restriction, preterm labour and intrauterine death. Delivery should take place in a tertiary centre. Although vaginal delivery is reasonable and does not appear to influence outcome, elective caesarean section may also be an option in order that delivery takes place in a more controlled environment and timing of neonatal surgery can be better planned. Large omphaloceles are probably best delivered by caesarean section because of the possibility of trauma or soft tissue dystocia during a vaginal delivery.

The aim of surgery is to reduce the herniated viscera into the abdomen and to close the fascia and skin to create a solid abdominal wall with a relatively normal umbilicus. However, treatment can vary depending on the size and type of defect, the size of the baby, and any associated neonatal problems. Many surgeons prefer primary closure whenever possible. However, large defects with significant visceral herniation may require a more gradual or phased approach using silos to achieve reduction over a period of time before the abdominal wall is finally closed.

Gastroschisis [12–14]

This anomaly is believed to result secondary to an ischaemic insult to the developing abdominal wall. A full-thickness defect occurs secondary to incomplete closure of the lateral folds during the sixth week of gestation. The right paraumbilical area is usually affected. The incidence of gastroschisis is between 0.4 and 3 per 10 000 births and appears to be increasing. It has a strong association with young maternal age (<20 years), cigarette smoking, illicit drugs (cocaine), vasoactive over-the-counter drugs (such as pseudoephedrine) and environmental toxins. The diagnosis is usually obvious on ultrasound, often during the first-trimester (11–14 weeks) nuchal translucency scan, with free floating bowel or rarely the liver floating in the amniotic fluid without a covering membrane. Differential diagnoses include ruptured omphalocele sac or limb–body wall complex.

Associated anomalies occur in 10–20% of cases and most of these are in the gastrointestinal tract. It has been proposed that gastroschisis should be classified as simple (if isolated) or as complex (if associated with intestinal atresia, perforation, stenosis or volvulus). Chromosomal abnormalities or genetic syndromes are very rare. There is a slight increase in the incidence of cardiac abnormalities but this is not as high as seen in omphalocele. There is an increased incidence of preterm labour (30%), fetal growth restriction (70%), oligohydramnios (25%) and fetal death (5%). The cause of fetal growth failure is unclear but could be partially due to increased protein loss from the exposed viscera. The herniated bowel is at risk from volvulus and long-segment necrosis and/or more localized atretic and stenotic segments. Increasing bowel dilation, progressive oligohydramnios or decreased growth velocity may all be indicative of a fetus that is at increased risk of intrauterine death or greater neonatal complications. Early referral to a tertiary centre with multidisciplinary management is essential. Fetal echocardiography should be performed due to the increased association with cardiac anomalies. Serial scans should be performed to assess fetal growth and liquor volume, degree of bowel dilatation and bowel wall thickness. There is no contraindication for vaginal delivery but, as for omphalocele, elective caesarean section may also be an option to facilitate neonatal care. Bladder herniation and significant bowel dilatation may be risk factors for intrapartum fetal compromise (fetal distress) requiring operative delivery. Most centres now advocate delivery by 37 weeks given the increased risk of fetal demise after this gestation.

The ideal treatment of gastroschisis is immediate reduction of the herniated bowel back into the abdominal cavity and closure of the abdominal wall (primary reduction and repair). However, if reduction is likely to cause an abdominal compartment syndrome or significant respiratory difficulty, then staged repair is preferred. This involves applying a plastic silo around the bowel to progressively push the herniated viscera into the abdominal cavity over a number of days until definitive closure is possible. Overall survival is good (90–95%), with most deaths occurring in babies who have significant bowel loss, sepsis or long-term complications of short bowel syndrome. There is a 10% risk of hypoperistalsis syndrome, which may require longer hospitalization

and hyperalimentation. Gastrointestinal reflux occurs in 10% of cases and there is a 5–10% risk of obstruction due to adhesions in the longer term. A significant number of cases will also develop inguinal hernias due to increased intra-abdominal pressure post surgery. The risk of recurrence is small but exposure to vasoactive substances should be avoided in any subsequent pregnancy.

Genitourinary tract anomalies [15,16]

Congenital anomalies of the kidney and urinary tract account for one-third of all anomalies detected by routine fetal ultrasonography. In humans, fetal glomeruli develop by 8–9 weeks, tubular function commences after week 14 and nephrogenesis is largely complete by birth. After 20 weeks, the kidneys provide over 90% of the amniotic fluid. Any bilateral renal malformation can be associated with oligohydramnios/anhydramnios, lung hypoplasia, joint contractures and facial abnormalities collectively termed the Potter sequence.

Renal agenesis [17,18]

Unilateral renal agenesis has an incidence of 1 in 500–1000 births compared with bilateral renal agenesis, which occurs in 1 in 5000–10 000 births. Bilateral renal agenesis is not compatible with extrauterine life. It occurs more commonly in males and there is also an increased incidence in twins. Poorly controlled maternal diabetes or ingestion of renotoxic drugs are other aetiological factors. The diagnosis is usually made at the mid-trimester fetal anomaly scan. Although earlier diagnosis is sometimes possible, it is often difficult in the first trimester as the amniotic fluid volume is not significantly reduced at that stage. Anhydramnios is usually present by mid-trimester in bilateral renal agenesis. The liquor volume is usually normal in unilateral agenesis and the normal kidney can be larger due to compensatory hypertrophy.

There is an increased incidence of additional anomalies, particularly in the genital (blind vagina, uterine malformations, seminal vesicle cysts), cardiovascular and gastrointestinal systems in up to 44% of fetuses with renal agenesis. If the diagnosis of bilateral renal agenesis is made antenatally, the parents must be counselled about the dismal outcome and offered termination of pregnancy. Karyotyping and post-mortem is essential to help diagnose aneuploidy or a specific syndrome. Ultrasound of parental kidneys should be considered and genetic counselling offered. The risk of recurrence is low in unilateral renal agenesis (2–4%) but can be as high as 6–10% in bilateral cases.

Multicystic dysplastic kidney [19,20]

Unilateral multicystic dysplastic kidney (MCDK) has an incidence of 1 in 3000–5000 live births compared with 1 in 10 000 for bilateral dysplasia. It is one of the commonest causes of an abdominal mass in the neonatal period. The abnormal kidneys contain undifferentiated cells and metaplastic elements such as cartilage. On ultrasound, large hyperechogenic kidneys containing multiple cysts of varying sizes are present. Contralateral renal abnormalities can occur in 30–50% of cases. The prognosis for the fetus depends on whether there is unilateral or bilateral dysplasia. Bilateral MCDK is often lethal, with fetuses dying from pulmonary hypoplasia after birth. Termination of pregnancy should be offered in these cases.

No specific fetal intervention is required in cases of isolated unilateral MCDK. Serial ultrasound scans to monitor size of the abnormal kidney and liquor volume should be performed. Occasionally, gradual resorption (autonephrectomy) of the abnormal kidney can occur. Karyotyping should be offered to exclude aneuploidy. The mode of delivery is based on standard obstetric criteria. The prognosis is usually good. There is a small risk of long-term hypertension and malignant transformation in the dysplastic kidney. Children with a normal solitary functioning kidney, with evidence of compensatory hypertrophy, have a small risk of future renal insufficiency. In addition, there is an increased risk of hyperfiltration injury, which may be marked by hypertension and proteinuria that warrants long-term surveillance. Children with MCDK have a higher risk of vesico-ureteric reflux compared with the general population, particularly if there are contralateral renal abnormalities. There is also a risk of abnormalities of the internal genitalia for both males and females with MCDK.

Lower urinary tract obstruction [21]

In male fetuses, posterior urethral valves are the most common cause (90%) of bladder outlet obstruction. In female fetuses, urethral atresia accounts for the majority of cases. Less common causes of congenital lower urinary tract obstruction include anterior urethral valves/anterior urethral diverticulum, prune belly syndrome, urethral atresia, prolapsed ureterocoele, syringocoele, megalourethra, megacystis–microcolon–hypoperistalsis syndrome, obstruction by a hydrocolpos in females with cloacal anomalies, or rarely obstruction by a tumour such as a sacrococcygeal teratoma.

Oligohydramnios and a large thick-walled bladder with a keyhole sign and bilateral hydroureters and hydronephrosis are usually evident on ultrasound. The prognosis is worse (95% mortality) in those diagnosed antenatally when mid-trimester oligohydramnios is present. Features that suggest poor prognosis include dilatation of the upper tract, increased bladder wall thickness, oligohydramnios and evidence of renal dysplasia (echogenic renal cortex and cystic renal change), especially before 24 weeks. Obstruction can be complete or partial and the

amount of liquor volume usually gives some idea as to the severity of the obstruction. In complete obstruction anhydramnios rapidly develops. In addition, renal dysplasia can occur from an early gestation if the obstruction is severe. Karyotyping is important as aneuploidy is present in up to 10% of cases. Termination of pregnancy is an option, particularly if there is severe oligohydramnios/anhydramnios, the diagnosis is made early in pregnancy or if there is evidence of renal dysplasia on ultrasound.

Fetal therapy is possible and includes serial vesicocentesis, percutaneous vesico-amniotic shunting (VAS) or cystoscopy. The rationale for VAS is to decompress the urinary tract and therefore relieve the back-pressure on the fetal kidneys and to hopefully prevent the development of renal dysplasia. Shunting also allows restoration of flow of fetal urine into the amniotic cavity and thus prevents pulmonary hypoplasia. Compared with VAS, fetal cystoscopy for cases with posterior urethral valves appears to be more effective in improving both the 6-month survival rate and renal function, while VAS was only associated with improvement in the 6-month survival rate with no effect on renal function. Fetal cystoscopy is more invasive than VAS and carries a 10% urological fistula rate following fetal laser ablation of the bladder outlet obstruction. The risk of requiring dialysis and subsequent renal failure is approximately 30–50% in several series. To date, fetal intervention has not significantly changed the long-term renal outcome for affected individuals. Additional long-term problems include reflux, recurrent infections, bladder compliance and voiding issues and sexual function.

Head and neck anomalies

Cleft lip and palate [22–24]

The incidence of cleft lip and palate varies with ethnicity and geographical region but in a Caucasian population it is approximately 1 in 800–1000 for cleft lip and palate and 1 in 100 for cleft palate alone. Orofacial clefts can be classified as non-syndromic (isolated) or syndromic based on the presence of other congenital anomalies. Approximately 20–50% of all orofacial clefts are believed to be syndromic. The diagnosis is often made following the mid-trimester fetal anomaly scan. Fetal three-dimensional ultrasound and/or fetal MRI may help in determining the extent of palatal involvement. The aetiology of cleft lip/cleft palate is complex and multifactorial, involving both genetic and environmental factors. Many environmental factors are associated with orofacial clefting, including maternal alcohol consumption and cigarette smoking. Folate deficiency is also associated with cleft lip/cleft palate and prenatal folic acid supplementation has been shown to decrease this risk. Maternal corticosteroid use causes a threefold to fourfold increase in orofacial clefting. Anticonvulsants, including phenytoin and valproic acid, also cause cleft lip and palate. Phenytoin causes a nearly 10-fold increase in the incidence of facial clefting.

Associated anomalies include brain, cardiac and limb/spine deformities. There is a high risk of cerebral anomaly with midline clefts. Karyotyping should be offered in all cases. All patients should be referred to a multidisciplinary craniofacial team early following fetal diagnosis, where all aspects of the baby's management including feeding, surgery and cosmetic results can be discussed with parents. It is important to exclude any underlying syndrome after birth and genetic counselling for the risk of recurrence should be offered.

Cystic hygroma/lymphangioma [25,26]

Cystic hygroma is a rare congenital malformation of the lymphatic system and has an incidence of between 1 in 6000 and 1 in 16 000 births. Among aborted fetuses the incidence may be as high as 1 in 300. Approximately 75% occur in the neck, usually in the posterior triangle more commonly on the left side, and 20% occur in the axillary region. Chromosome abnormalities are present in almost 70% of cases, with Turner's syndrome and Down's syndrome particularly common. There is also an association with non-chromosomal conditions (Noonan's syndrome, multiple pterygium syndrome). Once detected, a careful search for additional abnormalities is vital. Karyotyping should always be offered. The presence of hydrops is a poor prognostic feature, with a perinatal mortality rate exceeding 80%. Fetal echocardiography should be performed. There is an increased incidence of preterm labour and polyhydramnios, particularly if the cystic hygroma impairs fetal swallowing. In very large lesions, obstruction of the pharynx and larynx may develop making intubation very difficult. The EXIT procedure (*ex-utero* intrapartum treatment) may be required before the umbilical cord is divided.

Skeletal system anomalies

Skeletal dysplasias are a heterogeneous group of genetic disorders characterized by differences in the size, shape and mineralization of the skeletal system that frequently result in disproportionate short stature. The diagnosis is usually made by clinical features, radiological criteria, family history and, increasingly, by genetic testing. It is estimated that 30–45 per 100 000 newborns have a skeletal dysplasia. Antenatal management depends on identifying the presence of a skeletal dysplasia and making an assessment of the lethality of the condition. Karyotyping should be offered, particularly in the presence of other abnormalities. DNA should be stored for future genetic testing. A precise diagnosis often needs to await postnatal or post-abortal radiology or molecular testing. Most cases of skeletal dysplasias are autosomal

recessive, for which genetic counselling is important. Others may be due to a new dominant mutation. Family history of skeletal dysplasia, malformations and short stature should be obtained. Termination of pregnancy is an option for most cases of skeletal dysplasias as many have a poor outcome. A narrow thorax or significant polyhydramnios in particular indicates a high chance of lethal pulmonary hypoplasia. Specific genetic mutations are known for some skeletal dysplasias – achondroplasia and thanatophoric dysplasia, *FGFR3* mutation; campomelic dysplasia, *SOX9* mutation; diastrophic dysplasia, *DTDST* mutation; and osteogenesis imperfecta, *COL1A* or *COL2A* mutation – and therefore prenatal diagnosis may be possible in selected cases.

Thoracic anomalies

Pulmonary development requires normal fetal breathing movements, an adequate intrathoracic space, sufficient amniotic fluid, normal intra-lung fluid volume and pulmonary blood flow. Maternal health, including nutrition, endocrine factors, smoking and disease, can also adversely influence fetal lung development. There are five stages of lung development: embryonic (0–7 weeks *in utero*), pseudoglandular (7–17 weeks *in utero*), canalicular (17–27 weeks *in utero*), saccular (28–36 weeks *in utero*) and alveolar (36 weeks *in utero* to 2 years postnatal).

Diaphragmatic hernia [27,28]

Congenital diaphragmatic hernia has an incidence of 1 in 3000–5000 births. It occurs more commonly on the left side (75–80%) than on the right side (20–25%). The combination of lung hypoplasia, lung immaturity and pulmonary hypertension and the presence of other malformations can result in high mortality for this condition. The degree of pulmonary hypoplasia depends entirely on the length of time and extent the herniated organs have compressed the fetal lungs. Associated abnormalities may be present in 30–60% of cases and can involve any organ system. Aneuploidy is present in 10–20% of cases and it may also be associated with some genetic syndromes (Fryn's syndrome, Beckwith–Wiedemann syndrome). Congenital diaphragmatic hernia should be suspected if the fetal stomach is not in its usual intra-abdominal position. Liver, mesentery and bowel and spleen may be present in the chest. Differential diagnoses include congenital cystic adenomatoid malformations, bronchogenic cysts, pulmonary sequestration or thoracic teratomas. Polyhydramnios and/or hydrops may sometimes be present. Increased liquor is usually due to impaired swallowing and hydrops may occur if there is significant cardiac compression. Liver herniation is a poor predictive factor for the development of pulmonary hypoplasia.

Management includes detailed assessment of the fetus for additional anomalies, karyotyping and fetal echocardiography. Fetal MRI or three-dimensional ultrasound can sometimes be considered to evaluate lung volume. Parents should be counselled by a paediatric surgeon regarding neonatal management. Termination of pregnancy is an option if significant visceral herniation (particularly liver) is present. The aim is to deliver at term. The mode of delivery is determined on standard obstetric criteria. However, it is essential that delivery takes place in a tertiary centre where the baby can be closely monitored to assess the degree of pulmonary compromise (hypoplasia and vascular hypertension) before surgery is undertaken. Prenatal intervention by fetoscopic endoluminal tracheal occlusion (FETO) is now an option, with the main objective of improving fetal lung growth. There is evidence that treatment *in utero* can increase postnatal survival for both left- and right-sided defects. However, prenatal treatment, only available in select fetal therapy centres, is associated with significant risk of preterm premature rupture of membranes and preterm birth.

Congenital pulmonary airway malformation [29–31]

Congenital pulmonary airway malformations (CPAMs), previously known as congenital cystic adenomatoid malformations, are rare developmental malformations of the lower respiratory tract. CPAMs account for 95% of congenital cystic lung abnormalities and are the most common cystic lung lesions diagnosed by prenatal screening. They are characterized by lack of normal alveoli and excessive proliferation and cystic dilatation of terminal respiratory bronchioles. The incidence of CPAM is between 1 in 11 000 and 1 in 35 000 live births and is slightly more common in males. They are usually unilateral (>85%) and usually involve only one lobe of the lung. Most (60%) are left-sided lesions. The diagnosis is usually made on antenatal ultrasound by the detection of enlarged hyperechogenic lungs sometimes containing cysts of varying sizes. Mediastinal shift, cardiac compression, polyhydramnios and hydrops may also be present. Between 45 and 85% of prenatally identified CPAMs will spontaneously regress. However, large macrocystic or solid lesions can cause hydrops, pulmonary hypoplasia, cardiac dysfunction and perinatal death. The majority of lesions follow a characteristic growth pattern that is highly dependent on gestational age. There is usually an increase in size between 17 and 26 weeks before possible regression after 30 weeks. Large lesions can cause pulmonary hypoplasia, impairment of fetal swallowing and polyhydramnios, cardiac compression and hydrops. Serial scans are essential to monitor the size of the lesion (particularly macrocystic CPAM), the development of cardiac compression and/or hydrops. Prenatal treatment options include the maternal administration of steroids, minimally

invasive procedures or, rarely, open fetal surgery. These interventions aim to alleviate the mass effect, prevent the progression of complications and improve the outcome for these fetuses. In selected macrocystic lesions, fetal therapy (either aspiration of the cyst or insertion of a shunt to drain the cyst) may be an option. Maternal steroid treatment has been reported to have a beneficial effect on large microcystic CPAMs. The mode and timing of delivery is on standard obstetric criteria. Postnatally, the baby will require careful monitoring and a chest X-ray. Surgery may be deferred for up to 24 months.

Pleural effusions [32,33]

Fetal pleural effusions have an incidence of between 1 in 10 000 and 1 in 15 000 pregnancies. Effusions may be primary (due to leak of chyle into the pleural cavity) or secondary (seen in hydrops). Complications include mediastinal shift, cardiac compression, hydrops and pulmonary hypoplasia. Affected fetuses are at significant risk for respiratory distress at birth. Once detected the patient should be referred to a fetal medicine unit for further investigations. The presence of other anomalies should be excluded. Fetal echocardiography should be performed as cardiac abnormalities are present in 5% of cases. Karyotyping should be offered as there is a significant association (10%) with aneuploidy. Maternal serology for infection should be performed. Serial scans should be arranged to assess the size of the effusion and for the development of hydrops or polyhydramnios as these are poor prognostic features. There are several treatment options. Firstly, a period of expectant observation is reasonable if the fetus is not hydropic and the effusion is small or moderate in size. Thoracocentesis or pleuro-amniotic shunting are other options. The risks associated with pleuro-amniotic shunting include miscarriage or preterm labour, rupture of membranes, blockage of the shunt and shunt migration. Survival after pleuro-amniotic shunting is approximately 80%.

Fetal tumours

Teratomas [34–36]

Teratomas are tumours that contain tissue from all three germinal layers (ectodermal, mesodermal and endodermal tissue). Most prenatally diagnosed teratomas are situated in the brain, oropharynx, sacrococcygeal region, mediastinum, abdomen and gonad. Teratomas are the most common perinatal tumour, comprising 37–52% of congenital neoplasms and having a yearly incidence of approximately 1 in 40 000 live births. The majority of teratomas occur in the sacrococcygeal region (60%), followed by the gonads (20%) and thoracoabdominal lesions (15%).

Sacrococcygeal teratomas are the most common neoplasm in the fetus and newborn, with an estimated prevalence of 1 in 30 000–40 000. There is a 3 : 1 female preponderance. The diagnosis is often made when a complex mass is detected at the base of the spine (sacrococcygeal region). It can be either predominantly solid and vascular or predominantly cystic with relatively little vascularity, or mixed with equal amounts of solid and cystic structures. Associated anomalies are present in 10–40% of cases. Arteriovenous shunting through the vascular component of the tumour can result in hydrops, polyhydramnios and high-output cardiac failure. Poor prognostic factors include large solid tumours (>10 cm), hydrops and polyhydramnios. Other complications include gastrointestinal or bladder outlet obstruction. Most sacrococcygeal teratomas are histologically benign, with malignancy more common in solid tumours and in males. Fetuses with large or rapidly growing tumours and polyhydramnios are more likely to experience a complicated outcome after birth.

Tumour dystocia, rupture and haemorrhage during delivery are the main causes of perinatal morbidity and mortality. Additionally, polyhydramnios can precipitate preterm delivery. Maternal complications including pre-eclampsia (mirror syndrome) can occur if there is significant placentomegaly and hydrops. Delivery should take place in a tertiary centre with facilities for immediate surgery. Elective caesarean section should be the mode of delivery, with particular care taken during delivery to avoid trauma to the tumour. Blood should be available in the delivery room in case of tumour haemorrhage. After birth, mortality due to haemorrhagic complications is relatively high and represents the leading cause of mortality in the neonatal period.

Fetal hydrops [37,38]

Hydrops is an end-stage process for a number of fetal diseases resulting in tissue oedema and/or fluid collection (ascites, pleural effusion, pericardial effusion) in various sites. Its aetiology may be either immune or non-immune depending on the presence or absence of red cell alloimmunization. Non-immune causes now account for more than 90% of all cases of hydrops. Congenital heart abnormalities, cardiac arrhythmias (supraventricular tachycardia, complete heart block), twin–twin transfusion syndrome, congenital anomalies, aneuploidy, infections, congenital anaemia and congenital chylothorax are all possible causes for hydrops. Regardless of aetiology, hydrops has a very poor outcome (>80% mortality). Early development of hydrops has a particularly poor prognosis. The mortality rate is highest among neonates with congenital anomalies (60%) and lowest

among neonates with congenital chylothorax (6%). Mortality is significantly higher in premature infants and those delivered in poor condition.

It is important to obtain a detailed family, medical, obstetric and genetic history. A history of prior exposure to possible viral infections (maternal rash, arthralgia/myalgia) is especially important. Detailed ultrasound to detect structural abnormalities, particularly cardiac and thoracic abnormalities, should be performed. The umbilical cord and placenta should be carefully examined to exclude vascular malformations. The fetal heart rate and rhythm should be examined to exclude fetal tachyarrhythmias or bradyarrhythmias. Maternal blood should be taken for full infection screen (CMV, parvovirus, rubella, herpes), *Toxoplasma* serology, blood group and antibody screen, and haemoglobin electrophoresis. Fetal anaemia should be excluded by middle cerebral artery peak systolic velocity monitoring. Fetal echocardiography should be performed in all cases. If anaemia is suspected the most likely cause is parvovirus infection. This is a treatable condition with usually a single fetal transfusion. Karyotyping is mandatory in all cases. Samples should be sent for cytogenetics and infection screen using PCR. If hydrops is secondary to fetal arrhythmia, maternal antiarrhythmic therapy may be of benefit. There is usually a delay in response because of the slow transplacental transfer into the fetal circulation. Occasionally, direct fetal treatment may be required in cases of fetal supraventricular tachycardia unresponsive to maternal treatment. If the hydrops is secondary to a structural anomaly (e.g. pleural effusion), *in utero* therapy (pleuro-amniotic shunting) may be necessary. Termination of pregnancy should be offered if hydrops is severe or if major malformations or aneuploidy are present. Parents should be counselled that untreated hydrops carries a very high (>80%) perinatal mortality rate and that outcome is likely to be poor.

Conclusions

When a fetal structural anomaly is identified, regardless of gestation, there are several key issues that must be considered. Firstly, it is crucial to remember that to the pregnant woman the detection of any anomaly is a source of great anxiety and stress. Women should receive information regarding the abnormal ultrasound findings in a clear, sympathetic and timely fashion, and in a supportive environment that ensures privacy. Whenever appropriate, referral to a tertiary fetal medicine unit should be made. A full and frank discussion with a senior obstetrician or fetal medicine specialist is important for explaining the diagnosis and further management of the pregnancy. Further testing (amniocentesis, chorionic villous sampling or fetal blood sampling) may be required. More complex imaging with fetal MRI may sometimes help delineate anatomy (particularly for CNS anomalies). Additional counselling by a genetic counsellor or geneticist may be necessary. Counselling should always be unbiased and respectful of the patient's choice, culture, religion and beliefs.

In many cases serial scans will be necessary to assess evolution of the abnormality and to attempt to detect other anomalies not previously identified, as this may influence counselling as well as the obstetric or neonatal management. In some cases parental imaging and testing may be required. Referral to an appropriate paediatric or surgical specialist should be considered to enable the woman to receive the most accurate information possible concerning the anomaly and the associated prognosis. It may be important to stress that, not infrequently, both major and minor structural anomalies, whether isolated or multiple, may sometimes be part of a genetic syndrome (despite a normal fetal karyotype) and that long-term prognosis will depend on the final diagnosis. Critically, it is important to stress that antenatal ultrasound is geared towards evaluating anatomy rather than function and that sometimes normal anatomy does not always correlate with normal function and vice versa.

Although fetal therapy is possible for some conditions, it is generally not an option for the majority of fetal structural anomalies. If early or urgent postnatal management is required, delivery at a centre that can provide the appropriate neonatal care should be considered. In cases of termination of pregnancy, stillbirth or neonatal death, the health professional should encourage the performance of a complete post-mortem by a perinatal pathologist to provide maximum information about the fetal anomaly. When a complete post-mortem is refused, at least a partial or external post-mortem (including X-rays and photographs) should be considered.

Summary box 20.2

- When an abnormality is detected consider further investigations, including karyotyping with microarray, parental testing, fetal MRI and fetal echocardiography.
- Counselling should be non-directive, sympathetic and wherever possible should include a paediatric specialist.
- For some conditions termination of pregnancy is an option but it must be broached sensitively.
- The importance of a post-mortem should be explained to parents.
- When appropriate, genetic input should be arranged.
- Pre-pregnancy counselling may be helpful for some parents.

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21

Multiple Pregnancy

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Multiple pregnancy has a global impact on both maternal and perinatal risk in any pregnancy and impacts on society in terms of both social and economic effects. Improvements in the health of the population, and in particular perinatal care, have led to a reduction in overall total pregnancy complications (both maternal and perinatal). However, the proportion of these attributed to twins and higher-order pregnancies is increasing and of significant importance. Almost every maternal and obstetric problem occurs more frequently in a multiple pregnancy and there are, in addition, a number of potential intrapartum considerations that complicate routine management. The modern management of a multiple pregnancy initially concentrates on the recognition of fetal risk, as mediated primarily by chorionicity, and then the monitoring of fetal growth and well-being using ultrasound. Attempts to reduce the risks of preterm delivery and pre-eclampsia in the mother are equally important and equally as frustrating (as in singleton pregnancy care), with little improvement in overall management of these conditions in the last 20 years. Recognizing the specialized nature of multiple pregnancy management has led to the publication of recommendations by two scientific study groups of the Royal College of Obstetricians and Gynaecologists (RCOG) [1,2] and the commissioning of recommendations of care for multiple pregnancies by the National Institute of Health and Care Excellence (NICE) in 2009 (and published in 2011) [3]. At the heart of care is the recommendation that such pregnancies are managed within specialist multidisciplinary teams and in designated multiple pregnancy clinics so as to organize antenatal, intrapartum and indeed postnatal care.

Incidence

The considerable geographical and temporal variation in the incidence of multiple pregnancy reflects factors including dizygotic twinning as the result of multiple ovulation [4]. The incidence of twinning ranges from 4 per 1000 births in Japan to as frequent as 54 per 1000 in some regions of Nigeria. In addition, this 'complication' is more prevalent in pregnancies with advancing maternal age (presumed to be secondary to the rise in follicle-stimulating hormone concentrations). Familial predisposition to multiple ovulations (usually dizygous twinning) may occur and is presently best explained by an autosomal dominant inheritance pattern. In contrast, monozygous twinning, the result of early cleavage division of a single blastocyst, occurs with a relatively constant incidence of approximately 3.9 per 1000.

Time trends in multiple pregnancy demonstrate a remarkable change in reproductive behaviour and consequence. Some of the first documented records from Scandinavia in the eighteenth century indicate that multiple pregnancy rates may have been higher than they are today, reaching a zenith of 17 per 1000 maternities [5]. However, during the twentieth century, twin pregnancy rates appeared to be in decline until the early 1970s, since when there has been a clear rise in prevalence [6]. Since the early 1980s, the twinning rate in the UK has risen from 9.8 to 13.6 and the triplet rate from 0.14 to 0.44 per 1000 maternities. Such an increase is reflected internationally, with the greatest rise being noted in the USA. Multiple pregnancies accounted for 1.6% of all births in the UK during 2007, with approximately 98% of these being twin births [6]. A considerable proportion of the

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increase is due to assisted reproductive technologies, such as superovulation (using antioestrogens or gonadotrophins) and *in vitro* fertilization (IVF) with embryo transfer. There is evidence that the number of multiple pregnancies is influenced by the number of embryo transfers and, as such, the number of multiple pregnancies associated with IVF has reduced since the recommendation that embryo transfer numbers be reduced. In addition, epidemiological evidence suggests that both types of assisted reproduction techniques increase the incidence of monozygous twinning by up to eightfold [7]. This is particularly associated with the techniques of 'blastocyst hatching'. Monochorionic twins comprise 20% of spontaneous and 5% of iatrogenic twin gestations. This is important as monochorionic twins have the greatest pregnancy-related complication rates.

However, it is also important to recognize other influences. The association between increasing maternal age (strongest at 30–39 years) and spontaneous dizygous twinning is worthy of note. The combined effects of delayed childbearing and high uptakes of assisted reproductive technologies at advanced maternal age have been responsible for this rise [6].

Perinatal loss

Cumulative fetal loss rate in twins is up to five times higher (and in triplets 10 times higher) than in corresponding singleton pregnancies. Rates of stillbirth and neonatal mortality for a multiple pregnancy are 14.9 and 19.8 per 1000 live births, respectively. This high perinatal fetal loss and morbidity is largely attributed to the increased risk of prematurity and also intrauterine growth restriction (IUGR) with associated iatrogenic prematurity (irrespective of chorionicity, see following section).

Cerebral palsy is approximately three times more common in twins and 10 times more common in triplets compared with singletons. These figures are per fetus, whereas the more relevant figure when counselling parents is the chance of their multiple pregnancies producing any one baby with these complications.

Chorionicity and zygosity

Approximately two-thirds of twins are dizygous and one-third monozygous. However, it is chorionicity rather than zygosity that mediates the degree of perinatal risk in any individual multiple pregnancy. This is most important as it is clinically identifiable. Cumulative fetal loss rates and perinatal mortality are up to five times higher in monochorionic twins compared with dichorionic twins [8]. This study, and a more contemporary one (during a period when modern management was possible including more widespread recognition of feto-fetal transfusion syndrome and its fetoscopically directed treatment [9]), noted that in monochorionic diamniotic twin pregnancies, 85% resulted in double survivors, 7.5% in a single survivor and 7.5% in no surviving baby. These deaths occurred spontaneously or iatrogenically. Perinatal morbidity appears similarly related, with prenatally acquired cerebral lesions evident in the early neonatal period on ultrasound in up to one-third of monochorionic twins compared with 3% of dichorionic twins delivered preterm [10]. Such excess morbidity and mortality is mediated predominantly (but not exclusively) through the inter-twin placental vascular anastomoses that connect the two fetal circulations.

Monozygotic pregnancies assume one of three placental configurations. Division within 3 days of fertilization results in separate dichorionic placentas, which in up to 50% of cases may have the appearance on ultrasound of being adjacent to each other and 'fused'. Splitting after formation of the inner cell mass at 4 days after fertilization results in a single monochorionic diamniotic placenta, whereas splitting after 7 days results in monochorionic monoamniotic twins. Approximately one in five of all twins are monochorionic.

Ultrasonic determination of chorionicity

Chorionicity may be clinically determined during pregnancy using ultrasound, with up to 90–100% accuracy in the first trimester. Ultrasound allows the following features to be ascertained.

- Determination of the number of constituent layers of the dividing membranes (and therefore of membrane thickness).
- Qualitative interpretation of the membrane as 'thick' (dichorionic) or 'thin' (monochorionic) appears as accurate as inter-twin membrane/septal measurement.
- Demonstration of a tongue of placental tissue within the base of the inter-twin membrane, known as the 'twin peak' sign, is diagnostic of a dichorionic pregnancy. In contrast, a thin septum with a single placental mass is suggestive of monochorionicity.
- Presence (or not) of a single placental mass.

Chorionicity should be determined on ultrasound in all multiple pregnancies, as a screening test, ideally within the first trimester between 11 and 14 weeks of gestation (when specificity and sensitivity are greatest). Digital or hardcopy images should be stored demonstrating the signs of chorionicity. This is because chorionicity is relevant to:

- counselling parents in relation to the risk of perinatal morbidity and mortality;

- counselling parents in relation to their risk of genetic and structural abnormalities;
- invasive testing and the management of discordant congenital anomaly;
- feasibility of multiple fetal pregnancy reduction;
- risk of complications that may occur in a multiple pregnancy and potential sequelae that may ensue;
- early detection and management of feto-fetal transfusion syndrome.

Such an examination should be routine and allow the stratification of prospective pregnancy care. In addition, ultrasonic visualization of the inter-twin membrane/septum and genitalia may be difficult later on in pregnancy or when there is significant oligohydramnios complicating the pregnancy. The first ultrasound allocation of chorionicity should be performed in the first trimester between 11 and 14 weeks at a time when increasing numbers of pregnancies are undergoing nuchal translucency screening [11]. Ultrasonic sexing is performed for medical rather than social reasons in multiple pregnancies and, as such, achieves a high degree of accuracy, usually between 16 and 20 weeks.

Zygosity determination

Monochorionic twins by definition are monozygotic, while discordant-sex twins are dizygous. In the remaining 50%, zygosity cannot be determined without DNA fingerprinting, such as the polymerase chain reaction technique that compares parental inheritance patterns of a number of dinucleotide and trinucleotide short tandem repeats which are highly polymorphic in copy number. Such determination is rarely performed prospectively in clinical practice. Just as placental chorionicity is rechecked at birth (usually by clinical or histopathological examination), cord blood zygosity studies may be offered to parents of twins where there is indeterminate zygosity. Not only are parents curious but knowledge of zygosity influences the twins' rearing, their sense of identity, their genetic risks and their transplantation compatibility. However, it is not routine to offer this in current practice within the NHS in the UK. Rarely there may be indications for zygosity testing *in utero* on invasive collection of fetal tissue, such as excluding contamination, deducing genetic risk or demonstrating dichorionicity in the presence of fetal compromise.

Miscarriage

Twins have a high incidence of spontaneous early pregnancy loss. Estimates suggest that approximately 12% of human conceptions start as twins [12]. Studies of ultrasound or miscarriage pathology indicate that twins are found at least twice as commonly in the first trimester as at birth. First-trimester early pregnancy loss and resorption of one previously indefinable twin on ultrasound is known as the 'vanishing twin' phenomenon and is estimated to occur in up to 20% of twin pregnancies [13]. Spontaneous first-trimester loss of one or more fetuses in high-order pregnancies is estimated to occur approximately 50% of the time. When one twin dies *in utero* in mid-trimester, a papyraceous fetus (the squashed paper-like remains of the baby) may be found alongside the placenta after delivery. In some cases, this is only identifiable histopathologically.

Prenatal diagnosis

The widespread use of ultrasound in the first trimester and for routine mid-trimester anomaly scanning to detect structural congenital malformations and Down's syndrome is relevant to all multiple pregnancies. Zygosity determines the risk of congenital abnormality and chorionicity what can be done if it is found to be present.

Zygosity may be deduced definitively in cases of monochorionicity or discordant external genitalia (dizygous), while in dichorionic concordant-sex twins the chance of dizygosity is 75–80%. Monozygous twins have a 50% increase in structural abnormalities per baby. In particular, they have twice the frequency of congenital heart disease (a fourfold increase per pregnancy). Women with dizygous twins can be counselled that the chance of their pregnancy producing a child with Down's syndrome is theoretically double their age-related risk, whereas women with monozygous twins simply have their age-related risk that both twins will be aneuploid. Serum screening is, in general, inapplicable to multiple pregnancies. In contrast, nuchal translucency and first-trimester ultrasound scanning as a fetal-specific screening test is readily applicable and recommended by the National Screening Committee in the UK. At 18–24 weeks, women with multiple pregnancies should be offered a mid-trimester fetal anomaly scan (which includes visualization of the four chambers of the heart and the great vessel outflow tracts) irrespective of chorionicity (as in singleton pregnancies). In countries with a gestational age limit for termination of pregnancy of 24 weeks, the anomaly scan should preferably take place before 22 weeks. In addition, in the first trimester between 11 and 13^{+6} weeks, all women with multiple pregnancies should be offered nuchal translucency screening for the detection of chromosomal anomalies (as well as the formal documentation of chorionicity). In dichorionic twins, the risk of aneuploidy is that of each of the individual fetuses. In monochorionic twin

pregnancies, the risk of aneuploidy is the average between the twins. The use of first-trimester serum screening as an adjunct to nuchal translucency, taking chorionicity into account, may slightly improve detection rates for Down's syndrome in twins, but the results of large prospective studies are awaited [14].

Screening for Down's syndrome using a maternal plasma sample to perform cell-free DNA sequencing, also known as non-invasive prenatal testing (NIPT), in monochorionic twins should be equally reliable as in singletons. However, reliable scientific data are still lacking. NIPT in dichorionic twins has been studied in small series, and appears promising, although with a higher failure rate and lower accuracy compared with singletons [15].

Invasive procedures

Invasive procedures in twins and other higher-order multiple pregnancies are potentially complex techniques and should only be performed in fetal medicine referral centres [15]. The *in utero* topography (placental and membranes) is mapped using ultrasound. The location of the fetuses, the placental site(s) and the plane of the dividing septum in three dimensions should be noted and recorded. Such is a prerequisite for interpretation of discordant results and for selective termination of pregnancy. The operator performing the diagnostic procedure should also undertake any selective termination so as to minimize uncertainty and obviate any need for confirmatory invasive testing.

In monochorionic twins, it is acceptable practice to sample only one fetus by either amniocentesis or chorionic villous sampling (CVS). However, rare cases of heterokaryotypic monochorionic twins may be missed (occurring in <1%). For this reason, amniocentesis on both amniotic sacs is worthy of consideration if monochorionic twins are discordant for structural anomalies, nuchal translucencies or growth.

In dichorionic twins, there has been controversy about whether CVS is less desirable than amniocentesis for performing karyotyping. Because of problems with contamination, some investigators suggest restricting CVS to high-risk cases such as monogenic disease or where there is an aneuploidy risk of greater than 1 in 50. The risk of contamination is likely to be higher than the published figures (2%) since the literature is confined to discordant-sex twins. Any benefits of CVS are outweighed by the potentially disastrous consequences of misdiagnosis due to contamination, with subsequent termination of a diploid fetus or the wrongful birth of a fetus with a chromosome abnormality. For these reasons, the RCOG guidelines [15] discuss potential advantages to amniocentesis as the preferred option for karyotyping in dichorionic twins. Such a decision has to be weighed against the increased risks of selective reduction at increased gestational ages. When performing fetal blood sampling, the intrahepatic vein may be sampled to avoid confusing the cord origins in twins.

There are no randomized controlled trials to indicate procedure-related loss rates in twins. However, background loss rates are appreciably higher. A recent systematic review of the literature relating to the risks of CVS and amniocentesis in twin pregnancies was published in 2012. This study noted that for CVS, nine studies fulfilled the inclusion criteria. The overall pregnancy-loss rate was 3.84% (95% CI 2.48–5.47; $N = 4$). The rate of pregnancy loss before 20 weeks was 2.75% (95% CI 1.28–4.75; $N = 3$) and before 28 weeks was 3.44% (95% CI 1.67–5.81; $N = 3$). For amniocentesis, the overall pregnancy-loss rate was 3.07% (95% CI 1.83–4.61; $N = 4$). The rate of pregnancy loss before 20 weeks was 2.25% (95% CI 1.23–3.57; $N = 2$), before 24 weeks was 2.54% (95% CI 1.43–3.96; $N = 9$) and before 28 weeks was 1.70% (95% CI 0.37–3.97; $N = 5$). Pooled data from four case–control studies showed a higher risk (2.59% vs. 1.53%) of pregnancy loss before 24 weeks following amniocentesis (relative risk, RR 1.81; 95% CI 1.02–3.19) [16].

In dichorionic twins discordant for fetal anomaly, selective termination of pregnancy by the induction of asystole using an abortifacient is associated with an 8% loss rate in the international registry, with lower rates if the procedure is performed before 16 weeks' gestation [17]. Selective termination of monochorionic twins cannot be performed using injection of an abortifacient as this would lead to death of the healthy twin due to sharing of the circulation along vascular anastomoses. However, a variety of cord occlusion techniques has been developed to render selective termination feasible. However, evidence shows that there is an associated increased risk of co-twin demise and co-twin morbidity when these procedures are performed [18]. Survival rates of the co-twin vary between 70 and 80% in reported single-centre series.

Maternal homeostatic responses

All the normal physiological adaptations, such as increased cardiac output, glomerular filtration rate and renal blood flow, are further increased in a multiple pregnancy. Women with twins increase their plasma volume by one-third more than women with singletons. Red cell mass increases approximately 300 mL more than in singleton pregnancies but because this is disproportionately less than the increase in plasma volume, haemoglobin and haematocrit values fall. Maternal iron stores are diminished in 40% of women with twins so

routine haematinic supplementation is recommended (usually as combined iron sulfate and folic acid supplementation).

Hyperemesis gravidarum is more common in multiple pregnancies and is managed as in singleton pregnancies. Severe cases may respond to maternal steroid therapy and require pyroxidine (B_6) supplementation. The majority of minor pregnancy complications such as backache, symphysis pubis dysfunction, oedema, varicose veins, haemorrhoids and stria are all increased as a result of both the physical effects of greater uterine size and greater placental hormone production [19].

Hypertensive disease of pregnancy and pre-eclampsia are up to 10 times more common in multiple compared with singleton pregnancies but are managed once diagnosed on standard principles (as in singletons). Consideration should be given to low-dose aspirin prophylaxis but there are no national/international recommendations to this effect. Maternal pregnancy-related hypertension remains a significant cause of maternal morbidity (and mortality) in multiple pregnancies and a significant cause of iatrogenic preterm delivery, increasing perinatal morbidity and mortality. This occurs in 15–20% of twin pregnancies, 25% of triplets and up to 60% of higher-order multiple pregnancies [20].

Postnatally, the physical difficulties and socioeconomic impact of coping with the demands of two or more babies are considerable. Postnatal depression is more common in women nursing twins than singletons [21]. With the high perinatal loss rates there are often associated problems of postnatal grieving and bereavement. Families of women who give birth to babies after a multiple pregnancy may require additional social support.

Intrauterine growth restriction

Ultrasound is the primary tool for monitoring growth in multiple pregnancies for several reasons. The risk of IUGR (~25%) is higher than in singleton pregnancy, and in two-thirds of cases growth will be discordant (affecting one twin only). In addition, abdominal palpation and symphysis–fundal height measurement are unreliable as indices of growth in individual fetuses as they reflect total intrauterine growth.

There is no proven agreement on the ideal frequency of ultrasound examination. However, it is common policy to scan dichorionic twins at up to 4-weekly intervals from 24 weeks' gestation with or without Doppler measurements as indicated. Monochorionic twins are often scanned more frequently, at 2-weekly intervals, from 16 weeks onwards, as recommended by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) practice guideline. At this gestational age, there is significant overlap in diagnosis between early twin–twin transfusion syndrome and selective IUGR. There is controversy as to whether singleton or twin biometric charts should be used. The former appears more sensible, as twins have a higher risk of IUGR with potential morbidity and the use of twin charts thus seems akin to using separate charts for other high-risk groups. Furthermore, increasing emphasis is placed on growth profile and fetal condition (i.e. liquor volume estimation and umbilical artery Doppler velocimetry). Many centres use the measurement of discordancy in estimated fetal weight (EFW, which can be estimated using varied ultrasound parameters) as an index of discordant IUGR:

$$\mathrm{EFW} = 100 \times \left(\mathrm{EFW}_{\mathrm{larger}} - \mathrm{EFW}_{\mathrm{Smaller}}\right) \Big/ \mathrm{EFW}_{\mathrm{larger}}$$

This parameter has some predictive value in monochorionic twins for bad outcome in feto-fetal transfusion syndrome and stillbirth [22], but in dichorionic twins it is a relatively poor predictor of perinatal death [23].

The standard principle of management of IUGR (i.e. delivery when the risks of continued intrauterine life outweigh those of extrauterine existence) needs modification in twin pregnancy to account for the risks to both twins. The latency between absent end-diastolic flow velocity in IUGR in twins is longer before 'pre-terminal' factors precipitate delivery than in singleton pregnancies. In addition, this latency is longest in monochorionic twins. However, careful and specialist surveillance of such pregnancies using cerebral, peripheral and intracardiac arterial and venous Doppler velocimetry is required. For example, cessation of fetal growth with pre-terminal arterial and venous Doppler studies may warrant delivery at 26 weeks in a singleton fetus. However, discordant IUGR at such an early gestation in dichorionic twins might better be managed by allowing the severely affected IUGR fetus to die *in utero*, sparing the healthy fetus the risks of iatrogenic prematurity. Such risks and the balancing of decision-making are always difficult and should be individualized. Decisions should be made in concert with parents and multidisciplinary teams (including neonatologists).

In monochorionic twins, such decisions are even more complex. There is some evidence that the presence or absence of umbilical artery Doppler flow during diastole is indicative of prognosis. Positive end-diastolic velocities indicate the best prognostic group when there is significant discordancy between monochorionic twins in terms of growth. Absent end-diastolic velocity indicates an intermediate risk group and so-called intermittent absent end-diastolic velocity indicates the worst prognostic group and, in particular, the worst outcomes in terms of perinatal morbidity [24]. Indeed, in

monochorionic twin pregnancies complicated by IUGR in one fetus, there is evidence that the 'larger' twin may have the highest morbidity in terms of neurodevelopmental sequelae. In some cases (of early onset) it may be necessary to consider selective cord occlusion rather than delivery of the whole pregnancy (depending on the gestational age of diagnosis). However, these again are difficult decisions evoking clinical complexity and parental anxieties. Management in a tertiary centre is therefore vital and individual discussions relating to procedure-related morbidity and mortality are essential.

Preterm labour

Multiple pregnancies contribute disproportionately to preterm deliveries. Recent data indicate that, overall, 52.2% of multiple births deliver before 37 weeks and 10.7% prior to 32 weeks [25]. This is the major cause of neonatal death in multiple pregnancies: mortality rates are up to seven times higher in twins than singleton pregnancies; in triplets and higher-order pregnancies, rates of nearly 40 per 1000 live births have been recorded [26]. The median gestational ages at delivery in twins and triplets is 37 and 34 weeks, respectively. However, the proportion of these pregnancies delivering before 30 weeks (twins 7%, triplets 15%) is much more concerning because of the associated long-term morbidity. Parents should be informed of the symptoms and signs of threatened preterm labour and the advisability of early presentation. The stimulus to this increased risk is not clearly defined. Certainly (as in polyhydramnios) there is increased uterine distension (i.e. stretch), which may influence autocrine and paracrine intramyometrial processes. There is also focus on the potential maternal–fetal endocrine interaction, which may predispose to this increased risk.

There is little evidence that the screening techniques available are highly predictive of preterm delivery (although some demonstrate promise); however, more reliable identification of twin pregnancies at risk of preterm birth may improve outcome if effective interventions are used. Management of preterm labour in multiple pregnancies differs little from that of singletons, except that the consequences of prematurity affect a greater number of babies. The following discussion concentrates on those aspects which appertain especially to multiple pregnancies.

Prediction

The prediction of preterm labour in twins and multiple pregnancies is as problematic as it is in singletons. One of the most promising methods of prediction of spontaneous labour in twins is the measurement of maternal cervical length using transvaginal ultrasound. A systematic review of 11 studies in the published literature (1436 pregnancies) has indicated the potential efficacy of cervical length in predicting risk of spontaneous preterm delivery in twins. Between 23 and 24 weeks' gestation, the mean maternal cervical length is similar to that of singleton pregnancies (38 mm). At this gestation, a cervical length of 25 mm or less will have a positive summary likelihood ratio of 5.02 (95% CI 3.21–7.61) and a negative summary likelihood ratio of 0.75 (95% CI 0.54–106) for delivery prior to 34 weeks. This correlates with a change from pretest probability of preterm birth of 18.5% to a post-test probability of 14.2% (12.9–15.9) with a negative test and 47.6% (38.9–56.4) with a positive test [27].

The use of home uterine activity monitoring or fetal fibronectin estimation [28] has not been demonstrated conclusively to be useful in prediction and therefore cannot be advocated.

Prevention

Preterm labour in a multiple pregnancy (as in polyhydramnios) is attributed to over-distension ('stretch') of the uterus. Accordingly, there is no specific preventive measure (aside from fetal reduction in higher-order multiple pregnancies as discussed below).

Although hospitalization for bed rest has been widely practised in the past, there is little evidence to support its use. Critical appraisal of the literature and meta-analysis of four randomized controlled trials indicate that bed rest in twins significantly increases the chances of preterm delivery, with a trend to greater perinatal mortality [29]. In contrast, a single randomized controlled trial in triplets demonstrated a non-significant trend to less premature delivery and fewer neonatal deaths but was based on a very small number of cases [30].

Meta-analysis of seven randomized controlled trials demonstrated that prophylactic β_2-sympathomimetic therapy was of no benefit in preventing preterm labour in twin pregnancies [31]. This was not surprising given its lack of efficacy in singleton pregnancies and is presumably due to tachyphylaxis. As in singleton pregnancies, this therapy is no longer used. In addition, cervical cerclage, and most recently vaginal progesterone therapy, has not been shown to be helpful and indeed may actually be harmful [32]. Indeed, an individual patient-level meta-analysis of randomized trials of cervical cerclage in women with a 'short' cervix (on ultrasound at 20–23 weeks) indicated an increased risk of preterm delivery prior to 35 weeks [33].

Most contemporary focus has fallen on the role of maternal administration of progesterone in potentially

reducing the risk of preterm delivery. The Study Of Progesterone for the Prevention of Preterm Birth In Twins (STOPPIT) was a randomized, double-blind, controlled trial to assess the role of daily vaginal progesterone (90 mg) for 10 weeks from 24 weeks' gestation [32]. This study indicated that progesterone did not reduce the composite outcome risk of delivery or intrauterine death before 34 weeks in women with twin pregnancy. This effect was independent of chorionicity (although there was a trend towards worsening of outcome in monochorionic twins). Such findings are in concordance with other studies demonstrating no efficacy [34,35], in which progesterone was administered as intramuscular 17-hydroxyprogesterone caproate (250 mg). Despite these findings, individual patient data analysis has indicated that vaginal progesterone may be effective in the reduction of adverse perinatal outcome in women with a cervical length of 25 mm or less; however, further research is warranted to confirm this finding [36].

Recently, there has been interest as to whether physical interventions, such as the fitting of an Arabin cervical pessary, reduces the risk of preterm birth in twin pregnancies with a short cervix (<25 mm). A recent study, performed under the collaborative umbrella of the Fetal Medicine Foundation found no significant improvement in the risks of preterm birth in the intervention group (compared to the conservative group).

As such, there is no evidence that prophylactic measures, either physical or pharmacological, prevent spontaneous preterm labour in multiple pregnancies.

Management

The use of β_2-sympathomimetic infusions in multiple pregnancy, along with steroids and fluid overload, are known risk factors for the rare but potentially fatal complication of pulmonary oedema. As in singleton pregnancies, such active tocolysis has all but been abandoned. Equally, tocolysis with maternally administered oral nifedipine or intravenous atosiban (an oxytocin receptor antagonist) only leads to a relatively modest prolongation of gestation and studies informing efficacy of use in multiple pregnancies are sparse. Certainly, as in singleton pregnancies, the use of such therapy is usually only advocated to allow prophylaxis with corticosteroids. This is exemplified in a retrospective cohort study of 432 twin pregnancies (1982–1986), which noted that 54% of twins were born after spontaneous preterm delivery; of these, 23% were associated with preterm premature rupture of membranes and a further 23% were iatrogenic [37]. In these iatrogenic indications, 44% were secondary to maternal hypertension, 33% secondary to fetal compromise and/or IUGR, 9% secondary to antepartum haemorrhage and 7% associated with one or more fetal deaths.

Maternal glucocorticoids have been clearly demonstrated to reduce the incidence of respiratory distress syndrome and its perinatal consequences in numerous randomized controlled trials [38]. However, only one uncontrolled study with separate data from multiple pregnancies suggested reduced benefits from antenatal corticosteroid administration in multiple pregnancies compared with singleton pregnancies [39]. The relative 'resistance' of multiple pregnancies to pulmonary surfactant maturation compared with singleton pregnancies has been postulated and has raised the possibility that a larger dose is required in multiple pregnancies but this remains to be objectively tested [40].

A report by Holmes *et al.* [41] has indicated that among 18% of 325 twin pregnancies delivering before 34 weeks' gestation, 70% did so within 24 hours of presentation, the usual interval required for maximal corticosteroid efficacy. It has therefore been proposed that corticosteroids be administered prophylactically. Such a proposal is controversial. It is certainly theoretically possible that this could do more harm than good, as such therapy would potentially need to be administered on a weekly basis and there is no evidence that repeat doses of steroids are of increased value. Furthermore, and not withstanding the safety of steroids in follow-up studies, there remain concerns about the potential adverse fetal effects of repeated steroid courses on glial formation and hippocampal development in children exposed *in utero*.

Complications of monochorionic twinning

Monochorionic twinning, which complicates 20% of all twin pregnancies, may be said to be a congenital anomaly of the placenta where the inter-twin circulations communicate through placental vascular anastomoses. These occur in almost all monochorionic twin pregnancies. Bidirectional superficial arterial–arterial or venous–venous anastomoses may potentially compensate for any haemodynamic imbalance created by deep unidirectional arterial–venous anastomoses. Relatively small inter-twin 'transfusions' are thus likely to be a normal physiological event in monochorionic twins. However, the imbalance of flow between twins may well be pathological and is always a potential risk in such pregnancies (increasing perinatal mortality considerably).

Acute feto-fetal transfusion

When one of a monochorionic twin dies *in utero*, there is a significant risk of ischaemic damage predominantly to

the fetal brain (18% in monochorionic twins), although there are reports of damage to pulmonary and hepatic systems, intestinal atresia, limb reduction and renal necrosis. For twin pregnancies overall, a recent systematic review derived a risk of 9% (95% CI 6–13) for neurological abnormality [42]. Death of one of a monochorionic twin substantially increases the risk of co-twin demise *in utero*. Again, a recent systematic review has reported that surviving monochorionic twin fetuses have a six times greater risk of intrauterine fetal death (12%) following single fetal demise after 20 weeks' gestation than initially surviving dichorionic twins (4%; OR 6, 95% CI 1.8–19.8) [42]. Gestational age at the time of intrauterine fetal death influences the extent and type of fetal brain injury. Single intrauterine fetal death after the second trimester can lead to periventricular leucomalacia, multicystic encephalomalacia or germinal matrix haemorrhage. In the third trimester of pregnancy, subcortical leucomalacia, basal ganglion damage or lenticulostriate vasculopathy may develop. There is debate about whether development of such central nervous system (CNS) anomalies are gestationally dependent. However, the long-term morbidity of such an event prior to 14 weeks is controversial and the association less pronounced.

Unlike dichorionic twins, discordant fetal compromise with risks of intrauterine demise in one twin have to be balanced against the potentially adverse effects of iatrogenic prematurity in the co-twin if delivery needs to be expedited in monochorionic twins. A balanced and sometimes complex discussion may ensue, not only to prevent intrauterine death in the potentially compromised twin but also to prevent sequelae in the co-twin. However, once single intrauterine fetal death has occurred in a monochorionic twin, delivery should not be immediate. The pregnancy should be evaluated for secondary sequelae, initially by the use of ultrasound. Such assessment should be within a tertiary fetal medicine centre. The assessment often includes the use of sequential ultrasound scanning (with increasingly the adjuvant investigation of fetal MRI) to prospectively evaluate the presence of CNS neuropathology that may develop up to 4 weeks after the sentinel event.

Chronic feto-fetal transfusion

Chronic feto-fetal transfusion syndrome (FFTS) occurs in approximately 15% of monochorionic pregnancies (twins and triplets). It is responsible for up to 40% of deaths in monochorionic twins, where it is more commonly known as twin–twin transfusion syndrome (TTTS). The underlying pathophysiology involves chronic shunting of blood from the donor twin to the recipient twin, leading to an inter-twin haemodynamic imbalance. Such a vicious circle of events leads to the 'donor' twin becoming hypoperfused, growth restricted and with associated oliguria and the development of anhydramnios. The co-twin, the 'recipient', becomes polyuric with often severe polyhydramnios and a hyperdynamic circulation that may cause both diastolic and systolic cardiac dysfunction, ending in the development of hydrops fetalis and death (if no treatment ensues). FFTS/TTTS is diagnosed when there is gross discordancy in amniotic fluid volume in monochorionic twins, with polyhydramnios in the recipient and anhydramnios in the donor sac. It constitutes severe disease if the onset is prior to 26 weeks. A staging system has been described and is useful in annotating the condition in a consistent manner but does not always denote a logical order of disease progression (Table 21.1). In general terms, the prognosis is better in early-stage disease (stages I and II) and worse in more advanced disease (stages III and IV). However, cardiac dysfunction may be present in up to 20% of fetuses with stage I disease (by Quintero staging) and as a consequence complicated monochorionic twin pregnancies may progress to the most adverse stages without warning.

Untreated, perinatal loss rates in the mid-trimester approach 95%. The principal clinical problem is severe polyhydramnios, which may be associated with premature rupture of membranes or preterm labour (or a combination of these) usually before 26 weeks' gestation. In addition, differences in inter-twin haemodynamics may be associated with single or double twin demise (with antecedent CNS morbidity). Fetoscopic laser ablation/coagulation of the inter-twin communicating vessels has been demonstrated by critical appraisal of the literature to be the optimal treatment in FFTS/TTTS [43]. This is therefore the treatment of choice in monochorionic twin pregnancies presenting with this complication prior to 26 weeks' gestation. Modification of the fetoscopic laser technique, using the SOLOMON method to ablate across the equatorial plane between arteriovenous anastomoses previously ablated using the selective sequential method, further reduces neonatal morbidity

Table 21.1 Staging system for FFTS/TTTS.

Stage I	Polyhydramnios /oligohydramnios with bladder of the donor still visible
Stage II	Bladder of the donor not visible
Stage III	Presence of absent end-diastolic flow velocity in the umbilical artery, reverse flow in the ductus venosus or pulsatile umbilical venous flow in either twin
Stage IV	Hydrops in either twin
Stage V	Demise of one or both twins

and, in particular, the complication of twin anaemia polycythaemia sequence (TAPS) [44].

Twin anaemia polycythaemia sequence

The incidence of TAPS occurring spontaneously in monochorionic diamniotic twins is up to 5%. However, it may complicate up to 13% of cases of TTTS following laser ablation. TAPS is believed to be due to the presence of miniscule arteriovenous anastomoses (<1 mm) which allow slow transfusion of blood from the donor to the recipient, leading to highly discordant haemoglobin concentrations at birth (Fig. 21.1). The postnatal diagnosis of TAPS is based on the finding of chronic anaemia (including reticulocytosis) in the donor and polycythaemia in the recipient. The criteria for diagnosis include a difference in haemoglobin concentration between the twins of more than 80 g/L and reticulocyte count ratio greater than 1.7 or small vascular anastomoses (<1 mm in diameter) in the placenta. The prenatal diagnosis of TAPS is based on the finding of discordant middle cerebral artery (MCA) Doppler abnormalities, including an MCA peak systolic velocity (PSV) more than 1.5 multiples of the median (MoM) in the donor, suggesting fetal anaemia, and an MCA PSV less than 1.0 MoM in the recipient, suggesting polycythaemia. Additional ultrasound findings in TAPS include differences in placental echogenicity and thickness, with a bright thickened section for the donor twin and an echolucent thin recipient section. The polycythaemic twin might have a 'starry sky' appearance of the liver due to diminished echogenicity of the liver parenchyma and increased brightness of the portal venule walls.

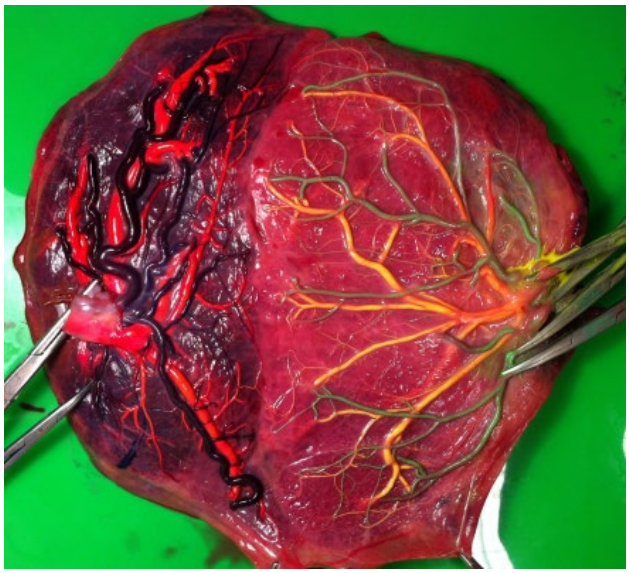

Fig. 21.1 TAPS is believed to be due to the presence of miniscule arteriovenous anastomoses (<1 mm). *Source:* Dr E. Lopriore. Reproduced with permission of Dr E. Lopriore. (*See also colour plate 21.1*)

The outcome of twin pregnancies complicated by TAPS is variable. Severe TAPS may result in intrauterine death of both twins. At the other end of the spectrum, mild TAPS may still allow the birth of two healthy neonates (apart from having a significant haemoglobin difference between the two). It appears that the main neonatal morbidity consists of anaemia (requiring transfusion) and polycythaemia (possibly requiring partial exchange transfusion). However, cases of severe cerebral damage have been reported in neonates with TAPS. Recent evidence suggests that in monochorionic twins complicated by TAPS, the risk of neurodevelopmental delay is increased (20%) Therefore, brain imaging during the third trimester and neurodevelopmental assessment at the age of 2 years are recommended.

The management options depend on the gestational age at assessment, parental choice, the severity of the disease and technical feasibility of intrauterine therapy. Therefore, the management of twin pregnancies complicated by TAPS should be individualized. The commonest options include conservative management, early delivery, laser ablation or intrauterine transfusion (IUT) for the anaemic twin, combined IUT for the anaemic twin and partial exchange transfusion to dilute the blood of the polycythaemic twin. In order to screen for TAPS, the MCA PSV should be measured from 20 weeks onwards in both fetuses, and during the follow-up of treated TTTS cases. Prevention of TAPS by modification of the fetoscopic laser ablation technique remains the best way to prevent morbidity.

Twin reversed arterial perfusion sequence

This rare condition (complicating 1 in 35 000 pregnancies) arises in monochorionic twins with two umbilical cords often linked by large arterio-arterial anastomoses. Flow from one, the 'pump' twin, supplies the other, the 'perfused' twin, in a retrograde fashion. The perfused twin almost always has associated significant congenital malformations, often including a rudimentary heart and aorta. The term 'twin reversed arterial perfusion (TRAP) sequence' is preferred, so named because reversed deoxygenated arterial supply is associated with only rudimentary development of the upper body structures within the fetus. Thus the acardiac twin is perfused by its co-twin (the pump twin) via the intertwin placental anastomoses. Perinatal mortality in the pump twin in untreated cases is approximately 50% due to associated polyhydramnios and cardiac failure that may ensue [45]. Although polyhydramnios may be elevated by amnioreduction, definitive treatments

that cause occlusion of the perfused (acardiac) twin's cord or rudimentary aorta may be achieved by a variety of fetoscopic or ultrasound-guided techniques (intrafetal laser ablation, radiofrequency thermal ablation and fetoscopic cord occlusion). There is still controversy whether to offer intervention electively, or only when signs of cardiac compromise occur, and at what gestational age intervention is best performed. Earlier intervention appears to be associated with a more advanced gestational age at birth. With careful case selection improved outcome for the pump twin is described in up to 85% [46,47]. Most significant complications include co-twin demise or hypoperfusion (with cerebral morbidity) and/or preterm ruptured membranes.

Monoamniotic twins

Of monozygotic twins, 1% lie in the same sac (monoamniotic) exposing them to the risks of cord entanglement. This may prove problematic most commonly (but not exclusively) in the intrapartum period. For this reason most cases are delivered by elective caesarean section. These twins also have higher reported overall perinatal mortality rates of approximately 30%. This appears largely related to the risk of sudden unexplained intrauterine death (often before 34 weeks' gestation). Therefore the timing of delivery of these twins is controversial. Anecdotal and cohort studies have suggested that use of prophylactic maternal sulindac (cyclooxygenase-2 inhibitor) to reduce fetal urine output and thus amniotic fluid volume reduces the risk of cord entanglement [48]. In combination with this, others have advocated hospitalization from 26–28 weeks onwards and elective premature delivery of these twins between 32 and 34 weeks' gestation. The most recent evidence indicates that the risk of these events are relatively low, with close outpatient surveillance being recommended rather than very early elective delivery [49–51]. However, the consensus view suggests a course of prophylactic corticosteroids followed by elective caesarean delivery by 33 weeks in these rare twin pregnancies.

Labour and delivery of twins and multiple pregnancies

Whatever the chorionicity of the twin pregnancy, it is best practice for intrapartum care to be discussed and a multidisplinary plan set out in the early third trimester of pregnancy. The indications for elective caesarean section are relatively few. Congenital anomalies associated with significant risk of cephalopelvic disproportion (including conjoined twins) would be an obvious indication and potentially monoamniotic twins would be another (see below). In addition, monochorionic pregnancies, complicated by placental anomalies associated with increased perinatal mortality (i.e. TTTS or TRAP), are generally delivered at 34–36 weeks and usually by caesarean section [2].

Perinatal mortality increases slightly after 38 weeks' gestation in twins and there are therefore many obstetricians who elect for delivery then. However, there are no data to indicate whether or not this rise in mortality applies to twins whose growth and well-being are known to be normal on ultrasound. Induction of labour is not contraindicated in twin pregnancies. Mode of delivery is decided on standard principles based on presentation of the first twin (cephalic in 70%, breech in 30%) and the documentation of optimal fetal growth and well-being. Those with previous caesarean section scars are probably best delivered by repeat caesarean section because of the greater risk of scar dehiscence/rupture due to both uterine distension and intrauterine manipulation of the second twin. Recent data have indicated that a planned elective caesarean section may achieve an up to 75% reduction in the risk of perinatal death compared with vaginal delivery by reducing risks of acidosis and anoxia (especially to the second twin) [52–55].

Caesarean section has been advised when the first twin is breech, which would obviate the rare risk of interlocking twins and entrapment of the head of a presenting breech above the second cephalic twin. The use of intrapartum ultrasound may allow detection of such problems with early recourse to emergency caesarean section. However, there is no evidence that vaginal delivery of a presenting breech that would otherwise satisfy criteria for vaginal delivery (EFW less than 3.5–4 kg, flexed head and not footling) is inappropriate in selected cases. The presentation of the second twin is of no importance until after birth of the first.

Even in twins where the first twin is cephalic presentation (at term), there may be the need for obstetric delivery of the second twin, with potentially an increased risk of perinatal morbidity. However, a Cochrane review (on delivery of the second twin not presenting cephalically) indicates that caesarean section increases maternal febrile morbidity without improving neonatal outcome [56]. This awaits critical appraisal.

For vaginal delivery, continuous cardiotocography of both twins is best achieved by a combination of internal and external monitoring on a dual-channel recorder. An intravenous line is sited and maternal blood drawn for group and save, in view of the increased incidence of caesarean section and postpartum haemorrhage.

Augmentation of labour with oxytocin may be used as in singletons. An epidural anaesthetic is strongly advised in case of the unexpected need for internal manipulation of the second twin. If one is not sited, an anaesthetist will be required at delivery with early recourse to spinal or even general anaesthesia. The place of delivery is debatable but there is an increasing trend for twins to be delivered in operating theatres so that there is immediate redress to emergency caesarean section if necessary.

Delivery of the first twin proceeds as for a singleton. Its cord is clamped to prevent fetal haemorrhage (from the second twin along any placental anastomoses). An experienced obstetrician discerns the presentation of the second twin, either by abdominal or vaginal examination or, increasingly, by the use of transabdominal ultrasound. Oblique or transverse lies are then converted to a longitudinal lie by external version and held in place by an assistant. Uterine contractions should be monitored and if necessary augmented using oxytocin. The membranes should be left intact to facilitate version. External cephalic version may be used to manipulate the fetal head over the pelvic inlet. Internal cephalic version is preferred as a primary procedure by many experienced obstetricians, as it seems to be associated with a higher success and lower complication rate than external cephalic version. One or preferably both feet are grasped and brought down into the vagina followed by an assisted breech delivery with contractions and maternal effort.

Historical series suggest that the risk to the second twin is increased the greater the delay until delivery. Classically, intervals of greater than 30 min are acceptable providing the cardiotocograph is satisfactory and the presenting part is descending. Uterine inertia with a longitudinal lying second twin is corrected by oxytocin infusion. This is a not uncommon occurrence in the intrapartum management of twins.

Fetal distress may be managed by ventouse delivery, even if the head is high or breech extraction. The already stretched vaginal tissues after the birth of the first twin allow these procedures in circumstances where they would normally be contraindicated. Caesarean section for second twin is occasionally indicated for disproportion, usually where the second twin is much bigger than the first. An oxytocin infusion is given prophylactically in the third stage of labour to minimize the risks of postpartum haemorrhage.

There is some evidence that the risk of perinatal loss is greater at the end of the third trimester in monochorionic twins compared with dichorionic twins. However, there is insufficient evidence that elective delivery before 36 weeks improves outcome. Most current consensus-based guidelines recommend delivery between 36 and 38 weeks' gestation [3].

Higher-order multiples

Perinatal and maternal risk increases exponentially with increasing fetal number. Most higher-order multiple pregnancies are the result of assisted reproductive technologies and thus should be preventable with closer monitoring of follicular response and single (or, at most, two) embryo transfers in IVF therapy. Indeed, there are proven arguments for restricting the number of embryos transferred to one in order to minimize twin and triplet risk, and this course of action appears to have limited adverse effect on live birth rates when more cycles are allowed [57,58].

Every woman/couple with a higher-order multiple pregnancy should have a discussion with a senior obstetrician relating to increased maternal and perinatal risks. This should involve the discussion and option of multiple fetal pregnancy reduction. In addition to perinatal mortality rates, parents should be counselled as to the mean gestational age at delivery (33 weeks for triplets, 31 weeks for quadruplets). In addition, 10% of triplets and 25% of quadruplets deliver before 28 weeks' gestation, with severe neurological sequelae rates of 12% and 25% (respectively) in survivors [59]. The chief perceived disadvantage of multiple fetal pregnancy reduction, usually accomplished by administration of a percutaneous fetal intrathoracic injection of abortifacient (commonly potassium chloride), is complete miscarriage. International registry data demonstrate that this is lowest with reduction to twins, with rates for starting triplets and quadruplets of 7% and 15%, respectively [60]. There is now a consensus that multifetal pregnancy reduction between 10 and 12 weeks should be recommended for quadruplets and higher multiples so as to lower both maternal and fetal risks.

The situation with triplets has been more controversial, with many considering this a social issue for parents. However, recent data indicate that in a fetal reduction group ($N = 482$) compared with an expectantly managed group ($N = 411$), the rate of miscarriage was significantly higher (8.1% vs. 4.4%, RR 1.83, 95% CI 1.08–3.16; $P = 0.036$) and the rate of preterm delivery lower (10.4% vs. 26.7%, RR 0.37, 95% CI 0.27–0.51; $P < 0.0001$) [61].

Higher-order multiple pregnancies should be managed in tertiary perinatal centres with a fetal medicine service. Care is almost always individualized. Management is along standard lines for twins but with greater emphasis on preventing preterm delivery and on monitoring fetal growth and well-being. Although there have been successful reports of triplets and even quadruplets being delivered vaginally, most higher-order pregnancies are now delivered by caesarean section. This alleviates difficulties with electronic fetal monitoring, avoids

unrecognized hypoxaemia (especially given the high incidence of IUGR) and prevents birth trauma from manipulative delivery of non-cephalic presenting fetuses. Given the higher incidence of preterm labour in the midtrimester, the option after delivery of the presenting fetus of conservative management with passive retention of residual fetus to prolong gestational age should be considered [62].

The concept of a multiple pregnancy clinic

Increasingly, there is consensus opinion that the management of multiple pregnancies should be concentrated in a designated 'multiple pregnancy clinic' with experienced midwifery and obstetric discussion and decision-making and with access to immediate diagnostic ultrasound and multidisciplinary opinions (i.e. anaesthetic, neonatal paediatric and psychological services). This care should be holistic in approach (in the widest sense) and could be organized regionally or in subregional centres depending on local population needs and numbers. Such clinics would allow the timely diagnosis of complications of multiple pregnancy along with an individualized plan of care for the prenatal, intrapartum and postnatal periods in women with multiple pregnancies.

Conclusion

The rate of multiple pregnancies appears to be rising, a phenomenon elevated by increased maternal age and the use of assisted reproduction technologies. Even so, the greatest proportion of multiple pregnancies are twins. Obstetric care should be undertaken with specialist teams in a multiples clinic so that prenatal care (influenced by chorionicity), intrapartum care and postnatal well-being may be discussed and planned prospectively. Such developments will hopefully minimize the increased maternal and perinatal risks that exist in such complex pregnancies.

Summary box 21.1

- The prevalence of twin and triplet pregnancies is increasing worldwide. This is associated with a significantly increased risk of maternal and perinatal adverse outcomes in such pregnancies.
- The modification of artificial reproduction techniques with transfer of single embryos reduces significantly (but not completely) the risk of multiple pregnancy.
- Chorionicity is an important factor to determine using ultrasound in the first trimester. Monochorionic twin pregnancies are associated with an increased risk of perinatal mortality and morbidity.
- Multiple pregnancies should be managed in designated multidisciplinary clinics where a holistic approach to pregnancy management can be adopted. This includes the discussion and planning of intrapartum care.
- In the postnatal period, women who have children from multiple pregnancies require increased support as they are at increased risk of emotional/psychological morbidity and this may also lead to socioeconomic stress.

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Part 5

Birth

22

Normal Mechanisms in Labour

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Parturition

The onset of labour is the result of a cascade of intrauterine biochemical events that culminates in cervical softening and dilatation and increased uterine contractility (Fig. 22.1). Alterations in the timing of birth are the leading cause of neonatal mortality and morbidity. The mechanisms involved in the onset of labour in women remain elusive and as a consequence the prediction and management of preterm labour are poor, resulting in potentially severe complications for the newborn, distress to the parents and high medical costs. Spontaneous preterm labour may or may not result from the same endocrine and intracellular pathways as the physiological onset of labour at term. Despite considerable improvements in special care baby units, the perinatal mortality rates for preterm birth remain steady, and there is a wide range of both short-term and long-term complications and handicap in the surviving infants [1,2]. On the other hand, our limited understanding of the physiological mechanisms can make induction of labour difficult. More than 25% of pregnant women will undergo an induction of labour for prolonged gestation (41 or more weeks), hypertensive disorders of pregnancy, pre-labour rupture of membranes, or other indications [3]. A combination of vaginal prostaglandins and intravenous oxytocin is a common method for induction of labour; moreover, oxytocin is used for augmentation of contractions after labour of spontaneous onset. Stimulation of contractility carries the risk of failure and increased chance of delivery by caesarean section: in a study of reasons for caesarean section in labour in nulliparous women, the majority (70%) were due to 'failed induction/dystocia', 29% were indicated for fetal distress and 1% were due to acute clinical emergencies (e.g. cord prolapse, placental abruption) [4]. Studies involving more than two million women in several countries show that the rates of caesarean section in induction of labour at term are 30–40%, contributing to a 50% increase in caesarean section deliveries over the past decade [5]. This compelling epidemiological evidence shows that induction of labour at term is a major contributor to maternal and neonatal morbidity and emphasize the need to improve our understanding of human parturition so that we can develop more efficient ways of inducing and augmenting labour.

Summary box 22.1

The ability of obstetric care providers to predict and prevent preterm labour and birth is poor, resulting in potentially severe complications for the newborn, distress to the parents and high medical costs.

Fetal signals

Fetal surfactant (a mixture of lipids and apoproteins) is a signal for parturition because it provides a link between fetal lung maturation, which is essential for extrauterine life, and the onset of labour through stimulation of prostaglandin production. Amniotic fluid surfactant, which reflects fetal lung maturation, is an important intrauterine source of arachidonic acid, and increases the rate of prostaglandin synthesis in the fetal membranes. This effect is due to the release of fatty acids, including arachidonate, from the lipids of fetal surfactant by the sequential action of phospholipase C and diglyceride lipase activities in amniotic fluid and by the transfer of arachidonate from surfactant phosphatidylcholine to phosphatidylethanolamine and phosphatidylinositol in amnion cells [6]. These lipid pathways provide a link between the process of maturation of the fetus in preparation for birth and the labour-initiating prostaglandin activation.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

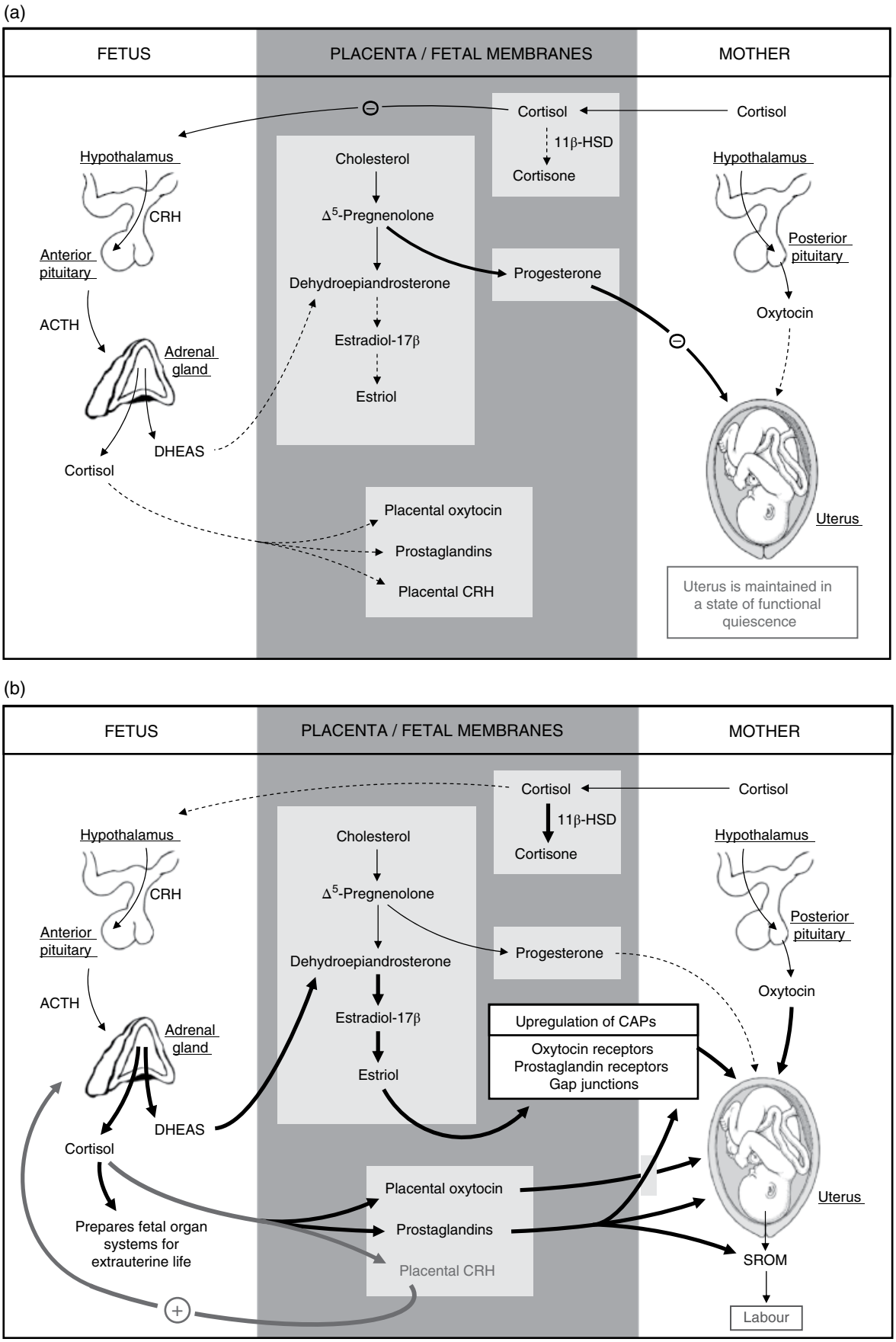

Fig. 22.1 Proposed 'parturition cascade' for the onset of labour at term. The spontaneous onset of labour at term is regulated by a series of paracrine/autocrine hormones acting in an integrated parturition cascade. The factors responsible for maintaining uterine quiescence throughout gestation (a) and for the onset of labour at term (b) are shown. This includes the withdrawal of the inhibitory effects of progesterone on uterine contractility and the recruitment of cascades that promote estriol production and lead to upregulation of the contraction-associated proteins within the uterus. ACTH, adrenocorticotrophic hormone (corticotrophin); CAPs, contraction-associated proteins; CRH, corticotrophin-releasing hormone; DHEAS, dehydroepiandrosterone sulfate; 11β-HSD, 11β-hydroxysteroid dehydrogenase; SROM, spontaneous rupture of membranes.

In addition to the effect of its lipid components, fetal surfactant is likely to be involved in the process of parturition through the effects of the surfactant-associated proteins SP-A and SP-D. These are multimeric molecules containing C-type lectin domains and collagen-like regions. SP-A and SP-D concentrations in amniotic fluid rise sharply from about 26 weeks' gestation to term and the proteins are found in the fetal membranes and decidua [7]. SP-A and SP-D perform innate immune functions in the lungs via macrophage activation, control of inflammation, and clearance of microbes and apoptotic and necrotic cells. These proteins have an important role in non-immune defence mechanisms in the amniotic cavity. SP-A interacts with toll-like receptors TLR-2 and TLR-4 on macrophages and increases the expression of interleukin (IL)-1β and nuclear factor (NF)-κB [8]. In mice, intra-amniotic injection of SP-A provokes premature delivery by a process which involves NF-κB activation [9]. SP-A has direct stimulatory effects on human myometrial cells through activation of NF-κB and mitogen-activated protein (MAP) kinase pathways [10]. On the other hand, SP-A appears to inhibit proinflammatory cytokine expression in the amniotic epithelium [11]. The role of SP-D in pulmonary host defence, particularly in the lungs of premature newborns, is well established. SP-D binds DNA from bacteria and on the surface of dying cells, enhancing the clearance of nucleic acids and limiting inflammatory reactions at sites of infection or apoptosis. SP-D is localized in the endometrium of the secretory phase and in placental villi and may have a role in the prevention of intrauterine infections at the time of implantation and during pregnancy [12].

Steroids

Steroids have complex and versatile metabolic pathways, with complementary distribution of enzyme activities in the different compartments of the human fetoplacental unit [13]. The fetal adrenal glands and liver, the maternal adrenal and liver and the placenta operate as integrated steroidogenic organs in pregnancy [14]. The fetal adrenals produce large amounts of dehydroepiandrosterone (DHA) and DHA-sulfate which, together with 16α-hydroxy metabolites from the fetal liver, are essential precursors for the synthesis of oestrogens in the placenta [15]. Moreover, fetal pregnenolone sulfate contributes significantly to placental progesterone production, complementing progesterone synthesis from maternal cholesterol. The complexity of the steroid metabolome in fetal and maternal blood has been reviewed elsewhere [16]. There are many steroid metabolites in the circulation reflecting fetal organ development and maternal responses for parturition. For example, the levels of conjugated androstenediol and of 16α-hydroxyandrostenedione rise sharply in fetal blood in the last few weeks of pregnancy [15]. On the other hand, several reduced progesterone metabolites including 5β-dihydroprogesterone, which bind to progesterone receptors and may contribute to uterine quiescence, decrease in late pregnancy, providing a functional progesterone withdrawal [17]. The search for steroid signals for parturition is difficult, given the metabolic complexity and the multiplicity of cellular effects on uterine and cervical tissues; however, few areas of physiology offer such clear functional integration among fetal and maternal organs in late pregnancy.

Placental corticotrophin-releasing hormone (CRH) plays a key role in stimulating steroid synthesis in pregnancy, specifically the production of DHA and other steroid sulfates in the fetal zone of the fetal adrenal. Increasing CRH levels in the maternal circulation has been proposed as a predictor of parturition and preterm labour [18], but the performance is poor [19]. The predictive value of measuring multiple steroid compounds simultaneously during late pregnancy and around parturition is likely to be better than measuring CRH alone [16].

Inflammatory responses

Decidual activation

Decidual cells, especially tissue macrophages, may have a role in the mechanism of labour by promoting the synthesis and release of prostaglandins and proinflammatory cytokines [20]. Prostaglandins are the final common pathway for parturition in many species and synchronize uterine activation and cervical ripening through a highly integrated transport system and specific receptor signalling pathways in decidua and myometrium [21,22]. Moreover, the decidua provides a place of immune tolerance and defence to protect the fetus and the placenta from infections. The output of prostaglandin (PG)$F_2\alpha$ by human decidual cells is higher in samples obtained after labour than before the onset of labour, whereas the output of other prostaglandins (PGE_2, PGD_2) and their metabolites remains relatively constant [23]. The release of the PGF isomer 9α,11β-PGF_2 from placenta, amnion and choriodecidua into the amniotic fluid increases at term [24]. $PGF_2\alpha$ and 9α,11β-PGF_2 have direct effects on the myometrial cells of the uterus, increasing intracellular calcium and promoting contractions through the stimulatory FP receptor [25]. The reason for the selective increase in PGF release with labour is not clear, but it appears to involve the action of cytokines produced by macrophages that migrate and settle in the decidua where they have important regulatory roles in pregnancy. Macrophages exhibit remarkable plasticity and their behaviour is influenced by the tissue microenvironment. Proinflammatory cytokines (IL-1; tumour necrosis factor-α, TNF-α) have strong paracrine and autocrine effects on decidual macrophages promoting the upregulation of prostaglandin synthase enzymes [24,26].

In some women, the premature release of prostaglandins provoked by decidual infection or haemorrhage can lead to very early delivery (before 30 weeks' gestation) with devastating consequences for the baby [27,28].

Inflammation and the onset of labour

The cellular disruption of inflammation, especially in the setting of infection, can lead to uterine activation and labour, but it should not be accepted as the general mechanism for the spontaneous onset of labour. In a study of more than 200 pregnant women undergoing caesarean section at term, the intrauterine site most commonly associated with histopathological inflammation was the decidua [29]. When caesarean sections were elective and carried out before the onset of labour, the incidence of deciduitis was low (6%) whereas in women operated on after the onset of labour deciduitis was much more frequent (29%). This could be interpreted as a cause–effect relationship between inflammation and spontaneous labour; however, most of the women with inflammation (86%) were in a group with cervical dilatation of 5 cm or greater. Decidual inflammation may be a consequence or labour, rather than its cause [29]. Inflammation of the fetal membranes is much more common in preterm deliveries than at term. A recent study detected acute chorioamnionic inflammation in 30% of preterm pregnancies but only 5.1 % of term pregnancies [30], confirming previous observations that there is an inverse relationship between gestational age and the frequency of bacteria in the fetal membranes or histological chorioamnionitis [31]. Many acute-phase response genes increase in myometrium due to factors unrelated to labour (e.g. surgical trauma, hypoxia, underlying pathology); these changes are likely to be due to secondary inflammatory responses late in labour, rather than changes required for the onset of labour [32]. Inflammation may be a trigger for spontaneous labour in infection-associated preterm deliveries, but it should not be accepted as the underlying mechanism for the onset of labour at term. The continuing search for the physiological pathways of parturition in women is important. New perspectives into decidual function and the timing of birth have been presented, highlighting the complex interaction of biological factors (prostaglandins, cytokines, growth factors and reactive oxygen species), genetic predisposition and immune defence mechanisms in the regulation of human parturition [33].

Summary box 22.2

Prostaglandins are the final common pathway of the parturition cascade. Prostaglandins given by any route to any species at any stage of gestation will result in pregnancy termination.

Endogenous mediators

Role of oxytocin

There are many genes potentially involved in the regulation of uterine contractility whose expression is modulated by oestrogens, progesterone and other pregnancy hormones. Oxytocin (OXT) is a member of an ancient nonapeptide hormone system and it is widely used in synthetic form for the induction and augmentation of labour because it stimulates uterine contractions. The pulse frequency of OXT secretion increases during human labour [34] and there is general agreement that it is important during the puerperium to facilitate uterine haemostasis after delivery and to initiate lactation. However, the role of OXT in the initiation of parturition is less clear. The high sensitivity of the uterus to OXT in pregnancy is due to a significant increase in the concentration of myometrial oxytocin receptor (OXTR) compared with the non-pregnant uterus [35,36]. The OXT sensitivity of the uterus remains very high at term but there is no clear increase at parturition; labour begins with no preceding warning and no change in the sensitivity of the uterus to circulating levels of OXT [37]. OXT has several roles in human parturition: one promoting uterine contractility to facilitate delivery and to prevent postpartum haemorrhage, and other roles preparing the uterus for the initiation of labour. In addition to stimulating contractility through the phospholipase C/calcium pathway in myometrial cells, OXT activates transcription factors of the NFAT (nuclear factors of activated T cells) family in a calcineurin-dependent manner [38]. The calcineurin–NFAT signalling cascade lies downstream of many cell surface receptors, including G protein-coupled receptors (e.g. receptors for OXT and prostaglandins in myometrium) and receptor tyrosine kinases (e.g. receptors for growth factors and cytokines), providing points of convergence and amplification for hormones, growth factors and other endogenous mediators involved in the preparation of the uterus and the cervix for parturition. NFAT is involved in OXT-mediated stimulation of PTGS2 (prostaglandin-endoperoxide synthase 2, also known as COX2) expression in human myometrial cells, regulating the rate-limiting step in prostaglandin synthesis. Moreover, OXT induces PTGS2 expression and stimulates prostaglandin release in human myometrial and amnion cells through other pathways, including the NF-κB complex, providing a link with the uterine response to cytokines and other inflammatory stimuli [39]. The influence of OXT on calcium homeostasis in human myometrial cells highlights its importance in normal labour [40,41].

Oxytocin receptors

OXT is a potent stimulatory peptide and it has been proposed that an increase in the concentration of OXTR in the uterus may be a trigger for parturition [35]. The implication is that low levels of OXTR expression in myometrium may favour uterine quiescence during ongoing pregnancy. However, the concentration of myometrial OXTR is very high in late pregnancy and there is no evidence that it increases further at the onset of labour [42–44]. It may be argued that uncoupling or blocking of OXTR may be a mechanism to inhibit contractility until parturition. However, the sensitivity of the human uterus to OXT remains relatively unchanged during the last few weeks of pregnancy and does not increase before the spontaneous onset of labour [37]. Both OXT- and OXTR-deficient mice have normal pregnancies and deliveries [45,46]. The accumulated evidence in mice suggests that inhibition of OXTR function is not responsible for uterine relaxation in pregnancy, although OXT retains important roles in luteal function [47], nursing response [46] and social behaviour [45,48]. Nevertheless, the design of OXTR antagonists is seen as a good approach for the management of preterm labour in women, because these drugs have relatively high uterine selectivity and few side effects [41,49,50].

Epidermal growth factor

The concentration of epidermal growth factor (EGF) increases in amniotic fluid during pregnancy [51]. EGF concentrations in maternal blood range from 70 to 800 pg/mL [52], whereas in cord blood the levels are higher (500–3000 pg/mL) [53]. EGF has traditionally been studied as a critical factor in fetal maturation and more recently it has been implicated in the pathogenesis of pre-eclampsia [52]. However, the role of EGF as a physiological mediator in parturition is less well established. EGF stimulates PTGS2 expression in human amnion [54] and myometrial cells [55] and the mechanism has been investigated in some detail. EGF operates through a specific receptor (EGFR, the first member of the ErbB tyrosine kinase family), which is the target of several clinically approved anticancer agents. In human myometrial cells, EGF stimulates PTGS2 expression through interaction of EGFR with members of the mitogen-activated protein kinase family, namely MEK1/2 and ERK1/2. This effect requires activation of protein kinase C [55]. Interestingly, OXT stimulates ERK1/2 in myometrial cells through a mechanisms that may involve transactivation of EGFR by OXTR and the effect of calcium [56]. The effect of EGF, and possibly other growth factors and cytokines, on prostaglandin release and acute-phase responses in the uterus is mediated by steroid receptor co-activator interacting proteins and by transcription factors [57]. OXT and EGF can stimulate PTGS2 expression and prostaglandin release through receptor transactivation and convergence of intracellular signals. These cooperative effects facilitate the preparation for labour in a physiological manner. Moreover, these pathways can be further stimulated by proinflammatory cytokines which amplify PTGS2 transcriptional responses via NF-κB and protein kinase C [39,55]. IL-1β and TNF-α stimulate not only PTGS2, but also the terminal prostaglandin synthases AKR1B1 (prostaglandin F synthase) and PTGES (prostaglandin E synthase) in human myometrial cells [58]. It is likely that the mechanism of labour is set to respond primarily to endogenous hormones and growth factors, with the system retaining the ability to react to inflammatory stimuli in an accelerated or premature manner (Fig. 22.2). Many studies rely on experiments using isolated uterine tissues *in vitro* and may not account for the full biological complexity of interacting maternal and fetal organs during parturition *in vivo*.

The uterus as a smooth muscle organ

The uterus provides a safe environment for the blastocyst to implant. The nutritious endometrial layer becomes receptive and encourages the development of a viable embryo and the trophoblast. Over a period of 40 weeks of gestation, the fetus, placenta and amniotic fluid increase their masses considerably, posing remarkable haemodynamic, metabolic and mechanical demands on the mother. At the same time, the uterus must expand and remain relatively relaxed, with a closed cervix, to allow the growth and differentiation of the fetus to a stage when it is ready to cope with extrauterine life. However, at the onset of labour the uterus is responsible for driving the process of birth through structural, biochemical and electrophysiological changes that result in cervical ripening and dilatation and the establishment of synchronized myometrial contractions. The process ends with the delivery of the newborn and the placenta, followed by an intense period of uterine remodelling and involution.

The myometrial layer contains specialized smooth muscle cells arranged in bundles embedded in a matrix of collagenous connective tissue. The collagen fibres facilitate the transmission of force generated by myometrial bundles. The process of cervical ripening involves changes in the connective tissue with an increase in collagen solubility and alterations in proteoglycans of the ground substance. This process has been regarded as an inflammatory reaction [59], with elevated levels of cytokines [60] and other proinflammatory molecules signalling through toll-like receptors (TLR2, TLR4) implicated in the mechanism of cervical remodelling in spontaneous labour [61].

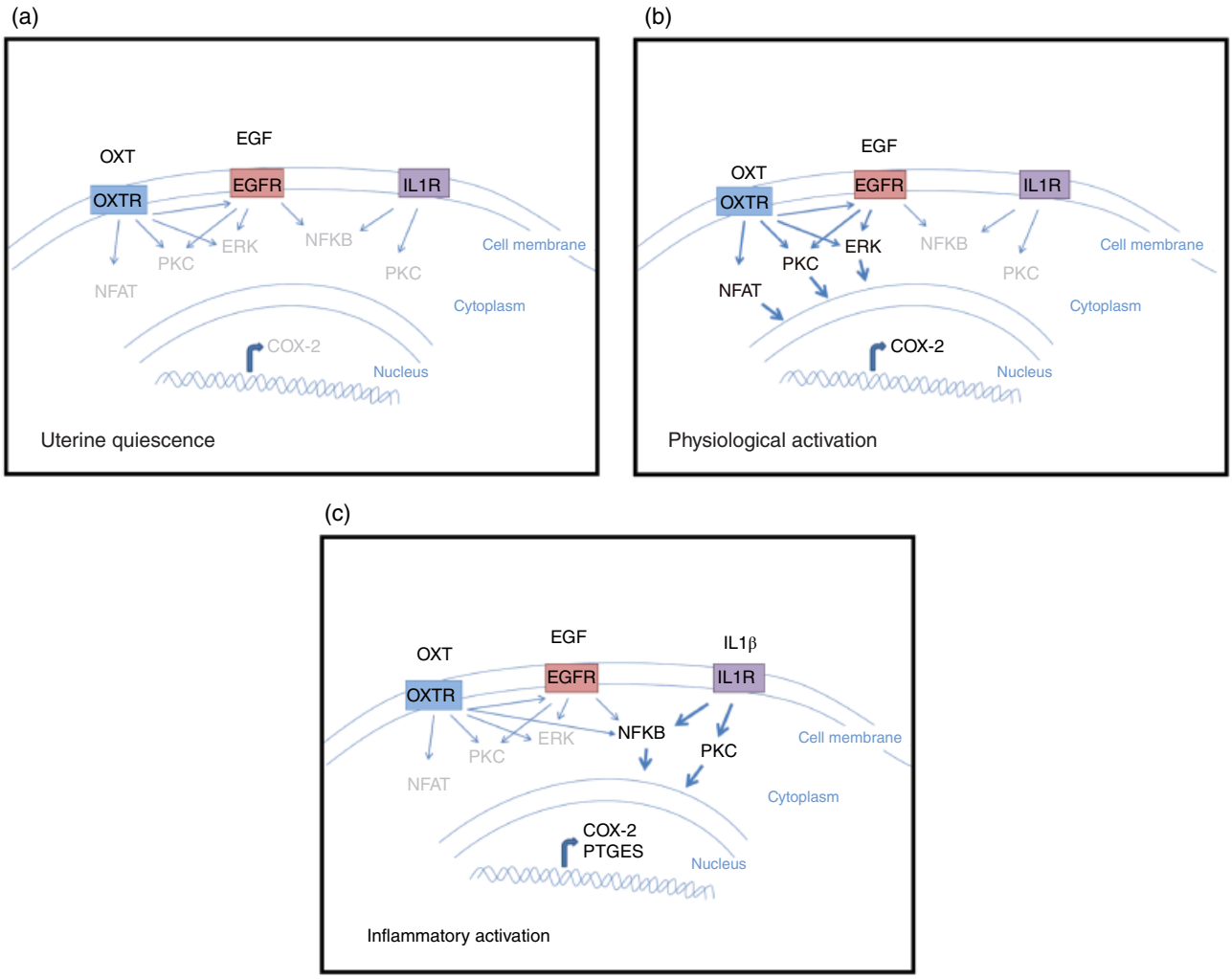

Fig. 22.2 Simplified mechanisms of uterine activation. (a) During pregnancy the uterus remains relatively quiescent with little prostaglandin synthesis because the inducible prostaglandin-endoperoxide synthase 2, also known as COX2, is expressed at low levels. (b) COX2 expression and prostaglandin output can be increased through stimulation of oxytocin receptors (OXTR) and epidermal growth factor receptors (EGFR) which act separately or coordinately via major signalling cascades involving mitogen-activated protein kinases (e.g. ERK), protein kinase C (PKC) and transcription factors such as NFAT (nuclear factor of activated T cells). (c) In the presence of inflammatory stimuli (leucocyte infiltration/macrophage activation following infection or haemorrhage) interleukin 1β receptors (IL1R) can increase prostaglandin release to very high levels through strong stimulation of COX2 and other terminal prostaglandin synthases (e.g. PTGES). The pathways involved include PKC and NFKB (nuclear factor of kappa B) and may involve disruption of OXTR and EGFR signalling.

The basis of uterine contractility

Myometrial smooth muscle cells contain actin (thin filaments) and myosin (thick filaments) in a less organized fashion than in striated muscle, but nevertheless forming efficient contractile units due to their intricate cytoskeletal organization [62]. Mammalian smooth muscle myosin belong to the class II myosins, which are characterized by a hexameric protein structure composed of two heavy chains (about 200 kDa) and two pairs of light chains: the 20-kDa regulatory myosin light chain (MYL_{20}) and the 17-kDa essential light chain. Functionally, myosin consists of three domains: the motor domain which interacts with actin and binds ATP, the neck domain which binds the light chains and is the site of calmodulin interaction, and the tail domain or anchoring domain which helps position the motor domain so that it interacts with actin [63]. Myosin generates contractile force by pulling actin filaments of opposite polarity towards one another (Fig. 22.3).

Myosin is both a structural protein and an enzyme (Mg-ATPase) capable of hydrolysing ATP to generate mechanical energy. The ATPase region of myosin is located in the head and is activated by actin; however, the level of activity is very low when MYL_{20} is unphosphorylated, but increases manifold upon phosphorylation of the regulatory chains. The enzyme responsible for MYL_{20} phosphorylation is the calcium-calmodulin

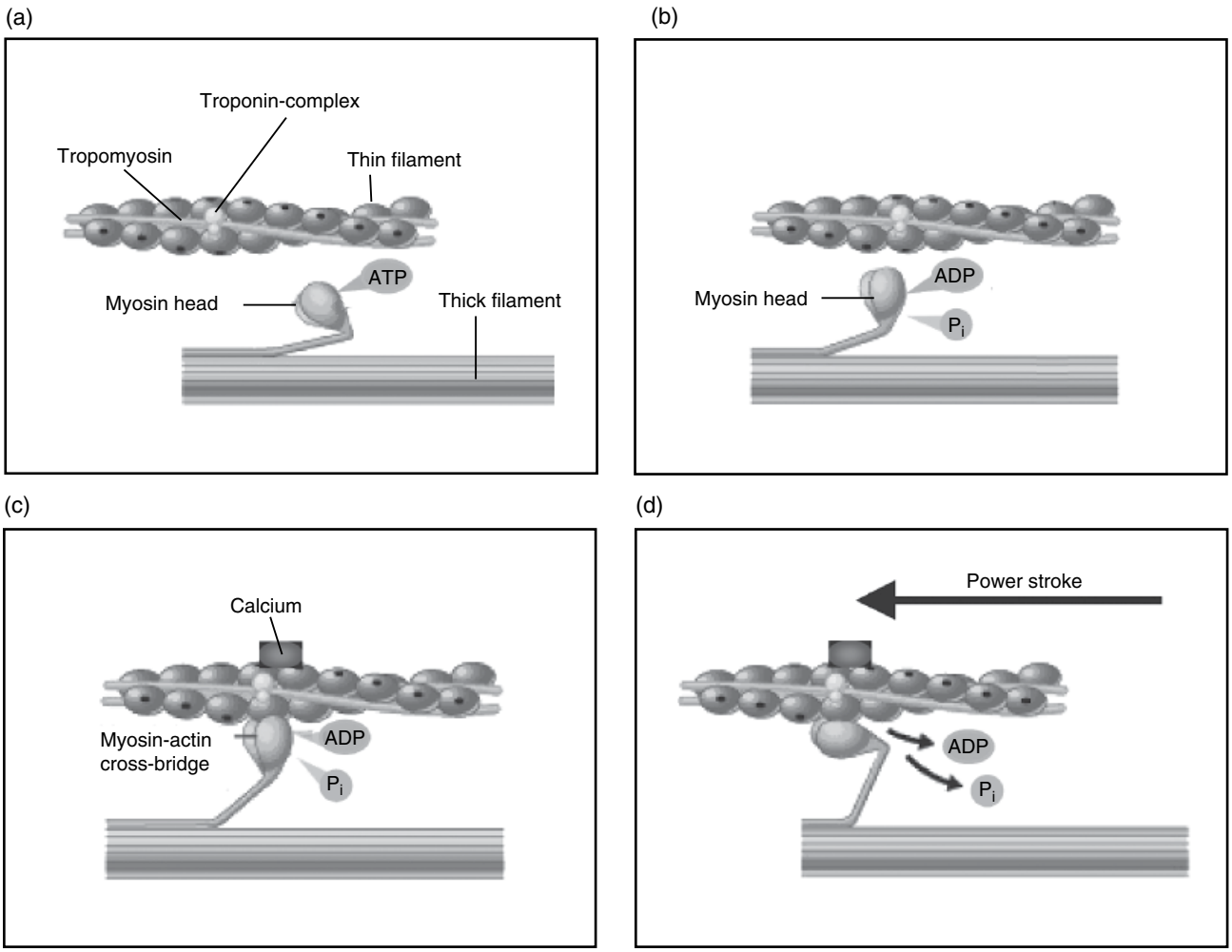

Fig. 22.3 Mechanics of muscle contraction. (a) Appearance of the contractile unit in the resting state. The thick filament refers to myosin; the thin filament is actin. Myosin-binding sites on the actin filaments are covered by a thin filament known as tropomyosin that obscures the myosin-biding sites, therefore preventing the myosin heads from attaching to actin and forming cross-bridges. Adenosine triphosphate (ATP) is hydrolysed into adenosine diphosphate (ADP) and inorganic phosphate (Pi). The troponin complex is attached to the tropomyosin filament. (b) As intracellular calcium concentrations increase, calcium binds to the troponin complex resulting in a conformational change that allows binding sites between actin and myosin to be exposed with the formation of actin–myosin cross-bridges. (c) Formation of actin–myosin cross-bridges results in release of Pi and ADP, causing the myosin heads to bend and slide past the myosin fibres. This 'power stroke' results in shortening of the contractile unit and generation of force within the muscle. (d) At the end of the power stroke, the myosin head releases the actin-binding site, is cocked back to its furthest position, and binds to a new molecule of ATP in preparation for another contraction. The binding of myosin heads occurs asynchronously (i.e. some myosin heads are binding while other heads are releasing the actin filaments), which allows the muscle to generate a continuous smooth force. Cross-bridges must therefore form repeatedly during a single muscle contraction.

dependent myosin light chain kinase (MYLK). There are three types of MYLK, the skeletal, cardiac and smooth muscle enzymes. The three types have a common conserved serine threonine kinase domain, but smooth muscle MYLK has unique immunoglobulin and fibronectin domains [64]. Despite its name, smooth muscle MYLK is expressed in almost all tissues and is involved not only in contractions but in many other cellular activities. Kinases are often portrayed as promiscuous enzymes with multiple substrates; however, despite its ubiquitous expression, the only known substrate of MYLK is myosin. Human myometrium expresses 137-kDa and 218-kDa isoforms of MYLK in both non-pregnant and in term pregnant uterine tissue [65,66]. Interestingly, a small 19-kDa non-catalytic C-terminal fragment of MYLK called telokin is highly expressed in pregnant compared to non-pregnant myometrium, suggesting it may have a regulatory role in gestation [66]. Smooth muscle MYLK has an actin-binding domain at the N-terminus which binds to purified polymeric actin (F-actin); however, the affinity of MYLK for myofilaments, which contain myosin II and many other proteins in addition to F-actin, is much higher. MYLK also has myosin- and calmodulin-binding domains. Purified MYLK can only

bind to calmodulin in the presence of calcium. The protein structure of MYLK suggests that it is a long and flexible molecule capable of attaching itself to actin through its N-terminus, and to the neck region of myosin through the C-terminal telokin domain. In this position the catalytic core of the enzyme is able to phosphorylate MYL_{20} in the thick filaments while being tightly anchored to the thin filaments. MYLK can itself be phosphorylated, modulating its activity during myometrial contractions.

Generation of uterine contractions

Myometrial smooth muscle is myogenic: it can generate contractions spontaneously without the need for external stimulation. Contraction of myometrial cells is initiated by action potentials that depolarize the cell membrane, allowing the rapid entry of calcium through voltage-operated channels (Fig. 22.4). The rise in intracellular calcium concentration ($[Ca^{2+}]_i$) is detected by

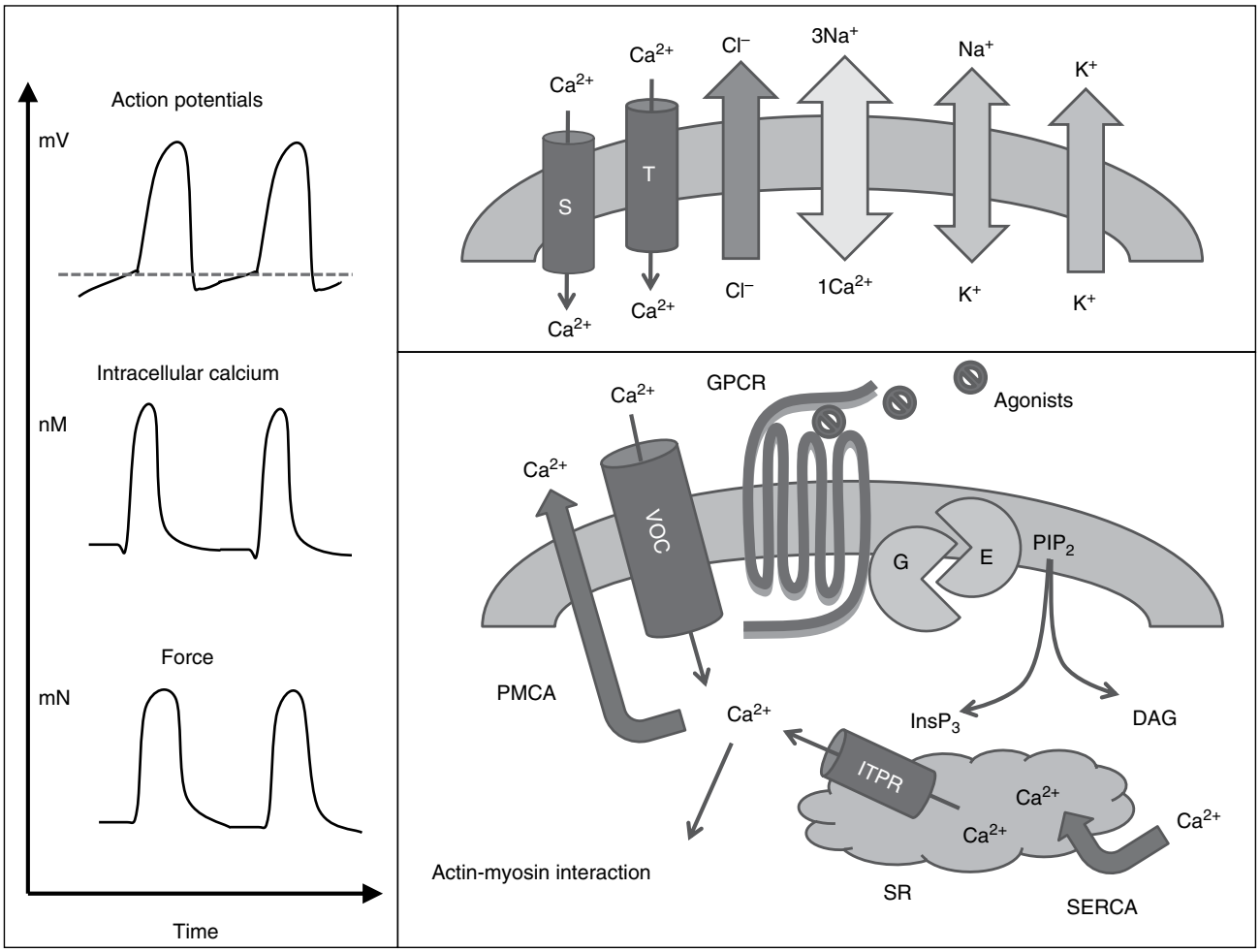

Fig. 22.4 The physiological basis of myometrial contractility. Action potentials are generated by pacemaker depolarization of the cell membrane (top) which is regulated by a complex interaction of several channels and ion pumps. These include store-operated (S) and T-type calcium channels as well as calcium-sensitive chloride (Cl^-) channels, all of which contribute to membrane depolarization. This is balanced by the Na^+/Ca^{2+} exchanger, and the strong hyperpolarizing effect of the Na^+/K^+ pump and the calcium-sensitive K^+ channels. Action potentials (measured in mV) provoke rapid entry of Ca^{2+} into the cell by opening voltage-operated L-type channels (VOC); the increase in intracellular Ca^{2+} levels (typically from 100 to 500 nM) provokes tension (measured in mN) by enhancing actin–myosin interaction. Stimulatory agonists such as oxytocin operate through G protein-coupled receptors (GPCR) which activate G protein effector complexes (G/E). A common G/E interaction involves G_q/phospholipase C which generates two second messengers from membrane phosphatidylinositol 4,5-bisphosphate (PIP_2), namely inositol 1,4,5-trisphosphate ($InsP_3$) and diacylglycerol (DAG). $InsP_3$ stimulates contractility by releasing Ca^{2+} from intracellular stores in the sarcoplasmic reticulum (SR) through ITPR channels. DAG stimulates protein kinase C. The phasic nature of myometrial contraction requires rapid Ca^{2+} extrusion mechanisms to lower intracellular Ca^{2+} and decrease tension. Ca^{2+} is transported out of the cell by plasma membrane Ca^{2+}-ATPases (PMCA) and taken up by the SR through smooth endoplasmic reticulum Ca^{2+}-ATPases (SERCA). Phospholamban is a protein that inhibits SERCA, but this inhibition can be blocked by phosphorylation of phospholamban by cyclic AMP-dependent kinases. *Sources:* adapted from Noble *et al.* [83], Berridge [84] and Sanborn [89].

the Ca^{2+} sensor calmodulin, which activates MYLK and provokes the phosphorylation of MYL_{20}. The activity of myometrial MYLK is very sensitive to minor changes in $[Ca^{2+}]_i$ around the 100–200 nM range and it is thought that the enzyme reaches maximal activity at lower Ca^{2+} concentrations than in other types of smooth muscle. Phosphorylation of MYL_{20} stimulates the formation of cross-bridges between actin and myosin filaments and the generation of force [65,67]. The phasic nature of myometrial contractions (recurrent episodes of force separated by intervals of relaxation) at parturition is necessary to allow vascular flow in the placenta and exchange of oxygen and waste products with the fetus during several hours of labour. In order to promote relaxation between contractions, myometrial cells have efficient Ca^{2+} extrusion mechanisms that include Ca^{2+} pumps and Na^+/Ca^{2+} exchangers in the cell membrane, as well as Ca^{2+} entry into intracellular stores, for example sarcoplasmic reticulum (SR) [68,69] (Fig. 22.4).

The increase in steroid hormones and placental-derived growth factors in pregnancy has important effects on the structure of the uterus. Myometrial tissue becomes more vascularized and there is hyperplasia and hypertrophy of myometrial cells. The cellular content of actin and myosin and of the actin-binding proteins caldesmon and calponin increases several fold compared with non-pregnant cells [65]. The increased expression of caldesmon protein in pregnancy has been described as a 'brake' on the myosin motors of the contractile filaments by a mechanism of Ca^{2+} desensitization [70]. Comparisons between pregnant and non-pregnant myometrial strips *in vitro* show that the relationship between the level of MYL phosphorylation and the amount of force is more favourable in pregnant tissue [65].

Calcium homeostasis

The phasic nature of uterine contractions is an intrinsic property of uterine smooth muscle and is related to the capacity of myometrial cells to modify $[Ca^{2+}]_i$ through reversible activation/inhibition of membrane receptors, ion channels and Ca^{2+} pumps. The main source of Ca^{2+} is the extracellular fluid, but intracellular stores such as the SR have important regulatory functions [71].

Myometrial cells are depolarized by action potentials which provoke the influx of Ca^{2+} through voltage-operated channels [72,73]. Interestingly, spontaneous action potentials in pregnant human myometrial cells are inhibited in sodium-deficient or calcium-free solutions [74–76]. This is due to the essential role of extracellular Ca^{2+} and of membrane Na^+/Ca^{2+} exchangers in the generation of action potentials and myogenic contractility. Magnesium sulfate is a natural calcium antagonist and a potent L-type calcium channel inhibitor. Nifedipine is a commonly used pharmacological blocker of external Ca^{2+} entry which also acts on L-type channels. In the presence of nifedipine both spontaneous and OXT-induced contractions in myometrial strips from term pregnant women are virtually abolished, confirming the essential role of external Ca^{2+} in the development of phasic uterine contractions in late pregnancy. L-type calcium channels have been targeted pharmacologically in the management of preterm labour, using magnesium sulfate or nifedipine; these drugs are effective at relaxing the uterus but they lack myometrial selectivity and can cause side effects. The role of T-type channels in the transmission of action potentials and in the regulation of contraction frequency in myometrial cells has been investigated, but the ubiquitous expression of these channels makes them a poor pharmacological target for the control of uterine activity [77,78].

Intracellular calcium stores

The study of calcium stores in smooth muscle has benefited from the development of fluorescent calcium indicator dyes that allow the measurement of transient rises in free Ca^{2+} in discrete cellular compartments. A number of general observations have been made across many tissues [79] which are relevant to human myometrium.

1) Sporadic increases in $[Ca^{2+}]_i$ occur as a consequence of Ca^{2+} release from intracellular stores (e.g. SR) rather than Ca^{2+} entry through the plasma membrane.
2) These increases are usually very transient and are followed by Ca^{2+} entry into the cells through voltage-dependent channels; without Ca^{2+} influx the intracellular stores are rapidly depleted.
3) Two types of intracellular stores can be distinguished by the nature of their regulatory mechanisms: those containing the ryanodine receptors (RYRs), activated by ryanodine or caffeine, and the inositol 1,4,5-trisphosphate receptor (ITPR)-containing stores. The latter are associated with activation of G protein-coupled receptors (GPCRs) in the cell membrane and activation of phospholipase C.
4) Refilling of intracellular stores may be facilitated by their close proximity to the cell membrane and may be linked to the generation of depolarizing currents.

Several isoforms of RYR and ITPR have been described in human myometrium [42,80]. The RYR acts as a Ca^{2+} channel and studies using human myometrial cells have confirmed the presence of functional RYRs in this tissue [81]. Ryanodine and cyclic ADP-ribose (cADPR) promote intracellular Ca^{2+} release in myometrial preparations *in vitro* and potentiate oxytocin-induced $[Ca^{2+}]_i$ increases by facilitating Ca^{2+} entry from the extracellular medium through 'calcium-induced calcium release' [82]. Interestingly, inflammatory mediators such as TNF-α induce CD38 expression in myometrial cells; this

suggests that inflammation may potentiate the parturition cascade by promoting the cADPR system [82].

ITPRs also act as intracellular Ca^{2+} channels and are activated by inositol 1,4,5-trisphosphate ($InsP_3$) generated when endogenous myometrial stimulants such as OXT, endothelin or α-adrenergic agonists bind GPCRs coupled to proteins of the G_q family which activate phospholipase C. $InsP_3$ binds to myometrial ITPRs and promotes Ca^{2+} release [42,71]. Experiments using myometrial strips from late pregnant women [71] and imaging techniques that allow the visualization of discrete Ca^{2+} fluxes in lipid microdomains [69] suggest that ITPR channel activation is an early event in uterine activation by OXT; however, in the absence of extracellular Ca^{2+} the development of force is short-lived because intracellular Ca^{2+} stores are soon exhausted; in other words, the development of phasic uterine contractions is absolutely dependent on the availability of extracellular Ca^{2+} to myometrial cells. Under normal physiological circumstances, for example in the absence of inflammation, ITPR channels in the SR appear to be more important for myometrial function than RYR channels [71]. Experiments using myometrial strips from late pregnant women showed that ryanodine had little effect on spontaneous or OXT-induced contractions [71], suggesting no functional role for RYR in this preparation. Moreover, blocking SR Ca^{2+} uptake with cyclopiazonic acid, an inhibitor of Ca-ATPase in myometrium, increased contractile force and $[Ca^{2+}]_i$.This suggests that the SR may normally contribute to lowering $[Ca^{2+}]_i$ during the relaxation phase of the contractions [71]. The complex role of intracellular Ca^{2+} stores requires further investigation because, in addition to acting as a trigger for agonist-induced Ca^{2+} mobilization, the SR may act as a 'sink' for Ca^{2+} during stimulation and, by enhancing plasma membrane Ca^{2+} efflux, may contribute to homeostatic Ca^{2+} relaxation mechanisms [83].

Electrophysiological mechanisms

A model for the activation of human myometrium based on electrophysiological and receptor mechanisms has been proposed [84], partly based on available experimental evidence [69,85,86]. In this model, activation of uterine contractility during labour is driven by action potentials initiated by slow depolarization of clusters of pacemaker myometrial cells. The action potentials trigger Ca^{2+} entry into the cells through L-type voltage-operated channels and the rise in $[Ca^{2+}]_i$ provokes contractions, thus linking the electrical signal with force (excitation–contraction coupling). This model envisages that the balance of depolarization and hyperpolarization in the cell membrane is controlled by multiple pumps and channels, including a Na^+/Ca^{2+} exchanger; a Na^+/K^+ pump, and Ca^{2+}-activated K^+ channels that contribute to relaxation (hyperpolarization). On the other hand, Ca^{2+}-sensitive chloride channels, T-type channels, and a putative channel that senses whether the level of Ca^{2+} in the SR store is low (store-operated channel, SOC) can tip the balance of the 'pacemaker' towards depolarization [84]. GPCR agonists like OXT can initiate depolarization by generating $InsP_3$ and emptying the SR store through ITPR channels, thus activating SOC, whereas RYR channels would contribute to contraction directly by increasing $[Ca^{2+}]_i$. Further regulatory refinement of myometrial activation can be provided by Ca^{2+}-ATPases that promote Ca^{2+} extrusion through the plasma membrane (PMCA) or Ca^{2+} uptake into the SR (SERCA).

Some aspects of this model have been reinforced by the abundant experimental evidence in favour of a role for L-type Ca^{2+} channels as the major route for Ca^{2+} entry into myometrial cells and the unquestionable involvement of the GPCR/phospholipase C/$InsP_3$ pathway activating ITPR channels in human myometrium [76,87]. However the role of RYR channels in human myometrium is questionable. The presence of Ca^{2+}-activated K^+ channels in this tissue has been demonstrated but their role in phasic myometrial activity during labour is not clear. An interesting interaction between Ca^{2+}-activated K^+ channels and α_2-macroglobulin has been described in myometrial cells whereby in the presence of OXT α_2-macroglobulin induces oscillations in Ca^{2+}-activated K^+ channel activity and promotes Ca^{2+} entry via SOC [88]. A number of endogenous Ca^{2+}-ATPase modulators has been described, including phospholamban, a membrane-associated protein that inhibits SERCA-mediated Ca^{2+} uptake into the SR. Interestingly, phospholamban can be phosphorylated by cAMP-dependent kinases leading to its inactivation and the liberation of SERCA activity [83].

Receptor-regulated myometrial contractility

In addition to the spontaneous uterine activity driven by action potentials, there is strong evidence that receptors and their cell signalling pathways have a physiological influence on the regulation of uterine contractility. The uterus has a rich variety of receptors, many of which are upregulated in pregnancy, and responds to classical hormones and transmitters (e.g. OXT, 5-hydroxytryptamine) as well as local modulators (e.g. prostaglandins and thromboxanes). The link between the myometrial cell membrane receptor and the initiation of a signalling cascade is, in most cases, a regulatory GTP-binding protein. G proteins can activate effector enzymes such as phospholipase Cβ (PLCB), adenylyl cyclase (ADCY) or phosphoinositide 3-kinase. The PLCB pathway is activated by receptors usually coupled to G_q which stimulate myometrial contractility. Endogenous agonists include peptide hormones (OXT, endothelin), prostanoids ($PGF_2\alpha$,

thromboxane A_2), catecholamines, muscarinic agents and inflammatory mediators (bradykinin, serotonin). The response is initiated by the hydrolysis of a receptor-sensitive pool of phosphatidylinositol 4,5-bisphosphate (PIP_2) in the cell membrane. The breakdown of PIP_2 generates two molecules with potent signalling effects: $InsP_3$, which releases calcium form the SR, and 1,2-diacylglycerol (DAG), which activates protein kinase C (PRKC) and stimulates the phosphorylation of many target proteins. Potential substrates of PRKC include ion channels, calcium pumps, and proteins involved in GPCR function and coupling to phospholipase C, ITPR regulation and elements of the contractile machinery [89]. In addition, DAG has PRKC-independent effects, for example in human myometrial cells DAG analogues facilitate store-operated or receptor-operated Ca^{2+} entry through the cell membrane via L-type channels and Na^+/Ca^{2+} exchangers [90].

Some ligands can activate more than one type of myometrial receptor, creating complex responses depending on the relative abundance and affinity of each receptor subtype and the presence of other agonists competing or interacting with related receptors. For each receptor, the effect on myometrial contractility will depend on the integration of these signals and on the physiological state of the organ under different endocrine influences. Changes in myometrial sensitivity to agonists are likely to be important mechanisms for maintaining the balance between uterine quiescence and contractility. The uterus is very sensitive to OXT, which is commonly used for the induction and augmentation of labour; however, many uncertainties remain about its mechanism of action. For instance, analysis of the Ca^{2+}–tension relationship in pregnant myometrial strips reveals a strong component of 'Ca^{2+} sensitization' during OXT-induced contractions [91,92], probably involving inhibition of myosin phosphatase. The pathways involve small GTP-binding proteins of the Rho family and activation of Rho-dependent kinases [93].

Uterine relaxation

The physiological mechanisms responsible for the transition of the pregnant uterus from a long period of relative relaxation to a short period of active contractions in labour remain unknown. Greater understanding of the factors involved in the loss of uterine quiescence may assist in the anticipation and prevention of preterm labour. Therapeutic approaches to inhibit uterine contractility in women in preterm labour remain rudimentary [94], based on the use of drugs that are not effective or have potentially serious side effects. We need to increase our understanding of the endocrine and physiological control of parturition in women.

Role of cyclic nucleotides

The importance of cyclic nucleotides (cGMP and cAMP) in smooth muscle function cannot be over-emphasized. These molecules provide rapid intracellular responses to a variety of signals and have profound effects on regulatory proteins through the activation of specific protein kinases. The role of cyclic GMP as a mediator of nitric oxide (NO) [95] effects in myometrium is a matter of controversy. Initial studies suggested a link between NO production, cGMP generation and uterine relaxation [96]. However, cGMP has a much more potent inhibitory role in tracheal and vascular smooth muscle than in myometrium [97,98]. Intravenous nitroglycerin has been used to relax the uterus during postpartum emergencies [99,100] but the use of NO donors for routine tocolysis is not recommended [101].

Cyclic AMP is produced from ATP in response to activation of GPCRs positively coupled to ADCY, and is known to influence a wide range of physiological events including relaxation of myometrial smooth muscle [102]. The actions of cAMP in myometrial cells, as in other cell types, result from the dynamic interplay of multiple ADCY, phosphodiesterases and protein kinase A (PRKA) isoforms that allow spatial and temporal changes in cAMP levels to be translated into compartmentalized responses within the cell. Most of the effects of cAMP are due to its ability to bind to PRKA. The localization of PRKA activity within cells depends on reversible interactions with 'A kinase anchor proteins' (AKAP). Although the evidence that agonist-mediated increases in cAMP result in uterine relaxation is strong, the mechanism of action of cAMP in myometrium is not well known. PRKA–AKAP complexes have been described in pregnant human myometrium [103–105], but there is little information about the physiological targets that become phosphorylated during cAMP-induced relaxation. New lines of research suggest that cAMP interacts with progesterone receptors to regulate COX2 expression in human myometrial cells [106].

G protein-coupled receptors and their second messenger pathways

The uterus has GPCRs for many endogenous agonists and responds with contraction or relaxation depending on the type of G protein and second messenger pathway activated. In general, receptors coupled to G_q are stimulatory through activation of PLCB and receptors coupled to G_s are inhibitory (promote relaxation) via stimulation of ADCY (Table 22.1). Some ligands can activate more than one type of myometrial receptor, creating complex responses depending on the relative abundance and affinity of each receptor subtype and the presence of other agonists competing or interacting with related receptors. G proteins are heterotrimers ($\alpha\beta\gamma$ subunits)

Table 22.1 Examples of G protein-coupled receptors in myometrium and their signalling pathways.*

Endogenous ligands	Receptors	G protein class	Signalling pathway	Effect on myometrial contractility
Amines				
Catecholamines	ADRA1	$G_{q/11}$	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB ↑PLCD/ $InsP_3$–Ca^{2+}	Stimulation
	ADRA2	$G_{i/o}$	↓ADCY/cAMP/PRKA	Stimulation
	ADRB2	G_s	↑ADCY/cAMP/PRKA	Inhibition
	ADRB3	G_s $G_{i/o}$	↑ADCY/cAMP/PRKA ↓ADCY/cAMP/PRKA	Inhibition
Histamine	HRH1	$G_{q/11}$	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation
	HRH2	G_s	↑ADCY/cAMP/PRKA	Inhibition
Serotonin	HTR1,2	$G_{i/o}$ $G_{q/11}$	↓ADCY/cAMP/PRKA ↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation
	HTR4,7	G_s	↑ADCY/cAMP/PRKA	Inhibition
Eicosanoids				
Prostaglandin D_2	PTGDR	G_s	↑ADCY/cAMP/PRKA	Inhibition
Prostaglandin E_2	PTGER1	$G_{q/11}$	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation
	PTGER2	G_s	↑ADCY/cAMP/PRKA	Inhibition
	PTGER3	$G_{i/o}$ G_s $G_{q/11}$	↓ADCY/cAMP/PRKA ↑ADCY/cAMP/PRKA ↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation/inhibition
	PTGER4	G_s	↑ADCY/cAMP/PRKA	Inhibition
Prostaglandin $F_{2\alpha}$	PTGFR	$G_{q/11}$	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation
Prostacyclin	PTGIR	G_s	↑ADCY/cAMP/PRKA	Inhibition
Thromboxane A_2	TBXA1R	$G_{q/11}$ $G_{12/13}$	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB ↑ARHGEF/RHOA/ARF6/PLD	Stimulation
Peptides				
Angiotensin	AGTR2	$G_{12/13}$	↑ARHGEF/RHOA/ARF6/PLD	Stimulation
Bradykinin	BDKRB2		↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB	Stimulation
Calcitonin-related	CL-RAMP	G_s	↑ADCY/cAMP/PRKA	Inhibition
Endothelin	EDNRA	$G_{q/11}$ G_i	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB ↓ADCY/cAMP/PRKA	Stimulation
Oxytocin/vasopressin	OXTR/ AVPR1A	$G_{q/11}$ G_i	↑PLCB/$InsP_3$–Ca^{2+}/DAG–PRKCB ↓ADCY/cAMP/PRKA	Stimulation

*This table is not exhaustive and other receptors require further study in human pregnant myometrium [127–129].
ADCY, adenylyl cyclase; ARF6, ADP-ribosylation factor 6; ARHGEF, RHO guanine nucleotide exchange factor; DAG, 1,2-diacylglycerol; GRK, G protein-coupled receptor kinase; $InsP_3$, inositol 1,4,5-trisphosphate; PLCB, phospholipase Cβ; PLCD, phospholipase Cδ; PRKA, protein kinase A; PRKCB, protein kinase Cβ.

and the effects of Gα subunits on PLCB, ADCY and other effectors are modulated by the interaction of Gβγ subunits, especially those liberated from $G_{i/o}$ or G_{12}, with the same or with other effector proteins including ADCY, ARF6, GRK, PLCB, PLCD, phosphatidylinositol kinases and ion channels. For each receptor, the effect on myometrial contractility will depend on the integration of these signals and on the physiological state of the organ under different endocrine influences. Changes in myometrial sensitivity to agonists may be an important mechanism for maintaining the balance between uterine quiescence and contractility. For example, pregnancy induces an increase in the myometrial response to OXT [35] and histamine [95] and a decrease in the response to tachykinins in women [95]. More research needs to be done on the responses of pregnant and non-pregnant human myometrium to selective GPCR agonists and antagonists to build a complete picture.

Receptor-mediated uterine relaxation

The β_2-adrenoceptor (ADRB2) has been a pharmacological target to relax the uterus for many years, using beta-mimetic drugs. Exposure of human pregnant myometrial strips to the β_2 agonist isoproterenol *in vitro* results in a significant decrease in contractile force and in the frequency of spontaneous contractions. Similar effects have been obtained with ritodrine, a beta-mimetic used as a tocolytic agent in preterm labour [107,108]. Table 22.2 lists a number of endogenous ligands that can relax the uterus. Some of these, for example catecholamines and prostaglandins, have complex stimulatory and inhibitory effects due to the presence of multiple receptors in myometrium. Inhibitory receptors such as ADRB2 or the prostaglandin PTGER2 receptors have in common the coupling through $G\alpha_s$ to ADCY. Receptors coupled to $G_{i/o}$ (e.g. α_2-adrenoceptors, ADRA2) inhibit ADCY and decrease cAMP production, favouring uterine contractions; however, in many systems prolonged stimulation of $G_{i/o}$-coupled receptors provokes sensitization of ADCY to subsequent stimulation by other G_s-coupled receptors (heterologous sensitization) [109].

Changes in the sensitivity to endogenous agonists (catecholamines, prostaglandins) operating through ADRB2, PTGER2 and other receptors coupled to cAMP production may be responsible for the transition from uterine quiescence to the onset of labour. This is an attractive hypothesis, although it requires more evidence to support it. Beta-mimetics (ritodrine, terbutaline, salbutamol) were among the earliest agents used clinically to inhibit uterine contractions, but their efficacy is questionable [110]. ADRB2 receptors are widely expressed in many organs, and consequently the use of beta-mimetics in pregnancy is associated with potentially serious cardiovascular, neuromuscular and metabolic side effects. There is contrasting new information to be considered before the possible clinical use of PTGER2 agonists to relax the uterus [111].

Table 22.2 Endogenous and exogenous factors affecting myometrial contractility during labour.

Uterine stimulants
Endogenous
Oxytocin
Prostaglandins
Endothelin
Epidermal growth factor
Exogenous
Oxytocin
Prostaglandins
Uterine relaxants
Endogenous
Relaxin
Nitric oxide
L-Arginine
Magnesium
Corticotrophin-releasing hormone
Exogenous
β-Adrenergic agonists (ritodrine hydrochloride, terbutaline sulfate, salbutamol, fenoterol)
Oxytocin receptor antagonist (atosiban)
Magnesium sulfate
Calcium channel blockers (nifedipine, diltiazem, verapamil)
Prostaglandin inhibitors (indometacin)
Phosphodiesterase inhibitor (aminophylline)
Nitric oxide donor (nitroglycerin, sodium nitroprusside)

Desensitization of GPCRs

Sustained stimulation of GPCRs typically causes desensitization (a reduction in response in the face of a constant stimulus), which protects cells from overstimulation and involves numerous adaptive mechanisms in characteristic time frames. Within seconds to minutes of stimulation, most GPCRs desensitize as a consequence of receptor phosphorylation by G-protein receptor kinases (GRKs) or second-messenger regulated protein kinases which are very abundant in human myometrium [112]. This phosphorylation can inhibit G-protein activation (i.e. cause receptor desensitization), but the most important effect of GRK-mediated phosphorylation is to facilitate the binding of arrestin proteins [113]. This not only prevents G-protein activation but also targets the desensitized receptor for internalization. The consequent reduction in cell surface receptor number can also underlie desensitization in the intermediate time frame of minutes to hours. Over longer periods (hours to days), numerous adaptive processes serve to either reinforce or reverse the earlier desensitization by changing rates of synthesis and degradation of receptors and downstream effectors. Arrestins have many other roles, including acting as scaffolds to facilitate receptor-stimulated activation of mitogen-activated protein kinases (MAPKs) in discrete cellular compartments. This mechanism has been confirmed for bradykinin B_2 receptors in human myometrial cells [114].

One of the difficulties with the use of agonists for $G\alpha_s$-coupled receptors to promote uterine relaxation is the tendency of GPCRs to desensitize and downregulate. This process has been particularly well studied for the ADRB2 receptor but it has long been known to occur with other utero-relaxing receptors such as PTGER2 and PTGIR [115]. The loss of tocolytic effect of ritodrine in women in preterm labour has been known for many years [116].

Summary box 22.3

G protein-coupled receptors are useful pharmacological targets to manipulate uterine activity but the risk of side effects must be considered.

Gap junction proteins

Uterine relaxation in pregnancy may be due to lack of electrical and metabolic coordination between myometrial smooth-muscle cells. Gap junctions are specialized protein channels that facilitate the propagation of electrical activity and the exchange of small molecules between cells. The appearance of gap junctions in myometrium is thought to herald the onset of labour in animals and humans [117–119]. GJA1 (connexin 43) is one of the main structural proteins in gap junctions; its expression in myometrium is stimulated by estradiol and inhibited by progesterone [120]. Studies of *GJA1* gene regulation indicate that the family of activator protein-1 transcription factors is critical in determining the level of GJA1 expression in myometrial cells [121,122]. Retinoic acid upregulates GJA1 expression in human endometrial and myometrial cells probably through nuclear receptors [123,124]. The function of gap junctions is tightly regulated through phosphorylation of specific serine residues at the C-terminus of GJA1. A number of protein kinases are involved in the functional regulation of GJA1, including PRKA, PRKC and MAPK1. Phosphorylation at Ser-368 seems important for translocation of GJA1 from the cytosol and its assembly on the plasma membrane. On the other hand, phosphorylation of GJA1 and other connexins may also trigger internalization and degradation. Activation of MAPK1 in pregnant rat myometrium leads to phosphorylation of GJA1 at Ser-255 and this causes loss of amplitude and synchronization of uterine contractions [125]. In mice, conditional deletion of the *GJA1* gene causes a dramatic delay in parturition [126]. A better understanding of the pathways that regulate GJA1 expression and phosphorylation in human myometrium will clarify the role of these proteins during pregnancy and labour.

Mechanics of normal labour at term

Labour and delivery are not passive processes in which uterine contractions push a rigid object through a fixed aperture. The ability of the fetus to successfully negotiate the pelvis is dependent on the complex interaction of three variables: the powers, the passenger and the passage.

The powers

The powers refer to the forces generated by the uterine musculature. Uterine activity is characterized by the frequency, amplitude (intensity) and duration of contractions. It can be assessed by observation, palpation, external monitors (such as external tocodynamometry, which measures changes in shape of the abdominal wall as a function of uterine contractions and is therefore more qualitative than quantitative), and direct measurement of intrauterine pressure (which requires insertion of a pressure transducer directly into the uterine cavity usually through the cervix after rupture of the fetal membranes). It is generally believed that the more optimal the powers, the more likely a woman is to have a successful vaginal delivery; however, there are few data to support this statement. Classically, three to five contractions in 10 min has been used to define 'adequate' uterine activity in labour, and is seen in around 95% of women in spontaneous labour at term. Various units have been devised to objectively measure uterine activity using an intrauterine pressure transducer, the most common of which is the *Montevideo unit* (the average strength of contractions in mmHg multiplied by the number of contractions per 10 min), which is a measure of average frequency and amplitude above basal tone; 200–250 Montevideo units defines adequate labour [130,131]. The ultimate measure of uterine activity is a clinical one. If uterine contractions are 'adequate', one of two events will occur: either the cervix will efface, dilate and the fetal head will descend, or there will be worsening caput succedaneum (scalp oedema) and/or moulding (overlapping) of the skull bones. The latter situation suggests a diagnosis of cephalopelvic disproportion.

The passenger

The passenger is the fetus. There are several fetal variables that may influence the course of labour and delivery.

1) Fetal size: can be estimated clinically through the use of the four Leopold manoeuvres or by ultrasound.
2) Fetal lie: refers to the longitudinal axis of the fetus relative to the longitudinal axis of the uterus.
3) Fetal presentation: refers to the fetal part that directly overlies the pelvic inlet.
4) Attitude: refers to the position of the head with regard to the fetal spine (i.e. the degree of flexion and/or extension of the fetal head).
5) Position of the fetus: refers to the orientation of the fetal presenting part relative to the maternal pelvis.
6) Station: a measure of descent of the presenting part of the fetus through the birth canal.

The presence of a multifetal pregnancy increases the probability of abnormal lie and malpresentation in labour.

The passage

The passage consists of the bony pelvis (sacrum, ilium, ischium and pubis) and the resistance provided by the pelvic soft tissues (cervix and muscles of the pelvic

floor). Measurements of the various parameters of the female bony pelvis have been made with great precision, both directly in cadavers and through the use of imaging (CT and MRI) in living women, and four distinct shapes have been defined (gynecoid, anthropoid, android and platypelloid). In practice, however, the use of clinical pelvimetry to assess the pelvic shape and capacity is of limited value. The only way to determine whether a given fetus will be able to pass safely through a given pelvis is for a woman to undergo a trial of labour.

Stages of labour

Although labour is a continuous process, for reasons of study and to assist in clinical management, it has been divided into three stages as described by Friedman (Fig. 22.5) [132,133]. The first stage refers to the interval between the onset of labour and full cervical dilatation (10 cm). It has been subdivided into several phases according to the rate of cervical dilatation. The duration and rate of cervical change during the second stage of labour varies between nulliparous and multiparous women (Table 22.3). The second stage refers to the interval between full cervical dilatation and delivery of the infant. The third stage, which refers to delivery of the placenta and fetal membranes, usually lasts less than 10 min, but up to 30 min may be allowed in the absence of excessive bleeding before active intervention is considered.

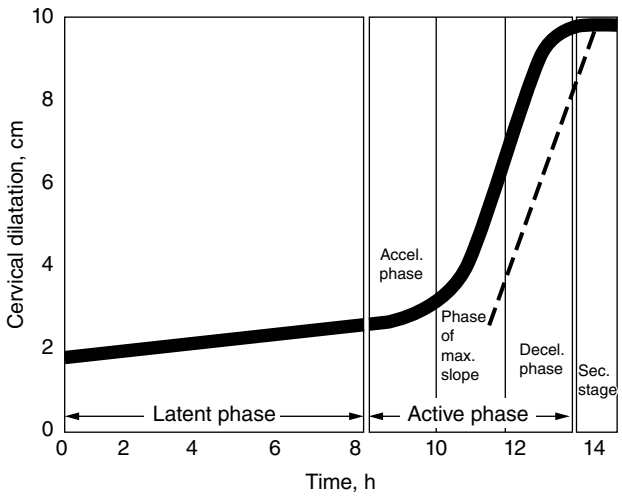

Fig. 22.5 Characteristics of the average cervical dilatation curve for nulliparous labour. The 2-hour 'action line' is shown as a stippled line. *Source:* Friedman EA. *Labor: Clinical Evaluation and Management*, 2nd edn. New York: Appleton-Century-Crofts, 1978. Reproduced with permission of Appleton-Century-Crofts.

Table 22.3 Progression of spontaneous labour at term.

Parameter	Mean	Fifth percentile
Nulliparas		
Total duration of labour (hours)	10.1 hours	25.8 hours
Duration of first stage of labour	9.7 hours	24.7 hours
Duration of second stage of labour	33.0 min	117.5 min
Duration of latent phase	6.4 hours	20.6 hours
Rate of cervical dilatation during active phase	3.0 cm/hour	1.2 cm/hour
Duration of third stage of labour	5.0 min	30 min
Multiparas		
Total duration of labour (hours)	6.2 hours	19.5 hours
Duration of first stage of labour	8.0 hours	18.8 hours
Duration of second stage of labour	8.5 min	46.5 min
Duration of latent phase	4.8 hours	13.6 hours
Rate of cervical dilatation during active phase	5.7 cm/hour	1.5 cm/hour
Duration of third stage of labour	5.0 min	30.0 min

Source: data from Friedman EA. *Labor: Clinical Evaluation and Management*, 2nd edn. New York: Appleton-Century-Crofts, 1978. Reproduced with permission of Appleton-Century-Crofts.

Cardinal movements in labour

The mechanisms of labour, also known as the cardinal movements, refer to the changes in position of fetal head during its passage through the birth canal. Because of the asymmetry of the shape of both the fetal head and the maternal bony pelvis, such rotations are required for the fetus to successfully negotiate the birth canal. Although labour and birth is a continuous process, seven discrete cardinal movements of the fetus are described: engagement (which refers to passage of the widest diameter of the presenting part to a level below the plane of the pelvic inlet), descent, flexion, internal rotation, extension, external rotation (also known as restitution) and expulsion (Fig. 22.6).

Summary box 22.4

Labour is a clinical diagnosis characterized by regular phasic uterine contractions increasing in frequency and intensity and resulting in effacement and dilatation of the uterine cervix. The ability of the fetus to successfully negotiate the pelvis is dependent on the complex interaction of three variables: the powers, the passenger and the passage.

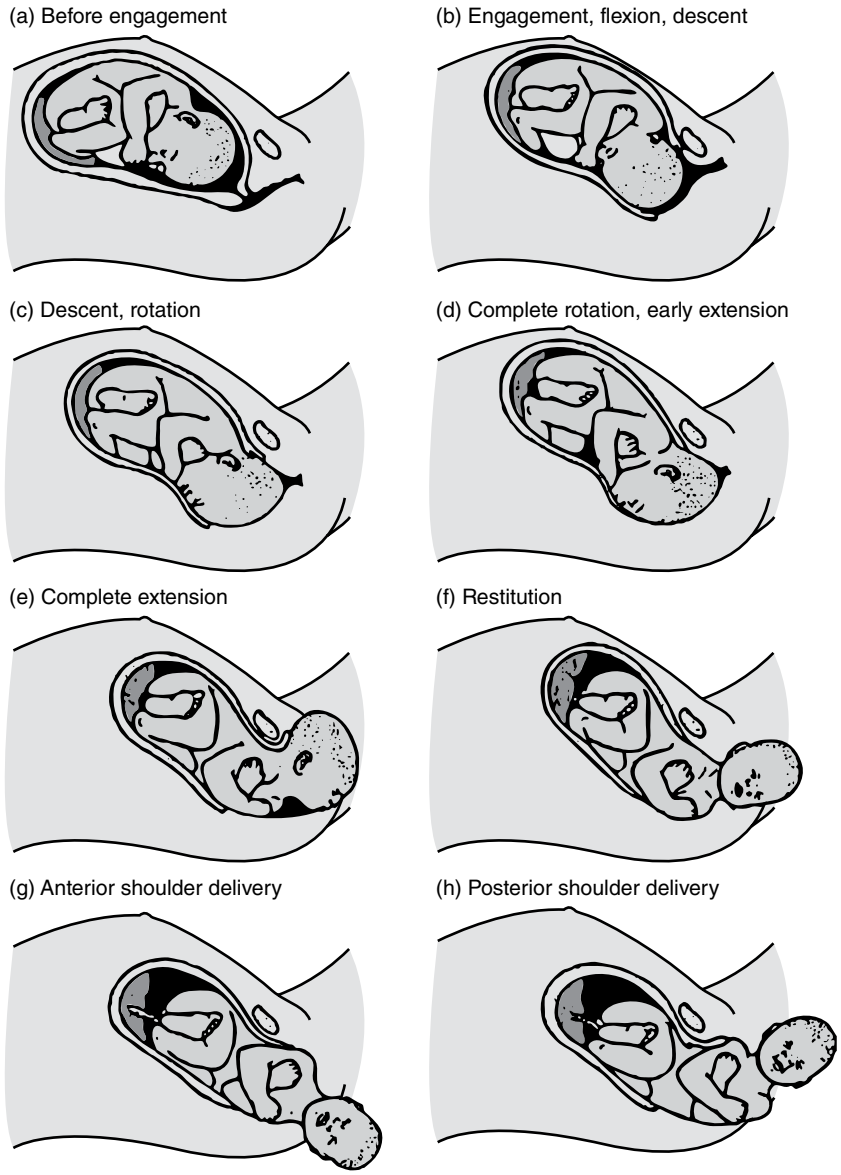

Fig. 22.6 Cardinal movements of the fetus during labour and birth.

Management of uncomplicated labour and delivery

Intrapartum management

Initial assessment in labour should include a focused history (time of onset of contractions, status of the fetal membranes, presence or absence of vaginal bleeding, perception of fetal movement), physical examination and routine necessary laboratory testing (full blood count, blood type). Physical examination should include documentation of the patient's vital signs, notation of fetal position and presentation, an assessment of fetal well-being, and an estimation of the frequency, duration and quality of uterine contractions. The size, lie, presentation and engagement of the fetus should be assessed by abdominal palpation. If there are no contraindications to pelvic examination, the degree of cervical dilatation, effacement, status of the fetal membranes, and the position and station of the presenting part should be noted. If the practitioner is still uncertain about fetal presentation or if the clinical examination suggests an abnormality (such as a multifetal pregnancy, low amniotic fluid volume or intrauterine growth restriction), an ultrasound examination is indicated. Assessment of the quality of uterine contractions and degree of cervical dilatation should be performed at appropriate intervals in order to follow the progress of labour. Vaginal examinations should be kept to a minimum to avoid promoting intra-amniotic infection. Pain management should be

discussed and implemented when desired. The fetal heart rate should be recorded before, during and after a uterine contraction at least every 30 min in the first stage of labour and every 15 min in the second stage.

Clinical assistance at delivery

Preparation for delivery should take into account the patient's parity, presentation of the fetus and the progression of labour. The goals of clinical assistance at delivery are the reduction of maternal trauma, prevention of fetal injury and initial support of the newborn if required. When the fetal head crowns and delivery is imminent, pressure from the practitioner's hand is used to hold the head flexed and to control delivery, thereby preventing precipitous expulsion, which has been associated with perineal tears as well as intracranial trauma. Once the fetal head is delivered, external rotation (restitution) is allowed to occur. If the cord is around the neck, it should be looped over the head or, if not reducible, doubly clamped and transected. Use of suction to clear secretions from the fetal mouth, oropharynx and nares has not been shown to reduce the incidence of meconium aspiration syndrome [134] and, as such, is not routinely recommended. Thereafter, a hand is placed on each parietal eminence and the anterior shoulder of the fetus is delivered with the next contraction by downward traction towards the mother's sacrum in concert with maternal expulsive efforts. The posterior shoulder is then delivered by upwards traction. The infant should be held securely and wiped dry with a sterile towel. The timing of cord clamping is dictated by convenience and is usually performed immediately after delivery.

Delivery of the placenta and fetal membranes

The third stage of labour can be managed either passively or actively. *Passive management* involves waiting for the three classic signs of placental separation (lengthening of the umbilical cord, a gush of blood from the vagina signifying separation of the placenta from the uterine wall, and a change in the shape of the uterine fundus from discoid to globular with elevation of the fundal height) before applying traction to the umbilical cord. *Active management* of the third stage has been shown to reduce total blood loss and the incidence of postpartum haemorrhage [135], but can complicate management in cases involving an undiagnosed second twin or placenta accreta. In active management, uterotonic agents such as OXT are administered at birth to hasten delivery of the placenta. Two techniques of controlled cord traction are described to facilitate separation and delivery of the placenta: (i) the Brandt–Andrews manoeuvre, in which an abdominal hand secures the uterine fundus to prevent uterine inversion while the other hand exerts sustained downward traction on the umbilical cord; or (ii) the Créde manoeuvre, in which the cord is fixed with the lower hand while the uterine fundus is secured and sustained upwards traction applied using the abdominal hand. Care should be taken to avoid avulsion of the cord.

After delivery, the placenta, umbilical cord and fetal membranes should be examined. A missing placental cotyledon or a membrane defect may suggest retention of a portion of the placenta, which can lead to postpartum haemorrhage or infection. In this setting, manual and/or surgical exploration of the uterus may be required to remove the offending tissue. The cervix, vagina and perineum should also be carefully examined for evidence of birth injury. If a laceration is seen, its length and position should be noted and repair initiated. Adequate analgesia (either regional or local) is essential for repair. Special attention should be paid to repair of the perineal body, the external rectal sphincter and the rectal mucosa. Failure to recognize and repair rectal injury can lead to serious long-term morbidity, most notably faecal incontinence.

Conclusions

The timely onset of labour and birth is an important determinant of perinatal outcome. Labour is a physiological and continuous process. The factors responsible for the onset and maintenance of labour at term are not completely understood, and continue to be under active investigation. A better understanding of the mechanisms responsible for the onset of labour will further our knowledge about disorders of parturition, such as preterm and prolonged (post-term) labour, and will improve our ability to secure a successful pregnancy outcome.

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23

Post-term Pregnancy

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Gestational age is an important determinant of perinatal outcomes. Most attention to this issue has been focused on predicting and preventing preterm births, defined as delivery prior to 37 weeks of gestation. This seems entirely appropriate as preterm birth is the greatest cause of perinatal morbidity, mortality and costs [1,2]. However, post-term births are also associated with increased perinatal morbidity and mortality [3]. Furthermore, post-term pregnancy is easily preventable by delivery of the neonate by induction of labour. Thus this potentially problematic condition of pregnancy deserves further attention, research and careful consideration. This chapter discusses what is known about the existing epidemiology of post-term birth and associated outcomes, the methodological issues related to studying post-term pregnancy, that complications associated with post-term pregnancy rise in a continuous manner as opposed to suddenly at any specific threshold, and the management and prevention of post-term births and future directions for research and clinical care.

Definitions

Post-term pregnancy is currently defined as a pregnancy progressing to 42 weeks (294 days) of gestation or beyond [4]. Other terms such as 'prolonged' or 'post-dates' have also been used but for the sake of nomenclature 'post-term' should be used [5]. Further, although 42 weeks is the current threshold designation for post-term pregnancy, up until the 1980s 43 weeks was the threshold while many clinicians currently use the term to describe pregnancies of 41 weeks' gestation and beyond.

It is sensible that there should be a term to describe the range of 41 to 41^{+6} weeks of gestation, and recently the designation 'late term' was agreed upon and endorsed by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal–Fetal Medicine (SMFM) in the USA. This term is in contrast to 'full term', describing pregnancies from 39^{+0} to 40^{+6} weeks of gestation, and 'early term', describing pregnancies from 37^{+0} to 38^{+6} weeks of gestation [6].

Given the wide range of terminology, it is best to always include the gestational age along with the descriptor for clarity, for example 'post-term pregnancy at 42^{+1} weeks gestation' or 'late term pregnancy at 41^{+2} weeks gestation'.

Incidence

In order to accurately determine the 'natural' incidence of post-term pregnancy, there must be meticulous early pregnancy dating, universal follow-up of all pregnancies, and absence of obstetric intervention.

The 14% post-term pregnancy rate quoted for the Hawaiian island Kauai [7] may be regarded as informative because of low rates of obstetric intervention and full follow-up, but lacks correction for potential gestational age dating error. In the UK, the fall in incidence of post-term pregnancy from 11.5% in 1958 [8] to 4.4% in 1970 [9] illustrates the effect of the rise in rates of induction of labour from 13 to 26% over the same period. More recently, in the USA in 2005, 14% of all pregnancies progressed beyond 41 weeks of gestation and just under 6% progressed beyond 42 weeks of gestation [10]. This is lower than the approximately 18% of pregnancies beyond 41 weeks and 10% beyond 42 weeks in 1998, with these changes attributed to increases in the use of induction of labour, but are also partly due to improved early gestational age dating [11,12]. An analysis of 171 527 births in residents of the North-east Thames region in 1989–1991 gave an incidence of 6.2% for post-term pregnancy [13]. In a study of 1514 healthy pregnant women in whom the discrepancy between date of last menstrual period (LMP) and dating based on first-trimester crown–rump

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

length (CRL) was less than –1 to +1 days, the duration of pregnancy was estimated using time-to-event analysis: non-elective delivery was taken to be the event while elective delivery was taken to be censoring [14]. The median time to non-elective delivery was 283 days from LMP. The life-table graph published in this study gives an incidence of post-term pregnancy of about 6%. This study likely underscores the importance of accurate dating in the actual incidence of post-term pregnancy.

As noted earlier, accuracy of gestational age is an important component of determining whether a pregnancy is post-term. This has been demonstrated in several studies of pregnancy dating. For example, one study found that reliance on menstrual dates gave an incidence of post-term pregnancy of 10.7%, whereas the use of basal body temperature (BBT) charts gave a much lower rate of 4.7% [15]. In another study, the routine use of ultrasound to confirm pregnancy dating decreased the overall incidence of post-term pregnancy from 12 to 3% [16]. The impact of BBT or ultrasound dating is likely because women are far more likely to be oligo-ovulatory and have delayed ovulation than polyovulatory with earlier ovulation. Delayed ovulation in any given menstrual cycle would place a pregnancy at an earlier gestational age than that predicted by the first day of the LMP.

Other studies have demonstrated that the use of ultrasound to establish gestational age lowers the incidence of post-term pregnancy. Eik-Nes *et al.* [17] showed that adjustment of dates following measurement of the biparietal diameter at 17 weeks' gestation led to an incidence of post-term pregnancy of 3.9%. Three other studies of routine ultrasound examination for dating have demonstrated a reduction in the rate of false-positive diagnoses of post-term pregnancy, and thereby the overall rate of post-term pregnancy, from 10–15% to approximately 2–5% [18–20]. In a Cochrane review of randomized trials of routine versus selective second-trimester ultrasound, routine second-trimester biometry was found to reduce the number of pregnancies classified as post-term [21].

Moreover, early ultrasound for pregnancy dating may be superior to mid-trimester ultrasound in this regard. In a small prospective randomized trial, Bennett *et al.* [22] demonstrated that routine first-trimester ultrasound for pregnancy dating reduced the incidence of post-term pregnancy from 13% to 5% compared with second-trimester ultrasound dating. In another study, it was demonstrated that not only did first-trimester ultrasound dating lead to lower rates of post-term pregnancy beyond 42 weeks' gestation, but the same was true for diagnosis of pregnancy beyond 41 weeks' gestation [23]. Improved dating also reveals a greater difference in the rate of perinatal complications between term and post-term pregnancies. This is due to the misclassification bias that usually occurs with misdating. Such misclassification of women who are term as post-term and women who are post-term as term both lead to a smaller difference in the rate of complications between term and post-term pregnancies. Thus, older studies of women whose pregnancies did not have dating confirmation by ultrasound underestimate the rates of complications seen in post-term pregnancies. The multicentre First and Second Trimester Evaluation for Aneuploidy Trial (FASTER) studied 3588 women undergoing first-trimester ultrasound [24]. Gestational age determination using CRL as opposed to LMP reduced the apparent incidence of pregnancies greater than 41 weeks' gestation from 22.1 to 8.2% (P <0.001). Of note, ultrasound at 12–14 weeks' gestation, while considered early, can often lead to worse estimates of gestational age than ultrasound at 18–22 weeks. Thus, reliance on standard nuchal translucency ultrasound over an earlier first-trimester ultrasound may be problematic and requires further research.

Summary box 23.1

- Post-term gestation is defined as 42 weeks of gestation and beyond.
- Many other terms, such as 'post-dates' and 'prolonged pregnancy', are used interchangeably with 'post-term'.
- It is likely that many so-called post-term pregnancies are due to misdating.
- Pregnancies with dating confirmed by ultrasound are less likely to become post-term.
- First-trimester ultrasound is even better than second-trimester ultrasound with respect to the prevention of misdiagnosed post-term pregnancy.

Aetiology

It is likely that the majority of post-term pregnancies represent the upper range of a normal distribution. Further, as noted above, the most common 'cause' of post-term pregnancy is inaccurate pregnancy dating. However, it does appear that there are specific associations with a range of predictors that may help point to potential aetiologies of post-term pregnancy.

Rare but classically described causes of post-term pregnancy include placental sulfatase deficiency (an X-linked recessive disorder characterized by low circulating estriol levels), fetal adrenal insufficiency or hypoplasia, and fetal anencephaly (in the absence of polyhydramnios) [25,26].

Genetic factors may also play a role in prolonging pregnancy. In one study, women who were the product of a pregnancy beyond 41 weeks' gestation were more likely themselves to have a pregnancy progress beyond

41 weeks' gestation (relative risk, RR 1.3) [27]. Similarly, women who have had a prior post-term pregnancy are more likely to have another such pregnancy [27,28]. For example, after one pregnancy beyond 41^{+0} weeks of gestation, the risk of a second such pregnancy in the subsequent birth is increased 2.7-fold (from 10 to 27%). If there have been two successive prolonged pregnancies, the incidence rises to 39% [29]. Paternal genes expressed in the fetoplacental unit also appear to influence length of gestation. In a recent Danish case–control study [30] of women with two consecutive births, the risk of a second post-term pregnancy among 21 746 women whose first delivery was post-term was 20% as compared with 7.7% among 7009 women whose first delivery was at term. However, the risk of recurrent post-term delivery was reduced to 15% when the first and second child had different fathers (odds ratio, OR 0.73, 95% CI 0.63–0.84).

Low vaginal levels of fetal fibronectin at 39 weeks are predictive of an increased likelihood of post-term pregnancy [31]. Ramanathan *et al.* [32] showed how transvaginal measurement of cervical length at 37 weeks predicts both post-term pregnancy and failed induction. These observations suggest that a defect or delay in the remodelling of the cervix that takes place prior to successful initiation of labour may cause post-term pregnancy and may also be associated with some of the apparent increase in dystocia associated with post-term pregnancy.

Post-term pregnancy could result from variations in the corticotrophin-releasing hormone (CRH) system during pregnancy, such as alteration in the number or expression of myometrial receptor subtypes, altered signal transduction mechanisms or increase in the capacity of CRH-binding protein to bind and inactivate CRH. Prospective longitudinal studies have shown that women destined to deliver before term tend to have a more rapid exponential rise in CRH in mid-pregnancy while women who go on to deliver post-term babies have a slower rate of rise [33]. Efforts currently directed towards researching the initiation of labour before term may lead to greater understanding of the aetiology of post-term pregnancy.

Epidemiology

There are a number of risk factors associated with post-term pregnancy which may have biological causal association. First among these is nulliparity, with a greater proportion of nulliparas reaching 40, 41 or 42 weeks' gestation and the median duration of pregnancy being 2 days longer in nulliparas compared with multiparas. Recent data have also shown an association with male fetuses [34]. Additionally, it has been described that African-American women have higher rates of preterm delivery [35], raising the possibility that race/ethnicity may be associated with overall gestational age and prolonged pregnancy in particular. One recent study found a decreased risk of post-term pregnancy among African Americans, Asians and Latinas compared with white women [36]. Further, some effects of race/ethnicity have been described to vary between obese and non-obese patients [37]. Obesity has been found to be associated with post-term pregnancy in several studies [38,39]. The association may have actual causality: studies have demonstrated this finding consistently and have shown a dose–response effect, with greater response among women who are obese than those who are overweight.

The theoretical mechanisms for the association between obesity and post-term pregnancy remain unclear. Since adipose tissue is hormonally active [40] and since obese women may have an altered metabolic status, it is possible that endocrine factors involved in the initiation of labour are altered in obese women. The long-noted associations between lower pre-pregnancy body mass index (BMI) and increased spontaneous preterm birth [41,42] are consistent with our findings and may be explained by a common, as yet unknown, mechanism regarding parturition, potentially related to circulating levels of oestrogen or progesterone. Since, evolutionarily, as a species we have evolved to face the environmental pressures of food scarcity, it is likely that the outcomes of a post-term pregnancy rarely served as an evolutionary pressure related to obesity 10 000 years ago when we existed primarily as nomadic tribes with a lower median BMI than today. Thus there is likely little benefit to the fetus for the pregnancy to proceed beyond 42 weeks' gestation, and such post-term pregnancies may be a product of current intrinsic and environmental factors.

Summary box 23.2

Post-term gestation is seen more commonly with:

- anencephaly;
- placental sulfatase deficiency;
- fetal adrenal hypoplasia;
- male fetuses;
- previous post-term pregnancy;
- maternal obesity;
- nulliparity;
- white race.

The aetiology of post-term pregnancy appears to have both a maternal and fetal component. It seems likely that there is some genetic predilection towards post-term pregnancy.

Risks associated with post-term pregnancy

Perinatal mortality

Post-term pregnancy is associated with an increased risk of perinatal mortality, both antepartum stillbirth as well as infant death. There is an important methodological distinction to make when measuring complications by gestational age. Some complications can only happen to women and infants who are delivered at that week of gestation. Other complications can occur to all women who are pregnant at that week of gestation, both those delivering as well as those who remain pregnant. For example, an antepartum stillbirth can occur in anyone who is pregnant at a given gestational age, i.e. in ongoing pregnancies. Alternatively, a neonatal death can only occur to the group that actually delivers at that week of gestation [43]. When considering the outcomes related to post-term pregnancy, we see the association with antepartum stillbirth regardless of how the effect is measured, but when the appropriate denominator of ongoing pregnancies is used, we see the risk of antepartum stillbirth begin to increase earlier at 39 and 40 weeks' gestation. Yudkin *et al.* [44] questioned the validity of using perinatal mortality rates as a means of relating outcome to gestational age, arguing that the population at risk of intrauterine fetal death at a given gestational age is the population of fetuses *in utero* at that gestational week and not those delivered at that week. However, the population at risk of intrapartum and neonatal complications such as cord prolapse or meconium aspiration syndrome is clearly the population of babies delivered at that week of pregnancy [45]. These issues are clearly explained by Smith [45], who related the perinatal risks at each gestational week to the appropriate denominators. Antepartum deaths were related to the number of ongoing pregnancies, intrapartum deaths to all births at that gestational age, excluding antepartum stillbirths, and neonatal deaths were related to the number of live births. Yudkin *et al.* [44] expressed the prospective risk of stillbirth for the next 2 weeks of the pregnancy; Hilder *et al.* [13] expressed the risk as a rate over the next week; Cotzias *et al.* [3] generated considerable controversy [46,47] by expressing the risk of prospective stillbirth for the remainder of the pregnancy. This is a counter-intuitive concept for most obstetricians, whereas many find the concept of the prospective risk of stillbirth over the coming week an accessible concept, particularly in pregnancies of 40–42 weeks' gestation ('If this woman remains undelivered in the next 7 days, what is the chance of a fetal death occurring *in utero*?').

In the broad range of literature, studies which dichotomize gestational age at 42 weeks demonstrate increased perinatal mortality (Table 23.1). The outcomes presented in this table compare pregnancies fulfilling the epidemiological definition of post-term pregnancy with those delivered at 'term'. In modern obstetric practice, women with epidemiological and obstetric risk factors are more likely to be delivered before 42 weeks. Thus women with twin pregnancies, pre-eclampsia, diagnosed intrauterine growth restriction, antepartum haemorrhage or previous perinatal death are likely to be over-represented in the 37–41 week population and under-represented among those delivered at 42 weeks and later, potentially underestimating the increased risks from progressing to the post-term period.

Studies have also examined these outcomes by week of gestation across all term pregnancies by week and demonstrate similar findings (Table 23.2). Specifically, this table addresses the argument that the duration of pregnancy is a continuum and that perinatal risks are unlikely to alter abruptly on day 294 of a pregnancy. Outcomes are presented by week of gestational age from 37 weeks up to and including 43 weeks' gestation. Outcome statistics are presented in a variety of forms as discussed above.

At first sight, it might seem that whether studies have used thresholds like 42 and 43 weeks of gestation or

Table 23.1 Perinatal mortality rates in term versus post-term pregnancies.

Reference	Source	Outcome	37–41 weeks	42 weeks and over
Campbell *et al.* [58]	444 241 births Norway 1978–1987	Relative risk of perinatal death	1	1.30 (1.13–1.50)
Fabre *et al.* [133]	547 923 births Spain 1980–1992	Stillbirth rate	3.3	3.6
		Early neonatal mortality rate	1.7	2.8
		Perinatal mortality rate	4.9	6.4
Olesen *et al.* [28]	78 033 post-term pregnancies, Danish birth register 1978–1993, 5% sample of deliveries at term	Adjusted odds ratio: stillbirth	1	1.24 (0.93–1.66)
		Adjusted odds ratio: neonatal death	1	1.60 (1.07–2.37)
		Adjusted odds ratio: perinatal death	1	1.36 (1.08–1.72)

Table 23.2 Perinatal outcomes by week of gestation, 37–43 weeks.

Reference	Source	Outcome	38–39	39–40	40–41	41–42	42–43	≥43
Bakketeig & Bergsjo	157 577 births, Sweden 1977–1978	Perinatal mortality rate	7.2	3.1	2.3	2.4	3	4
Ingemarsson & Kallen [51]	914 702 births, Sweden 1982–1991	Stillbirth rate in nulliparas	2.72	1.53	1.23	1.86	2.26	
		Neonatal mortality rate nulliparas	0.62	0.54	0.54	0.9	1.03	
		Stillbirth rate in multiparas	2.1	1.42	1.35	1.4	1.51	
		Neonatal mortality rate multiparas	0.55	0.45	0.53	0.5	0.86	
Divon *et al.* [134]	181 524 singleton pregnancies, reliable dates, ≥40 weeks, Sweden 1987–1992	Odds ratio for fetal death			1	1.5	1.8	2.9
Hilder *et al.* [13]	171 527 births, London 1989–1991	Stillbirth rate	3.8	2.2	1.5	1.7	1.9	2.1
		Infant mortality rate	4.7	3.2	2.7	2	4.1	3.7
		Stillbirth rate per 1000 OP*	0.56	0.57	0.86	1.27	1.55	2.12
		Infant mortality rate per 1000 OP	0.7	0.83	1.57	1.48	3.29	3.71
Caughey & Musci [54]	Hospital based, California 1992–2002, 45 673 births after 37 weeks	Fetal death rate per 1000 OP	0.36	0.4	0.26	0.92	3.47	
Smith [45]	700 878 births in Scotland 1985–1996, multiple births and congenital anomalies excluded	Cumulative probability of antepartum stillbirth	0.0008	0.0013	0.0022	0.0034	0.0053	0.0115
		Estimated probability of intrapartum and neonatal death	0.0006	0.0005	0.0006	0.0006	0.0006	0.0008

OP, ongoing pregnancies.

examined complications by week was only a matter of whether the strata required increased subgroup sample size due to needs for increased statistical power. However, examining these outcomes by threshold or in a continuous fashion is an important methodological issue. If complication rates increase as gestational age increases, then one would see an increase regardless of what threshold was chosen. And it is true, if one examines stillbirth rates before and after 39, 40, 41, 42 or 43 weeks, there is always a higher rate beyond the threshold. More importantly is how such information can be utilized to inform clinical management. Thus, a comparison of one week to the next is truly what needs to be examined. Are the risks higher of delivering at a given gestational age or of waiting an additional week of gestation? For such comparisons, examining complications week by week is of more use than simply comparing before and after a given threshold.

There are other methodological problems with this literature. Of course, there may be errors or biases in recording of information relating to gestational age. Women with uncertain dates have been repeatedly shown to be at increased risk of perinatal mortality [48,49]. Their inclusion may inflate the apparent perinatal risks of post-term pregnancy. Older studies of perinatal outcome in post-term pregnancy showed that about 25% of the excess mortality risk in post-term pregnancy relates to congenital malformations [25]. Of the studies quoted in Tables 23.1 and 23.2, only that by Smith [45] specifies that cases of lethal congenital malformation have been excluded from the analysis. Hilder *et al.* [46] reanalysed the data presented in their 1998 study [13] after correcting for congenital malformation, showing that the outcomes presented were not biased by fetuses with congenital malformation being preferentially represented among post-term pregnancies. Another potential bias is the interval between intrauterine death and delivery. A fetus that dies *in utero* at 41 weeks and is delivered at 42 weeks will be counted as a perinatal death at 42 weeks' gestation. If this happened regularly, this would suggest that perinatal mortality risks actually increase half a week to a week earlier.

Both tables show that post-term pregnancy is associated with an increased risk of perinatal death. However, there is no consistency between studies as to the timing of that increased risk from fetal death before labour, to antepartum death to early neonatal death or even infant mortality. The studies summarized in Table 23.1 suggest that an increased risk of neonatal death is the main source of the increased perinatal risk. This has been further substantiated by a recent study from California which finds higher rates of infant death in births at

41 weeks and beyond even in a low-risk population [50]. However, Table 23.2 shows that when pregnancies ending at 42 weeks are compared with those delivered at 41 weeks, every adverse outcome is increased with the exception of the 'estimated probability of intrapartum and neonatal death' from the Smith study [45]. When pregnancies ending at 41 weeks are compared with those ending at 40 weeks, this outcome is again unchanged, as is the neonatal mortality rate in multiparas in the Ingemarsson and Kallen series [51] and the infant mortality rate in the Hilder series [13]. All other outcomes deteriorate from 40 weeks to 41 weeks and again from 41 weeks to 42 weeks.

Perinatal morbidity

Epidemiological studies identify birth after 41 weeks or after 42 weeks as a risk factor for a variety of adverse neonatal outcomes. One retrospective cohort study of all low-risk, term, cephalic and singleton births delivered at the University of California, San Francisco, between 1976 and 2001 examined the incidence of adverse neonatal morbidity outcomes at 40, 41 and 42 weeks' gestation and compared these with the rates in pregnancies delivered at 39 weeks' gestation, after controlling for maternal demographics, length of labour, induction, mode of delivery and birthweight (except macrosomia) [52]. Compared with the outcome at 39 weeks' gestation, the relative risk of meconium aspiration increased significantly from 2.18 at 40 weeks to 3.35 at 41 weeks and 4.09 (95% CI 2.07–8.08) at 42 weeks. A composite outcome of 'severe neonatal complications', including skull fracture and brachial plexus injuries, neonatal seizures, intracranial haemorrhage, neonatal sepsis, meconium aspiration syndrome and respiratory distress syndrome, increased from a relative risk of 1.47 at 40 weeks to 2.04 at 41 weeks to 2.37 (95% CI 1.63–3.49) at 42 weeks. Similar findings have been demonstrated in multiple other studies that examined perinatal morbidity including pre-eclampsia, meconium, meconium aspiration syndrome, macrosomia, neonatal acidaemia, need for neonatal mechanical ventilation, caesarean delivery and perinatal infectious morbidity [53–57].

For example, dystocia, shoulder dystocia and obstetric trauma are all increased in post-term pregnancy [58]. Here, the risks increase with increasing fetal weight, but gestational age remains a risk factor independent of birthweight. In a case-matched study of 285 women with uncomplicated singleton post-term pregnancy and spontaneous onset of labour and 855 women with uncomplicated singleton term pregnancy, Luckas *et al.* [59] showed that caesarean delivery was significantly more common in women with post-term pregnancy (RR 1.90, 95% CI 1.29–2.85). The increase was equally distributed between caesarean deliveries performed for failure to progress in labour (RR 0.74, 95% CI 1.02–3.04) and fetal distress (RR 2.00, 95% CI 1.14–3.61). This finding is consistent with the hypothesis that some cases of post-term pregnancy are associated with a defect in the physiology of labour, in addition to any increase in risk of fetal hypoxia. However, the possibility of bias in management arising out of the knowledge that a pregnancy is post-term cannot be excluded as a factor in the increase in caesarean delivery rates.

A strong association between neonatal seizures and delivery at 41 weeks' gestation or more has also been identified in previous case–control studies. Minchom *et al.* [60] found that delivery after 41 weeks' gestation was associated with an odds ratio of 2.7 (95% CI 1.6–4.8). Curtis *et al.* [61] studied 89 babies with early neonatal seizures delivered after 42 weeks' gestation in Dublin; 27 were delivered after 42 weeks' gestation compared with 6 of 89 controls (OR 4.73, 95% CI 2.22–10.05).

Cerebral palsy

Neonatal encephalopathy may be followed by the development of cerebral palsy, while other cases of cerebral palsy may occur following a clinically normal neonatal period. It is accepted that the presence of neonatal encephalopathy indicates that a neurological insult has taken place during labour or the early neonatal period, while its absence is thought to indicate an insult at some earlier time in pregnancy [62]. Gaffney *et al.* [63] examined the obstetric background of 141 children from the Oxford Cerebral Palsy Register; 41 children whose cerebral palsy was preceded by neonatal encephalopathy were compared with 100 who had not suffered from neonatal encephalopathy. The babies with neonatal encephalopathy were more likely to have been delivered at 42 weeks' gestation or more (OR 3.5, 95% CI 1–12.1). Babies born at 42 weeks or more to nulliparous women were at particular risk of this sequence of events (OR 11.0, 95% CI 1.2–102.5).

Effect of parity and birthweight

Whether these outcomes, their rates, peaks and nadirs are affected by other demographics such as maternal age, race/ethnicity, socioeconomic status and medical complications of pregnancy has been minimally studied. However, it has been examined by parity. One series [51] shows that the increasing risks of adverse outcome associated with advancing age of gestation are more marked in nulliparas than in multiparas (Table 23.2). The aetiology for the modification of these outcomes by parity is unclear and could be due to true biological differences or perhaps differences in dating accuracy between the two

groups. Birthweight has also been examined as a modifier of outcomes by gestational age. In an analysis of 181 524 singleton pregnancies with reliable dates delivered at 40 weeks or later in Sweden between 1987 and1992, birthweight of two standard deviations or more below the mean for gestational age was associated with a significantly increased odds ratios for both fetal death (OR 7.1–10.0) and neonatal death (OR 3.4–9.4) [51]. A Norwegian cohort [58] also showed that small-for-gestational age babies were more vulnerable to the risks of post-term pregnancy. In this study, babies weighing less than the 10th centile had a relative risk of 5.68 (95% CI 4.37–7.38) of perinatal death at 42 weeks' gestation or later compared with babies between the 10th and 90th centile at the same gestational age. In this series, birthweight above the 90th centile was associated with the lowest relative risk of perinatal death (RR 0.51, 95% CI 0.26–1.0). These findings make biological sense in that one might suspect that there would be a subgroup of fetuses whose growth is affected due to intrauterine factors that increase the risk for fetal or neonatal demise. The practice pattern of delivering such fetuses at an earlier gestational age is thus supported by such findings.

Summary box 23.3

Post-term gestation is associated with:

- stillbirth;
- caesarean delivery;
- fetal macrosomia;
- meconium-stained amniontic fluid;
- birth trauma;
- neonatal acidaemia;
- cerebral palsy;
- neonatal/infant mortality.

A key methodological point when examining outcomes by gestational age in term and post-term pregnancies is properly determining the population at risk, i.e. *ongoing pregnancies* (all women pregnant at a particular gestational age) or *pregnancies delivered* (just the women who deliver at a particular gestational age). While the outcomes listed are all more frequent in pregnancies at 42 weeks' gestation and beyond, they are also increased (though not as high) in pregnancies at 41 weeks' gestation.

Management

Management of post-term pregnancies actually starts before a pregnancy becomes post-term. The goals of managing such otherwise low-risk pregnancies is to prevent the complications of post-term pregnancy and to prevent post-term pregnancy itself. Thus, the mainstay of management involves the use of antepartum testing to reduce risks of complications from expectantly managing these pregnancies. It also includes reducing the risk of post-term pregnancy through good pregnancy dating, outpatient cervical ripening and induction of labour, all before a pregnancy becomes post-term. These broad topics are discussed next.

Antenatal testing

The evidence of increased perinatal mortality and morbidity in late term and post-term pregnancy compared with delivery at 39 or 40 weeks' gestation inevitably leads to the conclusion that some cases of post-term pregnancy could be prevented by earlier delivery. It would seem logical to use screening tests to identify pregnancies destined to have an adverse outcome and to intervene selectively in these cases.

The ideal test of fetal well-being in post-term pregnancy would allow identification of all fetuses at risk of adverse outcome, at a stage where delivery would result in a universally good outcome. Thus a 'negative' test would indicate that the fetus is safe *in utero* for an interval of a few days until either delivery or a repeat test is performed and that the woman would eventually deliver with a good outcome. At present, no method of monitoring post-term pregnancy is backed up by strong evidence of effectiveness. There is some observational evidence that some pregnancies at risk of adverse outcome can be identified, but less evidence that prediction of the adverse outcome confers prevention.

Fetal movement counting

The least invasive monitoring is maternal assessment of fetal movements, also known as fetal kick counts. This test is used commonly in the supervision of term and post-term pregnancies (Table 23.3) but is not supported by firm evidence of efficacy. Generally, women are asked to count fetal movements once or twice per day and are expected to experience four to six such movements in 20–30 min. Two randomized trials have addressed the question of whether clinical actions taken on the basis of fetal movement improve fetal outcome [64,65]. The larger of these trials involved over 68 000 women [65]. These trials collectively provide evidence that routine formal fetal movement counting does not reduce the incidence of intrauterine fetal death in late pregnancy. Routine counting results in more frequent reports of diminished fetal activity, with a greater use of other techniques of fetal assessment, more frequent admission to hospital and an increased rate of elective delivery. It may be that fetal movement counting in post-term pregnancy will perform more effectively than it does in low-risk

Table 23.3 Randomized trials of routine versus selective induction at 41–42 weeks' gestation.

Reference	No.	Gestation at trial entry (days)	Method of induction	Method of fetal surveillance	Perinatal deaths
Augensen *et al.* [135]	409	290	Oxytocin and amniotomy	CTG	0
Bergsjo *et al.* [123]	188	284	Membrane sweep, oxytocin, amniotomy	Fetal movement, ultrasound, urinary estriol	1 in induction arm 2 in selective arm
Cardozo *et al.* [124]	363	290	PGE_2, oxytocin, amniotomy	Fetal movement, CTG	1 in selective arm 1 in induction arm
Chanrachakul & Herabutya [136]	249	290	Amniotomy and oxytocin	CTG, AFI	0
Dyson *et al.* [121]	302	287	PGE_2, oxytocin, amniotomy	CTG, AFI	1 in selective arm
Hannah *et al.* [111]	3407	287	PGE_2, oxytocin, amniotomy	Fetal movement, CTG, AFI	2 in selective arm
Heden *et al.* [137]	238	295	Amniotomy, oxytocin	CTG, AFI	0
Henry [122]	112	290	Amniotomy and oxytocin	Amnioscopy	2 in selective arm
Herabutya *et al.* [138]	108	294	PGE_2, oxytocin	CTG	1 in selective arm
James *et al.* [139]	74	287	Extra-amniotic saline if Bishop score <5; membrane sweep, amniotomy and oxytocin	Fetal movement, BPS	0
Katz *et al.* [120]	156	294	Amniotomy, oxytocin	Fetal movement, amnioscopy, oxytocin challenge	1 in each arm
Martin *et al.* [140]	22	287	Laminaria, oxytocin	CTG, AFI	0
NICHD [141]	440	287	CTG, oxytocin, amniotomy	CTG, AFI	0
Roach & Rogers [142]	201	294	PGE_2	CTG, AFI	0
Suikkari *et al.* [143]	119	290	Amniotomy, oxytocin	CTG, human placental lactogen, estriol, AFI	0
Witter & Weitz [144]	200	287	Oxytocin, amniotomy	Estriol, oxytocin challenge	0

AFI, amniotic fluid index; BPS, biophysical profile scoring; CTG, cardiotocography.

pregnancies. However, in the end, if this test did demonstrate reduction in perinatal morbidity or mortality, it is likely that such a protocol also leads to maternal anxiety and high rates of false positives.

Cardiotocography

Antenatal cardiotocography (CTG), also known as a non-stress test, has been widely used for more than 20 years to monitor moderate- to high-risk pregnancies. Observational studies have reported very low rates of perinatal loss in high-risk pregnancies monitored in this way [66,67]. Six randomized controlled trials comparing CTG with other methods of antepartum fetal monitoring have been the subject of a Cochrane review [68]. Women with post-term pregnancies were included in these trials. On the basis of the information presented in this review, the antenatal CTG has no significant effect on perinatal outcome or on interventions such as elective delivery. Miyazaki and Miyazaki [69] reported a series of 125 women with post-term pregnancies where a reactive CTG was recorded within 1 week of delivery. Ten adverse outcomes were reported from this group: four antepartum deaths, one neonatal death, one case of neonatal encephalopathy and four cases of fetal distress on admission in early labour. The poor performance of antenatal CTG in this series and in the randomized trials may relate to errors in interpretation or excessive intervals between tests. Numerical analysis using computerized calculations of the baseline rate and variability may reduce the potential for human error [70]. Weiner *et al.* [71] compared the value of antenatal testing with computerized CTG, conventional CTG, biophysical profile scores and umbilical artery Doppler; 337 pregnant women who were delivered after 41 weeks' gestation and who had 610 antenatal tests were included in this study. Of 12 fetuses with reduced fetal heart rate variation on computerized CTG, 10 had a trial of labour. Of these 10 fetuses, nine had fetal distress during labour. Of the 12 fetuses with reduced fetal heart rate variation, seven were acidotic at delivery (umbilical artery pH <7.2).

Overall, there were 10 acidotic fetuses at delivery in the study group. Only two of them had an umbilical systolic/diastolic ratio above the 95th percentile, three had an amniotic fluid index greater than 5, and five had fetal heart rate decelerations before labour. Fetuses who demonstrated an abnormal intrapartum fetal heart rate tracing or who were acidotic at delivery had a significantly higher rate of reduced fetal heart rate variation or decelerations before labour. The authors conclude that computerized CTG may improve fetal surveillance in post-term pregnancy. The obvious criticism of this study is the circular argument of using an antepartum CTG abnormality to predict an intrapartum CTG abnormality.

Ultrasound assessment of amniotic fuid

Ultrasound monitoring of amniotic fluid volume was first described in 1980 when a subjective classification of 'normal', 'reduced' or 'absent' amniotic fluid was described, based on the presence or absence of echo-free space between the fetal limbs and the fetal trunk or the uterine wall [72]. To test the value of the classification, 150 patients with pregnancies of 42 weeks or more underwent ultrasound examination in the 48 hours prior to delivery. The patients classified as having reduced or absent amniotic fluid had a statistically significant excess incidence of meconium-stained liquor, fetal acidosis, and birth asphyxia and meconium aspiration. Manning *et al.* [73] described a semi-quantitative method based on the largest vertical pool of amniotic fluid and used a 1-cm pool depth as the cut-off for intervention in a population of babies with suspected growth restriction. This was subsequently modified to 2 cm to improve detection of the growth-retarded infant [74]. Crowley *et al.* [75] found an increase in adverse outcomes in post-term pregnancies where the maximum pool depth was less than 3 cm. Fischer *et al.* [76] found that a maximum vertical pool of less than 2.7 cm was the best predictor of abnormal perinatal outcome.

Phelan *et al.* [77] described the amniotic fluid index (AFI), the sum of the maximum pool depth in four quadrants. Fischer *et al.* [76] found that maximum pool depth performed better than AFI in predicting adverse outcomes in post-term pregnancies. Alfirevic and Walkinshaw [78] randomly allocated women with post-term pregnancy to monitoring using either maximum pool depth or AFI. Both groups underwent computerized fetal heart rate monitoring every 3 days in addition to amniotic fluid measurements. The threshold for intervention was a maximum pool depth of less than 1.8 cm or an AFI of less than 7.3 cm. These figures had been identified as the third centiles for the local population. The number of women found to have an abnormal AFI was significantly higher than the number found to have an abnormal maximum pool depth and more women underwent induction of labour in the AFI arm of the trial. There were no perinatal deaths and no statistically significant differences in perinatal outcome between the two groups.

Morris *et al.* [79] performed an observational study of 1584 pregnant women at or beyond 40 weeks' gestation in Oxford. Women underwent measurement of amniotic fluid, using both the single deepest pool and AFI. The results of these ultrasound measurements were concealed from caregivers. These authors agreed with Alfirevic and Walkinshaw [78] that more women 'test positive' using AFI than with single deepest pool; 125 women (7.9%) had an AFI of less than 5 cm in contrast to 22 women (1.4%) who had single deepest pool less than 2 cm. There were no perinatal deaths. There were seven cases of severe perinatal morbidity, an incidence of 0.44%. Two of these had an AFI below 5 cm and four had an AFI of less than 6 cm. None of the seven cases had a deepest pool measurement of less than 2 cm, thus emphasizing the trade-off between specificity and sensitivity.

Locatelli *et al.* [80] conducted a similar study, but measured AFI twice weekly from 40 weeks until delivery. A composite adverse outcome of fetal death, 5-min Apgar score less than 7, umbilical artery pH less than 7 and caesarean delivery for fetal distress occurred in 19.8% of those with an AFI below 5 compared with 10.7% of those with an AFI above 5 ($P = 0.001$).

These studies of amniotic fluid after 40 weeks suggest some association between reduction in volume and adverse outcome, but overall it performs with poor sensitivity and specificity. There is no evidence to suggest that it can be relied on as a means of monitoring pregnancies after 41 weeks' gestation. In a meta-analysis of studies on the relationship of amniotic fluid with adverse fetal outcome, Chauhan *et al.* [81] concluded that there was some association between oligohydramnios and an increased risk of caesarean delivery for non-reassuring fetal heart rate patterns and low Apgar scores; however, the data relating to neonatal acidosis were insufficient. Fundamentally, while there is biological plausibility that decreases in amniotic fluid volume may pre-date complications in the term and post-term pregnancy, there are inadequate data to definitively state that such assessment followed by intervention will necessarily affect perinatal outcomes, by how much and with what timing. Furthermore, confidence in ultrasound assessment of amniotic fluid volume is undermined by studies which show a poor correlation between ultrasound AFI and actual amniotic fluid volumes measured by dye-dilution studies [82,83]. Development of a better test to identify the senescent placenta or changing fetal–placental–maternal physiology at term and post-term that will prevent perinatal complications is paramount.

Biophysical profile

Observational studies indicate that low biophysical scores identify babies at higher risk of adverse outcome [84]. However, evidence of ability to predict adverse outcome must not be interpreted as proof of the ability to prevent these outcomes.

A systematic review of four trials, comparing biophysical profile scoring with other forms of antepartum fetal monitoring, yields insufficient data to show that the biophysical profile is better than any other form of fetal monitoring [85]. Only one of these randomized controlled trials deals specifically with post-term pregnancy [78]. This trial compares monitoring of post-term pregnancy using a modified biophysical profile score (consisting of computerized CTG, AFI and the rest of the components of the conventional biophysical profile) with simple monitoring using CTG and measurement of amniotic fluid depth. The more complex method of monitoring post-term pregnancy is more likely to yield an abnormal result, but does not improve pregnancy outcome as evidenced by umbilical cord pH.

An observational study of biophysical profile scoring in the management of post-term pregnancy showed that 32 of 293 women who had abnormal biophysical profiles had significantly higher rates of neonatal morbidity, caesarean delivery for fetal distress and meconium aspiration than the women with reassuring biophysical profiles [86]. A further observational study of 131 post-term pregnancies showed that a normal biophysical profile score was highly predictive of normal outcome, but an abnormal test had only a 14% predictive value of poor neonatal outcome [87].

Doppler velocimetry

Two studies of routine umbilical artery Doppler velocimetry [88,89] in post-term pregnancy indicate that it is of no benefit. In a small observational study comparing the predictive values of CTG, AFI, biophysical profile scoring and the ratio of middle cerebral artery (MCA) Doppler to umbilical artery Doppler, Devine *et al.* [90] found that the ratio of MCA Doppler to umbilical artery Doppler was the best predictor of 'adverse outcome' in this study, defined by meconium aspiration syndrome or caesarean delivery for fetal distress or fetal acidosis.

Prevention of post-term pregnancy

The prevention of post-term pregnancy centres around efforts to ensure that a misdiagnosis is not made from improper pregnancy dating and encouraging the onset of labour prior to post-term pregnancy developing. While the first demands public health action to ensure that all patients have the option to obtain first-trimester ultrasound dating confirmation, widespread adoption of this practice seems limited at this point. However, most women undergo second-trimester ultrasound, which also reduces the risk of being misdiagnosed with a post-term pregnancy, though not as much as first-trimester ultrasound.

Post-term pregnancy can absolutely be prevented by simply inducing all patients before they reach 42 weeks of gestation. This appears to be a reasonable approach, but does carry some costs due to the prolonged admissions to labour and delivery units for induction of labour. A better way of preventing such post-term pregnancies would use techniques to encourage spontaneous labour. Several minimally invasive interventions have been recommended to encourage the onset of labour at term and prevent post-term pregnancy, including membrane stripping, unprotected coitus and acupuncture. *Stripping or sweeping of the fetal membranes* refers to digital separation of the membranes from the wall of the cervix and lower uterine segment. This technique, which likely acts by releasing endogenous prostaglandins from the cervix, requires the cervix to be sufficiently dilated to admit the practitioner's finger. Although stripping of the membranes may be able to reduce the time interval to spontaneous onset of labour, there is no consistent evidence of a reduction in operative vaginal delivery, caesarean delivery rates, or maternal or neonatal morbidity [91–93]. *Unprotected sexual intercourse* causes uterine contractions through the action of prostaglandins in semen and potential release of endogenous prostaglandins similar to stripping of the membranes. Indeed, prostaglandins were originally isolated from extracts of prostate and seminal vesicle glands, hence their name. Despite some conflicting data, it appears that unprotected coitus may lead to the earlier onset of labour, reduction in post-term pregnancy rates, and less induction of labour [94–96]. In one small randomized trial which attempted to address this question, women were randomized to a group advised to have coitus versus a control group which was not. In this study, the women advised to have coitus did so more often (60% vs. 40%), but there was no measurable difference in the rate of spontaneous labour in this underpowered study [97]. Similarly, the efficacy of *acupuncture* for induction of labour cannot be definitively assessed because of the paucity of trial data and requires further examination [98,99].

Ultrasound to establish accurate gestational age

The first step towards managing post-term pregnancy is to reduce the number of cases of post-term pregnancy by providing ultrasound verification of gestational age for all pregnancies. A systematic review shows that routine second-trimester ultrasound reduces the number of cases of post-term pregnancy [21]. A recent randomized controlled trial of first- versus second-trimester ultrasound showed a lower rate of post-term pregnancy in pregnancies dated by first-trimester ultrasound [22].

A secondary analysis of data from the FASTER trial showed that first-trimester ultrasound determination of gestational age by CRL as opposed to LMP reduces the apparent incidence of pregnancies greater than 41 weeks from 22.1% to 8.2% [24]. It does seem that obtaining a first-trimester ultrasound to assess viability and gestational age at the first visit is a good idea and may impact the overall number of diagnosed post-term pregnancies.

Induction of labour for post-term pregnancy

Given that a patient cannot have a stillbirth at 42 weeks if she is induced at 41 weeks, induction of labour has been identified as the principal intervention to reduce perinatal morbidity from post-term pregnancy. However, there is concern that such inductions of labour are in turn driving up the caesarean delivery rate. Thus, obstetric providers have responded in various ways to the apparently increased perinatal mortality and morbidity associated with post-term pregnancy. Such potential clinical options include induction at term to prevent pregnancies reaching 42 weeks, routine induction at 41 or 42 weeks or shortly before, and selective induction at 41 or 42 weeks in cases identified by tests as being at risk of adverse outcome. Fortunately, the benefits and hazards of some of these strategies have been evaluated in randomized controlled trials. Randomized or quasi-random trials comparing elective induction at term versus expectant management, and elective induction after 41 weeks versus monitoring of post-term pregnancies were identified using the search strategy described by the Cochrane Pregnancy and Childbirth Group and formed the basis of a systematic review of management options in post-term pregnancy [100]. The main outcomes of interest are those already identified in the analysis of post-term pregnancy risks: perinatal mortality, neonatal encephalopathy, meconium-stained amniotic fluid, caesarean delivery. In addition, evidence was sought relating to the effect of the various management options on maternal satisfaction. Subsequently, there have been other systematic reviews of randomized trials comparing induction of labour with expectant management in pregnancies of 41 weeks' gestation and more [101] or 41 weeks' gestation or less [102].

One major concern regarding induction of labour has been that of increased risk of caesarean delivery. However, this conclusion has not been universally accepted [103]. One component of the concern regarding induction of labour is the large number of retrospective studies which demonstrate higher rates of caesarean delivery in the induced patients [104,105]. The methodological problem with these studies is that they generally compare women who are induced to those in spontaneous labour [106]. A recent study which compared women who were induced with those who underwent expectant management actually found lower rates of caesarean delivery in the women who were induced [107]. Further, in a recent meta-analysis of three small studies of elective induction of labour prior to 41 weeks' gestation, induction of labour led to lower rates of caesarean delivery [108].

An alternative approach to the prevention of post-term pregnancy is selective or preventive rather than routine induction of labour at an earlier gestational age. In a small preliminary study of active management of risk in pregnancy at term (AMOR-IPAT) in which induction of labour at 41 weeks was recommended for all women with risk factors for cephalopelvic disproportion or intrapartum non-reassuring fetal testing, Nicholson *et al.* [109] were able to decrease the caesarean delivery rate from 17% in the expectantly managed group (induction rate, 26%) to 4% in the risk-factor managed group (induction rate, 63%).In a recent, prospective, randomized controlled trial, there was a trend towards lower caesarean rates in the risk-factor managed group, but the study was underpowered for this outcome [110]. However, it did find lower rates of admission to neonatal intensive care and an improved adverse outcome index in the risk-factor managed group, which was induced in the majority of cases.

Induction of labour at 41 weeks

Sixteen randomized trials comparing 'routine' induction of labour at a specified gestational age with a policy of selective induction of labour in response to an abnormal antepartum test are summarized in Table 23.3. These trials form the basis of a systematic review by Sanchez-Ramos *et al.* [101]. Twelve of them had been previously included in the Cochrane review by Crowley [100]. One trial is larger than all others and contributes considerable weight to both meta-analyses [111]. Both meta-analyses adopt an inclusive approach and include trials of variable size and quality. The gestational age at trial entry varies from 287 to 294 days' gestation. A variety of methods of antepartum fetal testing are used to supervise pregnancies in the expectant arm of the trials.

As noted above, it could be costly to routinely induce all women at 41 weeks' gestation. However, a study found routine induction of labour at 41 weeks' gestation to be cost-effective (i.e. more costly than not, but worth the improved outcomes) when compared with expectant management [112]. Routine induction of labour at 41 weeks' gestation was also included in recent recommendations from ACOG to safely reduce the primary caesarean delivery [113].

Induction at or before 40 weeks

Pre-emptive induction of labour, where women with uncomplicated pregnancies were routinely offered induction at or before 40 weeks, was practised in some

obstetric units in some countries in the 1970s. Six randomized trials compare a policy of 'routine' induction at 39 weeks [114,115] or 40 weeks [116–119], with either 'expectant' management of an indefinite duration or expectant management until 42 weeks' gestation. These trials reveal no evidence of any major benefit or risk to 'routine' induction at 40 weeks. Two perinatal deaths of normally formed babies occurred in the expectant arm of these trials and none in the induction arm. Obviously, this is not a significant difference. There was no effect on rate of caesarean delivery (OR 0.60, 95% CI 0.35–1.03), instrumental delivery or use of analgesia in labour. Not surprisingly, given the relationship between gestational age and meconium staining of the amniotic fluid in labour, induction around 40 weeks reduces the incidence of meconium staining in labour (OR 0.50, 95% CI 0.31–0.86). Unfortunately, the authors of these trials did not address the important question of women's views of induction of labour at this stage of pregnancy. The authors therefore missed a golden opportunity in failing to measure women's satisfaction with their care. 'Routine' induction of labour at 40 weeks would no longer be considered a realistic option for the prevention of post-term pregnancy. The number of inductions at 40 weeks required to prevent an adverse outcome at 41 or 42 weeks would be excessive and intervention at this level would be unlikely to be welcomed by women, obstetricians or midwives. Currently, a large prospective trial of this question – routine induction of labour at 39 or 40 weeks' gestation versus expectant management – is being conducted in the USA.

Induction of labour and perinatal morbidity and mortality

Even the largest trial [111] has insufficient statistical power to detect a significant reduction in the perinatal mortality rate. To have an 80% chance of detecting a 50% reduction in a perinatal mortality rate of 3 per 1000, a sample size of 16 000 is required. Table 23.3 records the 13 perinatal deaths that occurred in the randomized trials, three among 3159 women allocated to induction and 10 among 3067 women allocated to selective induction. One normally formed baby, among those allocated to induction [120], died from asphyxia following emergency caesarean delivery for meconium-stained amniotic fluid and bradycardia 2 hours after induction of labour. The other two deaths among those allocated to routine induction occurred in babies with lethal congenital anomalies. Three further deaths occurred in babies with anomalies among those allocated to selective induction. The other seven deaths occurred in normally formed babies. Two deaths in the Canadian Post-term Pregnancy Trial [111] occurred despite adherence to the monitoring protocol of daily movement counting and three times weekly CTG and ultrasound assessment of amniotic fluid volume. These babies were both small, weighing 2600 and 3175 g. In the trial by Dyson *et al.* [121], a neonatal death from meconium aspiration occurred in a 43-week baby delivered for acute fetal bradycardia following spontaneous labour. Fetal heart rate monitoring and ultrasound assessment of amniotic fluid had been reassuring 48 hours before the spontaneous onset of labour. One of the deaths in the trial by Henry [122] was attributed to gestational diabetes. The second occurred due to meconium aspiration in a woman who refused induction following detection of meconium at amnioscopy. The deaths in the trials by Bergsjo *et al.* [123] and Cardozo *et al.* [124] were due to pneumonia and abruptio placentae, respectively.

The authors of systematic reviews adopt a different approach to the inclusion of perinatal deaths in babies with fetal abnormalities. These are excluded in the Cochrane review [100] and included by Sanchez-Ramos *et al.* [101]. Thus, the Cochrane systematic review shows that induction of labour is associated with a significant reduction in perinatal mortality in normally formed babies (OR 0.23, 95% CI 0.06–0.90), while Sanchez-Ramos *et al.* confirm the reduction in risk of perinatal death (0.9 vs. 0.33%) but with the 95% confidence intervals for the odds ratio of 0.41 crossing unity (95% CI 0.14–1.28).

Both systematic reviews report a significant reduction in the incidence of meconium-stained amniotic fluid but this does not affect the rate of meconium aspiration (0.82, 95% CI 0.49–1.37) [100]. There is no effect on fetal heart rate abnormalities during labour. The odds ratio for neonatal jaundice (3.39, 95% CI 1.42–8.09), based on the small number of trials that reported this outcome, indicate that it is increased by induction. The systematic reviews do not show any beneficial or hazardous effects on Apgar scores, neonatal intensive care admission or neonatal encephalopathy.

Effect of induction of labour on risk of caesarean delivery

Sanchez-Ramos *et al.* [101] report that induction of labour is associated with a reduction in the rate of caesarean delivery (OR 0.88, 95% CI 0.78–0.99). Crowley [100] reported a similar outcome, but interpreted it as evidence that a policy of 'routine' induction of labour does not increase the likelihood of caesarean delivery. She believed that a post-randomization bias in the Hannah trial [111] may have weighted the results towards a spurious reduction in risk of caesarean delivery. Women in the expectant arm of the Hannah trial who required induction because of abnormal antenatal tests were denied vaginal prostaglandins whereas those allocated to 'routine' induction were treated with prostaglandin E_2. This could potentially lead to an increase in dystocia or failed induction in those denied prostaglandins. However, this does

not account for the 8.3% rate of caesarean delivery for fetal distress in the selective induction arm of the Hannah trial compared with 5.7% in the routine induction arm. The effect of a policy of induction of labour on reducing the rate of caesarean delivery for fetal distress is consistent across the trials reviewed. No significant heterogeneity was detected by Sanchez-Ramos *et al.* [101]. These authors also performed funnel plots, which were symmetric, indicating no evidence of publications bias.

Because the reduced rate of caesarean delivery associated with induction of labour is contrary to a traditionally held view among obstetricians that induction of labour increases the likelihood of delivery by caesarean section, a number of secondary analyses were carried out by Crowley [100]. These showed that induction of labour for post-term pregnancy does not increase the caesarean delivery rate, irrespective of parity, cervical ripeness, method of induction or ambient caesarean delivery rates. As noted above, routine induction of labour at 41 weeks' gestation was also included in recent recommendations from ACOG to safely reduce the primary caesarean delivery [113].

Women's views of induction for post-term pregnancy

Regrettably, randomized trials give little information on women's views of induction versus conservative management. Only one trial assessed maternal satisfaction with induction of labour [124]. These authors showed that satisfaction was related to the eventual outcome of labour and delivery, rather than to the mode of onset of labour. Women's views are likely to be influenced by the local culture, by the attitude of their caregivers and by practical considerations such as the duration of paid maternity leave. Few obstetricians, midwives or childbirth educators are capable of giving women unbiased information about the risks of post-term pregnancy and the benefits and hazards of induction of labour. In a prospective questionnaire study of women's attitudes towards induction of labour for post-term pregnancy, Roberts and Young [125] found that despite a stated obstetric preference for conservative management, only 45% of women at 37 weeks' gestation were agreeable to conservative management if undelivered by 41 weeks. Of those undelivered by 41 weeks' gestation, 31% still desired conservative management. This significant decrease was unaffected by parity or certainty of gestational age. In a subsequent study, Roberts *et al.* [126] offered women a choice between induction and conservative management at 42 weeks; 45% of women opted for conservative management. Certainly, an intervention that is common practice in more than 20–25% of pregnancies in most developed countries deserves more study with respect to its impact on women as well as the neonates who are the product of these pregnancies.

Post-term pregnancy and home birth

There is a lack of good-quality epidemiological evidence on the outcome of post-term pregnancy when delivery occurs at home. Bastian *et al.* [127] used multiple methods of case identification and follow-up to assemble a population-based cohort of 7002 home births in Australia; 50 perinatal deaths occurred, giving a perinatal mortality rate of 7.1 per 1000. Of 44 perinatal deaths in women of known gestational age, seven (15.9%) occurred post-term (≥42 weeks). A study conducted among Native Americans examined an increase in perinatal mortality in home births attended by midwives compared with those attended by doctors and identified post-dates pregnancies, breech deliveries and twins as the source of the difference in mortality rates between the two groups [128]. Given these relatively weak findings combined with the overall evidence regarding post-term pregnancy and intrapartum complications and perinatal morbidity and mortality, many home birth providers will refer such patients to an in-hospital practice.

Summary box 23.4

Antenatal testing

The following tests are often started at 40–41 weeks of gestation:

- fetal movement or 'kick' counts;
- CTG or non-stress test;
- assessment of amniotic fluid volume;
- biophysical profile.

Post-term pregnancy

Post-term pregnancy may be prevented by:

- induction of labour;
- stripping/sweeping the membranes;
- vaginal intercourse;
- accupuncture.

While induction of labour has been asociated with caesarean deliveries in previous retrospective literature, current prospective literature supports the premise that caesarean delivery is lower among those induced at 41 or 42 weeks' gestation compared with those managed expectantly beyond these thresholds.

Clinical guidelines for management of post-term pregnancy

Following the publication of the Canadian Post-term Pregnancy Trial [111] and the Cochrane review on post-term pregnancy management [114], the Society of Obstetricians and Gynaecologists of Canada (SOGC) issued a clinical practice guideline [129] that recommended the following.

1) After 41 weeks' gestation, if the dates are certain, women should be offered elective delivery.
2) If the cervix is unfavourable, cervical ripening should be undertaken.
3) If expectant management is chosen, assessment of fetal health should be initiated.

The Royal College of Obstetricians and Gynaecologists (RCOG) issued a clinical guideline on induction of labour in 2001 that included recommendations on management of post-term pregnancy [130].

1) Ultrasound to confirm gestation should be offered prior to 20 weeks, as this reduces the need for induction for perceived post-term pregnancy.
2) Women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks.
3) From 42 weeks, women who decline induction of labour should be offered increased antenatal monitoring, consisting of twice-weekly CTG and ultrasound estimation of maximum amniotic pool depth.

The ACOG Practice Guidelines [5] are somewhat similar, but specifically include the following.

1) The definition of post-term pregnancy should remain at 42 weeks of gestation and beyond.
2) Women with post-term pregnancies who have unfavourable cervices can either undergo labour induction or be managed expectantly.
3) Prostaglandins can be used in post-term pregnancies to promote cervical ripening and induce labour.
4) Delivery should be effected if there is evidence of fetal compromise or oligohydramnios.
5) Despite a lack of evidence that monitoring improves perinatal outcome, it is reasonable to initiate antenatal surveillance of post-term pregnancies between 41 weeks and 42 weeks' gestation because of evidence that perinatal morbidity and mortality increase as gestational age advances.
6) Recent ACOG guidelines regarding reducing the caesarean delivery rate suggest that routine induction of labour at 41 weeks' gestation is indicated.

The SOGC guidelines provoked an impassioned response [103]. These authors challenged the evidence of increased morbidity and mortality as pregnancy advances and the evidence from randomized trials that induction of labour post-term does not increase caesarean delivery rates and may reduce perinatal mortality rates. In particular, they were concerned that the recommendation from SOGC and RCOG that induction should be 'offered' at 41 weeks' gestation would be interpreted as a policy of mandatory induction at 41 weeks' gestation.

Thus, these three professional organizations, each with presumably capable and thoughtful members, arrived at a range of varied conclusions. Certainly this suggests, at the very least, there is a need for further research in this area, both on the effects of induction of labour, but also in ways to screen and prevent complications in late term and post-term pregnancies.

Practical management of post-term pregnancy

The RCOG recommendations are an excellent guide to practice. Every effort should be made to ensure that dates are as accurate as possible. When a woman reaches 41 weeks she should meet with a consultant obstetrician. Women have a right to be informed of the small increase in risk associated with continuing the pregnancy after 41 weeks. Thornton and Lilford [131] showed that pregnant women are much more risk averse than their caregivers. Following a vaginal examination, induction of labour should be offered on a date after 41 weeks that is acceptable to both the woman's wishes and the hospital resources. The vaginal examination could be accompanied by sweeping of the membranes, provided women are warned about the discomfort associated with this and are agreeable to proceed. Membrane sweeping reduces the need for 'formal' induction of labour [93]. The vaginal examination allows the obstetrician to inform the woman of the likely ease and success of induction of labour. For women who have previously delivered vaginally and for women with a favourable cervix, induction of labour is unlikely to be a difficult process. Women who wish to avoid induction of labour should be supported but should be made aware of the lack of reliability of antenatal tests and the lack of evidence that avoiding induction of labour reduces the risk of caesarean delivery. As induction of labour with prostaglandins is associated with an increased risk of uterine scar dehiscence compared with spontaneous onset of labour [132], women who have had a previous caesarean delivery, especially those with no vaginal deliveries, require carefully individualized management at 41 weeks' gestation.

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24

Induction and Augmentation of Labour

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Definition

Induction of labour is defined as the artificial initiation of labour [1]. It is performed when it is considered that there are benefits to the baby and/or mother if the baby is delivered, compared with the alternative of the baby remaining *in utero*. Rates of induction of labour have increased over a 10-year per period in the UK, from 15.4% in 2003–2004 to 21.2% in 2013–2014 [1]. Rates of induction of labour for singleton pregnancy were 23.3% in the USA in 2010, but with modest declines in the following two years [2].

Indications for induction of labour

The UK, the USA and the World Health Organization (WHO) have produced guidelines on the indications and methods for this common clinical procedure [3–5]. Possible indications for induction of labour include a range of conditions associated with maternal or fetal compromise (Table 24.1), although the risks and benefits of induction in many of these particular scenarios have not been fully evaluated in randomized trials. In practice, the timing of induction requires careful clinical judgement, and it is not always obvious at which point in these disease or physiological processes that the interests of the mother or baby, or both, will be better served by ending the pregnancy by induction of labour.

In practice, clinical conditions are not the only factors affecting induction rates, with one recent study suggesting that over 25% of the variation in induction rates is unexplained by such factors [6]. This variation may reflect differences in physicians' willingness to induce labour for maternal or caregiver convenience, greater or lesser demand from women for induction of labour in different areas, or uncertainties about the benefits and risks of induction across a range of scenarios.

Contraindications to induction of labour

There is greater consensus about the contraindications to induction of labour. Contraindications relate either to factors which make labour or vaginal delivery unsuitable or to indications for immediate delivery (these latter include complete placenta praevia, vasa praevia, transverse fetal lie, umbilical cord prolapse and previous classical caesarean section). The American College of Obstetricians and Gynecologists (ACOG) also includes 'previous myomectomy entering the endometrial cavity' as a contraindication to labour induction [4]. These contraindications are absolute and are fairly uncontroversial. In clinical practice, however, a frequent but challenging scenario is the woman with a previous caesarean section; such women commonly present with recognized indications for induction but are at increased risk of uterine rupture. Their management is discussed further in the section on induction of labour in the presence of previous caesarean section.

Predicting success of induction of labour

Induction of labour is most successful when the cervix is 'ripe' at the time of labour induction [7,8]. Ripening is the process by which the cervix changes in consistency prior to the onset of labour: collagen content and cross-linking decline and water content increases [9]. Physiologically, this facilitates the cervix being progressively dilated by contractions of the myometrium once labour starts. Prior to the onset of labour, ripeness can be measured by using a strain gauge to determine the force required to dilate the cervix. In clinical practice, however, the most commonly used assessment of cervical ripening is the Calder modification of the Bishop score [8] (Table 24.2). This score comprises five components of the cervix, all

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 24.1 Potential indications for induction of labour.

Abruptio placentae
Chorioamnionitis
Fetal demise
Gestational hypertension
Pre-eclampsia, eclampsia
Pre-labour rupture of membranes
Post-term pregnancy
Maternal medical conditions
Fetal compromise
Advanced maternal age at term
Gestational diabetes at term
Large-for-gestational-age baby at term
Logistical

Source: adapted from ACOG Committee on Practice Bulletins [4] with further additions.

Table 24.2 Calder modification of Bishop score.

Score	0	1	2	3
Dilation (cm)	<1	1–2	2–4	>4
Length of cervix (cm)	>4	2–4	1–2	<1
Station (relative to ischial spines)	−3	−2	−1/0	+1/+2
Consistency	Firm	Average	Soft	–
Position	Posterior	Mid/anterior		

Source: Calder AA, Embrey MP, Tait T. Ripening of the cervix with extra-amniotic prostaglandin E_2 in viscous gel before induction of labour. *BJOG* 1977;84:264–268. Reproduced with permission of John Wiley & Sons.

assessed on vaginal examination: cervical length, dilation, position, consistency and its station relative to the ischial spines. Labour induction with an unripe cervix will require more uterine activity to effect cervical dilation, potentially causing a longer labour, more pain and stress for both mother and baby, a higher risk of uterine rupture and evidence of an increased odds ratio (OR) of delivery by caesarean section (2.29, 95% CI 1.53–3.41) [10]. Despite this, one systematic review has suggested that the Bishop score is a poor predictor of the outcome of induction of labour at term and should not be used [11].

Given the deficiencies of the Bishop score, ultrasound measurement of cervical length is a superficially more attractive option to predict success of induction of labour. A variety of cervical lengths, ranging from 16 to 32 mm, have been used to indicate cervical ripeness. When these varying cervical lengths are assessed together, a 'short' cervical length predicts success and a 'long' cervical length predicts failure of labour induction, with a likelihood ratio (LR) of success after a positive test of 1.66 (95% CI 1.20–2.31) and after a negative test of 0.51 (95% CI 0.39–0.67) [12]. These data are based on results from 19 trials and 3065 women, with 'success' in labour induction being defined variously as achieving vaginal delivery, achieving delivery with 24 hours of labour induction, or achieving the active stage of labour. Although there is a statistically significant association between an ultrasound measurement of short cervical length and the success of induction, the predictive value of these measurements do not support the clinical use of this test in practice. It is widely considered that a diagnostic test should have a positive LR of 5 or greater or a negative LR of 0.2 or less to be clinically useful; ultrasound measurement of cervical length for predicting success of induction of labour is clearly suboptimal when measured against this standard [13].

A systematic review of randomized controlled trials to compare Bishop score with any other method for assessing pre-induction cervical ripening in women admitted for induction of labour identified only two trials (both comparing transvaginal ultrasound with Bishop score) [14]. The total number of women recruited was less than 250. No superiority of one test over the other was demonstrated in total.

Analysis of cervico-vaginal fluid insulin-like growth factor-binding protein (IGFBP)-1 has also been used to predict the success of induction of labour in a population of 193 nulliparous women. IGFBP-1 is associated with an adjusted OR of 5.5 (95% CI 2.3–12.9) in predicting vaginal delivery, after adjustement for cervical length on ultrasound and Bishop score [15]. More studies need to be done to determine any potential role in clinical practice.

To summarize, neither the Bishop score nor (currently) transvaginal ultrasound are effective as tools to predict success of induction of labour. This does not mean that the Bishop score should be abandoned, as it may be useful in determining whether the cervix is ripe or whether further doses of prostaglandins are required to achieve ripeness. However, alternative, more effective tests to predict the outcome of induction of labour would undoubtedly be helpful.

Pharmacological and mechanical methods of induction of labour

In order to reduce the risk of adverse events associated with labour induction with an unripe cervix, induction is often preceded by strategies to induce cervical ripening. In the UK, this is most commonly achieved with prostaglandins, normally intravaginal prostaglandin (PG)E_2. There has been increasing use of prostaglandins in association with induction of labour in Scotland over the last three decades [16].

In the USA, a wider variety and routes of administration of prostaglandins are endorsed, including

Table 24.3 Pharmacological agents for cervical ripening.

Agent	Route of administration	Dose	Maximum dose
PGE_2 tablets	Intravaginal	3 mg every 6 hours	6 mg
PGE_2 gel (dinoprostone)	Intravaginal	1 mg every 6 hours	3 mg (4 mg in unfavourable primigravidae)
PGE_2 controlled-release pessary (dinoprostone)	Intravaginal	Pessary releases 10 mg in 24 hours	One
PGE_1 (misoprostol) tablets*	Intravaginal	25 μg every 3–5 hours	None stated
PGE_1 (misoprostol) vaginal delivery system	Intravaginal	200 μg released at rate of about 7 μg/hour over 24 hours	One
PGE_2 (dinoprostone)*	Intracervical	0.5 mg every 6–12 hours	1.5 mg

*US practice.

intracervical and intravaginal PGE_2 and intravaginal misoprostol tablets. Oral administration of prostaglandins is not normally recommended for labour induction at term because it is associated with gastrointestinal side effects. Commonly used dose regimens in the UK and USA are shown in Table 24.3.

Prostaglandins for cervical ripening and induction of labour

The efficacy of prostaglandins for cervical ripening was shown in a seminal paper by Calder *et al.* [17]. Although highly effective in this regard, the cervical ripening effects of prostaglandins cannot easily be separated from their stimulatory effect on uterine contractions and it is largely this that causes the potential adverse effects of induction of labour with prostaglandins. Excessive uterine contractions are termed 'hyperstimulation' and can be associated with abnormalities of fetal heart rate (FHR). In some women, an abnormal FHR may require immediate delivery by caesarean section.

There are now extensive trial data on the use of prostaglandins for induction of labour. Demonstrated benefits of PGE_2 for cervical ripening compared with placebo or no treatment include a 'probable' reduced risk of vaginal delivery not being achieved within 24 hours, a 'probable' reduced risk of caesarean section and an increased risk of uterine hyperstimulation with FHR changes (4.8% vs. 1.0%; risk ratio, RR 3.16, 95% CI 1.67–5.98] [18].

Summary box 24.1

Prostaglandins for induction of labour reduce the risk of the woman not being delivered within 24 hours of the start of induction and reduce the requirement for caesarean section, but increase the risk of uterine hyperstimulation with FHR changes.

When formulations of vaginal PGE_2 are compared, the latest Cochrane review suggests that 'tablets, gels and pessaries appear to be as effective as each other, any differences between formulations are marginal but may be important' [18].

In another Cochrane review, intracervical PGE_2 has been shown to be superior to placebo for cervical ripening, but inferior to vaginal prostaglandin in terms of the risk of not achieving vaginal delivery within 24 hours (RR 1.26, 95% CI 1.12–1.41) [14], leading the National Institute for Health and Care Excellence (NICE) to conclude that 'intracervical PGE_2 should not be used for induction of labour'.

The effects of vaginal or oral PGE_1 (commonly administered as misoprostol) are similar to those of PGE_2 when placebo is used as the direct comparator of each; in other words PGE_1 also reduces the risk of vaginal delivery not occurring within 24 hours compared with placebo [19,20]. However, direct comparison between vaginal PGE_2 and vaginal misoprostol shows that labour induction with vaginal misoprostol is associated with a lower likelihood of vaginal birth not occuring within 24 hours (RR 0.77, 95% CI 0.66–0.89) and a trend to a greater risk of uterine hyperstimulation with FHR changes (RR 1.43, 95% CI 0.97–2.09) [21]. A systematic review of randomized comparisons demonstrated lower caesearean section rates with oral misoprostol compared with vaginal PGE_2 (RR 0.88, 95% CI 0.78–0.99) [20]. This same systematic review suggested that trials comparing vaginal misoprostol with oral misoprostol showed fewer babies with a low Apgar score and lower rates of postpartum haemorrhage in the oral group, but heterogeneous results for vaginal delivery within 24 hours and caesearan section rates [20]. In a sytematic review and network meta-analysis comparing prostaglandins, the odds of failing to achieve a vaginal delivery were lowest with vaginal misoprostol and the odds of caesarean section were lowest with titrated oral misoprostol [22]. A newly marketed slow-release formulation

of misoprostol [23] now has licencing approval in the UK and some other European countries, but has not yet been comprehensively compared with other formulations of vaginal prostaglandin for labour induction.

Authorities in the UK and USA have come to different conclusions about the benefits of misoprostol over and above those of PGE_2. In the UK, NICE currently recommend that misoprostol not be used routinely except in the situation of intrauterine fetal death. In contrast, ACOG endorses the use of misoprostol for induction of labour in a woman with an unfavourable cervix (assuming there has been no previous uterine surgery) [4]. Cochrane suggests that if misoprostol is being used, that oral is 'safer' than vaginal, and a dose of 20–25 μg in solution is most appropriate [20].

Other methods of cervical ripening and induction of labour

Various alternative induction strategies have been investigated in order to avoid the stimulatory effects of prostaglandins on uterine contractions and hence avoid the adverse effects of prostaglandins in labour induction. Mechanical methods commonly involve extra-amniotic saline solution infusion and laminaria, the hygroscopic dilator or extra-amniotic Foley catheter placement or cervical ripening balloon. Enthusiasm for the Foley catheter as a cervical ripening/pre-induction agent has increased following the publication of a large randomized trial demonstrating similar section rates to those observed with PGE_2, but with fewer maternal side effects [24]. A subsequent randomized trial compared the Foley catheter to oral misoprostol for labour induction, and again showed similar rates of adverse effects [25]. Importantly, a network meta-analysis comparing the Foley catheter, misoprostol and dinoprostone for induction of labour showed the lowest rates of uterine hyperstimulation accompanied by FHR changes in association with Foley catheter use, although vaginal misoprostol was the most effective agent for achieving vaginal delivery within 24 hours [26].

Membrane sweeping is recommended on routine antenatal visits post-term as an adjunct to labour induction as it reduces the risk of pregnancy prolongation beyond 41 weeks [27]. Of the pharmacological methods, nitric oxide donors [28] and intracervical hyaluronidase [29] both appear to ripen the cervix without inducing myometrial contractility, but there is insufficient evidence as yet to recommend their use in clinical practice. Mifepristone, a progesterone antagonist, has less stimulatory effects on myometrial contractions than prostaglandins but insufficient evidence about safety currently precludes use with a live baby [3,30].

Once the cervix is ripe, continuation of labour induction may involve forewater amniotomy (artificial rupture of the membranes) with or without augmentation of labour with oxytocin. Forewater amniotomy for induction of labour (without PGE_2 but sometimes with oxytocin) is commonly used as a primary method of induction in women with a ripe cervix, but is not routinely advised because of the increased requirement for oxytocin augmentation [31] if used alone, and because of lower acceptability compared with prostaglandin if used in combination with oxytocin [3]. It is probably for these reasons that use of artificial rupture of membranes with or without oxytocin is now much less commonly used as the primary method of induction of labour in the UK.

Augmentation of labour

Augmentation of labour is the process of speeding up the first stage of labour. For decades, amniotomy with or without oxytocin has been the standard intervention in this scenario, but recent systematic reviews suggest that these practices may not be evidence based.

Amniotomy

A meta-analysis of 14 trials in nearly 5000 women indicated that routine amniotomy had no effect on the duration of the first stage of labour, maternal satisfaction or Apgar scores at delivery, but that there was a trend to increased risk of caesarean section (RR 1.26, 95% CI 0.98–1.62) [32]. These facts support the authors' conclusion that 'we cannot recommend that amniotomy should be introduced routinely as part of standard labour management and care'.

There is a little more evidence in support of the use of amniotomy with oxytocin for augmentation of labour. As with prostaglandins, oxytocin has to be used carefully because the myometrial contractions it induces cause a reduction in blood flow to the uterus. This reduction in blood flow can lead to fetal distress, especially if the fetus is already compromised. A Cochrane systematic review and meta-analysis showed that early amniotomy and oxytocin augmentation applied prior to any delay in labour being identified reduced the risk of caesarean section (RR 0.87, 95% CI 0.77–0.99) and shortened the duration of labour (average mean difference 1.28 hours, 95% CI –1.97 to –0.59) [33]. There were no differences in any neonatal outcomes or in maternal satisfaction rates.

Summary box 24.2

The use of oxytocin for augmentation of labour reduces the total duration of labour by about 75 min and the risk of caesarean section by just over 10%.

There is great variability in uterine response to oxytocin, both between different women and, during the course of labour, within individual women. Thus, if oxytocin is used, it should be started in a low dose initially, with increasing doses titrated against the clinical response, and the dose reduced in the presence of frequent contractions. Possible benefits of higher doses of oxytocin more rapidly escalated (compared with lower doses) include a faster labour and a reduced risk of caesarean section, at the expense of increased rates of hyperstimulation, but the evidence for this is weak [3,34]. Commonly suggested starting doses range from 0.0005–0.006 units/min to a maximum of 0.004–0.042 units/min. The British National Formulary (BNF) suggests a starting regimen of oxytocin of 0.001–0.002 units/min and notes that although the maximum licensed dose in the UK is 0.02 units/min, in clinical practice it is reasonable to administer oxytocin in doses up to a maximum of 0.032 units/min. Both the BNF and the NICE intrapartum care guideline [35] indicate that oxytocin should be increased at intervals not less than every 30 min. Regardless of the regimen used, the target frequency of uterine contractions is three to five every 10 min.

Complications of induction of labour

The most common complication of induction of labour is the risk that the procedure is not successful and that labour does not ensue, which occurs in around 15% of primigravidae with an unfavourable cervix, but less commonly in multiparous women or those with a higher Bishop score at the start of the induction process [36].

Caesarean section is considered by many clinicians a complication of induction of labour, although there is now good evidence that this is incorrect. Indeed, in the clinical scenario for which there is most evidence, that of post-term pregnancy, meta-analyses indicate that induction reduces the risk of caesarean section compared with expectant management [37,38]. A similar reduction in the risk of caesarean section was observed in a systematic review of randomized trials of induction compared with expectant management (OR 0.83, 95% CI 0.76–0.92) [39] and in our own large population-based observational study comparing elective induction with expectant management [16].

Hyperstimulation

The contractile response to prostaglandins varies from woman to woman and is not easily predictable. Thus it is not surprising that some women contract excessively after administration of standard doses of prostaglandins. Uterine hyperstimulation is defined as a contraction frequency of more than five in 10 min or contractions exceeding 2 min in duration; tachysystole occurs when uterine hyperstimulation is accompanied by an abnormal FHR pattern. NICE quotes a rate of hyperstimulation across a range of induction agents of 1–5% [3], although this may be less common with the low-dose PGE_2 regimens in use in the UK.

Profound alterations in FHR pattern may require immediate delivery by caesarean section. In the presence of less severe FHR alterations, tocolysis (e.g. with terbutaline 250 μg i.v. or s.c.) may be sufficient to treat hyperstimulation in the majority of women.

Monitoring and setting during induction of labour

Monitoring

The evidence base for monitoring of maternal and fetal well-being during induction of labour is sparse. Most authorities suggest that a cardiotocograph should be performed to confirm that the FHR is normal prior to prostaglandin insertion. Thereafter, the onset of labour can be identified by the presence of uterine contractions. If contractions do not ensue spontaneously, digital cervical assessment should be performed at intervals no more frequently than every 6 hours to determine if there has been any change in the Bishop score. The cardiotocographic assessement should be repeated when contractions begin, normally 2–6 hours after prostaglandin administration.

Setting

There is increasing interest in carrying out induction on an outpatient basis, with the induction agent being administered at home or being administered in hospital and the woman then going home to await the onset of labour. Indeed, a recent survey has suggested that 18% of UK obstetric units offer this option [40]. Although there is some evidence that outpatient cervical ripening is somewhat preferred by women [41], and that outpatient cervical ripening increases maternal satisfaction during the induction process [42], there is currently insufficient evidence to determine whether outpatient cervical ripening is safe to recommend in routine use. Additionally, one randomized trial has shown that more than 50% of women randomized to outpatient induction, and who needed cervical ripening, did not go home because of abnormalities in FHR monitoring [43], and a large observational study showed similar durations of hospital stay prior to delivery in both the home and the hospital cervical ripening groups [44].

Induction of labour at term (>37 weeks' gestation): risks and benefits

Post-term pregnancy

The highest-quality evidence on the risks and benefits of induction of labour relates to the scenario of post-term pregnancy. The cumulative risk of perinatal death rises progressively after 38 weeks of gestation [45] and many authorities have suggested that induction of labour might reduce perinatal death. A recent meta-analysis for the Cochrane collaboration, reporting on 17 randomized trials incorporating 7407 women, compared a policy of labour induction for women who were 'post dates' to a policy of awaiting spontaneous onset of labour [38]. The babies of women in the induction arm were significantly less likely to have either perinatal death or meconium aspiration syndrome or to be delivered by caesarean section (Table 24.4). There were no significant interactions by gestational age subgroups. Translating the above data into numbers needed to treat (NNT), 410 (95% CI 322–1492) women would have to be induced for post-dates pregnancy to prevent one perinatal death. However, these data should perhaps be interpreted with caution, as the total number of fetal or neonatal deaths was small, one in the induction group and 13 in the actively managed group in this most recent meta-analysis [38].

Taken together, these data suggest that induction of labour at or beyond 41 weeks reduces perinatal death without increasing the risk of caesarean section. For these reasons, many authorities (including NICE) suggest that induction of labour should be routinely offered at 41 weeks' gestation and beyond in order to improve neonatal outcome. Additionally, there is some evidence that the majority of women at this gestation prefer induction of labour to conservative management [46].

Summary box 24.3

Post-term induction of labour reduces perinatal death (estimated NNT, 410) and reduces the need for caesarean section.

Pre-labour membrane rupture

Another common indication for induction of labour is when the fetal membranes rupture at term prior to the onset of labour, but labour fails to start. If the pregnancy continues without the baby being delivered, there is a risk of ascending infection which could lead to chorioamnionitis and attendant fetal and maternal compromise. However, 95% of women will labour spontaneously within 24 hours of membrane rupture, and thus early recourse to induction of labour might involve the adverse consequences of induction of labour in a woman who would have laboured spontaneously with conservative management. Again, this issue has been subject to randomized trials. At 37 weeks of gestation or more, compared with expectant management (no active management for at least 24 hours), induction within 24 hours reduces the risk of chorioamnionitis (RR 0.74, 95% CI 0.56–0.97), endometritis (RR 0.30, 95% CI 0.12–0.74) and (for the baby) neonatal intensive care admission (RR 0.72, 95% CI 0.57–0.92) without increasing rates of caesarean section (RR 0.94, 95% CI 0.82–1.08) [47]. Importantly, women undergoing induction of labour were happier with their treatment than those managed expectantly. However, a conservative approach in order to await the onset of labour is justifiable if the woman wishes, given that induction does not significantly reduce rates of neonatal infection (RR 0.83, 95% CI 0.61–1.12). Current advice from NICE is that women with pre-labour rupture of the membranes at term (≥37 weeks' gestation) should be offered a choice of induction of labour or expectant management, and that if labour has not commenced approximately 24 hours after rupture of membranes, then induction of labour is appropriate [3]. In practice, management decisions are likely to be based on local organization of care and the individual woman's request.

For women who are preterm, at least for those who are 'late' preterm, a recent randomized trial has shown no difference in rates of neonatal sepsis (the primary outcome) in women at 34–36 weeks' gestation with pre-labour rupture of the membranes, suggesting that conservative management is probably most appropriate in this group [48].

Table 24.4 Effect of induction of labour for post-dates pregnancy.

Outcome	RR	95% CI	Amount of evidence
Perinatal death	0.31	0.12–0.81	17 trials, 7407 women
Meconium aspiration syndrome	0.50	0.34–0.73	8 trials, 2371 women
Caesarean section	0.89	0.81–0.97	21 trials, 8749 women

Source: data from Gulmezoglu *et al.* [38].

Maternal request

The most controversial area, and the issue for which there is little evidence from randomized trials, relates to induction of labour in the absence of any medical indications, i.e. induction of labour on maternal request. Women and their partners are increasingly able to control many aspects of their lives, and this wish to plan their lives extends (for many women) into where, when

and how they have their baby. Although maternal choice is promoted in the UK, at least in regard to place of delivery and more 'natural' childbirth (such as delivery under water), there is less support for women who opt for delivery by elective caesarean section or who wish to have their labour induced before 41 weeks' gestation unless there are 'medical' indications to do this. Elective caesarean section on request can increase the rate of some maternal complications and may also have resource implications for the health service; these issues have been comprehensively debated elsewhere.

Induction of labour on request (elective induction) might be a suitable compromise for women who wish to choose the date of delivery of their baby but who hope for a vaginal delivery. Popular mythology is that elective induction is associated with an increased risk of caesarean section. However, only three randomized trials, none of optimal quality, have assessed the effects of induction of labour prior to 41 weeks' gestation for this indication. Although the relative risk of caesarean section was 1.73 when data from these trials was combined, the confidence intervals cross unity and thus this apparent increase in caesarean section rate is not statistically significant (95% CI 0.67–4.50) [49]. Caughey *et al.* reviewed the observational data around elective induction of labour and found no significant increase in caesarean section rates from observational data when women having elective induction were compared with women undergoing expectant management. We subsequently completed a retrospective cohort study of over 300 000 women undergoing induction in Scotland between 1981 and 2007 and showed either no increase or a very modest increase in caesarean section rates in association with elective induction of labour after adjustment for confounding variables of age at delivery, parity, period of birth, deprivation quintile and birthweight [16]. Additionally, we showed a reduction in perinatal mortality, with NNT at 40 weeks' gestation of 1040 inductions for every one perinatal death prevented. This beneficial effect on perinatal death reduction was achieved at the expense of one extra admission to the neonatal intensive care unit for every 131 women induced. We believe that these data provide support for a policy of agreeing to an individual woman's request for elective induction of labour, and for extending choice to the timing of delivery.

Summary box 24.4

There is no evidence that induction of labour 'on request' for women with an uncomplicated pregnancy and without a previous caesarean section increases the risk of caesarean section compared with a policy of expectant management.

Prevention of shoulder dystocia

In the scenario where birthweight is expected to be high (e.g. babies already diagnosed with macrosomia or babies of diabetic mothers), a strategy of induction has been hypothesized to prevent further intrauterine growth, thus reducing the risk of both fetal macrosomia and shoulder dystocia and increasing the chance of vaginal delivery. A recent systematic review (1190 women, four trials) has shown that induction of labour near term for babies with a suspected birthweight of more than 4000 g reduces the risk of shoulder dystocia (RR 0.60, 95% CI 0.37–0.98) and any fracture (RR 0.20, 95% CI 0.05–0.79) but not brachial plexus injury nor caesarean section [50]. These results are different from previous systematic reviews on this topic, and are not yet reflected in national guidelines. If women are being offered induction of labour because of macrosomia, they should be informed of the increased rate of pelvic floor damage seen in the induction group.

Advanced maternal age

As described above, induction of labour at term reduces the risk of perinatal mortality, with no significant difference in this effect for women induced at 39–40 weeks compared with 41+ weeks' gestation. The risk of stillbirth rises progressively with age and, taken together, these data have prompted the Royal College of Obstetricians and Gynaecologists (RCOG) to issue a Scientific Impact Paper stating that 'there is therefore an argument for offering induction of labour at 39–40 weeks of gestation to women ≥40 years of age', with NNT of 550 to prevent one stillbirth [51]. A subsequent randomized trial of the effect of elective induction at 39 weeks' gestation to women aged 35 years or more, and powered to evaluate the effect on caesarean section rather than perinatal mortality or stillbirth, showed that a policy of elective induction in women aged 35 years or more does not increase the risk of caesarean section, and there were no differences in women's experience of childbirth between the two groups [52].

Intrauterine fetal death

In the absence of induction of labour, 90% of women will spontaneously deliver within 3 weeks of intrauterine fetal death. The risks of conservative management include disseminated intravascular coagulation and (particularly in the presence of ruptured membranes) ascending infection. Additionally, many women with a diagnosis of intrauterine fetal death will wish to deliver the baby as soon as possible. There are no randomized trials comparing a policy of induction with

conservative management in this situation, and NICE recommends that conservative management is reasonable if 'the woman appears to be physically well, her membranes are intact and there is no evidence of infection or bleeding' [3].

In the presence of intrauterine fetal death, mifepristone 200 mg three times daily significantly reduces the induction to delivery interval [53]. In practice, a single dose of mifepristone (200 mg) followed by either low-dose vaginal misoprostol (e.g. 25–50 μg 4-hourly up to six doses) or vaginal PGE_2 is commonly used for induction of labour with intrauterine fetal death at 24 weeks or greater; higher doses of prostaglandin may be needed at earlier gestations and lower doses should be used if the woman has had a previous caesarean section.

Induction of labour in the presence of previous caesarean section

Women with a previous caesarean section who undergo induction of labour are considered to have an increased risk of repeat caesarean section and uterine rupture compared with those who labour spontaneously. There is some evidence for this: one systematic review showed that women with a previous caesarean have a risk of caesarean delivery of 24% (range 18–51%) during a spontaneous labour but a risk of 48% (range 28–51%) following induction of labour with PGE_2 [54]. One large cohort study indicated increased odds of uterine rupture when labour was induced with prostaglandins compared with spontaneous labour (OR 2.9, 95% CI 2.0–4.3) [55]. In 14% of women with uterine rupture the baby suffered a perinatal death. In another large cohort study, we analysed outcomes in women with one previous caesarean section [56]. We compared outcomes for women undergoing induction of labour with those having expectant management and those having elective repeat caesarean section. Compared with expectant management, induction of labour was associated with lower odds of caesarean delivery (adjusted OR 0.81, 95% CI 0.71–0.91), higher odds of neonatal unit admission (adjusted OR 1.29, 95% CI 1.08–1.55), and no impact on perinatal morality. In contrast, elective repeat caesarean section was associated with lower perinatal mortality than induction of labour (adjusted OR 0.23, 95% CI 0.07–0.75).

In view of these data, induction of labour in women with a previous caesarean section should be undertaken with caution and in an environment where uterine rupture can be rapidly diagnosed and treated if necessary. Some clinicians may feel that the possible risks of induction of labour in the presence of a previous caesarean section are too great, and that such women are best delivered by elective caesarean section if immediate delivery is indicated. Such decisions need to be made on an individual patient basis, given the lack of randomized trials in this area [57]. Although there are insufficient randomized trials to help decision-making on the best induction agent [58], the Foley catheter deserves investigation as the method of choice, given the reduced risk of hyperstimulation.

Pre-eclampsia

The final indication for induction of labour is the scenario of mild pre-eclampsia. Severe pre-eclampsia at term is an absolute indication for delivery, either by caesarean section or attempting to expedite vaginal delivery by induction of labour. Mild pre-eclampsia is often managed conservatively, but there is evidence from a recent paper that liberal induction of labour after 36 weeks' gestation in women with mild pre-eclampsia or gestational hypertension improves maternal outcomes expressed as a composite of maternal mortality, maternal morbidity, progression to severe hypertension or proteinuria, and major postpartum haemorrhage (RR 0.71, 95% CI 0.59–0.86) [59]. In contrast, for women with mild hypertension at 34–37 weeks' gestation, expectant management appears to be a better strategy [60].

Summary

Induction of labour is one of the most commonly undertaken procedures in obstetric practice. Prostaglandins are the agents most commonly used, with good evidence that they speed up the process of induction of labour. Further randomized trials are required to determine the effects of induction in a variety of clinical scenarios. Meanwhile, clinicians should discuss the current literature and its implications with pregnant women prior to making decisions about their management.

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25

Obstetric Emergencies

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This chapter details how to minimize the risks as well as the consequences of an obsteric emergency and how to manage various scenarios. We then discuss aspects of emergency skills training before including some algorithms: these are consistent with other more succinct algorithms but contain more detail as this is a reference textbook and additional information can be assimilated rather than just reproducing the 'checklist' type flow diagrams.

General principles for minimizing the risk of an emergency occurring

Promote good antenatal health

Good general health and a supportive home environment promote good health during pregnancy. The UK Confidential Enquiries into Maternal Deaths over many triennia [1–3] remind us of the increased risks not only of those with pre-existing disease, including mental illness and obesity, but also of socially excluded and vulnerable women including immigrant women, those abusing substances, and those in abusive relationships. Good antenatal care is paramount in promoting health: women should be screened for a variety of risk factors and any problems that are identified should be acted on [4]. We know from the confidential enquiries over the years that we sometimes fail to recognize, communicate or act on risk factors which are apparent in the antenatal period. This makes it even more important, when considering intrapartum care, to make every effort to review a woman's antenatal health to identify any such risks, and pay heed to any instructions made in the antenatal period.

Organized intrapartum care

Poor teamwork is directly associated with preventable morbidity and mortality for mothers and babies. The senior sister in charge and the senior obstetrician on the delivery suite should work together as a team to coordinate clinical activity. It is worthy of mention that when some people are in charge of a delivery suite, no matter how busy it is, things are calm and in control, while at other times even a quiet day can feel hectic. The skills required to coordinate workload and staffing are multiple and often acquired over years, but if you recognize either of the above characteristics in those you work with, take a moment or two to try to define what they are doing differently and try to emulate the one and avoid features of the other.

Triage

The principles behind effective triage have hinged on the ABC approach to prioritizing casualties according to whether they have an airway (A) problem (which can lead to death within minutes if left untreated) through difficulties with breathing (B) to circulatory disorders (C). Although this can also be useful in obstetrics, it does not address the fact that obstetricians have to prioritize between two patients: the mother and the baby. Indeed there is little written about obstetric triage [5,6] and how to fit the fetus (F) into the equation. Clearly it is not as easy as ABCF and emergency care to save a baby may take priority over a less than life-threatening maternal condition. However, it is true to say that in most societies the life of the mother is given priority over that of an unborn baby and, most importantly, the fetus is best treated by adequate, rapid and effective resuscitation or stabilization of the mother anyway [5].

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Summary box 25.1

Hints for keeping the workload under control

- Keep your mind open to all the activity going on.
- Try to coordinate activity so that things happen in sequence and not all at the same time.
- Listen to your midwives' and doctors' concerns and address them.
- Prioritize according to risk (triage).
- Get simple things done quickly, as once resolved they relieve staff.
- Do not defer decisions unnecessarily (work just builds up).
- Give each woman a carer with the appropriate skills to match the complexity of the clinical problem.
- Recognize if a doctor or midwife is out of their depth: support them and encourage them to call for help.
- Regularly revisit women with risk factors to check the situation is not deteriorating (do not assume you will be called).

General principles for minimizing adverse consequences resulting from an emergency

If risk factors have been identified, preparations can be made to deal with the anticipated problem and staff should be informed, briefed and their roles defined. It is not uncommon that when such problems are prepared for, everything goes smoothly: this does not mean that staff are over-cautious; it means they did their job well. Sadly, things do not always go smoothly, or an unexpected emergency occurs, and in such situations there are some features of general care which are important:

Communication and team working

A recent review of teamworking in maternity care [7] identified that good team communication, coordination and leadership were all evident in the best functioning teams. In one study of simulated eclampsia [8], more efficient teams were likely to have stated (recognized and verbally declared) the emergency (eclampsia) earlier, using closed-loop communication (task clearly and loudly delegated, accepted, executed and completion acknowledged).

Integrating and teaching these simple team behaviours in clinical drills appears to be clinically effective [9]. This has been reiterated in a US study, which reported a statistically significant and persistent improvement of 37% in perinatal morbidity for the hospital exposed to a programme combining team training and clinical drills, whereas there were no improvements in the hospital exposed to team training only, or the control.

Good leadership is often invoked by reports, but can be nebulous in practice. Recent studies have demonstrated that leadership may best be established by the person who has the most experience of the emergency [10] and leadership may be more effective when the leader knows all the members of the multiprofessional maternity team and their relevant roles – before the emergency happens – from previous training together or from handover. Once again the leader should be mindful of the same three components of the situation as the rest of the team (team, situation, patient focus): establish the setting (using SBAR, i.e. situation, background, assessment, recommendation), allocate critical tasks with closed loops (directed–acknowledged–confirmed) and, if necessary, pass leadership to team members who are more experienced for the specific emergency at hand [11].

Women and their families also want similar information in an emergency. In recounted experiences, companions often informed women of the situation and the aims of treatment because they had heard loud and clear messages about the cause of the emergency, the condition of the baby, and the aims of immediate and ultimate management [11].

Local multiprofessional training for all staff annually, with teamwork training integrated into the clinical training, appears to be the most effective method of improving teamwork.

Summary box 25.2

Aids to good communication

- Someone needs to take the lead role and coordinate activity in a systematic way such that staff work together as a team.
- Establish the situation and voice it to the team.
- The skills of any unknown staff need to be clarified.
- Roles need to be allocated which match the skills of the staff concerned.
- Specific jobs need to be given to specific people to avoid duplications and omissions.
- When someone is asked to do something, it is worth checking that they understand and are happy with what is being asked of them, and then they should confirm when it has been completed.
- Someone needs to document timings and actions.
- Someone needs to talk to the patient (and her partner) even if only briefly to keep them calm and informed and help them feel confident and supported.

Documentation

This has already been mentioned briefly, but in all emergencies it helps to have someone looking at the clock, holding pen and paper, who is responsible for documenting the important facts as they happen. Remember that if, as is often the case, this person is fairly junior, he or she may not understand exactly what is going on and may fail to document key activity, and therefore it is imperative that senior members of the team ensure that all essential information is communicated. Once the emergency is over, notes should be written carefully and comprehensively and signed legibly. This is the best time to account for what has happened, and any relevant diagnosis, follow-up care plan and prognosis for future pregnancies should be spelt out clearly whenever possible at this stage.

Risk management

After the emergency is over, reviewing the event with staff is hugely appreciated and very important: this is usually multidisciplinary but will sometimes be in small groups. Healthcare assistants and porters may need this support too and should not be forgotten. If everything went well, everyone should be congratulated; if some things were less than perfect, discussing why the difficulties were encountered and what might make things easier/work better another time is often helpful. This is a time for positive critical reflection; any negative feedback can wait and be dealt with privately.

Duty of candour

If the event has resulted in harm to the patients (woman/baby), then even if care was exemplary a senior doctor should speak personally to her and/or her partner/relative to express regret that the incident occurred and empathy for the current situation or outcome, and explain that such cases are reviewed to check everything was done that should have been and in a timely manor. Such dialogue should be recorded together with an offer to provide feedback to the patient/family should they so wish. This transparency and heightened communication and caring approach is directly driven from the NHS Litigation Authority and the Care Quality Commission with a statutory duty of candour for healthcare providers to comply since 2015 [12].

Emergency training

Over the last two decades the reduced duration of junior doctors' training, combined with the dramatic cuts in their working hours, it is unsurprising that their clinical experience of obstetric emergencies is much less than that of their predecessors. They rely increasingly on training away from the bedside and there is no doubt that improving training for intrapartum emergencies is at least part of the potential solution to improving outcomes in the UK and further afield.

A review of effective training for obstetric emergencies published in 2009 [13] concluded that many of the courses then reviewed had common features: institution-level incentives to train; multiprofessional training of all staff in their units; teamwork training integrated with clinical teaching and use of high-fidelity simulation models. These themes have been echoed in a more recent review for obstetric training [14] that concluded that all maternity and neonatal health professionals should participate in in-service training sessions. Furthermore, on-site 'in-house' training with low-tech, highly realistic models is more readily implementable than offsite training at simulation centres and training integrated into institutional clinical-governance and quality-improvement initiatives is likely to have better results.

The various regional and national multidisciplinary training courses have different emphases, complement each other and supplement local training. A few illustrations of these specialist courses are listed here.

- ALSO (Advanced Life Support in Obstetrics). This course is geared to midwives, obstetric senior house officers and junior specialist registrars and deals with the main obstetric emergencies in a structured systematic fashion. Candidates should gain a sound understanding of the problems and the structured approaches in how to manage them (www.also.org.uk).
- mMOET (Managing Medical and Obstetric Emergencies and Trauma). This course is geared to a more senior and multidisciplinary group: obstetric consultant and senior specialist registrars (post MRCOG and at least specialty training year 5), anaesthetic consultant and senior specialist registrars, and senior accident and emergency doctors. These courses can also include midwives and obstetric physicians whose presence emphasizes and promotes the team approach that is so important in the obstetric emergency. This course runs candidates through approximately 25 emergency scenarios and skills and deals with more advanced and complex aspects of emergency obstetrics and emergency behaviour (www.moet.org.uk).
- MOSES (Multidisciplinary Obstetric Simulated Emergency Scenarios). This course focuses on emergency behaviour and team-working dynamics

as they apply to the obstetric patient, rather than training on knowledge or techniques. It involves midwives, anaesthetists and obstetricians who often attend together from the same department. This course is very different from, and complements, MOET or ALSO (blsimcentre@bartsandth-elondon.nhs.uk).

- PROMPT (PRactical Obstetric Multi-Professional Training). A training programme for maternity units, it was developed in Bristol, UK and can be purchased by maternity units, who then deliver the teaching locally.

Effects of emergency training

Whilst we increasingly rely on these training programmes, the current evidence supports an annual, local unit-based, multiprofessional approach as these are most likely to translate into improved clinical outcomes. Not all training is productive and even the same teaching material delivered in different settings can have opposite results [15] but the best improvements to date have been reported from the PROMPT group, where there is evidence of significantly reduced preventable birth injury [16–19] and an associated 90% reduction in litigation costs [20]. These reductions have been replicated in pilot sites across the world, including developing world settings.

Collapse

Collapse as it presents to the obstetrician can be due to a variety of causes, from the sometimes innocent vasovagal faint through to cardiac arrest, but the initial assessment and management of the patient is remarkably similar and requires a systematic disciplined ABC approach combined with manual uterine displacement of the uterus or lateral tilting of the pregnant patient to minimize aortocaval compression. The essential steps of how to approach the apparently lifeless patient are summarized in Fig. 25.1, and aim to make the crucial diagnosis of cardiac arrest (as opposed to reduced consciousness due to another cause) so that cardiopulmonary resuscitation (CPR) can be commenced early. Most other conditions require basic resuscitation with attention to airway and breathing combined with intravenous access and circulatory support while the cause of the problem is diagnosed and then treated (Table 25.1).

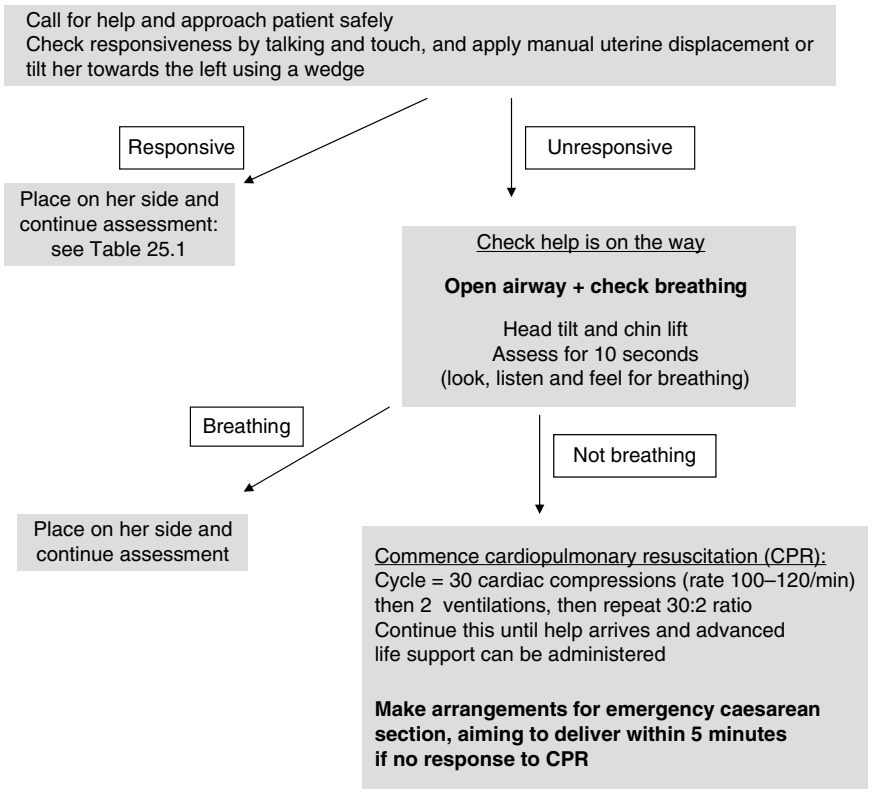

Fig. 25.1 Basic life support: approaching and treating the apparently lifeless patient.

Table 25.1 Causes, features and initial treatment of collapse in the obstetric patient (distinguishing features in bold).

	Cause/risk factors	Specific clinical features	Specific treatment points: all need ABC + lateral tilt if undelivered
Adrenal insufficiency	Inadequate or absent steroid cover in someone previously taking steroids	Drug history can be sought Hypotensive collapse Metabolic imbalance	Supportive with intravenous fluids (check electrolytes, especially sodium may be low) Hydrocortisone (200 mg i.v. stat) Check BM: may need glucose
Amniotic fluid embolism	Uterine tachysystole Syntocinon hyperstimulation Previous uterine surgery Multiparity Polyhydramnios	Restless, shortness of breath and cyanosis **Vaginal bleeding follows within 30 min due to disseminated intravascular coagulation** [2]	Oxygen + ventilate Deliver the baby as soon as possible Hydrocortisone (200 mg i.v. stat) (Aminophylline, diuretics, adrenaline, morphine)*
Anaphylaxis	Drug administration, e.g. antibiotics, Voltarol, anaesthetic agents, Haemaccel, latex	History of drugs/latex Rash Stridor Oedema	Adrenaline (1 mL of 1 in 1000 i.m. or 1 mL of 1 in 10 000 i.v. repeated as needed) with intravenous fluids Hydrocortisone (200 mg i.v. stat) Chlorpheniramine (20 mg i.v.)
Aspiration (Mendelson's syndrome)	Inhalation after vomiting/ passive regurgitation (reduced consciousness with unprotected airway)	Shortness of breath, restlessness, cyanosis **Bronchospasm**	Oxygen + ventilate (Aminophylline, steroids, diuretics, and antibiotics)*
Bacteraemic shock	Overwhelming sepsis due to especially Gram-negative rods or streptococci	Hypotensive **Warm/fever/blotchy**	Sepsis care bundle: replenish circulation, systems support Antibiotics intravenously (e.g. imipenem)
Cardiogenic shock	Congenital or acquired disease Cardiomyopathy	History Restless, **shortness of breath, chest pain**	**Sit up** Oxygen + frusemide
Eclampsia	Associated with cerebrovascular events or pulmonary oedema or magnesium toxicity	Hypertensive Proteinuria	Magnesium sulfate (antidote is calcium gluconate) Control blood pressure with hypotensives
Hyperglycaemia	Diabetes	Hyperventilation and **ketosis**	Intravenous fluids, insulin (and potassium)
Hypoglycaemia	Diabetes, Addison's disease, hypopituitary, hypothyroid	**Sweating/clammy** Loss of consciousness	Intravenous glucose
Intracerebral bleed	Arteriovenous malformation	Fits, CNS signs and **neck stiffness**	Supportive and urgent neuro-imaging
Massive pulmonary embolism	Usually deep pelvic thrombosis	Restless, cyanosis, **elevated jugular venous pressure**	Lie down, oxygen, IV fluids, anticoagulation/thrombolysis
Neurogenic	Vasovagal (uterine inversion)	**Vaginal examination**	Intravenous fluids ± atropine Reduce uterine inversion
Oligaemic	Haemorrhage (can be concealed)	**Tachycardia, pale and cold**	Restore circulation and turn off the tap [24]
Pneumothorax Pneumomediastinum	Previous history of labour/ pushing	Chest pain, shortness of breath	Aspirate/drain

*These treatments should be undertaken under anaesthetic supervision in a high-dependency or intensive care unit.

Cardiac arrest (Fig. 25.1)

CPR is not only difficult to administer but is particularly inefficient in the pregnant patient due to the following:

- Difficulties in performing CPR in pregnancy: the uterus needs to be manually displaced; if there are insufficient pairs of hands, the patient must be tilted.
- Increased oxygen requirements in pregnancy (20% increase in resting oxygen consumption).
- Decreased chest compliance due to splinting of the diaphragm (20% decrease in functional residual capacity).
- Reduced venous return due to caval compression limits cardiac output from chest compressions (stroke volume 30% at term compared with non-pregnant state).
- Risk of gastric regurgitation and aspiration (relaxation of cardiac sphincter).

For these reasons and to improve the chance of maternal survival it is considered appropriate to empty the uterus by performing a peri-mortem caesarean section within 4–5 mins if CPR (performed with uterine displacement or lateral tilt) is ineffective [5]. To achieve this the obstetrician at such an arrest should be preparing for caesarean section almost immediately. It is reiterated that the point of emptying the uterus is to aid in the resuscitation of the mother and is not for fetal reasons. Fetal viability issues should not delay this procedure, which is worthwhile when the pregnancy is of sufficient size to compromise resuscitation; as a guide, if the uterus has reached the level of the umbilicus it should be considered.

To perform a peri-mortem caesarean section rapidly, the skin incision should be that with which the operator is most familiar, and the uterine incision will be influenced by the gestation of pregnancy. These details matter little compared with the pressing need to evacuate the uterus and render the mother more receptive to life-saving resuscitation techniques. A large caesarean section pack is unnecessary and *in extremis* all the obstetrician needs is a scalpel to commence the procedure whilst other instruments are being collected.

It is stressed again that this is not done for fetal reasons but there is no doubt that at more advanced gestations fetal viability is more likely the more quickly the baby is delivered: 70% survive intact if delivered within 5 min, falling to 13% after 10 min [21].

To detail the management of each possible condition that can cause maternal collapse is beyond the scope of this chapter, but Table 25.1 summarizes the different possibilities and those features specific to them in terms of risk factors, clinically distinguishing features and specific points of treatment. More detailed accounts can be found in references in the MOET manual [5] but a few summary points are highlighted here.

Airway problems

The airway of an obstetric patient is more vulnerable than in the non-pregnant state. Not only is there more likely to be swelling and oedema, but the progestogenic effects that reduce gastric emptying and relax the cardiac sphincter increase the chance of regurgitation and subsequent aspiration of gastric contents. For these reasons the management of any obstetric patient with reduced consciousness requires careful attention to maintaining and protecting the airway, and this should involve an anaesthetist. In simple circumstances, the patient should at the very least be nursed on her side, and a jaw thrust and chin lift can aid in bringing the tongue forward to open the airway. Severe laryngeal oedema due to pre-eclampsia or anaphylaxis are examples of situations that can critically compromise the airway in the obstetric patient, and in these circumstances an anaesthetist is needed extremely urgently to establish and maintain the airway (usually by a cuffed endotracheal tube).

Breathing problems

If the airway is patent but breathing is laboured or consciousness impaired, then supplementary oxygen is vital. This should be given by face-mask with a reservoir bag, and the oxygen should be turned up to maximum at the wall in the emergency situation. Raised respiratory rate, restlessness and confusion are all signs of hypoxaemia, can precede collapse and should be taken extremely seriously. Oxygen saturation should be measured in air by a pulse oximeter, and arterial blood taken for gas analysis if there is any concern, and results of these should be reviewed with the anaesthetist on duty.

Circulatory problems

Circulatory problems can be due to cardiac disease (where the resulting pathology is usually pulmonary oedema and low-output failure), inadequate venous return with resultant low-output failure (massive pulmonary embolus) or an underfilled circulation (hypovolaemia, due to haemorrhage or sepsis). Early intravenous access with large-bore cannulae is vital, but treatment needs to be specific to the cause. Cardiac failure patients do not require (and indeed may be killed by) volume expansion, but are helped by being sat up and given diuretics, and may need inotropic support. On the other hand, a woman with a pulmonary embolus or one who is hypovolaemic needs volume expansion and to be lain down flat. Distinguishing between these conditions is vital as the management of

each would clearly be dangerous to the other. Hypovolaemia, which can be due to loss from the intravascular compartment (e.g. haemorrhage) or due to relative underfilling caused by vasodilatation (e.g. sepsis), is managed by volume expansion. Fluid replacement strategies with crystalloid or colloid remain controversial but the use of crystalloids in critically ill patients is supported by a Cochrane review [22] and Hartmann's solution is preferable to dextrose [23].

Haemorrhage

Obstetric haemorrhage is one of the most common causes of major maternal morbidity and mortality [24,25] and successive confidential reports in the UK show that it accounts for approximately 0.5 deaths per 100 000 maternities [3]. Over the years these confidential enquiries have highlighted a variety of substandard care issues and emphasis is placed on the importance of clear local procedures and policies to trigger rapid and appropriate responses which should be rehearsed regularly. Furthermore, there should be senior input in high-risk cases, especially women with a previous caesarean section and a low-lying placenta, as their risk of a morbidly adherent placenta is increased. In such cases antenatal and intrapartum multidisciplinary consultant input is advocated, with clear plans for surgery and with conservative options for treatment considered in advance [26].

Summary box 25.3

Care bundle components for women with suspected placenta accreta

- Consultant obstetrician involved in antenatal plan and present at delivery.
- Consultant anaesthetist involved in antenatal plan and present at delivery.
- Blood and blood products available on site.
- Multidisciplinary involvement in preoperative planning.
- Consent to include possible interventions.
- Level 2 critical care bed available.

Clinical care should concentrate on identifying risk factors for haemorrhage in all women to enable preparations and avoiding action to be taken. However, once massive haemorrhage occurs management should follow a logical sequence of diagnostic and therapeutic options as illustrated in Figs 25.2 and 25.3.

Summary box 25.4

Hints to minimize morbidity from haemorrhage

- Antepartum haemorrhage: if it is due to severe abruption with an accompanying bradycardia, the urgency of delivery is clear and an interval from decision to delivery of 20 min or less is associated with reduced neonatal adverse outcome [27].
- The descriptions 'heavy lochia' or 'she's trickling' are dangerous and should not be accepted: the woman should be reviewed and the problem resolved before it develops into a bigger problem.
- A bedside haemoglobin assessment in the acute phase of haemorrhage can be falsely reassuring (as dilution does not occur until there has been fluid resuscitation) and circulatory volume and blood replacement should be based on the amount of blood lost, the vital signs and the likely ongoing clinical scenario, *not* the haemoglobin [24].
- Continued vaginal bleeding with a contracted uterus is due to either retained placenta/membrane/clot or trauma and needs to be managed actively and not ignored. The problem will only get worse, so the woman should undergo examination under anaesthesia while she is well.
- Hypotension is a very late sign: blood pressure is maintained until very late in the obstetric patient who is bleeding, and tachycardia, peripheral perfusion, skin colour and urine output should be heeded early.
- Small women have relatively smaller circulating blood volumes and so allowance for body habitus should be made when estimating the significance of the estimated loss [24].
- If the lower segment of the uterus or the cervix fills up with blood or clot, it can cause vagal stimulation producing a bradycardia that can mislead. Vaginal examination should be done if in doubt.
- Bleeding can be concealed:
  - A uterus filling up is suggested by a rising fundus.
  - Intra-abdominal bleeding: massive volumes of blood can be accommodated within the peritoneal cavity without affecting girth measurements, which are unhelpful and can be falsely reassuring.
  - The uterus that is not central but shifted to one side should raise alarm bells: it suggests a broad ligament haematoma.
  - Whilst a tachycardia can aid in the recognition of concealed haemorrhage this can be inhibited by beta-blockers, and also sometimes by the intraperitoneal blood stimulating a vagal response.
- Petechiae suggest disseminated intravascular coagulation [28].

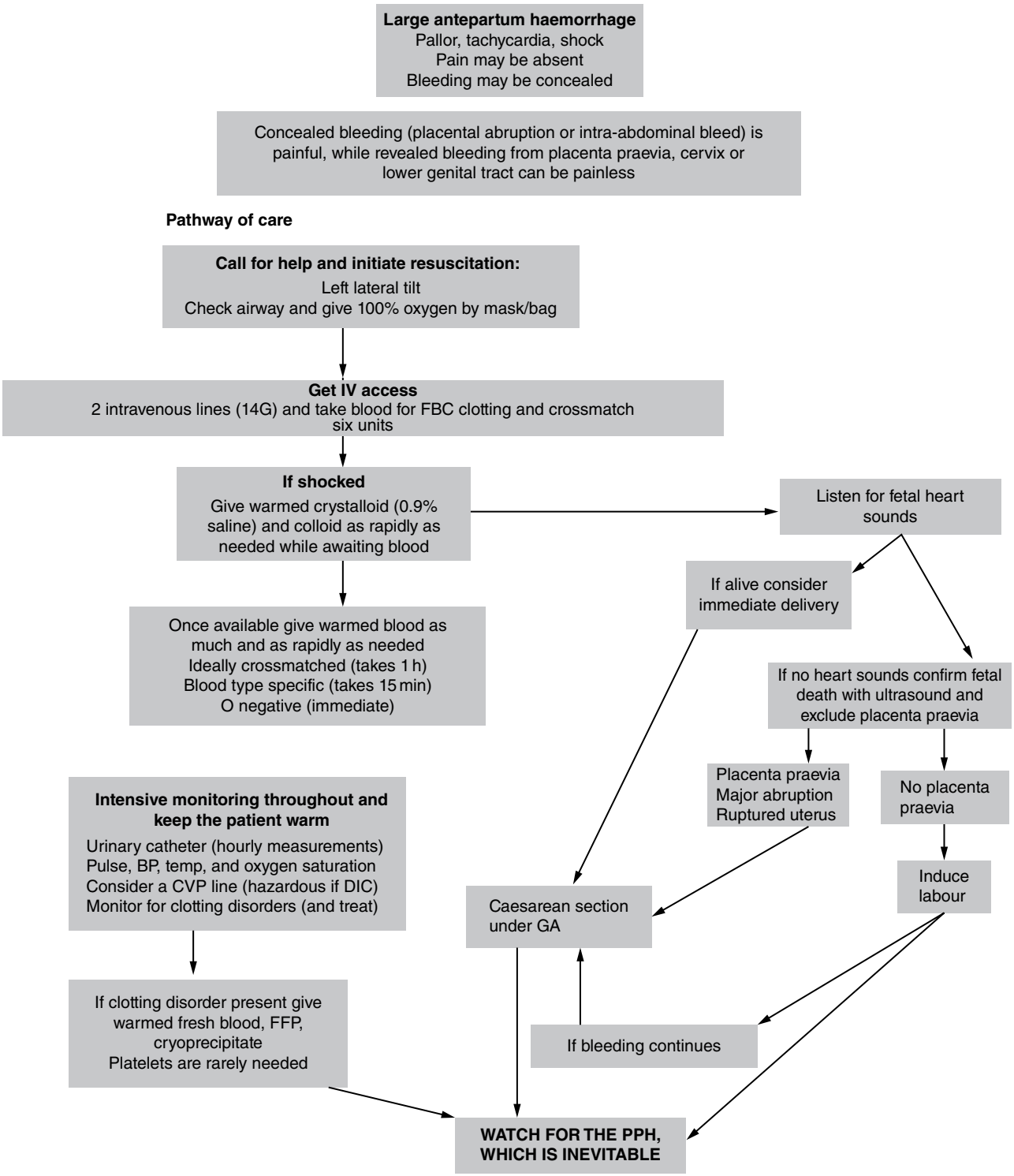

Fig. 25.2 Large antepartum haemorrhage. BP, blood pressure; CVP, central venous pressure; DIC, disseminated intravascular coagulation; FBC, full blood count; FFP, fresh frozen plasma; GA, general anaesthesia; PPH, postpartum haemorrhage.

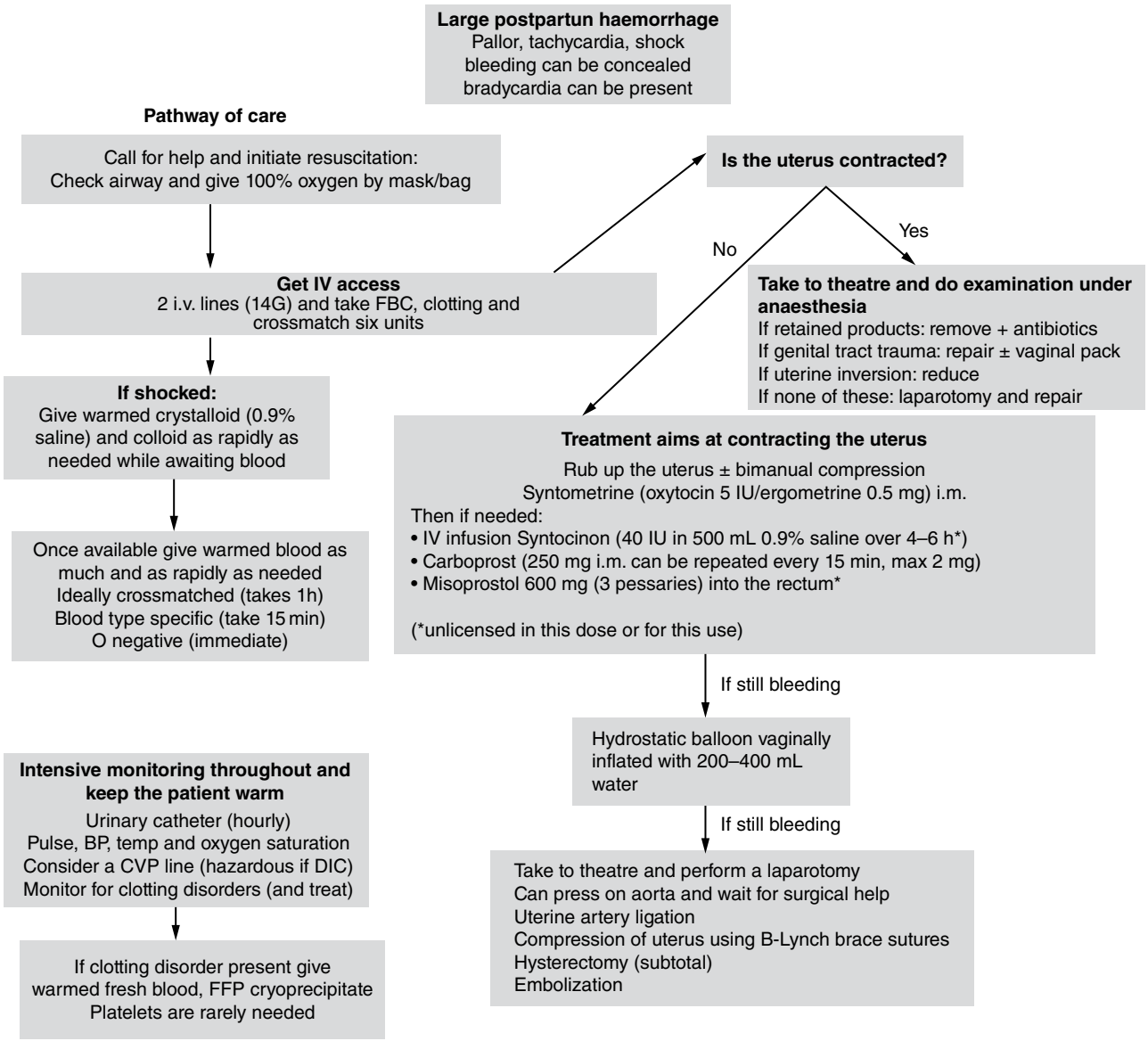

Fig. 25.3 Large postpartum haemorrhage. BP, blood pressure; CVP, central venous pressure; DIC, disseminated intravascular coagulation; FBC, full blood count; FFP, fresh frozen plasma.

Life-saving measures and advanced techniques for massive postpartum haemorrhage

Resuscitation with volume, blood and clotting factor replacement

Rapid replacement of circulating volume with *warmed* crystalloid and colloid while awating blood will maintain the circulation temporarily, but blood together with clotting products are needed urgently and should be given in anticipation of, and should attempt to minimize, the coagulopathy that is almost inevitable in the face of massive haemorrhage. To this purpose a ratio of 1 : 1 blood/fresh frozen plasma (FFP) is needed; if bleeding continues, cryoprecipitate should be given empirically while awaiting clotting studies [24,29]. Platelets should be given if levels fall below 50×10^9/L.

Tranexamic acid reduces death from PPH and early treatment optimises the benefits. Ig should be given intravenously and repeated, if bleeding continues or restarts (from 30 mins to 24 hrs later) [30].

Aortic compression

If bleeding is out of control and the anaesthetist needs to stabilize the patient, it is worth trying aortic compression while waiting for senior or specialist help to arrive. In the woman who has been delivered vaginally tilt the uterus forward and press a closed fist down onto the abdomen just

below the umbilicus. If the abdomen is already open, sweep the small bowel mesentery up towards the liver and with a swab on a stick or with finger and thumb squeeze the aorta. The effect is dramatic and can be life-saving.

Uterine packing

This is useful for placental bed bleeding but can also be used with uterine atony when there is an element of uterine tone present. The technique is not new, but rather than using a gauze pack an inflatable balloon has the advantage of being quick and expandable. Various balloon catheters have been reported for this technique including the Sengstaken–Blakemore and specifically designed ones, but the urological Rusch balloon catheter is cheaper and effective [31]. Some have used a condom attached to the end of a urinary catheter, but the balloon of a normal urinary catheter itself is not suitable as its capacity is far too small. The volume needed is very dependent on the individual and the key is to insert the balloon catheter and gently fill it whilst keeping the uterus as contracted as possible. As a rough guide approximately 200–400 mL or so is usually required, and as the balloon is inflated resistance is met and bleeding is seen to reduce. If bleeding is controlled, the balloon is usually left in for approximately 24 hours and then – again an advantage over the traditional uterine pack – it can be deflated in stages. If bleeding continues despite the balloon being inflated, then further steps need to be taken to turn off the tap. Whatever is used to pack the uterus, antibiotic cover should be given for the procedure and until the pack/balloon is removed; similarly the bladder should be catheterized until the pack is removed.

Brace suture

The B-Lynch brace suture, first described in 1997 [32], can avoid hysterectomy in cases of bleeding from uterine atony. It aims to exert longitudinal lateral compression on the uterus combined with a tamponade effect and is performed by means of one long suture placed as illustrated in Fig. 25.4. The key to this technique is to check the hypothesis that it works by exteriorizing the uterus and compressing it (bleeding should be controlled) before continuing. Since its first description there have been many reports of its successful use but there have been modifications suggested that have confused the understanding of the principles behind it, and some of these have been associated with problems [33–36]. Longer-term complications have also been reported [37,38] and it is worth reiterating that the suture should be of a rapidly absorbable material to avoid the prolonged presence of free loops of suture material in the abdomen after the uterus involutes [37].

Interventional radiology

Arterial embolization is increasingly reported in the management of postpartum haemorrhage [39,40]. It is especially effective in achieving haemostasis in cases of genital tract trauma where surgical control has failed or the injury is inaccessible. However, it can also help in more non-specific haemorrhage such as uterine atony, when the internal iliac and uterine arteries can be cannulated and their tributaries can be embolized. Developing links with, and knowing contact details of, an interventional radiology department in advance of the emergency scenario makes the urgent referral all the easier. There is a report suggesting that morbidity is better if embolization is carried out before rather than after hysterectomy [41], but this will clearly depend on local facilities and arrangements and the stability of the patient. Embolization is extremely difficult if the internal iliac arteries have been tied off and therefore this technique, which also threatens trauma to the internal iliac vein (a vascular surgeon's nightmare), should rarely be attempted by the obstetrician. Complications from embolization have been reported, including necrosis of uterus and bladder [42], but long-term follow-up has demonstrated that fertility can be maintained but pregnancy outcomes are complicated by a 32% risk of recurrent severe postpartum haemorrhage [43].

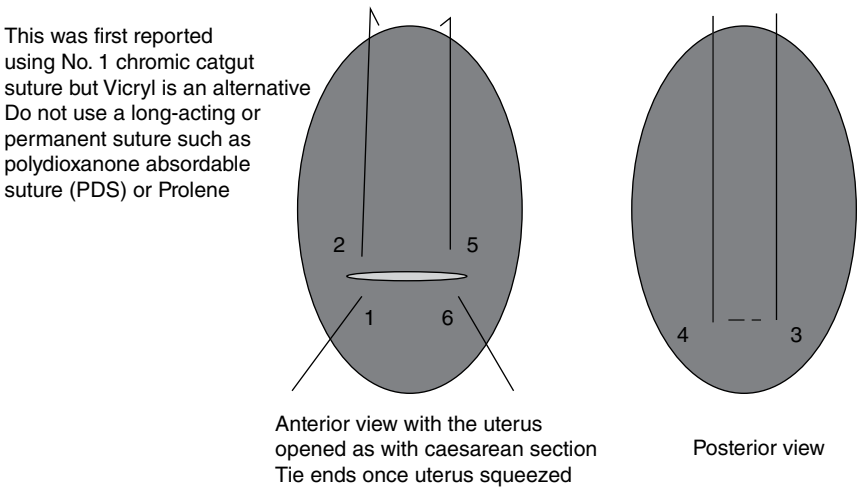

Fig. 25.4 B-Lynch 'brace' suture for treatment of bleeding due to uterine atony, but some uterine tone is needed.

Cell salvage

This technique of contemporary perioperative autologous blood salvage and retransfusion for use in obstetrics has been supported by the National Institute for Health and Care Excellence (NICE) [44], the Obstetric Anaesthetists Association [45] and the Royal College of Obstetricians and Gynaecologists (RCOG) [29,46]. A review confirmed its value and safety [47] and it is acceptable to Jehovah's witnesses [48,49].

Recombinant activated factor VII

There have been a few case reports of the value of giving this in the presence of severe clotting disorders in obstetric haemorrhage [50] but these treatments are still largely research based. It is expensive and only works if the patient has been given other clotting factors on which this can work. Practically speaking, this tends to be within research or on a named patient basis after discussion at consultant level between haematologist and obstetrician, whilst further evidence is collected. Initial reports were encouraging and the subject has been well reviewed [51] and is mentioned in the RCOG guidelines on blood transfusion in obstetrics [29] and postpartum haemorrhage [46].

Obstetric causes of collapse

Eclampsia

Eclampsia can present with collapse due to the fitting and post-ictal phase of the disease, an intracerebral catastrophe, magnesium toxicity or pulmonary oedema. The principles of treatment are as for any collapse and, in addition, blood pressure control, magnesium sulfate and strict fluid balance to avoid fluid overload provide the basis of good care. If the patient is antenatal then the mother must be stabilized before delivery (see Chapter 7). A summary flow chart of acute management of this condition is shown in Fig. 25.5.

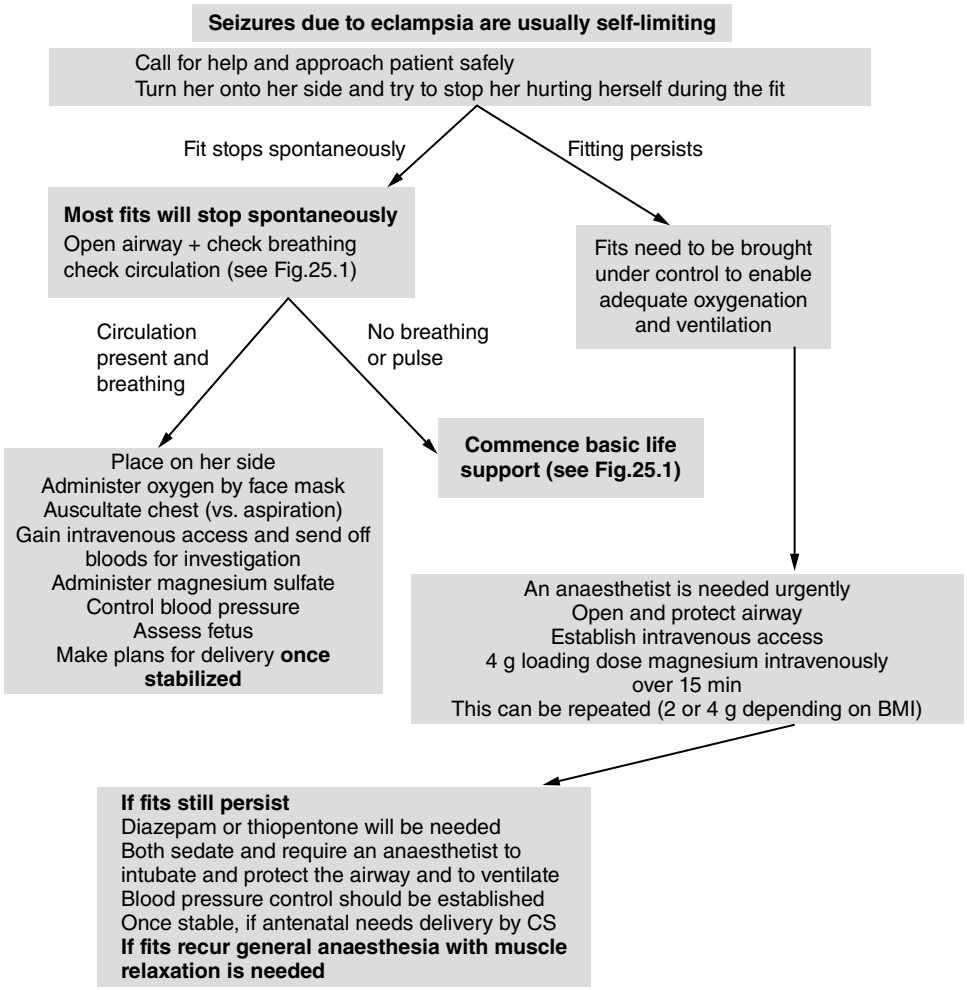

Fig. 25.5 Eclampsia. BMI, body mass index; CS, caesarean section.

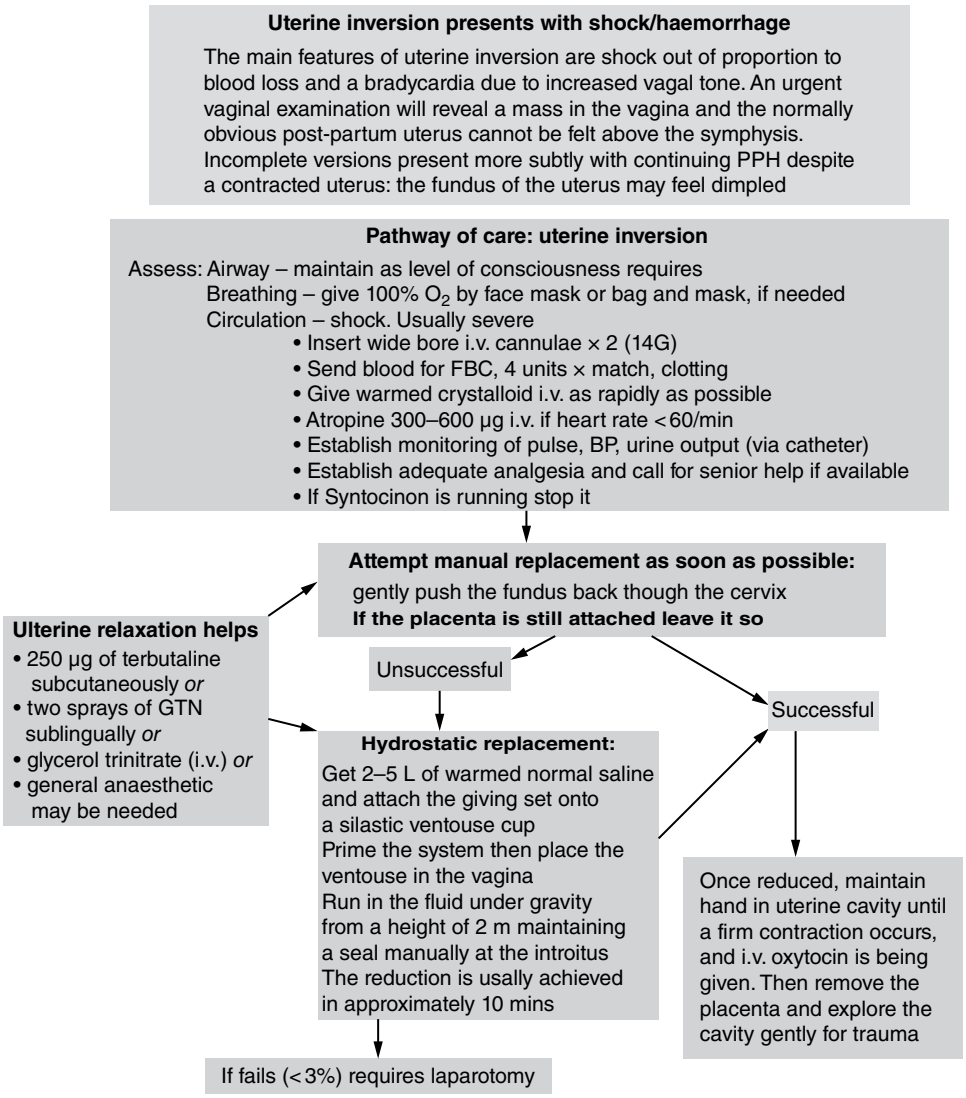

Fig. 25.6 Uterine inversion. BP, blood pressure; FBC, full blood count; GTN, glyceryl trinitrate; PPH, postpartum haemorrhage.

Uterine inversion and uterine rupture

Uterine inversion and uterine rupture can both contribute to maternal collapse and their management is illustrated in Figs 25.6 and 25.7. It is worth noting that 18 of the 42 cases of uterine rupture in the CESDI report had a laparotomy before a diagnosis was made [52]. Signs can be subtle and fetal heart abnormalities in the presence of a uterine scar should be taken extremely seriously and rarely, if ever, justify fetal blood sampling. Similarly, a multiparous patient with secondary arrest should arouse suspicion, and Syntocinon augmentation should only be decided after careful clinical assessment of the patient by the obstetrician to exclude obstructed labour.

Emergency obstetric deliveries

Most emergency operative deliveries (caesarean section, instrumental delivery, breech and twin deliveries and interventions for fetal distress) together with neonatal resuscitation are mentioned in the relevant chapters, but the management of shoulder dystocia and cord prolapse is illustrated in Figs 25.8 and 25.9 and discussed here.

Shoulder dystocia

Shoulder dystocia is every obstetrician's and midwife's nightmare, and rightly so. A lot of effort is now focused

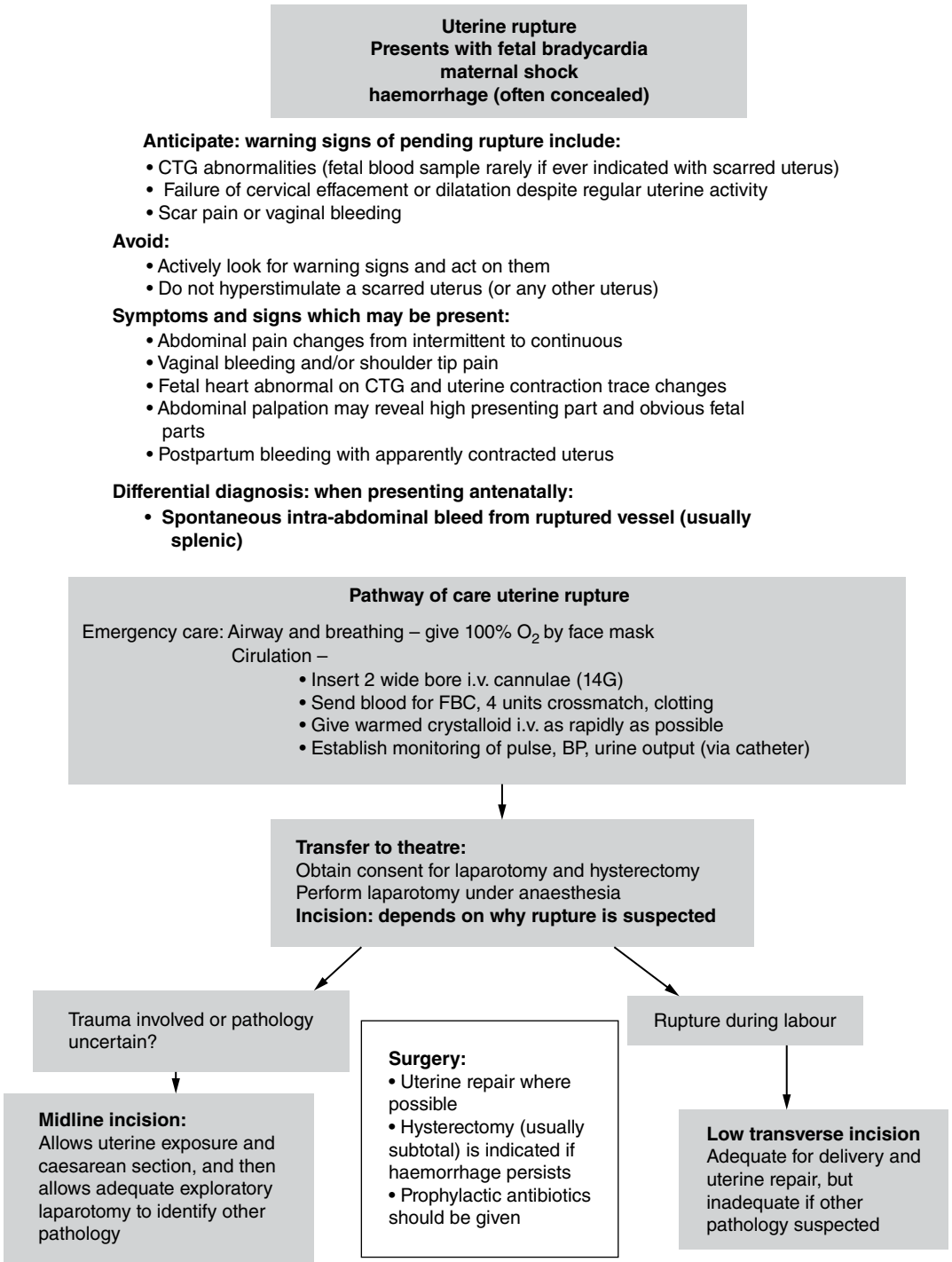

Fig. 25.7 Uterine rupture. BP, blood pressure; CTG, cardiotocography; FBC, full blood count.

on practical training using sophisticated mannequins [53] and this has resulted in improved clinical outcomes [17]. The flow chart in Fig. **25.8** highlights the processes and sequences of its management, but additional points to note include the following.

- Always remember that the problem is at the pelvic brim and pulling on the baby or pushing down on the fundus are both unhelpful and dangerous.
- Time is deceptive and what feels like a lifetime is only a few minutes (try to glance at a clock or get someone to note timings).

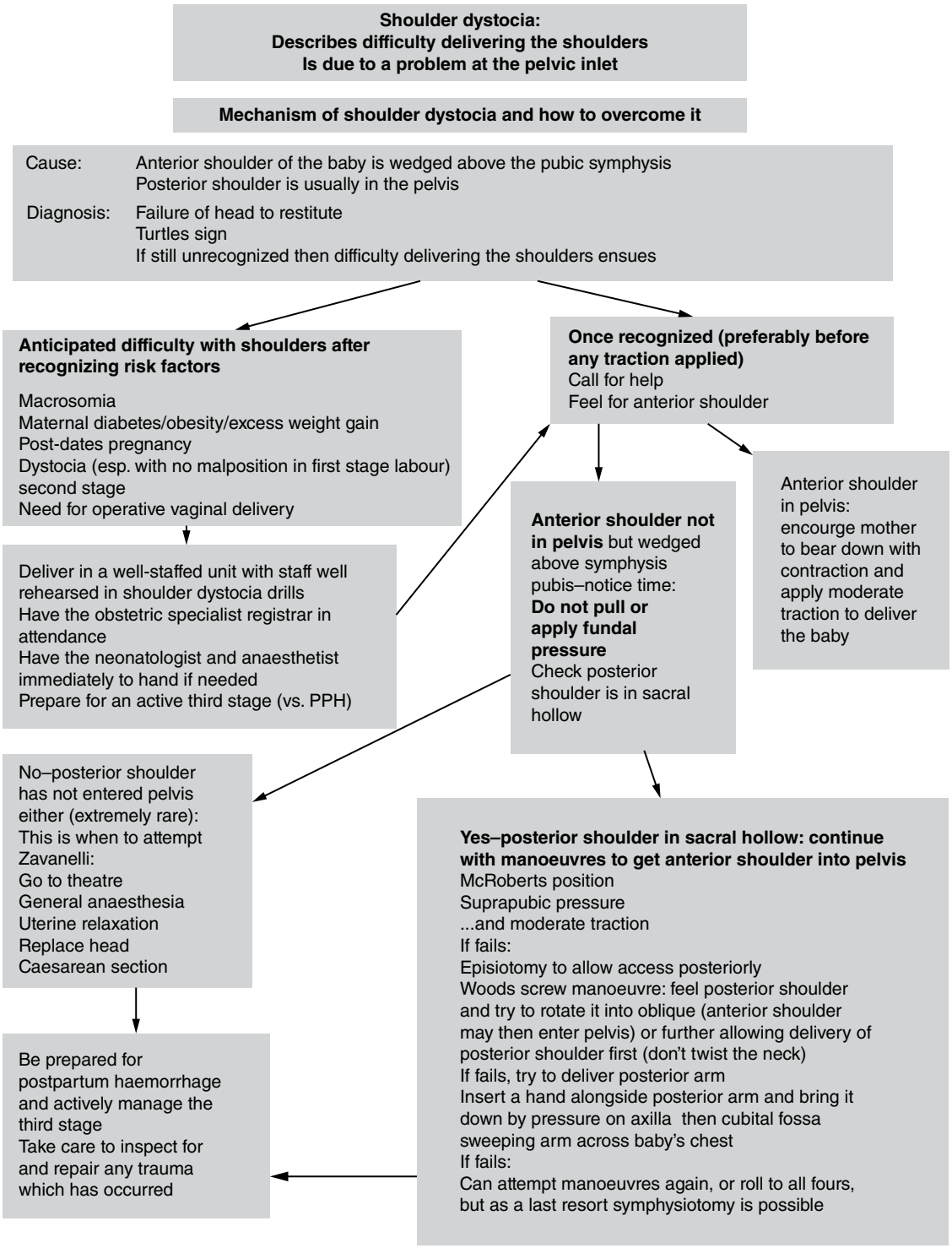

Fig. 25.8 Shoulder dystocia. PPH, postpartum haemorrhage.

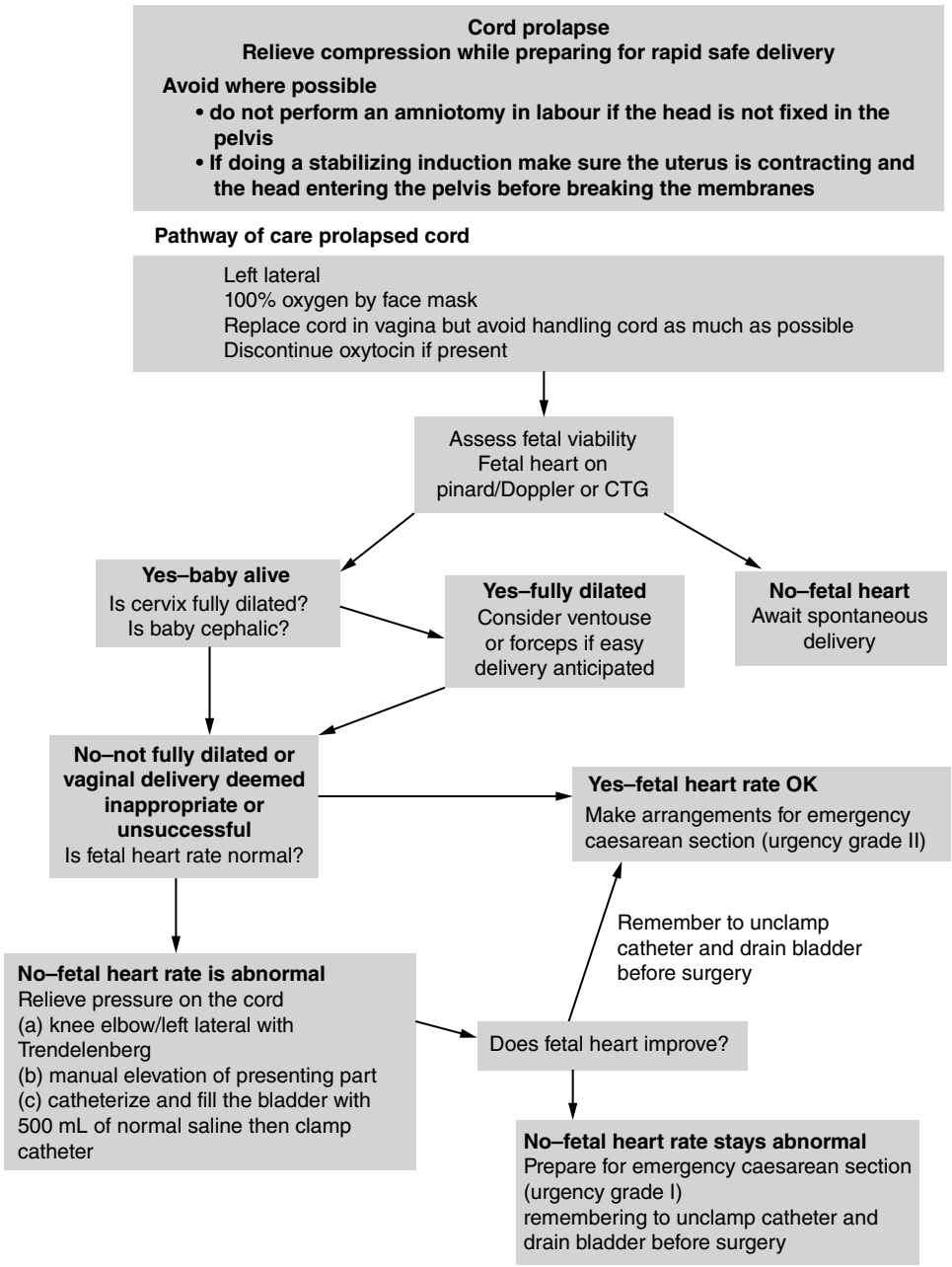

Fig. 25.9 Cord prolapse. CTG, cardiotocography.

- There remains a place for cephalic replacement [54] and occasionally symphysiotomy can be life-saving [55]. Check if the posterior shoulder is still above the pelvic brim or has entered into the pelvis and can be felt in the sacral hollow to help decide which of these manoeuvres would best suit.
- Careful and precise documentation is essential after the event.

Cord prolapse

Figure 25.9 highlights the main features of this emergency. The principles of treatment are as follows.

- Handle the cord as little as possible.
- If an operative vaginal delivery is proposed, it should be simple and achieved quickly; if it is not, it should be abandoned early.

- If there is no fetal bradycardia this need not be a panic delivery under general anaesthesia, and regional block administered with the patient lying on her side may be appropriate.
- If the bladder has been filled with saline, remember to empty it before surgery (just removing the spigot from the Foley catheter is not sufficient).

Summary

Good antenatal care, anticipating possible problems and preparing for them, and running a well-coordinated delivery suite are the mainstays of coping with obstetric emergencies. Training and drills help to focus on teamwork and provide a supportive system to reduce adverse consequences. Keep things simple and focus on the problem to hand. The ABC principle is a good one for dealing with any ill patient, but is particularly useful in the apparently lifeless patient and those who require resuscitation, although it is crucial to remember to manually displace the uterus or apply lateral tilt in anyone still pregnant. In any obstetric emergency keep the basic pathology in mind: why has this happened, what is the problem and how can it be treated?

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26

Malpresentation, Malposition, Cephalopelvic Disproportion and Obstetric Procedures

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Malpresentation, malposition and cephalopelvic disproportion

Definitions

The *vertex* is a diamond-shaped area on the fetal skull bounded by the anterior and posterior fontanelles and laterally by the parietal eminences. Vertex presentation is found in 95% of labours at term and is associated with flexion of the fetal head. Breech, brow, face and shoulder presentations constitute the remaining 5% and are collectively known as *malpresentations*. Their aetiology is usually unknown, but associations include macrosomia, multiparity, polyhydramnios, multiple pregnancy, placenta praevia, preterm labour, and anomalies of the uterus or pelvis (congenital or acquired, e.g. lower segment fibroids) and more rarely the fetus.

The *denominator* is a laterally sited bony eminence on the presenting part ('occiput' for vertex presentation, 'mentum' for face, 'acromium' for shoulder and 'sacrum' for breech). The *position* of the presenting part is defined by the relationship of the denominator to the maternal bony pelvis. The vertex enters the pelvis in the occipito-transverse (OT) position and during descent rotates to an occipito-anterior (OA) position in 90% of cases. This position is associated with a well-flexed head, allowing the smallest anteroposterior (suboccipito-bregmatic) and lateral (biparietal) diameters to pass through the pelvis (both 9.5 cm). *Malposition* occurs when the occiput remains in a tranverse or posterior position as labour progresses. Persistent malposition results in *deflexion* with a larger anteroposterior diameter presenting (occipito-frontal 11.5 cm). It is associated with increasing degrees of anterior or posterior *asynclitism*, with one of the parietal bones preceding the sagittal suture (in posterior asynclitism, the posterior parietal bone leads; Fig. 26.1). Significant degrees of asynclitism can result in labour dystocia and a higher risk of operative delivery [1].

In most cases, flexion occurs as the vertex descends onto the pelvic floor, leading to correction of the malposition and a high chance of spontaneous delivery. The *level* of the presenting part should be critically assessed as labour progresses. On abdominal examination, the head should descend until it is no more than 1/5 palpable in the late first stage. On vaginal examination the presenting part is assessed relative to the level of the ischial spines. Care must be taken to assess the level using the *lowest bony part*. Malposition is associated with increased moulding of the fetal skull and a large caput succedaneum, which may give false reassurance about the true degree of descent. In modern obstetric practice, operative vaginal delivery is not attempted if the leading edge of the skull is above the ischial spines (i.e. above '0' station; Fig. 26.2).

Malpresentations

Breech presentation

The incidence of breech presentation varies according to gestation: 20% at 30 weeks falling to 4% by term. The aetiology of most breech presentations at term is unclear but known factors to consider include placenta praevia, polyhydramnios, bicornuate uterus, fibroids and, rarely, spina bifida or hydrocephaly.

Types of breech presentation

Between 50 and 70% of breech presentations manifest with hips flexed and knees extended (extended breech) Complete (or flexed) breech is more common in multiparous women and constitutes 5–10% at term (hips and knees flexed; Fig. 26.3). Incomplete or footling breech (10–30%) presents with one or both hips extended, or

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

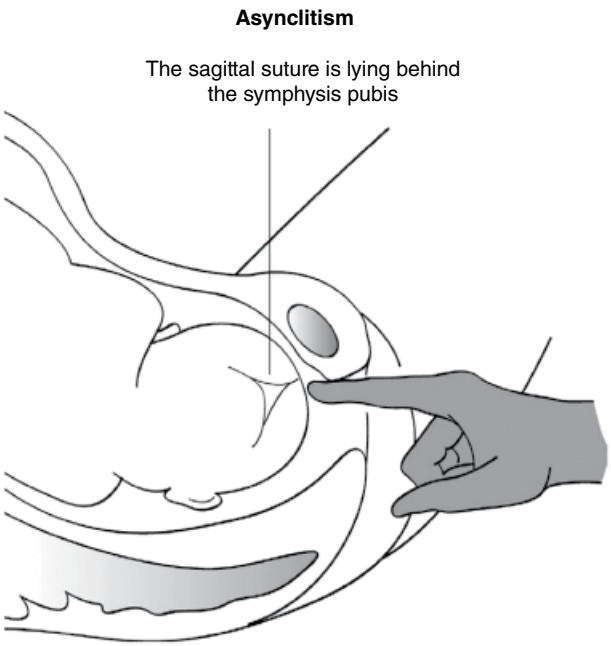

Fig. 26.1 Posterior asynclitism of the vertex: posterior parietal bone presenting below the sagittal suture.

one or both feet presenting and is most strongly assoiated with cord prolapse (5–10%). Knee presentation is rare.

Clinical diagnosis may miss up to 20% of breech presentations, relying on identifying the head as a distinct hard spherical hard mass to one or other side under the hypochondrium which distinctly 'ballots'. In such cases the breech is said to feel broader and an old adage reminds us: 'Beware the deeply engaged head – it is probably a breech!' Auscultation may locate the fetal heart above the maternal umbilicus and ultrasound confirmation should be considered.

Antenatal management

If breech presentation is suspected at 36 weeks, ultrasound assessment is recommended as it allows a comprehensive assessment of the type of breech, placental site, estimated fetal weight, confirmation of normality and exclusion of nuchal cord or hyperextension of the fetal neck.

External cephalic version (ECV) is encouraged after 36 or more weeks as the chance of spontaneous version to

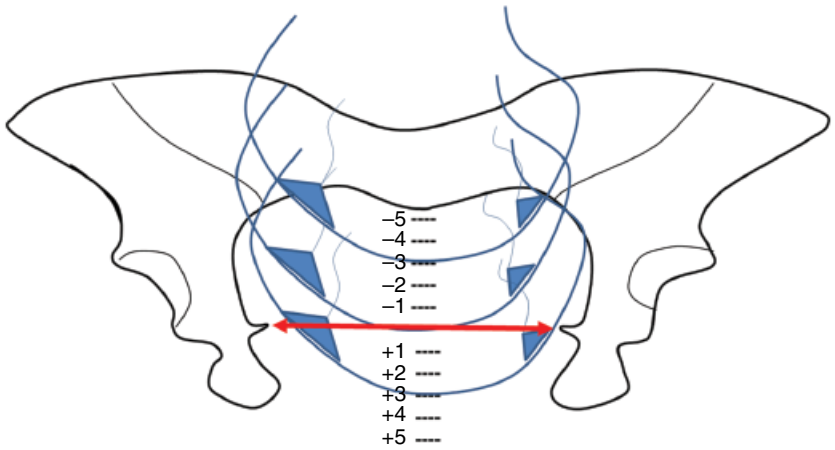

Fig. 26.2 Level of the presenting part relative to the ischial spines.

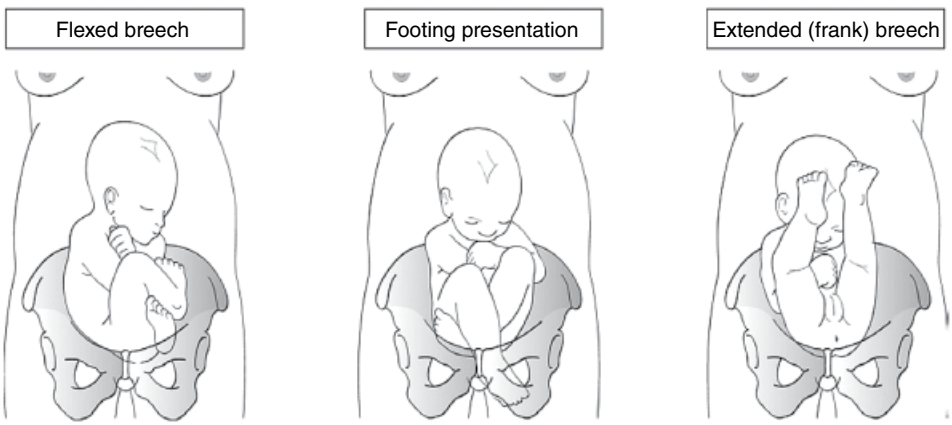

Fig. 26.3 The common types of breech presentation.

cephalic presentation after 37 weeks is only 8%. Absolute contraindications are relatively few but include placenta praevia, bleeding within the last 7 days, abnormal cardiotocography (CTG), major uterine anomaly, ruptured membranes and multiple pregnancy [2]. Couples should receive counselling about the procedure and its success rates and complications, and the subsequent management of persistent breech presentation. Tocolysis increases the likelihood of success, with average rates of 50% (range 30–80%). Women should be made aware that even with a cephalic presentation following ECV, labour is still associated with a higher rate of obstetric intervention than when ECV has not been required. ECV should be performed in a setting where urgent caesarean section (CS) is available in case of fetal compromise during or soon after ECV. CTG for 30–40 min prior to and after ECV should provide confirmation of fetal health. The chance of success is greater with multiparity, flexed breech presentation and an adequate liquor volume. The use of moxibustion at 33–35 weeks, in combination with acupuncture, may reduce the numbers of births by CS. Training specialist midwives is potentially cost-efficient with success rates comparable to consultant-led services (51–66%) [3].

The first step in ECV involves disengaging the breech by moving the fetus up and away from the pelvis, shifting it to a sideways position, followed by a forward somersault to move the head to the lower pole; if this fails a backward somersault can be tried. The need for emergency delivery by CS because of suspected fetal compromise is estimated to be 0.5%. Mothers who are rhesus-negative should have a Kleihauer–Betke test after the procedure and receive anti-D. If ECV is unsuccessful, women who are keen to avoid CS may be offered a repeat attempt under neuraxial blockade. This increases the chances of success (58.4% vs. 43.1%; relative risk, RR 1.44, 95% CI 1.27–1.64) and reduces the incidence of CS (46.0% vs. 55.3%; RR 0.83, 95% CI 0.71–0.97) [4]. Otherwise appropriate counselling about the options of elective CS or assisted vaginal breech delivery should be offered.

Deciding mode of delivery

Despite increasing evidence supporting elective CS for breech delivery at term, controversy and debate continue among professional groups.

1) *Breech presentation at term diagnosed antenatally*. The Term Breech Trial is the largest published randomized controlled trial where the primary outcome (serious perinatal morbidity and mortality) favoured planned CS over planned vaginal birth: 17/1039 (1.6%) versus 50/1039 (5.0%; RR 0.33, 95% CI 0.19–0.56; P <0.0001) [5]. The trial concluded that 'planned CS is better than planned VB for the term fetus in the breech presentation; serious maternal complications are similar between the groups'. This has significantly changed practice in many countries despite continuing debate and criticism about the trial design and intepretation of outcomes. However, the latest systematic review has confirmed a significant increased perinatal risk associated with planned vaginal birth [6].
2) *Breech at term diagnosed in labour and preterm breech delivery*. Observational trials of term breech 'undiagnosed' until presentation in labour confirm that this group has a high vaginal delivery rate with relatively low perinatal morbidity. In a similar vein, the evidence to guide best practice for delivery of the preterm breech remains equivocal, decisions often being based on individual interpretation of the data and local custom and practice.

Conducting a vaginal breech delivery

For women who wish to deliver vaginally, antenatal selection aims to ensure optimal outcome for mother and baby but remains relatively subjective. Women with frank and complete breech presentations (fetal weight <4000 g) encounter minimal problems, while those with footling breech are advised elective CS because of the increased risk of cord prolapse. CT or X-ray pelvimetry do not appear to improve outcome. Spontaneous onset of labour is preferred and labour management is similar to vertex presentation. Successful outcome depends on a normal rate of cervical dilatation, descent of the breech and a normal fetal heart rate (FHR) pattern. Where progress of labour is poor and uterine contractions are inadequate, oxytocin augmentation can be used juidiciously with early resort to emergency CS if progress remains slow (<0.5 cm/hour), particularly in the late first stage.

Epidural anaesthesia prevents bearing down before the cervix is fully dilated and is particularly important for labour with a preterm breech, when there is a real risk of head entrapment in the incompletely dilated cervix if pushing commences too early. For all breech labours, the mother should be encouraged to avoid bearing down for as long as possible. It is best to wait until the anterior buttock and anus of the baby are in view over the mother's perineum, with no retraction between contractions. Classically, the mother's legs are supported in the lithotomy position (the alternative upright breech technique is described later). Primigravidae will usually require an episiotomy with appropriate analgesia, although multigravidae can be assessed as the perineum stretches up.

The buttocks deliver in the sacro-tranverse position. The mother should be encouraged to push with contractions, aiming for an unassisted delivery up to and beyond the level of the umbilicus. There is no need to pull down

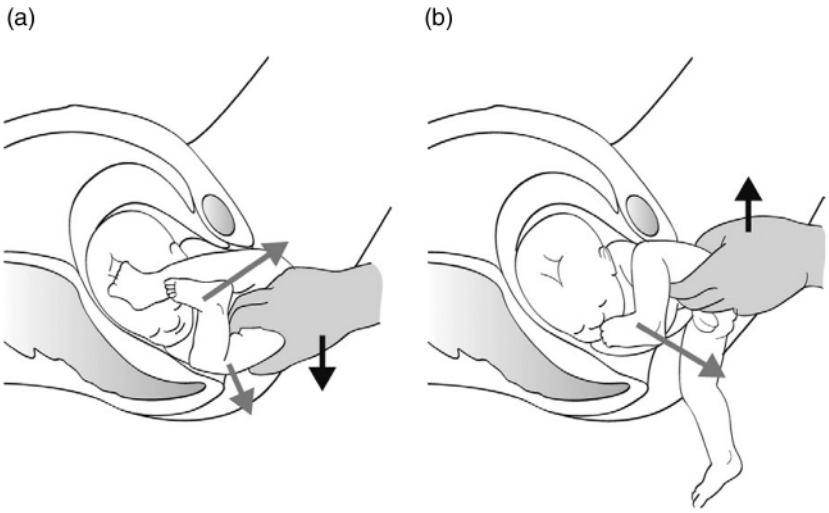

Fig. 26.4 Delivery of extended legs by gentle abduction of the thigh with hyperflexion at the hip, followed by flexion at the knee: (a) right leg; (b) left leg.

a loop of cord. The accoucheur should sit with hands ready, but resting on their own legs. Assistance is only required if the legs do not deliver. Gentle abduction of the fetal thigh whilst hyperflexing the hip, followed by flexing the lower leg at the knee will release the foot and leg (Fig. 26.4).

When the scapulae are visible with the arms flexed in front of the chest, sweep each arm around the side of the fetal chest to deliver using a finger placed along the length of the humerus. If the scapulae are not easily seen or if the arms are not easily reached, they may be extended above the shoulders. This can be resolved using the Løvset manoeuvre.

1) Hold the baby by wrapping both hands around the bony pelvis, taking care not to apply pressure to the soft fetal abdomen.
2) Rotate the baby 180° to bring the posterior shoulder to the front, i.e. to lie anteriorly (Fig. 26.5a).
3) Complete delivery of the anterior arm by gently flexing the baby laterally downwards towards the floor; the arm will deliver easily from under the pubic ramus (Fig. 26.5b).
4) Repeat the 180° rotation in the opposite direction, bringing the posterior shoulder to the front, then flex the baby laterally downwards to deliver the second arm.

Nuchal displacement (an arm trapped behind the fetal neck) is rare. If the left arm is trapped, the baby will need to be rotated in a clockwise direction to 'unwrap' the arm so that it can be reached. If the right arm is involved, anticlockwise rotation is needed.

Allow the head to descend into the pelvis, assisted by the weight of the fetus until the nape of the neck is visible under the symphysis pubis. Ensure slow controlled delivery of the head using one of four methods.

1) Mauriceau–Smellie–Veit manoeuvre: two fingers are placed on the maxilla, lying the baby along the forearm. Hook index and fourth fingers of the other hand over the shoulders with the middle finger on the occiput to aid flexion. Apply traction to the shoulders with an assistant applying suprapubic pressure if needed (Fig. 26.6).
2) Burns–Marshall method: grasp the feet, apply gentle traction and swing the baby gently up and over the maternal abdomen until the mouth and nose appear.
3) Forceps are applied to the head from below, with an assistant supporting the baby's body in the horizontal plane avoiding hyperextension. Kielland's forceps can be useful as they lack a pelvic curve. Apply traction, bringing the forceps upwards as the mouth and nose appear.
4) The upright breech technique is increasingly popular in midwifery deliveries. Mobility is encouraged with delivery on all fours, sitting (on a birth stool), kneeling, standing or lying in a lateral position. Delivery is spontaneous with no manual assistance in 70% of cases and a reduced incidence of perineal trauma (14.9%).

Entrapment of the aftercoming head

This rare complication occurs in two situations.

1) If the fetal back is allowed to rotate posteriorly, the chin may be trapped behind the symphysis pubis. Correction requires difficult internal manipulation to free the chin by pushing it laterally. McRoberts' manoeuvre and suprapubic pressure may help. Symphysiotomy is a last resort that can increase the available pelvic diameters.
2) In preterm delivery, the body can slip through an incompletely dilated cervix, with resulting head entrapment. If the cervix cannot be 'stretched up'

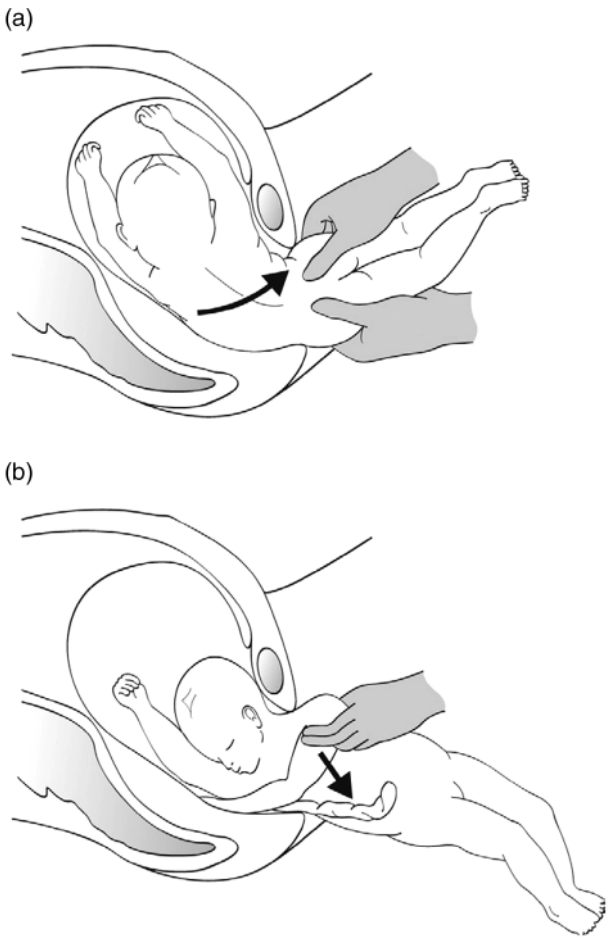

Fig. 26.5 Løvset's manoeuvre for extended arms: (a) rotation to bring the posterior (left) arm to the front followed by (b) delivery of the left arm (now anterior) from under the pubic ramus.

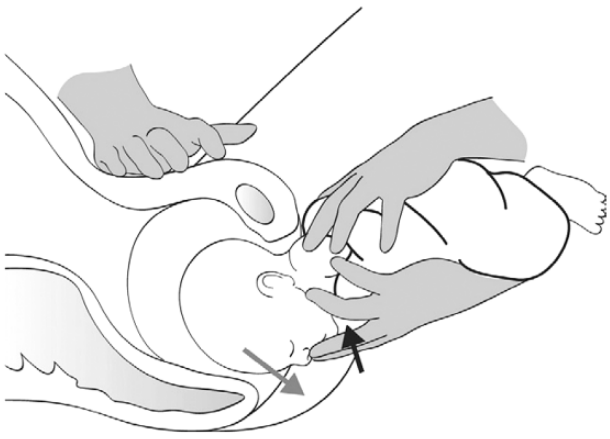

Fig. 26.6 Delivery of the head using the Mauriceau–Smellie–Veit manoeuvre assisted by suprapubic pressure.

digitally, surgical incisions are made in the cervical ring at 2, 6 and 10 o'clock (Dührssen incisions). Head entrapment in the contractile upper segment can occur at CS. Acute tocolysis and/or extension of the uterine incision may be required to release the head.

Women should be intimately involved in decisions about mode of breech delivery and the available evidence presented appropriately. A senior midwife or a doctor experienced in assisted breech delivery must be present. As vaginal breech deliveries decline, developing expertise in breech delivery now relies on simulation training and experience of breech delivery at CS.

Summary box 26.1

- ECV has a high success rate (51–66%) and should be encouraged.
- Ensure the fetal back does not rotate posteriorly during breech delivery.
- The most experienced accoucheur available should directly supervise vaginal breech delivery.

Brow presentation

Brow presentation occurs in 1 in 1500–3000 deliveries. The head is partially deflexed (extended), with the largest diameter of the head presenting (mento-vertical, 13.5 cm). The forehead is the lowest presenting part but diagnosis relies on identifying the prominent orbital ridges lying laterally. The eyeballs and nasal bridge may just be palpated lateral to the orbital ridges. Position is defined using the frontal bone as the denominator (i.e. 'fronto-'). Persistent brow presentation results in true disproportion, but when diagnosed in early labour careful assessment of progress is appropriate. Flexion to vertex or further extension to face presentation occurs in 50% and vaginal delivery is possible. Cautious augmentation with oxytocin should only be considered in nulliparous patients for delay in the early active phase of labour. If brow presentation persists, emergency CS is recommended. Vaginal delivery of a brow presentation is possible in extreme prematurity. Preterm labour is best managed in the same way as term labour, with delivery by CS if progress slows or arrests. Cord prolapse is more common and, though rare, uterine rupture can occur in neglected labour or with injudicious use of oxytocin. For this reason labour should not be augmented in multigravid patients with a confirmed brow presentation if progress is inadequate.

Face presentation

Face presentation occurs in 1 in 500–800 labours. The general causes of malpresentation apply for face presentation, but fetal anomalies (neck or thyroid masses,

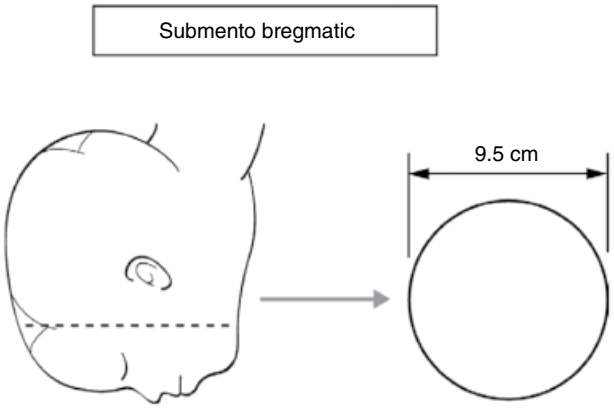

Fig. 26.7 The anteroposterior submento-bregmatic diameter of face presentation.

hydrocephalus and anencephaly) should be excluded. The fetal head is hyperextended and the occiput may be felt higher and more prominently on the same side as the fetal spine. However, face presentation is rarely diagnosed antenatally. On vaginal examination in labour, diagnosis relies on feeling the mouth, malar bones, nose and orbital ridges. Position is defined using the chin or mentum as the denominator. The mouth and malar bones form a triangle which can help differentiate face presentation from breech, where the anus lies in a straight line between the prominent ischial tuberosities. Face presentation is often first diagnosed in late labour. The submento-bregmatic diameter (9.5 cm) is compatible with normal delivery but only with the fetus in a mento-anterior position (60%) (Fig. 26.7). The same diameter presents with a persistent mento-posterior position (25%) but this cannot deliver vaginally as the fetal neck is maximally extended. Fetal scalp clips, blood sampling and vacuum extraction are absolutely contraindicated. Forceps delivery from low cavity can be undertaken for mento-anterior or mento-lateral positions by an experienced accoucheur but CS may still be required when descent is poor.

Shoulder presentation

The incidence of shoulder presentation at term is 1 in 200 and is found with a transverse or oblique lie. Multiparity (uterine laxity) and prematurity are common associations and placenta praevia must be excluded. The lie will usually correct spontaneously before labour as uterine tone increases, although prolapse of the cord or arm is a significant risk if membranes rupture early. For this reason, hospital admission from 38 weeks is recommended for persistent transverse lie. External version can be offered (and may also be considered for transverse lie presenting in very early labour). On vaginal examination, the denominator is the acromium but defining position can be difficult. If membrane rupture occurs at term with the uterus actively contracting, delivery by CS should be undertaken promptly to avoid an impacted transverse lie. If the uterus is found to be moulded around the fetus, a classical CS is recommended to avoid both fetal and maternal trauma. In cases of intrauterine death with a transverse lie, spontaneous vaginal delivery is possible for early preterm fetuses by extreme flexion of the body (spontaneous evolution). However, CS will usually be required beyond mid-trimester, although a lower segment approach may be used.

Malposition and cephalopelvic disproportion

In higher-income countries, cephalopelvic disproportion is usually 'relative' and due to persistent malposition or relative fetal size (macrosomia). Classically we consider these problems with regard to the passage, the passenger or the powers, either alone or in combination.

The passage

Absolute disproportion due to a contracted pelvis is now rare in higher-income countries unless caused by severe pelvic trauma and this should be known before the onset of labour. Caldwell and Moloy described four types of pelvis: gynaecoid (ovoid inlet, widest transversely, 50%), anthropoid (ovoid inlet, widest anteroposterior, 25%), android (heart-shaped inlet, funnel-shaped, 20%) and platypelloid (flattened gynaecoid, 3%). These can influence labour outcome but as pelvimetry is rarely used and clinical assessment of pelvic shape is inaccurate, this rarely influences clinical mangement in labour. The anthropoid pelvis is associated with a higher risk of persistent occipito-posterior (OP) position and relative disproportion.

The passenger and OP malposition

Fetal anomalies (e.g. hydrocephalus, ascites) where disproportion may be a problem in labour are usually assessed antenatally and delivery by elective CS considered. Fetal macrosomia is increasing, related to the rising body mass index (BMI) in many pregnant populations. The evidence for inducing non-diabetic women with an estimated fetal weight above the 90th centile (or >4000 g) in order to reduce cephalopelvic disproportion remains equivocal. Malposition is an increasingly common cause of disproportion and may be related to a sedentary lifestyle. OP position is associated with deflexion and/or asynclitism with a larger diameter presenting. Optimal uterine activity will correct the malposition in 75% of cases. Flexion occurs as the occiput reaches the pelvic floor with long rotation through 135° to an OA position and a high chance of normal delivery. Moulding of the

fetal skull and pelvic elasticity (related to changes at the symphysis pubis) are dynamic changes that facilitate progress in labour and delivery. Short rotation through 45° to direct OP can result in spontaneous 'face to pubes' delivery, although episiotomy may be required to allow the occiput to deliver. Persistent OP position occurs in up to 25% of cases and is associated with further deflexion. The risk of assisted delivery is high because of relative disproportion as the presenting skull diameters increase. Delivery in the OP position from mid-cavity (0 to +2 station) requires critical assessment to decide whether delivery should be attempted vaginally or abdominally and is discussed in later sections.

The powers

Disproportion is intimately related to dystocia and failure to progress in labour. National Institute for Health and Care Excellence (NICE) guidelines recommend that first stage delay is suspected with cervical dilatation of less than 2 cm in 4 hours when forewater amniotomy should be offered. Delay is confirmed if progress is less than 1 cm 2 hours later and oxytocin augmentation should be offered [6]. This shortens labour but does not affect operative delivery rates. High-dose oxytocin may reduce CS rates but larger trials are required before these regimens are used routinely. The decision to use oxytocin in labour arrest in multigravid patients must only be made by the most senior obstetrician and should always be approached with extreme caution as uterine rupture is a possible consequence.

In the second stage, particularly with epidural analgesia, passive descent for at least 1 hour is recommended, and possibly longer if the woman wishes, before encouraging active pushing. With regional analgesia and a normal FHR pattern, birth should occur within 4 hours of full dilatation regardless of parity [7]. Oxytocin may be commenced in nulliparous patients in the passive phase if contractions are felt to be inadequate and particularly with the persistent OP position. Failure of second-stage descent combined with excessive caput or moulding suggests disproportion and requires critical assessment to decide the appropriate mode of delivery.

Summary box 26.2

- OP position with deflexion of the head and asynclitism results in relative disproportion compounded by inadequate uterine activity.
- With epidural analgesia in place, passive descent should be encouraged for at least 1 hour.
- Augmentation with oxytocin should be used with extreme caution in multigravid patients with labour arrest.

Instrumental vaginal deliveries

Background

The incidence of instrumental vaginal delivery (IVD) varies widely and in Europe ranges from 0.5% (Romania) to 16.4% (Ireland), although there is no direct relationship with CS rates [8,9]. Epidural analgesia is associated with higher IVD rates. Allowing a longer passive second stage for descent results in less rotational deliveries and possibly a reduction in second-stage CS [10,11]. Common indications for IVD include delay in the second stage of labour due to inadequate uterine activity, malposition with relative disproportion, maternal exhaustion and fetal compromise. Women with severe cardiac, respiratory or hypertensive disease or intracranial pathology may require IVD to shorten the second stage (when forceps may be preferred).

Assessment and preparation for IVD

The condition of the mother and fetus and the progress of labour should be assessed prior to performing IVD. Personal introductions to the woman and her partner are essential, explaining the reason for IVD and ensuring a chaperone and enough support are available. The findings, plan of action and the procedure itself should be explained and the discussions carefully recorded. Verbal or written consent is obtained. The mother and her partner may be physically and emotionally exhausted and great care should be exercised in terms of behaviour, communication and medical action.

On abdominal examination, the fetal head should be no more than 1/5 palpable (preferably 0/5). A scaphoid shape to the lower abdomen may indicate an OP position. The FHR pattern should be assessed, noting any clinical signs of fetal compromise (e.g. fresh meconium). With acute fetal compromise (e.g. profound bradycardia, cord prolapse) delivery must be expedited urgently and this may only allow a brief explanation to be given to the patient and her partner at the time.

If contractions are felt to be infrequent or short-lasting, an oxytocin infusion should be considered in the absence of signs of fetal compromise. Both vacuum and forceps deliveries are associated with an almost threefold increased risk of shoulder dystocia compared with spontaneous delivery and this should be anticipated. However, it remains unclear whether this increased incidence is a cause or effect phenomenon [12].

On vaginal examination the cervix should be fully dilated with membranes absent. The colour and amount of amniotic fluid is recorded. Excessive caput or moulding may suggest the possibility of disproportion. Inability to reduce overlapping skull bones with gentle pressure is

designated 'moulding +++'; overlapping that reduces by gentle digital pressure is 'moulding ++', and meeting of the bones without overlap is 'moulding +'. Identification of position, station, degree of deflexion and asynclitism will help decide whether IVD is appropriate, where it should be undertaken and who should undertake the procedure.

Successful IVD is associated with station below the spines and progressive descent with pushing. If the head is 1/5 palpable abdominally, the leading bony part of the head is at the level of the ischial spines (mid-cavity). When the head is more than 1/5 palpable and/or when station is above the spines, delivery by CS is recommended.

Position is determined by identification of suture lines and fontanelles. The small posterior fontanelle (PF) lies at the Y-shaped junction of the sagittal and lambdoidal sutures but may be difficult to feel when there is marked caput. The anterior fontanelle (AF) is a larger diamond-shaped depression at the junction of the two parietal and two frontal bones. It can be differentiated from the PF by identifying the four sutures leading into the fontanelle. In deflexion (particularly OP positions) the AF lies centrally and is easily felt. Position can be confirmed by reaching for the pinna of the fetal ear, which can be flicked forwards indicating that the occiput lies in the opposite direction. Reaching the ear suggests descent below the mid-pelvic strait. The degree of asynclitism should be assessed (see Fig. 26.1), with increasing degrees suggesting disproportion and a potentially more difficult IVD. Assessment of level and position can be difficult with OP position and in obesity. If there is any doubt after careful clinical examination, ultrasound assessment is recommended. The fetal orbits are sought and the position of the spine is noted. This is simple to do and can reduce the incorrect diagnosis of fetal position without delaying delivery, although on its own may not reduce morbidity associated with IVD [13].

IVD is normally performed with the mother in the dorsal semi-upright position with legs flexed and abducted, supported by lithotomy poles or similar. The procedure is performed with good light and ideally aseptic conditions. The vulva and perineum should be cleansed and the bladder catheterized if the woman is unable to void.

Adequate analgesia is essential and requires careful individualized assessment. Epidural anaesthesia is advisable for mid-cavity IVD (i.e. station 0 to +2 cm below the ischial spines; see Fig. 26.2). In the absence of a pre-existing epidural, spinal anaesthesia may be considered. IVD at station +2 cm or below is termed 'low-cavity' and regional or pudendal block with local perineal infiltration (20 mL 1% plain lidocaine) can be used. Outlet IVD is performed when the head is on or near the perineum with the scalp visible without separating the labia. Descent to this level is associated with an OA position requiring minimal or no rotation and perineal infiltration with pudendal anaesthesia is effective.

When the vertex is below the spines, IVD is carried out with different types of forceps or vacuum equipment, depending on the position and station of the vertex and the familiarity and experience of the doctor. Overall, comparing outcomes is easier if designation is by station and position at the time of instrumentation (e.g. left OP at +3) rather than simply mid, low or outlet IVD [11,14].

Choice of instruments: forceps or ventouse

The choice of instrument depends on the operator's experience, familiarity with the instrument, station and position of the vertex. Therefore, knowledge of the station and the position of the vertex is essential. The fetus in an OA position in the mid/low cavity can be delivered using non-rotational, long or short-handled forceps or a vacuum device: silicone, plastic or anterior metal cups (with suction tubing arising from the dorsum of the cup) are all suitable. For the fetus lying OT at mid- or low-cavity, or lying OP position mid-cavity, Kielland's forceps or vacuum devices can be used to correct the malposition. Manual rotation is another technique to consider.

Low-cavity direct OP positions can be delivered 'face to pubis' but this may cause signifcant perineal trauma as the occiput delivers. For this reason, an OP vacuum cup (with the suction tubing arising from the edge of the cup) may be preferred. The cup will promote flexion and late rotation to OA often occurs on the perineum just prior to delivery. The Kiwi OmniCup® is an all-purpose disposable vacuum delivery system with a plastic cup and in-built PalmPump™ suitable for use in all positions of the vertex. Later models also display force traction to help the accoucheur avoid cup slippage (http://clinicalinnovations.com/portfolio-items/kiwi-complete-vacuum-delivery-system/)

Forceps delivery

Forceps come in pairs and most have fenestrated blades with a cephalic and pelvic curve between the heel and toe (distal end) of each blade. The heel continues as a shank which ends in the handle. The handles of the two blades sit together and meet at the lock. The cephalic curve fits along either side of the fetal head with the blades lying on the maxilla or malar eminences in the line of the mento-vertical diameter (Fig. 26.8a). When correctly attached, uniform pressure is applied to the head, with the main traction force applied over the malar eminences. The shanks are over the flexion point,

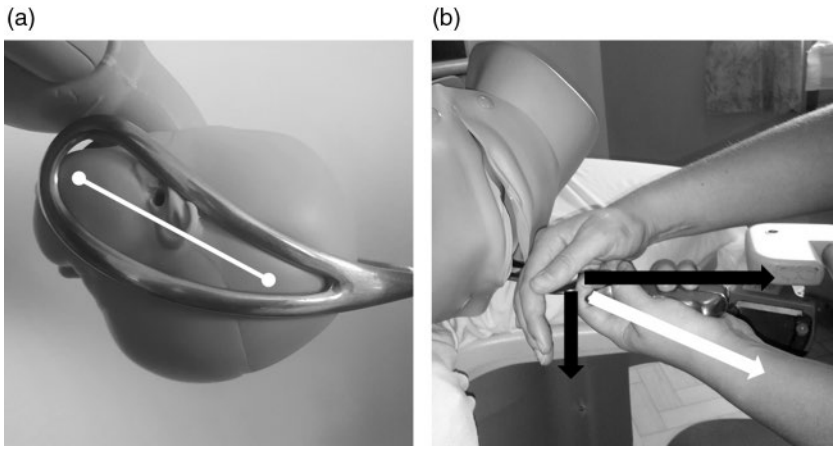

Fig. 26.8 (a) Malar forceps application showing mento-vertical diameter; (b) forceps traction (Pajot's manoeuvre).

allowing effective traction in the correct direction. Non-rotational forceps (the longer-handled Neville Barnes or Simpson, and the shorter-handled Wrigley's) have a distinct pelvic curve that allows the blades to lie in the line of the pelvic axis whilst the handles remain horizontal. Kielland's forceps have a minimal pelvic curve to allow rotation within the pelvis to correct malposition.

Prior to applying forceps, the blades should be assembled to check whether they fit together as a pair. All forceps have matching numbers imprinted on the handles or shanks and these should also be checked.

Non-rotational forceps can be applied when the vertex is no more than 45° either side of the direct OA position (i.e. right OA to left OA). Application and delivery in a direct OP position is also possible but not routinely recommended because of increased perineal trauma. The left blade is inserted first using a light 'pencil grip', negotiating the pelvic and cephalic curves with a curved movement of the blade between the fetal head and the operator's right hand, which is kept along the left vaginal wall for protection. Hands are swapped to insert the right blade using the same technique. Correct application results in the handles lying horizontally, right on top of left, and locking should be easy. Before applying traction, correct application must be confirmed: (i) the sagittal suture is lying midline, equidistant from and parallel to the blades; (ii) the occiput is no more than 2–3 cm above the level of the shanks (i.e. head well-flexed); and (iii) no more than a fingertip passes into the fenestration at the heel of the blade.

From mid- and low-cavity, Pajot's maneouvre should be used, balancing outward traction with one hand with downward pressure on the shanks with the other (Fig. 26.8b, white arrow). The handles are kept horizontal to avoid trauma to the anterior vaginal wall from the toes of the blades. Traction is synchronized with contractions and maternal effort, and the resultant movement is outwards down the line of the pelvic axis until the head is crowning. An episiotomy is usually needed as the perineum stretches up. The direction of traction is now upwards once the biparietal eminences emerge under the pubic arch and the head is born by extension. The mother will usually ask to have her baby handed to her immediately (unless active resuscitation is required). After completing the third stage, any perineal trauma is repaired and a full surgical count completed. The procedure, including plans for analgesia and bladder care, should be fully documented.

Rotational forceps

Kielland's forceps have a minimal pelvic curve allowing rotation of the head at mid-cavity. They are powerful forceps requiring a skilled accoucheur who is willing to abandon the procedure if progress is not as expected. The number of units able to teach use of Kielland's forceps to the point of independent practice is declining in the UK.

The forceps should match and are applied so that the knobs on the handles face the fetal occiput. Kielland's are used to correct both OT and OP positions using two methods of application.

1) Direct application involves sliding each blade along the side of the head if space permits, and is more easily achieved with OP positions.
2) Wandering application is useful in OT positions. The first blade is applied in front of the fetal face, from where it is gently 'wandered' around to lie in the usual position alongside the malar bone. The posterior blade is applied directly using the space in the pelvic sacral curve.

If application is difficult or the blades do not easily lock, the procedure should be abandoned. Correct application should be confirmed. Once locked, it is essential to hold the handles at a relatively steep angle

downwards in the line of the mid-pelvic axis in order to achieve easy rotation.

Asynclitism is corrected using the sliding lock, moving the shanks over each other until the knobs are aligned. Rotation should take place between contractions, using only gentle force. Rotation may require the fetal head to be gently disimpacted, either upwards or downwards but no more than 1-cm displacement is needed. Correct application should be checked again after rotation. Traction should result in progressive descent and an episiotomy is usually required. At the point of delivery, the handles of Kielland's are only just above the horizontal because of the lack of pelvic curve. If there is no descent with traction during three contractions with maternal effort, the procedure should be abandoned. Whether Kielland's delivery takes place in the delivery room or in obstetric theatre requires careful assessment of fetal and maternal condition, analgesia and labour progress. If there is any doubt, a formal trial of forceps should be arranged.

Vacuum delivery

Ventouse or vacuum delivery is increasingly favoured over forceps delivery for similar indications in the second stage of labour. The prerequisites to be satisfied before vacuum delivery are the same as for all forms of IVD. Vacuum delivery is contraindicated below 34^{+0} weeks and should be used with caution between 34^{+0} to 36^{+0} weeks [11]. Overall it is contraindicated for fetuses with possible haemorrhagic tendencies (risk of subgaleal haemorrhage) and before full dilatation [11]. Experienced practitioners may consider vacuum after 8 cm in a multigravid patient in some circumstances.

There are many types of vacuum cup in regular use, made of different materials and of differing shapes. Whichever cup is used, the aim is to ensure that the centre of the cup is directly over the flexion point. The flexion point is 3 cm in front of the occiput in the midline and is the point where the mento-vertical diameter exits the fetal skull [15]. Traction on this point promotes flexion, presenting the smallest diameters for descent through the pelvis: this is the optimum flexing median application (Fig. 26.9a). Other applications increase the risk of cup detachment, failed vacuum delivery and scalp trauma. In decreasing order of effectiveness, these are the flexing paramedian application (Fig. 26.9b), the deflexing median application (Fig. 26.9c) and the deflexing paramedian application (Fig. 26.9d).

It is vitally important to select the correct cup and this will vary depending on both the position and attitude of the fetus. The soft Silc, Silastic or anterior metal cups (where the tubing is attached on the dorsum of the cup) are not suitable for OT or OP positions, as their shape and configuration do not allow application over the flexion point. They are suitable for OA positions where the flexion point is accessible in the midline.

Metal cups come in different sizes, usually 4, 5 or 6 cm in diameter. In a systematic review they were more likely to result in successful vaginal birth than soft cups (RR 1.63, 95% CI 1.17–2.28), but with more cases of scalp injury (RR 0.67, 95% CI 0.53–0.86) and cephalhaematoma (RR 0.61, 95% CI 0.39–0.95) [16]. A specially designed cup should be used for OT and OP positions: metal OP cups have tubing emerging from the lateral aspect of the cup and the Kiwi OmniCup has a groove in the dorsum of the cup to accommodate the flexible stem. These cups can be manoeuvred more laterally or posteriorly to reach the flexion point. Hand-held vacuum is associated with more failures than metal ventouse [16], although a larger study suggested that the OmniCup has an overall failure rate of 12.9% [11].

Aldo Vacca (1941–2014) was the doyen of vacuum delivery and (with reference to the flexion point and cup application) his favourite quote was 'It's always more posterior than you think'. After ensuring flexion point application, the cup must be held firmly on the fetal scalp, and a finger should be run around the rim to ensure that no maternal tissue is entrapped. A vacuum of 0.2 bar (150 mmHg or 0.2 kg/cm^2 negative pressure) is created using a hand-held or mechanical pump, before

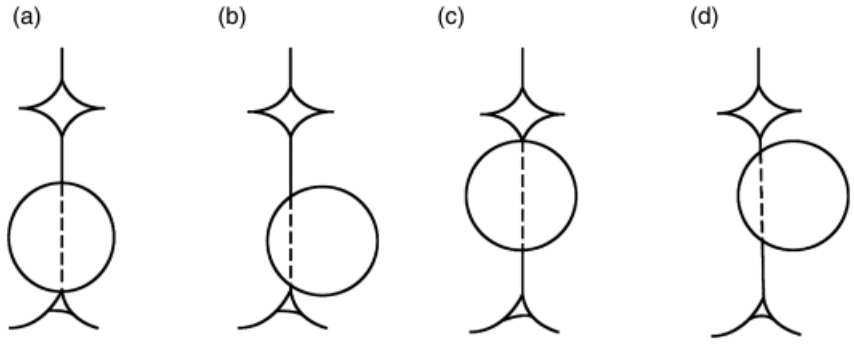

Fig. 26.9 Placement of the vacuum cup, from most favourable (a) to unfavourable (d). (a) Flexing median; (b) flexing paramedian; (c) deflexing median; (d) deflexing paramedian.

rechecking the position over the flexion point and confirming maternal tissue is not trapped. The vacuum is increased to 0.7–0.8 bar (500–600 mmHg or 0.8 kg/cm^2) in one step, waiting 2 min where possible to develop the 'chignon' within the cup. Axial traction in the line of the pelvic axis should be timed with uterine contractions and maternal pushing. A thumb should be placed on the cup, with the index finger on the scalp at the edge of the cup allowing the operator to feel any potential detachment before it is heard (by which point it is often too late to prevent detachment). Descent promotes autorotation of the head to the OA position and episiotomy is often not required. Parents should be reassured that the 'chignon' will settle over 2–3 days.

Manual rotation

Manual rotation for persistent OP position is an alternative to IVD. The procedure requires insertion of one hand into the posterior vagina to encourage flexion and rotation. Careful patient selection is essential and the operator must ensure that effective analgesia is in place. The right hand is inserted for a left OP position (insert left hand for right OP). Four fingers are placed behind the fetal occiput to act as the 'gutter' on which the head will rotate, with the thumb placed alongside the anterior fontanelle. When the mother pushes with a contraction, the thumb applies pressure to flex the head and rotation to an OA position should occur with minimal effort. In a series ($N = 61$) where OP position was managed in two groups, the spontaneous delivery rate increased from 27% to 77% in the group offered digital rotation ($P < 0.0001$) [17].

Complications of IVD

In a Cochrane review of 32 studies ($N = 6597$), forceps were less likely to fail to achieve a vaginal birth compared with ventouse (RR 0.65, 95% CI 0.45–0.94) [16]. Vaginal and perineal lacerations, including third- and fourth-degree tears, are more common with forceps than with vacuum. Infra-levator haematomas may occur occasionally and these should be drained if large or symptomatic. The risk of flatus incontinence or altered continence is also higher.

Follow-up of women who have had low or outlet IVD confirms normal physical and neourological outcomes for the vast majority of the newborn. In terms of neonatal outcome, cephalhaematoma is more common with vacuum but risk of facial injury is less. Facial and scalp abrasions are usually minor and heal in a few days. Unilateral facial nerve palsy is rare and resolves within days or weeks and is not usually related to poor technique. Skull fracture is rare and most need no treatment unless depressed, when surgical elevation may be indicated. Vacuum delivery may result in retinal haemorrhages, haematoma confined to one of the skull bones and neonatal jaundice. Severe scalp lacerations imply poor technique and are fortunately rare. Subgaleal haemorrhage may cause minor or severe morbidity and rarely mortality [18]. In reviewing morbidity associated with IVD, it is important to remember that the alternative option of second-stage CS is also associated with increased morbidity for both mother and baby.

Safe practice: sequential intrumentation and trial of instrumental delivery

For all IVDs, the procedure should be abandoned if there is 'no evidence of progressive descent with moderate traction during each contraction, or where delivery is not imminent following three contractions of a correctly applied instrument by an experienced operator' [11]. Sequential instrumentation is associated with increased neonatal morbidity and the decision to proceed must take into account the relative risks of delivery by second-stage CS from deep in the pelvis. It can be difficult to judge whether to proceed with IVD, especially in cases with mid-cavity malposition at the level of the ischial spines. In such cases a trial of instrumental delivery should be undertaken in theatre under regional anaesthesia, with the full theatre team and neonatal practitioner present. The estimated incidence of trial of instrumental delivery is 2–5%. It is vital to maintain awareness of the situation, with a clear willingness to abandon the attempt if progress is not as expected, proceeding immediately to CS. The couple should be advised of this strategy and appropriate consent obtained prior to the procedure, which should be undertaken by the most senior obstetrician available. In the presence of fetal compromise, it is prudent to consider delivery by emergency CS, rather than proceeding with a potentially difficult IVD. Paired cord blood samples should be taken and results recorded after every attempted IVD.

Contemporary developments in IVD

New methods are being developed to achieve IVD and include disposable plastic forceps with the ability to measure traction force (see http://www.medipex.co.uk/success-stories/pro-nata-yorkshire-obstetric-forceps/ and Fig. 26.10) and the Odon device where traction is applied using a plastic bag placed around the fetal head and neck. This device is undergoing trials led by the World Health Organization (see http://www.who.int/reproductivehealth/topics/maternal_perinatal/odon_device/en/).

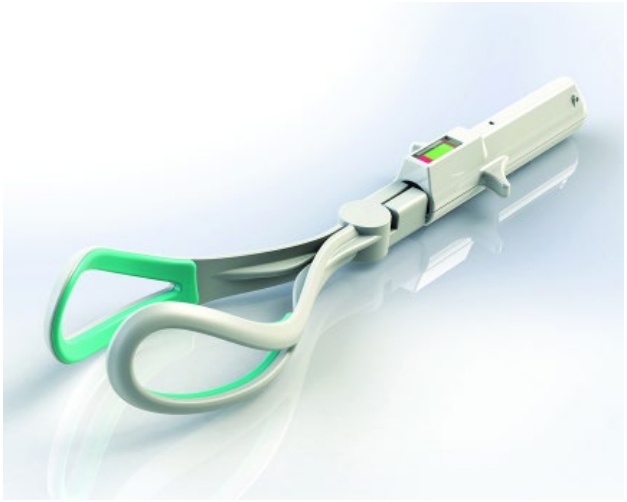

Fig. 26.10 Pro-Nata Yorkshire obstetric forceps. Reproduced with permission of Mark Jessup.

Summary box 26.3

- Level and position must be critically assessed before proceeding with IVD and ultrasound is a useful adjunct.
- Successful vaginal delivery is more likely when the correct vacuum cup is applied directly over the flexion point.
- Safe practice with IVD requires the operator to maintain a willngness to abandon the procedure at all times.

Caesarean section

CS rates vary widely across Europe, ranging from 14.8% in Iceland to 52.2% in Cyprus [8,9]. In 2015, the World Health Organization confirmed that CS rates higher than 10% are not associated with reductions in maternal and newborn mortality rates but acknowledged that the effects of CS rates on other outcomes (maternal and perinatal morbidity, paediatric outcomes, and psychological or social well-being) are still unclear and require further research [19]. This is very pertinent to obstetrics in the twenty-first century at a time when CS rates for non-obstetric indications are rising. This includes elective CS where the primary indication is maternal request, often reflected in significantly higher rates in the private sector.

Indications

The indications for CS are grouped into four categories depending on the urgency of the procedure [20,21].

- *Category 1*. There is immediate threat to the life of mother or fetus. Examples include abruption, cord prolapse, scar rupture, scalp blood pH below 7.20, and prolonged fetal bradycardia. Although a decision-to-delivery interval of 30 min is a useful audit tool to help review local practice, it does not correlate directly with poor perinatal outcome. Timing should be individualized and depends on the clinical urgency in each case. Those cases of utmost urgency require clear and timely communication between all members of the team. Team performance may benefit by practising rapid transfer to theatre using 'hot drill' simulation techniques [21].
- *Category 2*. There is no immediate risk to the life of mother or fetus. Delivery should be expedited in a timely manner but individual assessment remains critical. Examples include those with deteriorating CTG and a borderline scalp pH (especially in the early active phase of labour) or with slow progress in labour and poor maternal pain control. It is accepted that clinicians will categorize cases differently based on their interpretation of the clinical situation.
- *Category 3*. Requires early delivery but with no current maternal or fetal compromise. This group has a wide range of indications, including planned CS with ruptured membranes at term, not contracting or a growth-restricted fetus in the preterm period with abnormal venous Doppler but a normal FHR tracing.
- *Category 4*. The delivery is timed to suit the mother and maternity staff. This replaces the term 'elective CS' and should normally be delayed until 39 weeks to minimize the incidence of transient tachypnoea of the newborn.

Types of caesarean section

Lower uterine segment incision

The commonest CS procedure uses a transverse incision in the lower uterine segment (LUS). The abdomen is usually opened with a Pfannenstiel (transverse suprapubic) incision. The Joel-Cohen technique involves blunt digital stretching and separation of tissues using the natural tissue planes, with minimal sharp dissection and non-closure of both peritoneal layers. This has advantages over Pfannenstiel and traditional (lower vertical incision) techniques with improved short-term outcomes including shorter operating time, reduction in estimated blood loss and less pyrexia. Disposable double-ring retractors provide 360° circumferential atraumatic wound retraction and reduce superficial surgical site infection in gastrointestinal surgery by 45%. They give excellent access at CS and can be particularly useful in patients with a high BMI to support the panniculus during delivery and uterine repair. One of the flexible rings is inserted

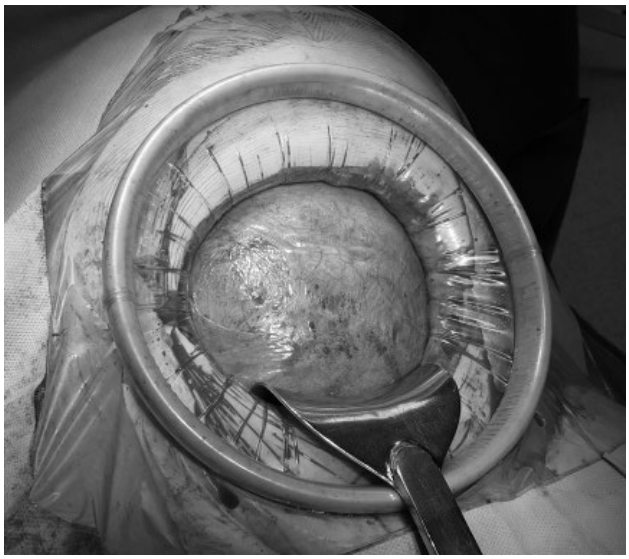

Fig. 26.11 Disposable retractor for caesarean section.

through the incision to lie under the abdominal wall and the surgeon and assistants roll up a thin polythene cylinder onto the second ring which lies outside the abdomen (Fig. 26.11).

Ensure that the uterus is not significantly dextrorotated. The utero-vesical peritoneum is divided, the bladder reflected caudally and a transverse incision is made in the LUS taking care to avoid injury to the fetus. Enlarging the uterine incision with scissors increases the risk of unintended extension compared with digital expansion. A recent systematic review confirmed that digital expansion in the cephalad–caudad direction rather than transversely further reduces the incidence of unintended extension, uterine vessel injury and major blood loss over 1500 mL [22]. In the later stages of labour, care should be taken to avoid making the incision too low, which can result in inadvertent delivery through the anterior vaginal wall below the level of the cervix.

A hand is inserted to guide delivery of the presenting part through the lower segment. Wrigley's forceps may be used to assist delivery in cephalic presentation. After delivery of the placenta, the uterine cavity should be checked to ensure it is empty. There is no advantage in inserting a finger through the cervix to facilitate drainage of lochia, even at elective CS. The CAESAR trial confirmed that single versus double closure of the uterus and non-closure versus closure of the peritoneum did not influence short-term morbidity, including infection [23]. However, it remains difficult to give definitive guidance because of the paucity of long-term morbidity data. At present, traditional two-layer repair is recommended based on observational data showing a fourfold increase in uterine rupture with single-layer closure, particularly if a locking suture technique is used. Whichever closure method is used, it is vital to ensure optimum alignment of all layers: decidua to decidua, myometrium to myometrium, and serosa to serosa. Blood loss is much less with lower-segment compared with upper-segment CS.

Before abdominal closure, undertake careful peritoneal toilet to remove excess blood and liquor and inspect both adnexa. Remember that handling the peritoneal layer may cause discomfort even under effective neuraxial blockade. The rectus sheath may be closed with a No. 1 polyglactin suture. In repeat CS or with BMI 30 and above, a delayed absorbable (polydioxanone) or non-absorbable polypropylene suture is recommended because it significantly reduces the risk of late wound dehiscence. The subcutaneous fat layer should be closed if it is more than 2 cm thick as this further reduces the risk of wound breakdown. Finally, subcuticular skin closure reduces the risk of superficial dehiscence compared with use of staples or clips. Prophylactic antibiotics and low-molecular-weight heparin to prevent thromboembolism are routinely administered. Enhanced recovery programmes provide an evidence-based approach to surgical recovery and include early mobilization and feeding. Removal of the urinary catheter and venous cannulae should be considered at 4–6 hours after surgery in uncomplicated cases.

Upper segment uterine incision

Classical CS involves a high midline vertical incision through the upper uterine segment (UUS). The vertical DeLee incision is sited one-third in the lower segment and two-thirds in the upper. UUS incisions have a higher risk of rupture in labour and elective CS is recommended in future pregnancies. There is also a small risk of spontaneous rupture in the antenatal period and elective CS is undertaken at 37–38 weeks (with prior steroid administration to promote fetal lung maturity). There are several indications for using the UUS approach, including impacted transverse lie with ruptured membranes, preterm CS with a narrow poorly formed LUS, large fibroids in the LUS, and in some cases of anterior placenta praevia with large vessels in the LUS. In the presence of an invasive placenta, it is vitally important to incise the uterus away from the placental site as this can lead to torrential life-threatening haemorrhage. A classical incision may be used if the invasive placenta involves the LUS, but a transverse incision at the fundus or even delivery via a posterior uterine incision may be required.

The UUS is often 2–3 cm thick and care must be taken on entering the cavity. However, the incision gives excellent access and delivery of the fetus is generally easy. Closure requires three layers of sutures and No. 1 or 0 polyglactin is recommended. An assistant holds the walls of the UUS together whilst individual sutures are inserted and tied. Interrupted figure-of-eight or Z stiches are

used for the first layer as these are more haemostatic. Subsequent layers may require interrupted sutures depending on the amount of bleeding. A non-suction tube drain can be left *in situ*. Postoperative morbidity (including paralytic ileus) is more common after UUS section and close observation is required.

Peri-mortem caesarean section (PMCS) or resuscitative hysterotomy

Cardiac arrest occurs in only 1 in 12 500 pregnancies. Peri-mortem CS is recommended if the gestation is greater than 20 weeks and return of spontaneous circulation does not occur after 4 min of effective cardiopulmonary resuscitation (CPR). The primary aim is to save the mother's life, as emptying the uterus improves venous return and facilitates resuscitation. Ideally, delivery should be completed within a further minute. This is rarely achieved in practice, but expediting delivery can be helped by following these simple steps: minimal skin preparation, avoiding full surgical 'scrub up' (i.e. a pair of gloves is all that is required) and a scalpel is the only instrument required. For clinicians unfamiliar with the Pfannenstiel incision and lower segment CS technique, a midline lower abdominal incision and vertical uterine incision approach is recommended. Bleeding will be minimal and the placenta can be left *in situ*. If resuscitation is successful, the patient will be anaesthetized and moved to theatre to complete surgery. Sadly in most cases, resuscitation is unsuccessful. In the UK, the appropriate legal entity must be informed (the coroner in England) and a post-mortem is likely to be required. For this reason, all tubes and cannulae present at the time of death must be left in place, the uterus left unsutured and the abdomen covered but not surgically closed. Appropriate support is essential for all family, relatives and staff involved.

Complications associated with caesarean section

Morbidity and mortality associated with CS cannot be totally avoided. Complications include haemorrhage, urinary tract damage, anaesthetic-related complications, infection and venous thrombosis. Simple bladder injury can be repaired in two layers with 2/0 polyglactin. The bladder should be left on free drainage via an indwelling urethral catheter which can be removed after 7–10 days. Ogilvie's sydrome (pseudo-colonic obstruction) is a rare complication following CS and presents with signs of intestinal obstruction (increasing pain and marked distension). A high index of clinical suspicion is required as vomiting is not a prominent feature. An urgent surgical opinion should be sought if abdominal X-ray confirms significant caecal dilatation. Caecal perforation is more likely with diameters over 10 cm and carries a mortality of 30–72%. Vesico-vaginal or uretero-vaginal fistulae are extremely rare. Maternal mortality with CS is estimated to be less than 0.33 per 1000 and is usually related to the reason the CS was done, major haemorrhage or more rarely anaesthetic complications.

Delivery of the deeply impacted head

The incidence of second-stage CS is increasing. It is a potentially complex and difficult procedure with significant maternal and fetal morbidity, including extension of the uterine incision and major postpartum haemorrhage. This is particularly so if the head is deeply impacted in the pelvis after an unsuccessful attempt at IVD. The surgeon may need to extend the uterine incision into the UUS using either a J-shaped extension from the lateral end, or an inverted-T starting at the middle of the incision. The latter results in a definite weak point in the uterine scar but in both situations elective CS will likely be recommended for future deliveries. Two main approaches have been used to help deliver the deeply impacted head, categorized as the push or pull techniques [24]. Routine or selective use of tocolytics has been recommended but there are insufficient data to confirm that uterine relaxation is effective [16].

The push technique

Some practitioners prefer to disimpact the head from below before proceeding with emergency CS. Others will ask an assistant to insert a hand into the vagina aiming to push up on the head after the uterine incision is made. It is important to await uterine relaxation. Rather than pushing up blindly, the assistant should confirm the position of the occiput, aiming to gently flex the head during disimpaction. This will allow smaller diameters to present as the head rises up through the pelvis. With flexion, the head will naturally rotate into an OT position as it rises through the mid/upper pelvis towards the pelvic inlet. Extension of the incision more often occurs on the same side as the occiput. This is probably because of the combined bulk of the fetal occiput lying in the surgeon's hand during manipulation, rotation and disimpaction.

The pull technique

This is also known as reverse breech extraction. The surgeon passes a hand into the upper segment and grasps both feet before gently pulling the fetus up to deliver the breech first. The chest and shoulders follow and the head is lifted out of the pelvis. In a systematic review comparing the push and pull methods, the pull technique was associated with a significant reduction in extension of the uterine incision, mean blood loss, operating time and infection [24].

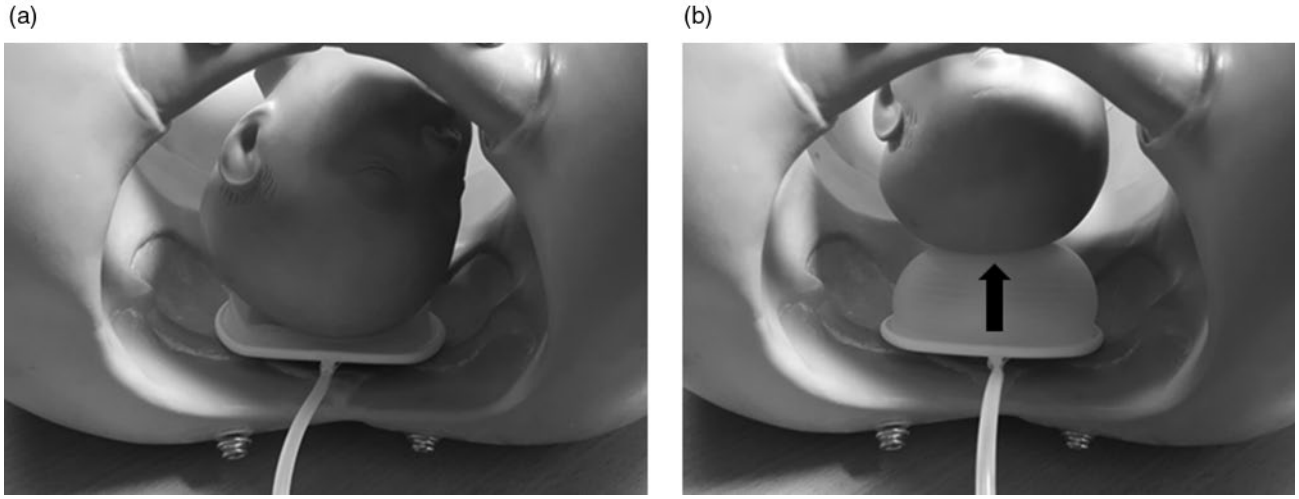

Fig. 26.12 Fetal Pillow to elevate the impacted fetal head: (a) deflated and (b) inflated.

Alternative techniques

The Patwardhan method was described in 1957 and relies on delivery of one or both shoulders first. It has traditionally been used on the Indian subcontinent. With the back anterior or lateral the uterine incision is made over the anterior shoulder and the order of delivery is as follows: shoulders (anterior then posterior, plus arms), trunk by flexion (with fundal pressure), legs, and finally the head is lifted out of the pelvis. This is modified when the back is posterior: anterior shoulder/arm, both legs, trunk by flexion, posterior shoulder/arm, head. It may have some advantages over the push method but there is insufficient evidence to offer definitive guidance.

Various fetal head-lifting devices are being developed and evaluated. The Fetal Pillow® has a soft foldable base plate with a balloon attached to one surface. It is inserted to lie beneath the fetal head and the balloon is filled with 180 mL of saline prior to incising the uterus. The fetal head is elevated by 3–4 cm (Fig. 26.12). In a non-blinded randomized trial ($N = 240$), use of the Fetal Pillow resulted in a significant fall in the number of major uterine wound extensions: 6 (5.0%) versus 39 (32.5%) (RR 0.23, 95% CI 0.11–0.48) [25].

Summary box 26.4

- CS rates vary widely but rates above 10% are not associated with improved maternal or neonatal outcomes.
- The primary aim of peri-mortem CS is to improve maternal survival when circulation is not re-established after 4 min of effective CPR (gestation >20 weeks).
- In the presence of an invasive placenta, incise the uterus away from the placenta to avoid life-threatening haemorrhage.
- In second-stage CS, pull techniques reduce the incidence of extension of the uterine incision.

Episiotomy and perineal lacerations

Perineal lacerations occur with normal delivery and IVD. Perineal tears are classified based on the involvement of the perineum.

1) First-degree tears involve the skin only.
2) Second-degree tears involve the skin and perineal muscle.
3) Injury to the anal sphincter is classified as a third-degree tear and is subdivided into 3a, involving less than 50% of the external anal sphincter (EAS); 3b, involving more than 50% of the EAS; and 3c, involving both EAS and internal anal sphincter (IAS). When the tear damages the sphincter and involves the anal epithelium, it is termed a fourth-degree tear. Collectively the group of injuries are referred to as obstetric anal sphincter injuries (OASI) [26].

Episiotomy

Episiotomy is a surgical incision of the perineum made after informed consent with the aim of increasing the soft-tissue outlet dimensions to help childbirth. Liberal use is not associated with reduction in OASI. Surprisingly, rates in Europe for women who deliver vaginally vary from 4.9% (Denmark) to 72.9% (Portugal), confirming that local custom rather than evidence guides most practice [9].

Episiotomy is used selectively in the UK. Midwives will consider episiotomy when (i) there is significant delay in delivery through a rigid perineum, (ii) in the presence of acute fetal compromise to expedite delivery, or (iii) to avoid significant perineal trauma. This is an individual decision based on clinical experience. Episiotomy facilitates IVD, although the need for an episiotomy is less with ventouse deliveries and with a distensible perineum. Judicious use of mediolateral episiotomy with IVD is associated with a sixfold decreased risk of OASI. When internal vaginal access is needed, as in some cases of assisted breech delivery and shoulder dystocia, episiotomy can improve access.

In the USA, a midline episiotomy starting from the fourchette and extending towards the anus is popular. This is associated with minimal bleeding, is easier to align for repair and requires less postoperative analgesia. However, the risk of OASI is higher and many countries prefer the mediolateral approach. Local anaesthetic infiltration of the perineum is effective for episiotomy with normal delivery and with outlet vacuum delivery but otherwise regional analgesia should be considered. It is important to check that analgesia is effective prior to episiotomy and additional local infiltration can be used when necessary. A single incision is made but the length is variable and depends on the size of the perineum and type of delivery. Blood loss is minimized by performing the episiotomy when the head crowns and the perineum is stretching up. The incision should be angled at 60° to the midline, in the direction of the ischial tuberosity. This is associated with a lower incidence of OASI, anal incontinence and perineal pain compared with the classical description at an angle of 45° [27]. Early repair after completion of the third stage prevents unnecessary blood loss; any profusely bleeding vessels are initially clipped then ligated.

Perineal repair

Effective analgesia should be checked again prior to repair. Additional tears requiring suturing may need further local infiltration. A thorough systematic examination should be undertaken before proceeding to ensure there is no occult sphincter damage and this may require a combined rectal and vaginal examination. Good light and optimal exposure are essential to achieve a good repair. Uterine bleeding may cause difficulty in visualizing the edges of the wound but this can be overcome by insertion of a tampon or vaginal swab with a tail.

Traditional repair is described in three layers, including a locking layer for the vagina, interrupted sutures for the perineal muscles and interrupted sutures for the skin. The two-stage technique is similar but skin edges are apposed but left unsutured (edges ≤0.5 cm apart). In contemporary practice the three-stage, continuous non-locking technique is recommended [28]. This is associated with the least short-term pain, is easily performed by the inexperienced operator and has economic advantages as only one suture is used. A rapidly absorbing polyglactin suture is recommended (2/0 gauge, 36-mm tapercut needle) although standard polyglactin may also be used. It is important to ensure that the initial anchoring stitch is placed above the apex of the incision. If there is an extension, placing a traction suture halfway up the vaginal tear can help to bring the apex into view. The vaginal mucosa and underlying tissue are approximated using a single continuous non-locking stitch. The hymenal ring acts as a useful marker to help align tissues as oedema results in asymmetry of the opposite sides of the incision. The perineal muscles are approximated with the same suture, which is also used to bring the skin into alignment by placing the suture below the skin surface in the subcutaneous fascia. A single knot is tied behind the hymenal ring. If the muscle layer is vascular, interrupted sutures may be required.

When the repair is complete, rectal examination should be performed to exclude accidental suture involvement of the rectum or anal canal (which if found should be removed and resuturing performed if necessary). A full count of instruments, needles and swabs is mandatory and must be recorded. Retention of vaginal swabs is a common cause of litigation and vaginal examination is essential to exclude inadvertent retention. The operative note should include full details of the repair, blood loss and plans for postoperative care. Pain relief should be prescribed and this may include administration of rectal diclofenac with consent. Observations should be continued, watching for excessive bleeding, pain or haematoma formation that may necessitate additional medical or surgical intervention. Later complications include infection, wound breakdown, pain, scarring or dyspareunia.

Obstetric anal sphincter injury

Reported rates of OASI in Europe vary from 0.1% (Poland and Romania) to 4.2% (Denmark and Iceland), although quality of reporting varies [9]. Unrecognized or inadequately repaired OASI can lead to long-term incontinence of faeces with or without flatus. OASI is best repaired in the operating theatre under regional anaesthesia. Good lighting, appropriate instruments, and an experienced surgeon and assistant are essential for successful repair. Thorough inspection is required to confirm the degree of sphincter and/or mucosal damage. It is important to exclude separate button-hole injuries of the rectal mucosa lying at a higher level. Anal

epithelium is repaired with continuous or interrupted 3/0 polyglactin sutures. The sphincter is repaired using monofilament 3/0 polydioxanone or braided 2/0 polyglactin with equivalent results [26]. An end-to-end technique should be used for all IAS repairs and for partial-thickness tears of the EAS (i.e. 3a and some 3b). Either end-to-end or the overlapping technique can be used for full-thickness EAS tears and these have equivalent outcomes [26].

Postoperative care should include antibiotics and physiotherapy support can be helpful. Routine use of laxatives is recommended to reduce the risk of wound dehiscence, but bulking agents should be avoided. At follow-up it is vital to enquire about incontinence of faeces or flatus, faecal urgency, pain and dyspareunia. Where facilities exist and when indicated, endo-anal ultrasound and/or anal manometry may be offered. If symptoms persist and cannot be improved by conservative measures, referral to a specialist gynaecologist and/or colorectal surgeon should be arranged.

Jango *et al.* [29] reviewed the effect of subsequent vaginal delivery on women who had suffered OASI. Those with faecal incontinence following OASI were recommended elective CS for future delivery. In those with no faecal incontinence, vaginal delivery carried a higher risk of deterioration of anal incontinence symptoms, although the risk of long-term faecal incontinence was not significantly increased.

Summary box 26.5

- Routine or liberal use of episiotomy is not recommended.
- Mediolateral episiotomies should be angled at 60° to the midline to reduce the risk of OASI.
- Exclude OASI by performing a systematic rectal and vaginal examination prior to all repairs.
- The continuous non-locking technique should be used for routine perineal repair.
- Isolated button-hole injuries should be sought and excluded during OASI repair.

Conclusion

The obstetrician in contemporary practice must be knowledgable about the various malpresentations and malpositions that arise and how they should be managed. We have emphasized the importance of accurate assessment of the position, attitude and station of the fetus within the maternal pelvis, a critical skill for the trainee to develop and the experienced clinician to maintain. These skills are brought to a focus in the management of malposition and second-stage arrest at the level of the ischial spines (i.e. at mid-pelvis). In this situation, ultrasound can be a useful adjunct to clinical skills. The operative techniques available to facilitate safe assisted delivery have been described (IVD, manual rotation and CS) and we encourage obstetricians to consider carefully the advantages and disadvantages of each method, selecting the safest and most appropriate to use in each case.

NICE intrapartum care guidance provides useful information about the management of abnormal labour [7] but there are still many controversies and unanswered questions that require further rigorous randomized trials. Simulation training can help to teach the technical skills required to perform intrapartum procedures safely, supported by direct supervision from senior clinicians and objective assessment of competence before moving on to independent practice. Intrapartum procedures can be stressful for the couple, the fetus and the clinician. Adequate knowledge, training, communication skills (before and after the procedure) and accurate record-keeping are essential to help alleviate the stress. Maintaining situation awareness, critical decision-making, clear communication and functional team-working are human factors and are the non-technical skills that must be embraced to ensure safe obstetric practice [30].

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27

Fetal Monitoring During Labour

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What this chapter cannot do is provide a comprehensive manual of fetal physiology, fetal heart rate interpretation and fetal monitoring techniques. While the main principles of these are discussed here, the reader is referred to other learning tools for fetal monitoring, including standard textbooks, the Royal College of Obstetricians and Gynaecologists (RCOG) e-learning program [1] and the online K2 fetal monitoring training system [2]. These e-learning systems are divided into sections which cover maternal and fetal physiology and pathophysiology, fetal heart rate and cardiotocography, and include a wealth of cases that can be worked through, asking the reader to interpret and make decisions which can be compared with those of experts.

Fetal physiology

Normal

The fetus is sustained by the uteroplacental unit and under normal circumstances provision is surplus to requirements, enabling the fetus to thrive, grow and build up energy reserves. Aerobic metabolism of glucose provides the fetus with its energy, and the oxygen which is vital for this process is usually plentiful. In normal pregnancy there is therefore more oxygen supplied by the uteroplacental unit than needed by the fetus and energy reserves in the form of glycogen are stored by the fetus.

Fetal compromise

The fetus can be compromised by a reduction in oxygen supply, an increase in oxygen requirements (e.g. in sepsis) or a reduced capacity to transport oxygen (severe fetal anaemia, e.g. rhesus disease, fetomaternal haemorrhage or some intrauterine infections such as parvovirus). The severity and duration of the insult will vary according to the cause, and similarly the effects on the fetus are equally wide-ranging, but the principal fetal responses are described below.

- *Acute*. If oxygen delivery falls, there is reduced oxygen in the fetal circulation (hypoxaemia); if levels fall further, hypoxia occurs (reduced oxygen in the fetal tissues). Two things occur in response to hypoxaemia and hypoxia: the circulation adapts to maintain supplies to vital organs (brain and heart) and anaerobic metabolism utilizing glucose released from the stored glycogen reserves provides continued energy supplies. The main consequences of anaerobic metabolism, which is almost 20 times less efficient than aerobic metabolism, are that fetal reserves are used up relatively quickly and the lactic acid, which is the waste product of this metabolism, results in a metabolic acidosis that can be harmful.
- *Chronic*. If there is uteroplacental disease and fetal supplies are limited, then glycogen stores may not accumulate and fetal reserves will be lacking. In chronic cases of reduced supply, the fetal circulation adapts as mentioned above with cranial sparing, and the peripheral circulation is effectively reduced. Depending on the severity and duration of this compromise, the pathophysiology results in decreased renal perfusion which in turn produces oligohydramnios (and, when more severe, anhydramnios) and reduced fetal growth. If there is further deterioration, anaerobic metabolism occurs and a metabolic acidosis develops.
- *Acute on chronic*. If an acute insult occurs in a fetus already compromised, it can withstand less hypoxia than a well-nourished fetus because it has less reserve and may have already made adaptations to conserve vital cerebral perfusion.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Thus the response and vulnerability of any fetus to a hypoxic insult will be largely dictated by (i) the condition of the fetus at the onset of that insult, (ii) the severity of that insult, and (iii) the duration of that insult. The fetal condition can deteriorate extremely quickly and defining the period of time beyond which damage will be sustained is impossible due to the individual circumstances of each fetus and each insult, but a normal well-grown and mature fetus that has good reserves can tolerate a short period of severe hypoxia, whereas the same insult can be catastrophic for a growth-restricted fetus.

Summary box 27.1

Progressive hypoxia with metabolic acidosis is accelerative. Hypoxia that has led to metabolic acidaemia indicates that:

- fetal reserves are spent;
- tissue hypoxia and acidaemia will be rapidly progressive;
- fetal damage becomes increasingly likely.

Metabolic acidaemia

Paired umbilical cord blood samples at delivery enable direct measurements of uteroplacental function (umbilical vein) and fetal acid–base status (umbilical artery). There are now a number of published series of routine paired cord samples [2–5] and results largely conform and are approximated in Table 27.1. The base deficit in the umbilical artery indicates the degree of fetal metabolic acidosis and values above 12 mmol/L suggest that there has been significant hypoxia and subsequent fetal damage may occur [6]. If venous pH and base deficit are normal, this rules out chronic hypoxia. The mean pH difference between artery and vein is 0.08 and if this difference is less than 0.03, it is likely that both samples have been taken from the umbilical vein. Timing of cord clamping after delivery can also influence cord samples [7].

Fetal and neonatal consequences of hypoxia

The damage that results from hypoxic insults varies according to the vulnerability of the fetus and the nature and duration of the insult, ranging from minimal clinical signs through brain damage to death. While neonatal complications tend to increase as cord arterial pH falls [8], especially at values below 7.0 [9–11], many born with such values do well [9,10,12] while approximately one-quarter suffer neurological morbidity or mortality [13].

Death

Intrapartum deaths do occur as a result of hypoxia, with an incidence in the UK of approximately 0.22 per 1000 [14], and intrapartum-related deaths (both stillbirths and neonatal deaths) account for 1 in 12 perinatal deaths [15]. While scrutiny of these cases has identified elements of substandard care, many cases are managed well and yet death still results. Confidential enquiries have shown that approximately half of intrapartum stillbirths are considered to be avoidable [16,17], with errors in care extending from a failure to recognize problems in the antenatal period and/or in labour to recognizing but failing to act on signs of fetal compromise [17].

Neonatal pathology

The paired umbilical cord gas results provide an objective measure of *in utero* fetal metabolism, reflecting the presence or absence of intrauterine hypoxia, but although they are associated with neonatal outcomes they are not predictive and do not indicate neonatal resuscitative needs. Indeed many babies born with low cord gases are vigorous at birth. On the other hand, the Apgar score is a subjective assessment of the need for neonatal resuscitation but does not indicate the cause of the problem. Resuscitation therefore occurs according to clinical need and the possible cause may then be clarified by the cord gases. A variety of neonatal problems can follow on from intrauterine hypoxia, including hypoglycaemia, disturbed thermoregulation and necrotizing enterocolitis, but the main worry is that of hypoxic brain injury due to the long-term morbidity associated with it.

Hypoxic–ischaemic encephalopathy

Neonatal encephalopathy is associated with a multitude of causes but hypoxic–ischaemic encephalopathy (HIE) is neonatal encephalopathy specifically caused by peripartum hypoxia. The centiles listed in Table 27.1 demonstrate that 2.5% of neonates are born with a cord arterial pH below 7.05. The incidence of more severe acidaemia (cord arterial pH <7.0) is approximately 3.7 per 1000 live births, while that of HIE at term is approximately 2.5 per 1000 live births [13]. The diagnosis of HIE requires evidence of intrapartum hypoxia and although there are various definitions [18–20], in essence there needs to be evidence of all of the following:

- an intrapartum insult (e.g. a sentinel event in labour or a pathological fetal heart recording);
- a metabolic acidosis at birth (pH <7.0 and base excess >12 mmol/L);
- moderate or severe neonatal encephalopathy;
- specific features on imaging in the neonatal period.

A spectrum of permanent brain injury can occur as a result of HIE [21] ranging from spastic quadriplegic

Table 27.1 Routine paired umbilical cord values.

	pH (median)	pH (2.5–97.5 centile)	Median base deficit (mmol/L)	Base deficit (mmol/L) (2.5–97.5 centile)
Umbilical vein	7.35	7.17–7.48	3.7	9.0–0.5
Umbilical artery	7.25	7.05–7.38	4.3	11.1–0.5

or dyskinetic cerebral palsy [18,20] to learning difficulties without motor impairment [22]. The incidence of cerebral palsy is 1–2 per 1000 deliveries and although the majority of these are due to antenatal complications, at least 10–15% result from events in labour [13].

Treatment and outcome of HIE

Severe acidaemia at birth (pH <7.0) does not always result in HIE, which in turn does not automatically result in cerebral palsy, but the more severe the metabolic acidosis at delivery and the more severe the HIE, the worse the prognosis for the baby. Individual clinical features and responses of the baby help inform the likely outcome as does cerebral imaging.

The greatest advance in this field is that of controlled total body cooling of term neonates with HIE. The cooling needs to start within 6 hours of birth and has been shown to improve intact neonatal survival (relative risk of cerebral palsy 0.67, 95% CI 0.47–0.96) with number needed to treat of 8 (95% CI 5–17) [23,24]. The obstetrician's role in this process is one of early communication and frank discussion with neonatal colleagues to help clarify the obstetric history and the likely diagnosis, which should help to promote early cooling or referral to a centre that provides this treatment if it is not available locally (see Chapter 32).

Summary box 27.2

Factors that reduce oxygen delivery to the fetus

Uteroplacental pathology
- Maternal demographics (age, smoking).
- Maternal diseases (hypertension, diabetes, sickle cell disease).
- Intrauterine growth restriction.
- Placental separation (marginal bleeds and abruptions).
- Post maturity.

Fetal pathology
- Fetal anaemia: rhesus isoimmunization, parvovirus infection, fetomaternal haemorrhage.

Labour
- Uterine contractions (especially if hypertonic or with prolonged labour).
- Cord compression.
- Maternal hypotension (aortocaval compression).
- Obstetric emergencies (maternal collapse, uterine rupture, abruptions, cord prolapse).

Midwives and obstetricians
- Injudicious use of prostaglandins or Syntocinon.

Labour

The rest of this chapter focuses on the normal physiology of labour and the fetal responses to labour, before highlighting abnormal labour patterns that increase fetal challenges and the problems which can arise from them. Without knowledge of the physiology and pathophysiology of labour, the anticipation and recognition of early signs of hypoxia may be missed. Failure to recognize the fetus at risk on entry to labour or failure to look for and then recognize early signs of hypoxia in labour can compromise the opportunity for prompt and timely action that may be crucial in avoiding irreversible damage.

The challenges of normal labour

Uterine contractions

In normal labour, the fetus is 'stressed' due to uterine contractions. The uteroplacental circulation is a low-pressure system and its perfusion ceases at the height of a uterine contraction in the first stage of labour (where intrauterine pressures reach about 90 mmHg) and throughout practically all of a contraction when the woman is pushing in the second stage of labour (intrauterine pressures up to 250 mmHg). Oxygen delivery to the fetus therefore effectively ceases during these periods.

A fetus in a normal pregnancy has adequate reserves of oxygen and can cope with this brief, temporary insult as long as the uterus relaxes enough between contractions for gas transfer to occur thus replenishing the supply of oxygen. The interval between the contractions is *crucial*

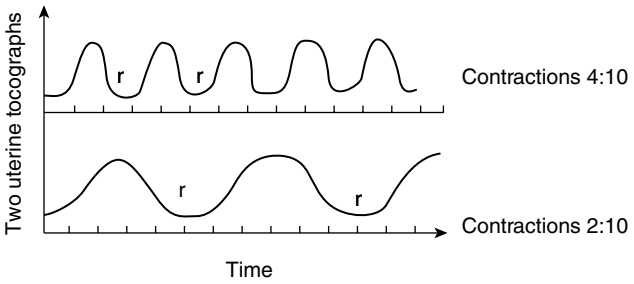

Fig. 27.1 Number of uterine contractions versus their duration in each 10-min period and how this influences the period of fetal recovery during uterine relaxation (r), both similar at approximately 4 min.

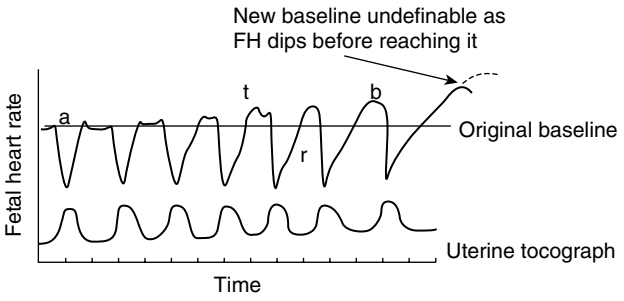

Fig. 27.2 Variable decelerations associated with cord compression demonstrating a typical dip (a). A rising baseline (b), a rebound tachycardia (t) and delayed recovery (r) are all suspicious signs.

to allow this recovery (Fig. 27.1), with 60–90 seconds of uterine relaxation needed between contractions [1].

A less well-nourished fetus does not have the same oxygen reserves even when the uterus is relaxed, and may have reduced or minimal energy reserves, so may not manage the episodic oxygen deprivation associated with each uterine contraction.

Head compression

The fetal head is subjected to pressure as it is compressed onto the cervix and through the pelvis by uterine contractions, and latterly this is exacerbated by maternal expulsive efforts. Head compression can produce a reflex bradycardia due to changes in intracranial pressure. This is a normal autonomic response, but clearly during any bradycardic episode the fetal circulation is reduced, so once again a baby already compromised will be more affected by this temporary reduction in oxygen delivery to the tissues due to the slower heart rate.

Cord compression

The umbilical cord lies in random fashion around the fetus *in utero* and can wrap around or lie in close proximity to any part of the fetus so that during a contraction it can become squashed. This is increasingly likely once the membranes have ruptured. The normal autonomic responses of a healthy fetus to an episode of cord compression is the result of baroreceptor and chemoreceptor stimulation and proceed as follows.

- Initially, the larger, less muscular, umbilical vein obstructs resulting in decreased cardiac return, which stimulates baroreceptors that cause a tachycardia.
- Hypoxia secondary to the umbilical vein obstruction stimulates chemoreceptors to trigger a parasympathetic response which produces a bradycardia.
- With further compression, umbilical artery obstruction raises peripheral resistance, exacerbating the bradycardia.
- As the contractions wear off, the process is reversed.

Cord compression, which is common, therefore produces a fairly classic pattern of fetal heart rate (FHR) decelerations as a normal autonomic response in a healthy fetus (Fig. 27.2, pattern 'a'). However, as mentioned above, every time a deceleration occurs the fetal circulation is reduced and therefore adequate uterine relaxation between contractions is vital to allow recovery of the fetal circulation with subsequent tissue perfusion. Prolonged or repetitive decelerations can have a cumulative effect over time: firstly the shouldering disappears, then there is a rebound tachycardia, delayed recovery from the decelerations and a rising baseline (Fig. 27.2). In the most severe type the baseline is undefined because the next contraction occurs before it is reached and the fetal heart decelerates again. Moreover, cord compression is more common when there is reduced Wharton's jelly to protect the umbilical vessels, as with a premature or growth-restricted fetus, and these are therefore more likely to suffer cord compression as well as being already compromised.

The challenges of abnormal labour

Infection

Pyrexia in labour is associated with an increased risk of fetal hypoxic damage and cerebral palsy [25,26]. The two processes of hypoxia and sepsis seem to potentiate each other rather than being simply additive, and this process can escalate quickly needing early recognition and appropriate action. One problem is that epidural anaesthesia is associated with a rise in core temperature and therefore mild pyrexias in labour are relatively common. This risks causing a rather relaxed attitude to fevers in labour rather than raising alarm bells. Clinical vigilance is needed, with proper assessment and appropriate treatment.

- If there are clinical signs of infection, even a mild pyrexia is significant.
- If there is no regional blockade, pyrexia of 37.5 °C is significant.

- Pyrexia of 38 °C with regional blockade is significant.
- Paracetamol alone is not a treatment for infection: it may lower the temperature by nature of its antipyretic effect and this is useful, but it does not mean that the infection is treated. 'Hiding' one of the signs of infection in this way can be dangerous.

In all these situations appropriate microbiology cultures should be taken and antibiotic treatment started. Clinical awareness of the infection and what it might mean to fetal condition, fetal reserve and the likely tolerance of the fetus to the remaining labour will all play a part in timing the delivery.

Prolonged labour

A fetus has to tolerate more uterine contractions during prolonged labour. This is common with fetal malpositions and, as such, is also associated with induced labour for post-term pregnancies or prolonged rupture of membranes, both of which increase the risks to the fetus (added risk of uteroplacental insufficiency or infection, respectively).

Excessive uterine activity

This comprises either tachysystole (more than five contractions in 10 min) or hypertonus (prolonged contraction or increased basal tone) and both can occur spontaneously or be iatrogenic. When excessive uterine activity occurs spontaneously, it can be extremely concerning because it is likely to be associated with pathology such as infection (additional risks and vulnerability already discussed) or bleeding. In the case of bleeding (which may be concealed retroplacental separation) there is the added insult of placental separation as well as failure of adequate uterine relaxation for the fetus to contend with. This situation is very dangerous and fetal deterioration is likely to be rapid.

Conversely, iatrogenic tachysystole and hypertonus are reversible if recognized and acted upon. These can result from prostaglandin sensitivity or overdose as well as oxytocin overdose. A common obstetric and midwifery aim when stimulating labour with oxytocin is for a certain number of contractions every 10 min but as this focuses attention on the contraction and not the relaxation, it is easy to see why excessive uterine activity is a relatively common problem [27–29]. If contractions last for 1 min, then aiming for four contractions in 10 min is reasonable, but if they last 2 min squeezing four into 10 min will cause fetal hypoxia (see Fig. 27.1). The added problem here is that oxytocin tends to be used in abnormal labour (e.g. prolonged rupture of membranes, post-term inductions, prolonged labour) so there are many other risk factors for fetal compromise. Tachysystole often goes unrecognized, with the Syntocinon infusion continuing or even being increased further until FHR abnormalities and thus hyperstimulation (tachysystole with FHR abnormalities) develops.

Uterine rupture

This results in catastrophic interruption to fetal oxygenation and delivery needs to be effected within minutes. However, even with this dramatic pathology, signs other than abnormal FHR monitoring may be subtle and the diagnosis is often not made until laparotomy [30]. Keeping the possibility in mind during problems with progress in labour or in those at increased risk may help to anticipate the diagnosis and lead to rapid action if needed.

Placental abruption

This may also be missed clinically as bleeding may be concealed and pain can be difficult to distinguish from labour, especially with a posterior placenta. Tachysystole and hypertonus are signs that are often missed because the focus of attention tends to be on the fetal heart and not the clinical signs and the tocograph. Therefore, again, the relatively later sign of an abnormal FHR pattern is often the only indication that there is something wrong.

Cord prolapse

Cord prolapse can also cause severe catastrophic cessation of fetal oxygenation requiring urgent delivery and is usually confirmed on vaginal examination after fetal heart abnormalities have been detected.

Cord compression becoming cord occlusion

Whilst an element of cord compression is relatively common in labour (and often self-corrects with alteration in maternal position, or rotation and descent of the fetal parts) it can deteriorate and lead to prolonged cord occlusion. This is a particular risk in the second stage of labour when the woman commences pushing and the head descends. In the presence of an FHR pattern in keeping with cord compression, it is therefore sensible to have made preparations for rapid delivery should the need arise, before commencing pushing.

Detecting the fetus with hypoxia

Recognizing fetal risk

As the ability of any fetus to cope with labour depends on its condition on entry into labour, antenatal recognition of risk is vital in planning safe delivery. Any woman identified as high risk for fetal compromise in labour can then be cared for accordingly, while those of low risk can be

monitored less intensively. Whichever technique is used, the aim of intrapartum monitoring of the fetus is to 'screen' for early signs of hypoxia in order to allow timely intervention and safe delivery before irreversible damage has been sustained. The priority with a low-risk pregnancy would be to have a detection system with a low false-positive rate so that unnecessary intervention is kept to a minimum; conversely, the priority for an at-risk fetus would be to have a detection system with a low false-negative rate and good sensitivity to identify the problem early.

The different techniques available for monitoring the fetus in labour are discussed in the following sections but it is worth pointing out that inevitably not all high-risk cases are detected antenatally and the unknown 'high-risk' fetus is especially vulnerable in labour because the index of suspicion is reduced. It is therefore important that with every woman and fetus admitted in labour, there is a deliberate effort to re-screen using history and examination to confirm normality before proceeding with the planned birth.

Summary box 27.3

Clinical scrutiny on admission in labour: be alert to clues for risk

- Antenatal risk factors may have been missed (revisit antenatal history).
- Risk factors may have developed since last seen (prolonged latent phase/rupture of membranes or bleeding).
- Examine carefully: fetal growth, liquor volume and colour, pyrexia.
- Labour characteristics: pattern of uterine contractions, fetal presentation and position.

Liquor and the passage of meconium

A good liquor volume is a reassuring sign that the fetus has not been subjected to chronic hypoxia in the antenatal period (discussed above). If no liquor is seen in labour after amniotomy (spontaneous or artificial), the safe assumption must be that there is oligohydramnios/anhydramnios and the case in question is an unrecognized growth-restricted fetus. All practising midwives and obstetricians will have seen the thick 'green-pea soup' meconium following the delivery of a baby who had not previously been recognized as being compromised. The clinical secret is to think about this possibility and be clear that absence of liquor indicates oligohydramnios/anhydramnios/growth restriction until proved otherwise (e.g. in the labour ward setting this can be assessed by an ultrasound scan).

The other sign in labour is that of the colour of the liquor. The National Institute for Health and Care Excellence (NICE) guidelines on intrapartum care discusses whether the presence of particulate meconium is significant or not [31,32], but working from pathophysiological principles seems a more logical way to interpret the signs.

- A term fetus may have passed meconium by nature of its maturity, but if this is 'innocent' the meconium should be diluted by adequate liquor.
- If the fetus is preterm, the passage of meconium is not normal and may suggest infection or hypoxia.
- If the meconium is thick, then by definition the liquor volume is reduced and reflects uteroplacental insufficiency and possible fetal compromise.
- If the liquor has been clear and then becomes meconium stained during labour, it suggests that the fetus may be compromised and this could be due to either hypoxia or infection.

Fetal monitoring in labour

Searching for signs and understanding the condition of the fetus and the normal stresses or pathophysiological insults it is exposed to is the single most important part of fetal monitoring in labour. Omitting this fundamental process on admission in labour and proceeding directly to FHR monitoring assumes that all babies have the same reserves and vulnerabilities. Our earlier discussions demonstrate how wrong such assumptions are: having an informed index of suspicion for a particular fetus and an understanding of any likely pathophysiology from the antenatal period and during labour increases the chance that signs of compromise will be detected early. Waiting until events are obvious is unthinking and dangerous as it may be too late to correct. To expect any monitoring system to dictate clinical decisions is unrealistic, illogical and hazardous.

The other point worth making before exploring the different techniques for monitoring the fetus in labour is that of the margin of error between the extremes of failing to recognize a fetus in difficulty (which will therefore sustain damage/death) and mistakenly identifying a healthy fetus as being in difficulty and subjecting it and the mother to an unnecessary operative delivery. When reviewing the different techniques of monitoring it is interesting to note that the trade-off is usually between increased operative delivery versus increased neonatal morbidity, and the relative risks of these will depend on the background prevalences of pathology; hence the recommendation from NICE that low-risk women be monitored differently to high-risk

women [31,32]. This does not remove an obligation to discuss the advantages and disadvantages with the pregnant woman in the antenatal period, so that she is informed and involved in the decisions surrounding her care in labour, particularly the fetal monitoring plan. The long-term outcomes of cerebral palsy and death are rare, and statistically significant differences have yet to be shown from the different monitoring modalities in low-risk pregnancies, although neonatal seizures are a significant concern and should not be ignored.

Historically, listening to the fetal heart has been the main method of monitoring the fetus in labour, but this is a step removed from the important information, which is whether oxygen supply is adequate for fetal tissue metabolism. If not and anaerobic metabolism has commenced, then by definition fetal hypoxia exists and is likely to get worse. The problem is that there is no direct continuous measure of fetal tissue pH, and even if there were it would be invasive and as such likely to be impractical for routine monitoring. Periodic fetal blood sampling (FBS) can be done in those showing signs of possible compromise, and to date this has been used when FHR pattern abnormalities have been found (discussed in more detail later). Fetal pulse oximetry has been explored as a means of measuring fetal oxygen saturation and is used in combination with FHR monitoring but randomized trials have failed to provide convincing evidence that it is helpful [33–35]. Near-infrared spectroscopy has also been explored [36,37] but has not yet been subjected to randomized clinical trials [38].

Fetal heart rate

FHR monitoring is the main technique used to supplement clinical scrutiny in intrapartum fetal monitoring. FHR is influenced by numerous factors that act largely through the two opposing divisions of the autonomic nervous system: the sympathetic nervous system, stimulation of which speeds up the rate, and the parasympathetic nervous system, stimulation of which slows it down. As such the heart rate is in a constant state of variation as these two influences oppose each other to maintain homeostasis. Both are responsive to the many stresses of labour, including changes in oxygen levels (via chemoreceptors), changes in fetal circulation (via baroreceptors) and infection, and these stresses are indirectly reflected in the FHR pattern. In addition, myocardial ischaemia also produces a fetal bradycardia. It is for these reasons that the FHR provides a reasonable indicator of fetal condition. This subject is well covered in the online RCOG and K2 teaching programmes [1,2].

Summary box 27.4

Fetal heart rate characteristics

- Baseline variability is the single most helpful parameter in screening for fetal hypoxia.
- Baseline heart rate rises with chronic stresses, including infection and hypoxia.
- Baseline heart rate should not fall during labour unless in response to treated infection; if it does, this reflects hypoxia.
- Accelerations are a healthy sign.
- Decelerations occur owing to:
  - head compression (uniform and should be in synchrony with uterine contractions, i.e. early);
  - cord compression (variable and should also be early; see Fig. 27.2); and
  - hypoxia (late and either uniform or exist as a delayed recovery or extension of the above decelerations).
- What happens to the right-hand side of the deceleration shows how the fetus is coping with the stress (Fig. 27.3).

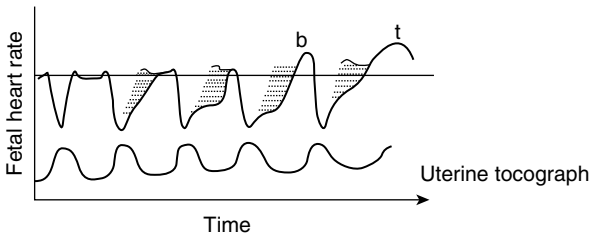

Fig. 27.3 Suspiscious signs that the fetus is becoming compromised. The recovery phase from each deceleration (right-hand side of each dip) takes longer with successive contractions (shaded areas) and the baseline rises (b) with a rebound tachycardia (t).

There are different classification systems to aid interpretation of FHR. The one most commonly used in the UK was the one described in the NICE intrapartum care guideline [31], which was updated in December 2014 [32]. In October 2015, the International Federation of Gynecology and Obstetrics (FIGO) also published guidelines for fetal monitoring [39–43]. Although virtually the same evidence base was reviewed for both, there are some differences between the two classification systems which has led to confusion, and some units in the UK have now opted to use the updated NICE guideline while others use the FIGO guidelines. The RCOG requested that NICE review their recommendations and further revisions were made in February 2017 which are illustrated in Table 27.2. Both systems classify features of the heart rate to assist with interpretation

of fetal well-being and give guidance on management (Tables 27.2 and 27.3). Although these systems differ slightly, the real issues are that one must understand fetal cardiac physiology and that the fetal heart trace is interpreted thoughtfully in the context of the full clinical picture, and changes over time are analysed carefully.

For example, the normal baseline values are taken from *populations* of healthy babies; it does not mean that the baseline of one fetus remains normal if it changes from, for example, 110 to 160 bpm or from 160 to 110 bpm over the course of labour. A small rise in the baseline (~20 bpm) during the course of labour is common due to sympathetic stimulation (via adrenaline) but more than

Table 27.2 Revised 2017 NICE classification of fetal heart features [32].

Feature	Normal	Non-reassuring	Abnormal
Baseline*	110–160	100–109 and 161–180	>180, <100
Variability*	5–25 bpm	<5 bpm for 30–50 mins or >25 bpm for 15–25 BPM	<5 bpm for >50 minutes or >25 bpm for >25 minutes, or sinusoidal
Decelerations*	None, early, or variable with no concerning features for <90 mins	Variable with no concerning features for >90 mins Variable with any concerning features in <50% of contractions for >30 mins Variable with any concerning features in >50% of contractions for <30 mins Late decelerations in >50% contractions for <30 mins with no other risk factors	Variable decelerations with any concerning features >50% contractions for 30 mins (less with risk factors) Late decelerations for 30 mins (less with risk factors) Acute bradycardia or single prolonged deceleration for >3 mins
Category*	All normal = normal/ reassuring	One non-reassuring with two normal features = non-reassuring	One abnormal or two non-reassuring features = abnormal
Management*		Consider the full clinical picture: explain/ escalate/conservative measures (position, contractions, fluids, paracetamol, antibiotics)	Escalate, conservative measures and further action such as FBS or delivery based on clinical picture Urgent delivery if prolonged bradycardia persists (if recovered by 9 min may reconsider)

*Concerning features include: decelerations lasting >1 minute, reduced variability, failure to return to baseline, biphasic shape and no shouldering.

Table 27.3 Summary of the FIGO classification of fetal heart features [42]: cardiotocography classification criteria, interpretation and recommended management.*

	Normal	Suspicious	Pathological
Baseline	110 – 160 bpm	Lacking at least one characteristic of normality, but with no pathological features	<100 bpm
Variability	5 – 25 bpm	Lacking at least one characteristic of normality, but with no pathological features	Reduced variability, increased variability, or sinusoidal pattern
Decelerations	No repetitive† decelerations	Lacking at least one characteristic of normality, but with no pathological features	Repetitive† late or prolonged decelerations during >30 min or 20 min if reduced variability, or one prolonged deceleration with >5 min
Interpretation	Fetus with no hypoxia/acidosis	Fetus with a low probability of having hypoxia/acidosis	Fetus with a high probability of having hypoxia/ acidosis
Clinical management	No intervention necessary to improve fetal oxygenation state	Action to correct reversible causes if identified, close monitoring or additional methods to evaluate fetal oxygenation‡	Immediate action to correct reversible causes, additional methods to evaluate fetal oxygenationc, or if this is not possible expedite delivery. In acute situations (cord prolapse, uterine rupture or placental abruption) immediate delivery should be accomplished

*The presence of accelerations denotes a fetus that does not have hypoxia/acidosis, but their absence during labour is of uncertain significance.
†Decelerations are repetitive in nature when they are associated with more than 50% of uterine contractions.
‡Fetal blood sampling.

this suggests it is secondary to stresses such as hypoxia or infection; baselines rarely fall in labour (unless sepsis is treated for example) and hypoxia should be suspected.

These baseline changes are important and worthy of a word of caution: paper cardiotocograph traces are usually folded up as they print and then are neatly tucked away, while computerized traces only display a short section of the heart rate pattern at any one time. In both situations proper review of a trace requires deliberate unfolding or scrolling back to the preceding trace in order to evaluate it fully. The consequence of failure to do this is that important signs of deterioration may be overlooked.

Heart rate monitoring techniques

How is it best to monitor the fetal heart? The options are between intermittent auscultation (directly using a Pinard stethoscope or a hand-held Doppler device) or continuous electronic recording via an abdominal Doppler transducer or fetal scalp electrode.

Intermittent auscultation

Listening directly to the fetal heart with a Pinard has been useful in the past, but although the device is small and cheap it has the disadvantage of only being heard by the person using it and the rate needs to be calculated by the listener. The hand-held Doppler machine is also small and portable but has the added advantages of magnifying the sound so that the woman and any other attendants can also hear the heart beat and it can also digitally display the heart rate. The only recording of these heart rates is done manually in the case notes. There is insufficient evidence to support one technique over the other, but one trial in Zimbabwe found more obstetric interventions and fewer neonatal complications when using the Doppler device compared with the Pinard stethoscope [44].

According to NICE [31,32], listening should be after a contraction for a full minute on each occasion: every 15 min in the first stage of labour and at least every 5 min in the second stage. FIGO also recommends auscultating the fetal heart every 15 min during the first stage of labour and every 5 min during the second stage, but recommends listening for at least 60 seconds 'during and for at least 30 seconds after a contraction' [41]. This approach will detect the benign early decelerations of head compression commonly present in the late first stage and second stage of labour, and may miss late decelerations. Both recommend commencement of continuous electronic fetal monitoring (EFM) in the presence of abnormality, but FIGO recommends auscultating over three consecutive contractions to confirm ongoing abnormality before commencing continuous EFM [41]. There are problems with intermittent auscultation: firstly, in clinical practice listening is often performed for less than 1 min [45] and, secondly, because the heart rate varies during the course of the minute, the recommendation is that the rate is averaged [31,32,41]. This latter point is worthy of comment: baseline variability and changes in the baseline are of paramount importance in assessing fetal well-being and thus averaging the heart rate removes both. Recording a range is common practice (e.g. 120–150 with accelerations and no decelerations) but a range without defining a baseline is not ideal; even on a trace it is difficult to distinguish accelerations and decelerations and it is much more difficult when just listening. This may explain why randomized controlled trials have consistently shown an increase in neonatal seizures in low-risk pregnancies monitored using intermittent auscultation compared with continuous EFM [31,46] (Table 27.4). However, as there is no statistically significant difference in rates of cerebral palsy or infant mortality, this disadvantage has to be weighed against the decreased risk of operative delivery associated with intermittent auscultation.

Admission cardiotocography

Because of the importance of assessment and risk stratification on admission in labour, and the potential disadvantages of intermittent auscultation, the concept of 'snapshot' cardiotocography (CTG) on admission to help differentiate the high-risk from the low-risk fetus is logical. Unfortunately, admission CTG in clinically low-risk pregnancies is not beneficial because it is associated with increased interventions without improved outcomes [47], and its use in the low-risk population is therefore not recommended [32,41].

Table 27.4 Randomized controlled trials that have compared electronic fetal monitoring and intermittent auscultation (values are relative risk with 95% confidence interval in parentheses).

	All women*	Low-risk pregnancies†
Neonatal fits	0.5 (0.31–0.80)	0.36 (0.16–0.81)
Perinatal mortality	0.85 (0.59–1.23)	1.02 (0.31–3.31)
Instrumental vaginal delivery	1.16 (1.01–1.32)	
Caesarean section	1.66 (1.30–2.13)	
Total operative deliveries		1.35 (1.09–1.67)

*In over 37 000 pregnancies (12 trials) [46].
†NICE subset of three trials of lo--risk pregnancies [31].

Cardiotocography

Electronic recording of the FHR with printout allows contemporaneous continuous recordings of the heart rate and a permanent record. The baseline and its variability are fairly easy to define and accelerations or decelerations from the baseline can be studied. As such it is a sensitive tool to document heart rate changes. Compared with intermittent auscultation its use improves fetal outcomes, with fewer neonatal seizures [45], but it impedes maternal mobility (unless telemetry transducers are used) and it tends to distract care from the woman to the monitor [44] and is associated with increased obstetric interventions (all forms of operative delivery).

The advantage of EFM is that it is very sensitive and detects the fetus at possible risk, but its poor specificity means that an abnormal trace does not mean the fetus is necessarily hypoxic. The need to improve the predictive value of EFM and reduce the disadvantage of increased operative delivery rates has focused research on additional techniques to supplement EFM when the trace is not normal. Pulse oximetry and near-infrared spectroscopy have already been mentioned briefly as not yet being clinically useful [33–37]. Whilst vibroacoustic stimulation for fetal assessment in the antenatal period looks promising, further research is still needed, including intrapartum studies to explore any potential benefits in labour [48]. The more invasive technique of intermittent FBS from the fetal scalp during labour is well integrated into intrapartum care as an adjunct to EFM and has been subject to clinical trials.

Fetal blood sampling

The value of FBS has been hotly debated in recent years [49,50] but currently remains an integral part of intrapartum fetal monitoring and is still recommended by NICE [32] and FIGO [42,43] except in acute fetal compromise (where emergency delivery is needed), maternal infection (e.g. HIV and hepatitis), fetal bleeding disorders and prematurity (<34 weeks).

Most FBS measurements examine pH and gas values, but more recently fetal lactate has been measured. This needs a smaller blood volume and so has potential advantages to pH estimation. This comparison between pH and lactate measurements using fetal blood has now been the subject of randomized controlled trials and while there were no differences in fetal outcomes or operative delivery rates, the success of FBS was greater in the lactate group due to the smaller volume of blood needed for analysis [51]. All FBS samples should be taken with the woman in the left lateral position to avoid aortocaval compression during the technique [31].

Interpretation of FBS results

The interpretation of the FBS result must include the clinical condition and the risk factors affecting the mother and fetus, and must allow for the fact that one result only reflects the pH/lactate at that moment. An isolated reading, even if normal, must not be taken as meaning there is no problem as the process of metabolic acidosis might only be starting (after hypoxaemia has proceeded to hypoxia, as described in detail earlier) and could yet accelerate quickly, depending on the cause. A pathological CTG requires repeat FBS even if the previous result was normal, to help assess the trend of fetal deterioration, and the timing of the repeat sample will depend on the nature of the CTG, the original result and, most importantly, the clinical features of the case. The NICE intrapartum guideline describes FBS classification and actions [31] (Table 27.5). The FIGO guideline [43] includes lactate measurements (Table 27.6).

The aim is to achieve delivery before irreversible fetal damage, and to wait until severe acidaemia occurs in order to justify intervention is illogical if the chance of vaginal delivery is remote and the fetal condition is already deteriorating. Hence two successive fetal blood samples, an hour apart, with pH of 7.35 and 7.25 should not be reassuring: this fetus is deteriorating rapidly and in another hour it is likely that the next pH value will be below 7.20. The clinical decision here will be largely determined by whether the woman is 9 cm dilated and progressing quickly (in which case repeat

Table 27.5 NICE classification of fetal blood samples [31].

pH	Interpretation	Action suggested by NICE [31]	Appropriate clinical action
≥7.25	Normal	Repeat within 1 hour if trace stays pathological or sooner depending on trace	Clinical features should also influence this timing and falling results indicate compromise (see text)
7.21–7.24	Borderline	Repeat within 30 min or sooner depending on trace	Clinical features will determine whether this repeat sample is sensible or whether delivery should be expedited (see text)
≤7.20	Abnormal	Ask for consultant obstetric advice	Delivery is needed and consultant should be informed but this should not delay delivery

Table 27.6 FIGO classification of fetal blood samples [43].

pH	Lactate (mmol/L)	Interpretation	Action
>7.25	<4.2	Normal	Repeat in 60 min if CTG still abnormal
7.20–7.25	4.2–4.8	Intermediate	Conservative measures; repeat in 20–30 min if not normalized
<7.20	>4.8	Abnormal	Conservative measures/rapid delivery

FBS within the next 30 min might allow progress to full dilatation and vaginal delivery) or whether she is still 4 cm dilated despite Syntocinon for the last 4 hours (in which case expediting delivery by caesarean section is likely to be more appropriate). This is why clinical judgement has to complement the basic rules suggested for guidance: such rules should not be followed unthinkingly.

Fetal blood sampling dilemmas

FHR abnormalities in the presence of oxytocin infusions cause enormous problems, and practice varies between stopping the oxytocin infusion to halt the FHR anomalies, stopping oxytocin until FBS is performed and found normal, or continuing the infusion and performing FBS. It should be remembered that contractions are needed for labour to progress, so the key decision is assessing the uterine contractions. The oxytocin infusion should continue if uterine contractions and relaxations are appropriate (see above) but if the fetal heart requires FBS, then proceed with it. NICE recommends stopping oxytocin if the trace is non-reassuring or abnormal until the FBS result is known; if it is normal, the oxytocin infusion can be restarted [32]. It needs to be remembered that FBS will need repeating to check that the fetus is not deteriorating with the augmented contractions.

FBS is rarely indicated at full dilatation as delivery is usually more appropriate for a pathological CTG, but a normal result can allow time for descent and rotation to convert what would have been a more complex operative delivery into a more straightforward one. If this is the plan, however, it should be remembered that the fetal condition deteriorates more quickly in second stage than in first stage (because of maternal expulsive effort) and such a policy is fairly high risk so the obstetrician should be on hand to effect delivery if the CTG deteriorates.

There is controversy regarding FBS in the presence of a uterine scar, because fetal heart anomalies are often the first sign of problems with scar integrity and FBS can be falsely reassuring prior to what might be very rapid fetal demise. On the other hand, scar rupture is a much rarer event than FHR abnormalities and not performing FBS and proceeding straight to caesarean section will inevitably lead to an increase in 'unnecessary' intervention. For these reasons, the decision to perform FBS in cases of vaginal birth after previous caesarean delivery should be taken at consultant level.

Decisions to perform FBS in early labour (≤3 cm dilated) or repeating the procedure on multiple occasions (≥3 cm) should be taken carefully and at a senior level, but may be appropriate and achieve safe vaginal delivery [52].

The dilemma faced when failing to obtain an adequate sample on attempting FBS (less of a problem when sampling for lactate) is whether to continue labour (unsafe if the FHR pattern is pathological) versus proceeding straight to delivery, but recent suggestions of scalp stimulation can help guide practice: if the scalp stimulation from the procedure produces accelerations and the trace normalizes, then this is reassuring [43].

Fetal ECG

ST analysis

Over the last couple of decades the use of computerized analysis of the fetal ECG, particularly the ST segment, has been introduced into clinical practice. The fetal ECG is detected by means of an internal electrode (attached to the fetal scalp) and the printout highlights when there is an ST event, namely elevation of the ST segment suggesting myocardial hypoxia. The original randomized trials [53–55] supporting this supplement to CTG monitoring suggested better neonatal outcomes with fewer operative deliveries, but the reality has been disappointing with a number of reports of problems when using this technique in routine clinical practice [56–58]. The eagerly awaited large randomized controlled trial from the USA showed that fetal ECG ST-segment analysis used as an adjunct to conventional intrapartum electronic FHR monitoring did not improve perinatal outcomes or decrease operative delivery rates [59]. These data are included in the most up-to-date Cochrane review, which is similarly unsupportive of ST analysis [60].

The difficulties with this method of monitoring arise because of the following:

- ST events are frequent among controls (50%) with normal CTG and normal cord gas values [58];
- ST events, together with abnormal CTG patterns, appear late in the hypoxic process and are inconsistent

(50% in moderate metabolic acidaemia, 67% in severe acidaemia) [58];
- if the ST event precedes the start of monitoring, it may not register [57].

A review of the first 1502 cases monitored in a teaching hospital in the UK showed no improvement in emergency operative delivery or neonatal encephalopathy rates [56]. The crux of the argument is that clinical decision-making when using this tool should include accurate CTG interpretation as well as registering the ST event, but the problem is that ST analysis has been marketed as reducing intervention because it is 'better' than CTG and it is therefore unsurprising that users have a tendency to disregard a pathological CTG if the ST event does not trigger [61].

Non-invasive fetal ECG

The other disadvantage of ST analysis is the internal spiral scalp electrode, which risks scalp trauma and transmission of infection. The signal pick-up and feasibility of external electrodes placed on the maternal abdomen has been explored [62] but is still in the research arena. This would avoid the spiral electrode problem, but difficulties remain with ST analysis and how to relate it to CTG interpretations in clinical practice and therefore further developing this technology is questionable.

Computerized CTG analysis

There is some evidence that computerized CTG analysis reduces perinatal mortality in the antenatal period [63], but the same is not so for intrapartum monitoring. Preliminary trials looking at adding an expert system to aid in the interpretation of the fetal heart trace and improve intervention rates and neonatal outcomes were underpowered [64] but a definitive, large, multicentre UK trial which randomized over 47 000 women to intrapartum CTG monitoring either with or without decision support [65] showed that there was no difference in outcomes for either mother or baby, except for a slightly increased incidence of FBS in the decision support group. The authors concluded that their hypothesis that substandard care is largely related to failure to identify pathological FHR patterns was not supported and that most adverse outcomes associated with preventable substandard care involved a failure to take appropriate management decisions once the CTG abnormality had been recognized.

The future

The conflict between the need to detect the fetus in danger and to expedite delivery while avoiding unnecessary intervention remains. The following suggestions or research examples demonstrate where further developments may improve this inexact science.

- Antenatal detection of growth restriction can be improved by the systematic use of growth charts to plot the symphysis–fundal height routinely and appropriate use of ultrasound and thorough antenatal care and admission assessments in labour will further help stratify women and their babies into lower- or higher-risk groups.
- Intermittent auscultation techniques for low-risk pregnancies could be further explored to establish whether neonatal outcomes can be improved by critically specifying the baseline (and variability from that baseline) rather than just recording an average rate or a range for FHR.
- Computerized CTG analysis is well established in, and has improved the accuracy of, antenatal EFM (where failing to fulfil the Dawes–Redman criteria is associated with acidaemia and intrauterine deaths) [63,66,67]. Development of this tool for intrapartum CTG application has had promising results [68], but results from the definitive INFANT trial [65] did not confirm any benefit. However, further development to include clinical parameters and not just pattern recognition designs may help return the focus to treating the baby not the CTG.
- Clinical flags that alert the clinician in real time during EFM and which take into account clinical factors as well as CTG parameters may all improve the detection of fetal compromise, but will never replace clinical acumen. Maintaining an alert, enquiring, critical review of the whole clinical picture will always be needed and highly valued. There is no place for complacency and the hope that machines will tell clinicians what to do is unrealistic.

Summary

Intrapartum fetal monitoring must start from a clinically inquisitive stance where all antenatal factors are assimilated and added to observations on presentation in labour. Distinguishing between low- and high-risk pregnancies will then tend towards one particular approach to fetal monitoring but it should be remembered that whichever technique is chosen, none is foolproof, and continued vigilance and awareness of clinical developments in labour are needed. This anticipation of hypoxia should help early recognition of problems so that appropriate action can avoid both unnecessary intervention and inappropriate inactivity which could lead to irreversible damage to the fetus.

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28

Preterm Labour

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Epidemiology

Definitions

Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy. Legally, in the UK, the 1992 Amendment to the Infant Life Preservation Act defined the limit of viability as 24 weeks. However, a small number of infants born at 23 weeks will survive. Mortality in preterm babies born after 32 weeks' gestation is similar to that of babies born at term. The risk of neonatal mortality or survival with handicap becomes significant in very preterm infants (defined as those born between 28 and 32 weeks) but is most significant in extremely preterm infants (defined as those born before 28 weeks) (Fig. 28.1). In modern obstetric practice assessment of gestational age is based principally on fetal biometry measured by first- or second-trimester ultrasound rather than the date of the last menstrual period. However, in the past, assessment of gestational age was not always accurate and paediatric statistics were based on birthweight rather than gestational age data. Low birthweight is defined as less than 2.25 kg, very low birthweight as less than 1.5 kg and extremely low birthweight as less than 1 kg. Using these definitions to describe outcome data leads to blurring of the distinction between preterm babies and small-for-gestational-age babies, particularly in the low birthweight category, and also fails to differentiate the normally grown preterm neonate from the neonate who is both preterm and small for gestational age.

Incidence

Globally, about 15 million babies are born preterm each year. The incidence of preterm birth varies significantly across the globe. In most developed nations the rate of preterm birth is below 10%, the UK rate is around 7% and in the USA the rate fluctuates between 9 and 12% with huge geographical or interstate variation. Countries with preterm birth rates exceeding 15% include Malawi, Congo, Comoros, Zimbabwe, Equatorial Guinea, Mozambique, Gabon, Pakistan, Indonesia, Mauritania and Botswana. The greatest numbers of preterm births occur in India, China, Nigeria, Pakistan, Indonesia and the USA [1].

Preterm birth rates are increasing in almost all countries with reliable data. Especially in the developed world, this is associated with assisted reproduction increasing the rates of multiple pregnancy and an increased tendency to obstetric intervention. Strategies in the USA to encourage obstetricians to reduce their reliance on elective preterm delivery to manage conditions such as growth restriction and pre-eclampsia have been associated with a significant local reduction in the preterm birth rate, although this applies largely to late preterm births.

The proportion of preterm births in each gestation or age week époque increases almost exponentially from about 32 weeks. This means that the great majority of preterm births occur at later gestations. In England some 15% of all preterm births occur before 32 weeks, whilst 70% occur between 35 and 37 weeks (Fig. 28.2). The UK rate of preterm birth prior to 32 weeks has remained relatively stable at 1–2%. About one-quarter of preterm births are elective deliveries, usually for pre-eclampsia, intrauterine growth restriction or maternal disease. The remainder are due to preterm labour and delivery.

The incidence of spontaneous preterm labour is at its lowest in women in their twenties. The risk is increased in teenagers and in women aged over 30. There is a higher incidence of preterm labour in first pregnancies. Higher parity alone is not a risk factor for preterm labour. Indeed there is a progressively lower risk with each successive term birth. Marital status, cigarette smoking, environmental stress, poor nutrition and use of alcohol, coffee and street drugs (especially cocaine) have all been

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

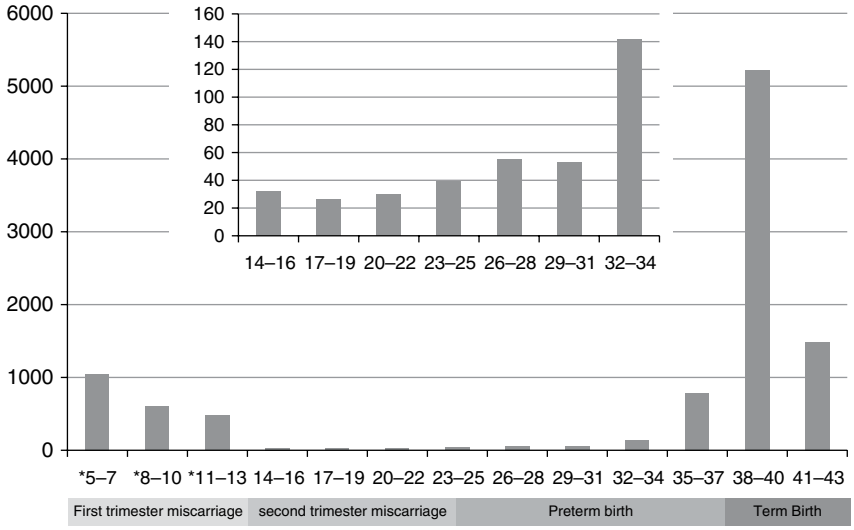

Fig. 28.1 Anticipated pregnancy outcome from 10 000 conceptions. The rate and timing of losses in the first trimester are derived from the CONCEIVE study (Foo FL, Collins A, McEniery CM, Bennett PR, Wilkinson IB, Lees CC. Preconception and early pregnancy maternal haemodynamic changes in healthy women in relation to pregnancy viability. *Hum Reprod* 2017;32:985–992). The outcomes in the second and third trimester are from the UK Office for National Statistics.

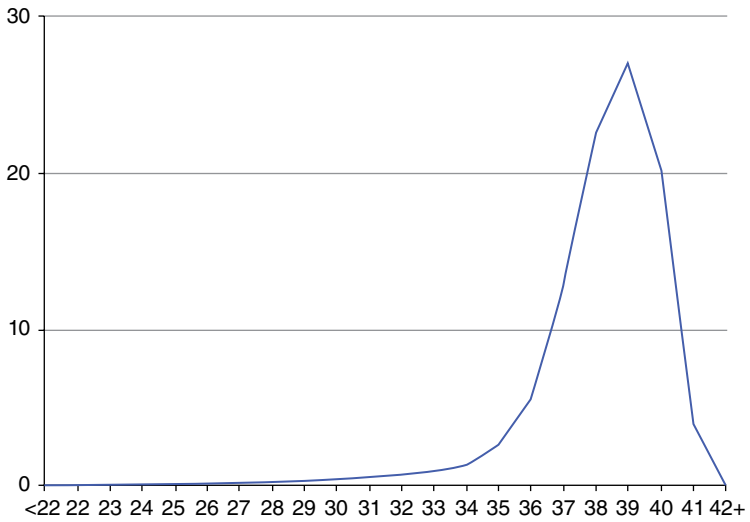

Fig. 28.2 Live birth percentages by gestation, 2011 birth cohort, England and Wales. *Source:* UK Office for National Statistics.

linked to an increased risk of preterm birth. However, many of these factors are interlinked and all are factors associated with social disadvantage. There does appear to be an association between race and risk of preterm delivery. In the UK the risk of preterm birth is 6% in white Europeans but 10% in Africans or Afro-Caribbeans, although it is difficult to differentiate genetic variation from social deprivation. In studies of populations where black and white women have similar lifestyles, levels of income and access to medical care (e.g. in US Army personnel), preterm delivery rates show a less marked ethnic variation. However, the identification of specific genetic polymorphisms that increase the risk of preterm labour does suggest that genetic as well as environmental factors may be involved, which explains the increased risk of preterm labour in certain ethnic populations. Intervention studies have shown that antenatal smoking cessation programmes reduce the risk of preterm birth, although there is no evidence currently that other interventions, such as increased frequency of antenatal care, dietary advice or an increase in social support, reduces the risk of preterm labour.

Summary box 28.1

- Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy.
- Globally, about 15 million babies are born preterm each year.
- Risk factors include primigravida, older maternal age, smoking, illicit drug use and cervical surgery.

Neonatal outcomes after preterm birth

As of 2014, preterm births became the single largest cause of death of children under the age of 5 throughout the world [2]. Of the 6.3 million children who died before the age of 5 years in 2013, 52% died from infection and 44% died in the neonatal period. The three leading causes of death were complications of preterm birth (15.4%), pneumonia (14.9%) and complications of labour and delivery (10.5%). Previously infection had been the largest cause of death in this age group but global improvements in the management of pneumonia, diarrhoea and measles since the turn of the century has substantially reduced the impact of these diseases on childhood mortality.

Globally, there are dramatic differences in survival rates for preterm infants depending on where they are born. Over 90% of extremely preterm babies (<28 weeks) born in low-income countries die within the first few days of life, while less than 10% of babies born at this gestation die in high-income settings, a 10 : 90 survival gap. The risk of a neonatal death due to complications of preterm birth is more than 12-fold higher for an African baby than for a European baby.

In developed nations, and in particular the UK, survival rates for preterm babies have improved steadily over the past three decades principally due to the introduction of surfactant therapy, improvements in neonatal respiratory management and more widespread use of antenatal steroids (Fig. 28.3). The Epicure study, which examined extremely preterm infants born in 1995, reported mortality rates of 100%, 90% and 80% for preterm infants admitted to neonatal units at 21, 22 and 23 weeks' gestation, respectively. The subsequent Epicure II study repeated this exercise in a similar cohort born in 2006 and found that although rates of survival of babies born between 22 and 25 weeks' gestation has increased since 1995, the pattern of major neonatal morbidity and the proportion of survivors affected are unchanged. Therefore improved survival for very preterm infants has been associated with an increase in the proportion of children with cerebral palsy who were born preterm. Neonatal mortality rises gradually between 32 and 28 weeks, from 2 to 8%, and then more dramatically and exponentially to 80% at 23 weeks (Table 28.1).

In the past, surfactant deficiency leading to neonatal respiratory distress syndrome (RDS) was the major cause of morbidity and mortality in preterm infants. Alveolar surfactant production begins at 30–32 weeks' gestation. Therefore preterm infants born prior to 30 weeks are at highest risk. The impact of RDS on neonatal morbidity and mortality has been dramatically reduced in the past three decades through use of antenatal corticosteroids and exogenous surfactant replacement. The risk of chronic lung disease, defined as a need for ventilation or oxygen supplementation at 36 weeks after conception, has however continued to rise because of the increased survival of extremely preterm infants. The fetal and neonatal brain is especially susceptible to injury between 20 and 34 weeks. The greatest risk of long-term neurodevelopmental problems is in infants born before 28 weeks or at birthweights of less than 1000 g. The Epicure study showed that in infants born before 26 weeks' gestation, approximately half had some disability at 30 months and approximately one-quarter had severe disability [3]. Cerebral palsy may be related to periventricular haemorrhage, post-haemorrhagic hydrocephalus

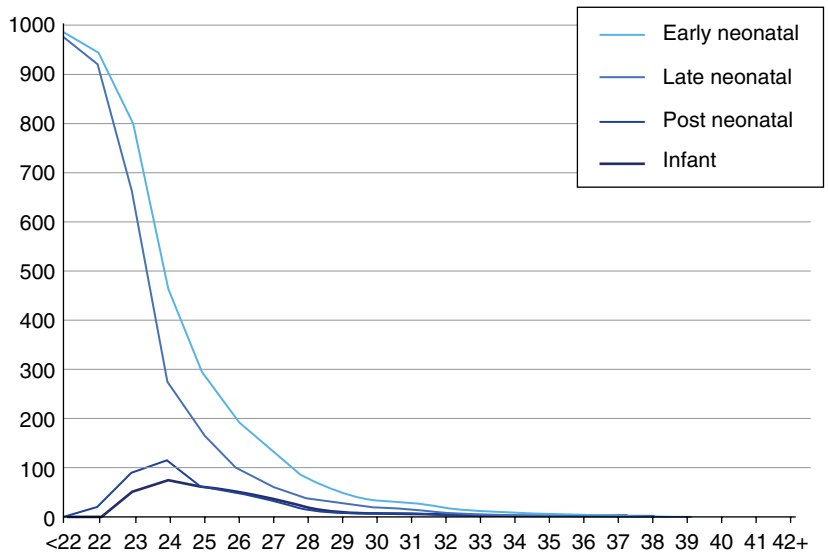

Fig. 28.3 Infant mortality rate by gestation, 2011 birth cohort, England and Wales. *Source:* UK Office for National Statistics.

Table 28.1 Prediction of survival for preterm births by weight and gestational age.

Gestational age (weeks)	Weight 5th centile (g)	Weight 10th centile (g)	Weight 90th centile (g)	Survival (%)	Survival without major morbidity (%)
23	600	450	970	6	2
24	700	550	1180	15	5
25	790	620	1250	45	15
26	880	700	1350	60	20
27	960	780	1450	75	50
28	1080	820	1600	85	60
29	1220	940	1720	90	80
30	1400	1050	1900	93	85
31	1600	1180	2100	96	90
32	1760	1300	2300	97	92
33	1980	1480	2500	97	95
34	2200	1650	2700	98	97

Source: adapted using data from Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ* 1999;319:1093–1097.

and periventricular leucomalacia. Hypoxia–ischaemia is a major risk factor for neonatal cerebral damage. However, there is growing evidence for a strong link between chorioamnionitis, fetal inflammation and the risk of periventricular leucomalacia.

The overall risk of cerebral palsy associated with preterm birth at any gestational age (i.e. 23–36 weeks) is increased sevenfold over that of babies born at term; however, with decreasing gestational age this risk increases dramatically, with relative risks of 14, 46 and 70-fold, in infants born before 34, 31 and 28 weeks, respectively. The risk of visual impairment due to retinopathy of prematurity is inversely related to gestational age at birth and directly related to the concentration and duration of oxygen treatment. The risk of retinopathy of prematurity rises dramatically from less than 10% at 26 weeks to above 50% in infants born at 24 weeks. About 3% of infants born before 28 weeks' gestation will require a hearing aid and 50% will be found to have learning difficulties at school requiring additional educational support.

Preterm birth is associated with an increased prevalence of other medical disabilities, learning difficulties, and behavioural and psychological problems even in those without cerebral palsy. The risks of autism and mental retardation are increased 10-fold in preterm infants born before 28 weeks, and that of schizophrenia is increased fivefold. Difficulty with cognitive processes contributes to an increased risk of school problems in children born preterm. Only half of children born before 28 weeks are able to enter preschool with their peer group. The proportion of children born preterm who experience academic difficulties increases with age as the complexity of the schoolwork increases. Even in adults born preterm and who have no apparent medical problems, there are lower rates of high-level education and higher rates of low income and dependence on social security benefits.

Mothers of infants born preterm are at increased risk of experiencing depressive symptoms. The length of time that the newborn preterm infant must stay in the hospital also affects the ability of the mother to fulfil her role in the family. Families caring for a child born preterm face long-term and multiple challenges. The impact on families is long term, with parents, siblings, finances and family functioning all affected. Families will need to continue to manage the effects of prematurity when the children are toddlers, reach school age, become adolescents and, in some cases, into adulthood. The parent's marital relationship is likely to become stressed, often leading to divorce and consequent worsening of parenting difficulties. Parents will experience higher stress levels through difficulties in supervision of the child, the child's peer relationships and self-esteem, the impact of the child's difficulties on family routines, and worrying about the child's future. Siblings are affected because of the decreased attention that they receive from their parents. The family as a unit is affected by the greater likelihood of not having additional children, the financial burden, limits on family social life, high levels of family stress and dysfunction, and parents' difficulty in maintaining employment.

Summary box 28.2

- Preterm birth is the single largest cause of death of children under the age of 5 throughout the world.
- The overall risk of cerebral palsy associated with preterm birth at any gestational age is increased sevenfold over that of babes born at term. It is 70-fold higher in infants born before 28 weeks.
- Over 90% of extremely preterm babies (<28 weeks) born in low-income countries die within the first few days of life while less than 10% of babies born at this gestation die in high-income settings, a 10 : 90 survival gap.

Endocrinology and biochemistry of labour

To effectively predict and prevent labour requires a good understanding of the endocrinology and biochemistry underlying the onset of labour in humans, both at term and preterm [4,5] (Fig. 28.4). Our understanding of the mechanisms leading to the onset of labour in the human remains incomplete, in part because the mechanisms of the onset of parturition in different species appear to have evolved differently, making the direct extrapolation of data from animal models to the human not necessarily valid.

Labour as an inflammatory process

Throughout pregnancy the uterine cervix needs to remain firm and closed whilst the body of the uterus grows by hypertrophy and hyperplasia but without significant fundal dominant contractions. For labour to be successful the cervix needs to be converted into a soft and pliable structure that can efface and dilate and the uterus needs to become a powerful contractile organ. There is no single endocrine or biochemical switch in the human that changes the uterus from its not-in-labour state to its in-labour state. The onset of labour is a gradual process which begins several weeks before delivery itself with changes in the lower pole of the uterus which cause cervical ripening and effacement. The onset of clinically identifiable contractions is a relatively late event in this process. Cervical ripening occurs through breakdown of collagen, changes in proteoglycan concentrations and an increase in water content. The lower segment of the uterus also stretches and relaxes and behaves physiologically more like the cervix than like the contractile upper segment of the uterus. These changes in the lower segment of the uterus are associated with an increase in the production of inflammatory cytokines, particularly interleukin (IL)-8 and prostaglandins from the overlying fetal membranes and decidua and from the cervix itself. Cervical ripening is associated with an influx of inflammatory cells into the cervix which release matrix metalloproteins that contribute to the anatomical changes associated with ripening. The later increase in fundally dominant contractility in the upper segment of the uterus is associated with an increase in the expression of receptors for oxytocin and prostaglandins, in gap junction proteins, which mediate electrical connectivity between myocytes, and in more complex changes in the intracellular signalling pathways which increase the contractility of the myocytes.

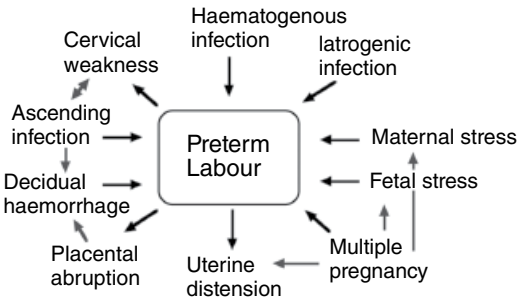

Fig. 28.4 The interplay of the causes of the preterm labour syndrome.

Roles of progesterone, corticotrophin-releasing hormone and oxytocin

In many species progesterone is thought to play an important role in suppressing the onset of labour [6]. Progesterone has a generally anti-inflammatory action within the uterus. As discussed above, many of the biochemical events associated with cervical ripening and the onset of labour are similar to those seen at sites of inflammation. In most species the onset of labour is heralded by withdrawal of progesterone.

So, for example, in the rodent, prostaglandin-mediated regression of the corpus luteum leads to a fall in progesterone concentrations immediately prior to the onset of labour. In the sheep increased production of cortisol from the fetal adrenal signals fetal maturation and induces placental 17α-hydroxylase, which increases synthesis of oestrogen at the expense of progesterone, again leading to progesterone withdrawal immediately prior to the onset of labour. There is no systemic withdrawal of progesterone in the human prior to the onset of labour, although there is an increase in the expression of genes formerly repressed by progesterone, which has led to the hypothesis of a 'functional progesterone withdrawal' mediated by changes in the expression or function of progesterone receptors or of cofactors needed for the function of the progesterone receptor. Another hypothesis is that inflammatory events seen within the uterus at

the time of labour are associated with increased activity of the transcription factors nuclear factor (NF)-κB and AP-1 (transcription factors strongly associated with inflammation in other contexts such as asthma, inflammatory bowel disease or arthritis). NF-κB and AP-1 repress the function of the progesterone receptor and so could mediate functional progesterone withdrawal. Although in the mouse progesterone concentrations fall due to luteolysis just prior to labour, there is still sufficient circulating progesterone concentrations to activate progesterone receptors. In the mouse it appears that the final event leading to parturition is the increased production of surfactant protein A from the fetal lung, which stimulates the activity of NF-κB within the uterus leading to an influx of inflammatory cells, an increase in inflammatory cytokine synthesis and depression of the residual function of the progesterone receptor. It is an attractive hypothesis that pulmonary maturation in the human may signal the final phase of the onset of labour but there is at present no direct evidence that this mechanism applies in the human.

Circulating levels of corticotrophin-releasing hormone (CRH), synthesized in the placenta, increase progressively throughout pregnancy and especially during the weeks prior to the onset of labour. CRH-binding protein concentrations fall with advancing gestational age such that, approximately 3 weeks prior to the onset of labour, the concentration of CRH exceeds that of its binding protein. Unlike in the hypothalamus, placental CRH is upregulated by cortisol. Several studies have linked placental production of CRH with the timing of birth and have demonstrated that a premature rise in CRH is associated with preterm delivery. The upregulation of CRH by cortisol suggests a mechanism by which the fetus, through increased adrenal cortisol production, may signal its maturation and control the timing of birth [7]. For much of pregnancy the CRH receptor expressed by the myometrium is linked to second messenger systems that promote relaxation. Near to term, however, CRH may enhance the contractile response to oxytocin and may stimulate the production of prostaglandins from the fetal membranes and the placenta.

In the monkey, uterine contractions occur only at night. In the days preceding labour and delivery there are nocturnal non-fundal dominant contractions which have been termed 'contractures'. The conversion from contractures to contractions is mediated by an increase in the production of oxytocin from the maternal posterior pituitary gland [8]. In the monkey, therefore, while the fetus might signal its general readiness to be born through increased cortisol production from the adrenal, the precise timing of birth is signalled by the mother. This may be a mechanism of defence against predators which ensures that delivery is always at night. Contrary to the experience of many obstetricians, this phenomenon does not apply to the human. There is no increase in the production of oxytocin associated with the onset or progression of either preterm or term labour. There is, however, an increase in the expression of oxytocin receptors within the uterus and there is local production of oxytocin in the uterus, decidua and fetal membranes. Although oxytocin probably does not play an important role in the precise timing of parturition in the human, increases in the density of oxytocin receptors suggests that oxytocin does play a role in mediating contractility. Recent studies have shown that oxytocin acts not only to stimulate the uterus to contract, but also to upregulate inflammatory mediators within the uterus, therefore adding an additional 'pre-labour' mechanism of action for the hormone. Oxytocin also plays important postnatal functions in mediating the milk-let down reflex, contracting the uterus to prevent postpartum haemorrhage and having a effect on maternal bonding with the baby.

Causes of preterm labour

Preterm labour is not a single disease entity but is a syndrome that may have one or more causes [9,10]. Research into the prediction and prevention of preterm labour has to some extent been made more difficult because many investigators have treated the syndrome as if it is a single disease. With the exception of studies specifically in multiple pregnancy and in populations of women with a short cervix, most clinical studies of interventions to prevent or delay preterm labour have not attempted to differentiate subjects on the basis of the underlying cause. Similarly, many studies which have attempted to identify biomarkers for preterm labour have not taken into account its multiple aetiology.

Preterm labour has been linked to cervical incompetence, abnormalities of haemostasis, infection within the uterus, placental abruption or decidual haemorrhage, fetal or maternal stress and multiple pregnancy. These various factors may act together to increase the likelihood of preterm delivery or to affect the gestational age at which preterm delivery occurs. Multiple pregnancy probably leads to preterm delivery through at least three mechanisms. Over-distension of the uterus leads to premature upregulation of contraction-associated proteins and of factors which mediate cervical ripening, all of which have been shown to be sensitive to mechanical stretch. Multiple pregnancy is associated with multiple placentas and therefore with an earlier rise in placental CRH concentrations in the circulation. The development of multiple corpora lutea may lead to increased production of relaxin and to premature cervical ripening. The incidence of multiple pregnancy has increased due to the trend of delayed

childbirth, since multiple births occur with a greater frequency amongst older mothers. However, the principal contributing factor has been the linked increase in the use of assisted reproductive technologies. This has been controlled to some extent in the UK by restricting the number of embryos transferred at *in vitro* fertilization, although poorly controlled ovulation induction therapies may continue to contribute to the problem.

Cervical function

With improved survival at early gestational ages, there is now overlap between second-trimester pregnancy loss and early preterm delivery. Historically, cervical incompetence was diagnosed in women who experienced persistent, often rapid and painless, late second-trimester pregnancy loss. More recently, the concept of cervical competence as a continuum has evolved. It is probable that cervical length and strength, together with the quality of the cervical mucus, contribute towards cervical function, both to retain the pregnancy within the uterus and to exclude potential bacterial pathogens from ascending from the vagina. Numerous studies have demonstrated a strong relationship between cervical length and the risk of preterm delivery. The cervix may be damaged (or completely removed) by surgery in the treatment of cervical cancer or, rarely, during a difficult instrumental vaginal delivery, or caesarean section at full dilatation. Historically, there were associations between diethylstilbestrol exposure *in utero* and developmental anomalies in the genital tract and cervical weakness. This ceased to be a problem in modern obstetric practice since the cohort of women exposed to the drug in the 1960s are now beyond reproductive age. A short or partially dilated cervix may allow bacteria to ascend into the lower pole of the uterus where, acting through the Toll-like receptors of the innate immune system which recognize bacterial components, they stimulate production of inflammatory cytokines, prostaglandins and the inflammatory response. This then leads to cervical ripening and shortening, which in turn decreases the ability of the cervix to act as either a mechanical or microbiological barrier and, ultimately, leads to the development of either localized or generalized chorioamnionitis and to preterm delivery. A short or weak cervix may therefore contribute to preterm delivery not only by leading to simple second-trimester miscarriage but also by contributing to a risk of ascending infection leading to a more classical spontaneous preterm labour. Delivery by caesarean section at or close to full dilatation of the cervix is now recognized as a risk factor for preterm birth. The probability is that difficult delivery leads to mechanical damage to the cervix, through the trauma from failed instrumental delivery, through a uterine incision made within cervical rather than lower segment tissue, or through damage to the cervix caused by the need to disimpact a deeply engaged fetal head.

There is an association between risk of preterm delivery and cervical intraepithelial neoplasia (CIN) [11]. The greatest risk is in those women with CIN who have had a particularly deep large loop excision of the transformation zone (LLETZ) or a cold knife cone biopsy. In women who have had a deep LLETZ or a cold knife cone biopsy, mechanical damage to the integrity of the cervix is probably a major aetiological factor in their risk of preterm labour. However, there is a smaller underlying risk associated with CIN alone. It may be that human papillomavirus (HPV) infection is an independent risk factor for preterm birth. It is also possible that the underlying factors associated with the development of CIN following HPV infection in an individual woman may also be factors which increase her risk of preterm birth.

Genital tract infection

There is a strong correlation between infection within the uterus and the onset of spontaneous preterm labour. As discussed, activation of inflammatory mediators is a central part of the normal biology of parturition. Therefore infection within the uterus has the potential to activate all the biochemical pathways, ultimately leading to cervical ripening and uterine contractions. It has been estimated that approximately 40% of all preterm births are associated with bacterial infection. The most likely source of infection is bacteria ascending from the vagina through the cervix into the lower part of the uterus. However, bacteria may also gain access to the amniotic cavity through haematogenous spread or by introduction at the time of invasive procedures. Following preterm delivery histological chorioamnionitis is usually more common and severe at the site of membrane rupture than elsewhere, such as overlying the placenta or umbilical cord. In virtually all cases of congenital pneumonia, inflammation of the fetal membranes is also present. Bacteria identified in the majority of cases of congenital infection are often also found in the maternal lower genital tract and, following twin preterm delivery, chorioamnionitis is more common and severe in the presenting twin than in the second twin (although this is not always the case). These factors all suggest that ascending infection from the lower genital tract is the commonest mechanism for chorioamnionitis.

The most common microbes isolated from the amniotic cavity of women in preterm labour are *Ureaplasma urealyticum*, *Fusobacterium* and *Mycoplasma hominis*. More than 50% of patients in preterm labour will have more than one microorganism isolated from the amniotic cavity. Microorganisms can be identified in the fetal membranes of the majority of women delivering both

preterm and at term. It is probable that some cases of spontaneous preterm delivery are due to an excessive inflammatory response to a lesser degree of bacterial invasion of the amniotic cavity. So, for example, bacterial vaginosis (see below) may be a greater risk factor for preterm labour in women who carry a high secretory form of the tumour necrosis factor (TNF)-α gene.

There is now considerable interest in the role of the microbial communities in the vagina in the aetiology of preterm birth. The collective term for the range of bacterial species in the vagina is 'vaginal microbiota'. The collective term for all the bacterial genes present is 'vaginal microbiome' (although the term 'microbiome' is often used interchangeably with 'microbiota' to define a microbial community occupying a reasonably well defined habitat which has distinct physicochemical properties). The study of the bacterial genes present in the vaginal microbiome is described as metagenomics.

In reproductive life the vaginal microbiota is usually dominated by the presence of lactobacilli, representing more than 90% of bacterial species present. Lactobacilli secrete lactic acid, which maintains a low pH hostile to other microorganisms and which has anti-inflammatory actions. Lactobacilli also excrete specific antimicrobial proteins. A minority of women will have a *Lactobacillus*-depleted vaginal microbiota, and this may allow overgrowth of bacterial vaginosis (BV)-associated anaerobic organisms such as *Gardnerella vaginalis*, which creates a biofilm that allows other opportunistic bacteria to thrive. The increased oestrogen concentrations of pregnancy increase the availability of vaginal mucosal glycogen, a source of energy for lactobacilli. Therefore, in general, the proportion of lactobacilli increases in the vagina during pregnancy. The relationship between the structure of the vaginal microbiota and the risk of preterm birth varies from population to population. In some but not all populations in the USA, where *Lactobacillus* depletion is common, a dysbiotic *Lactobacillus*-depleted BV-like vaginal microbiota is a risk factor for preterm birth. In the UK, prevalence of a dysbiotic vaginal microbiota in pregnancy is low but is probably still a risk factor. However, the dominance of one particular species, *Lactobacillus iners*, appears to be a risk factor for both cervical shortening and preterm birth. *Lactobacillus iners* has less ability to excrete anti-inflammatory isomers of lactic acid or antimicrobial proteins, and may represent a transitional organism between healthy vaginal microbiota and vaginal dysbiosis or bacterial vaginosis.

Haemorrhage

Placental abruption may lead to the onset of preterm labour. This is thought to be through release of thrombin, which stimulates myometrial contractions by protease-activated receptors but independently of prostaglandin synthesis. This may explain the clinical impression that preterm labour associated with chorioamnionitis is often rapid whereas that associated with placental abruption is less so because there is no pre-ripening of the uterine cervix. Generation of thrombin may also play a role in preterm labour associated with chorioamnionitis when it is released as a consequence of decidual haemorrhage.

Fetal and maternal stress

There is evidence that both fetal and maternal stress may be risk factors for preterm labour. Fetal stress may arise in association with abnormal placentation and growth restriction. Maternal stress could be due to environmental factors. In both cases it is postulated that over-secretion of cortisol leads to upregulation of CRH production in the placenta.

Summary box 28.3

- Preterm labour has been linked to cervical incompetence, abnormalities of haemostasis, infection within the uterus, placental abruption or decidual haemorrhage, fetal or maternal stress and multiple pregnancy.
- There is an association between risk of preterm delivery and deep LLETZ or cold knife cone biopsy.
- Colonization of the vagina with *Lactobacillus iners* or with a *Lactobacillus*-depleted high-diversity community structure are risk factors for preterm pre-labour rupture of membranes and preterm birth.

Prediction of preterm labour

In the majority of cases of preterm labour obstetric management consists principally of attempting to suppress contractions in women who are already in established labour. As discussed in more detail later, this strategy is essentially ineffective. Obstetric strategies to reduce perinatal morbidity and mortality associated with preterm labour should ideally involve the early identification of women at risk and the use of prophylactic therapies. Prediction of preterm labour can be considered in two broad scenarios. Firstly, there is prediction at a time removed from the labour event itself, intended to direct possible prophylactic therapy. Secondly, there is the prediction of delivery in women who are symptomatic, essentially intended to differentiate those who are genuinely in preterm labour from those who have preterm contractions but are not at risk of imminent delivery.

Attempts have been made to devise risk scoring systems based on socio-demographic characteristics,

anthropomorphic characteristics, past history, patient behaviour and habits and factors in the current pregnancy. None of these systems has been found to have positive predictive values or sensitivities which make them clinically useful in identification of individual women at risk. Most systems rely heavily on past obstetric history and are therefore irrelevant to women having their first baby. At present there are no screening tests which are routinely applied to primigravid women, or to multigravid women who are not at high risk for preterm labour. Women at high risk of preterm labour will initially be detected based solely on past obstetric history. Having had a single previous preterm delivery increases the risk of preterm delivery in a subsequent pregnancy four times when compared to a woman whose previous delivery was at term. A past obstetric history which consists of a term delivery followed by a preterm delivery confers a higher risk of preterm delivery in the third pregnancy than a past obstetric history that consists of a preterm delivery followed by a term delivery. This may be because the latter group contains a disproportionate number of women whose preterm delivery was for 'non-recurring' causes such as placental abruption, whereas in the former group the preterm delivery following the term delivery may be due to damage to the cervix during the original term delivery.

Ultrasound measurement of cervical length

There is very good evidence that transvaginal sonographic measurement of cervical length can be used to identify women at risk of preterm labour in both low- and high-risk pregnancies and in women who are symptomatic [12] (Fig. 28.5). Transabdominal measurement of cervical length is unreliable because of the need for a full bladder, which may compress the cervix leading to an overestimate of its length, and because it is more difficult to obtain adequate views of the cervix with this technique. Transvaginal ultrasound should be performed with the bladder empty. The probe is placed in the anterior fornix of the vagina without undue pressure on the cervix and optimally the internal and external os and the echogenic endocervical mucosa should be identified along the length of the canal. For identification of risk in asymptomatic women (those who do not have symptoms of labour) two broad strategies are currently in common use: a single measurement in the mid-second trimester, or serial measurement of cervical length throughout the second and early third trimester of pregnancy.

A single measurement of cervical length, usually at the time of a routine ultrasound scan between 18 and 22 weeks, has been widely used to identify subjects at high risk of preterm birth for inclusion into intervention trials. If a screening strategy using a single ultrasound

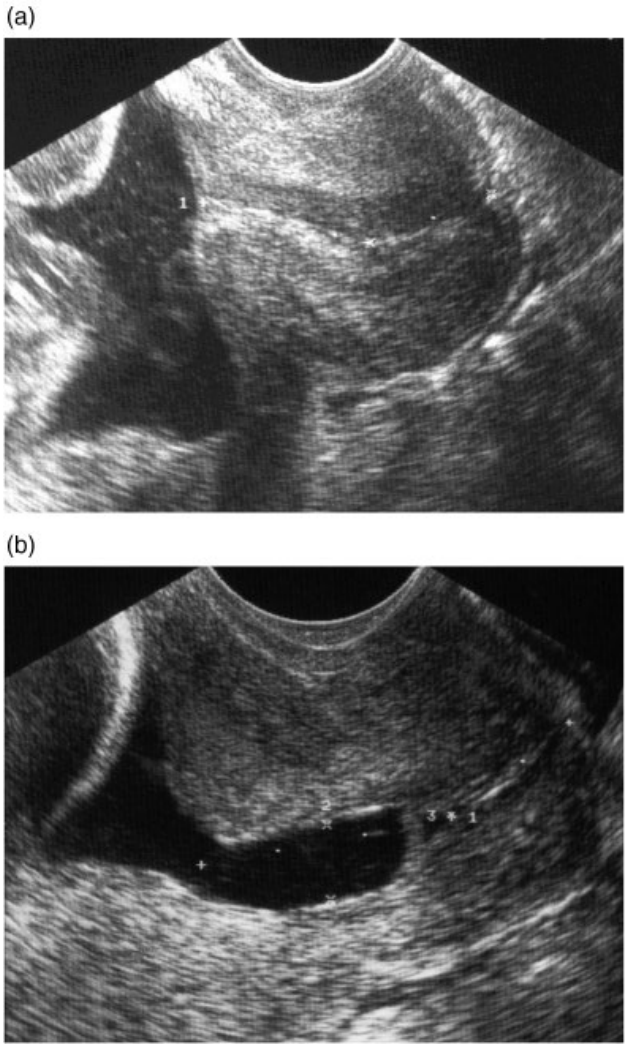

Fig. 28.5 Appearance of the cervix on transvaginal ultrasound: (a) normal cervix; (b) funnelling leading to a short cervix.

measurement of cervical length is used, then assessment between 21 and 24 weeks' gestation appears to be better than assessment prior to 20 weeks' gestation in predicting the risk of preterm labour. However, this is to a certain extent a self-fulfilling prophesy since clearly the closer to the actual onset of preterm labour the assessment of cervical length is made, the more likely it is that the cervix will be found to be short. It is arguable that identification of a risk of preterm labour as late as 23 weeks may be too late for any potential prophylactic therapies to be fully effective. In addition, such a strategy is unable to detect any of the women whose pregnancy loss or preterm delivery occurs prior to 23 weeks. A large number of studies have examined the relationship between gestational age, cervical length and the risk of preterm delivery (Fig. 28.6). Many studies have used single cut-off values. So, for example, a cervical length of

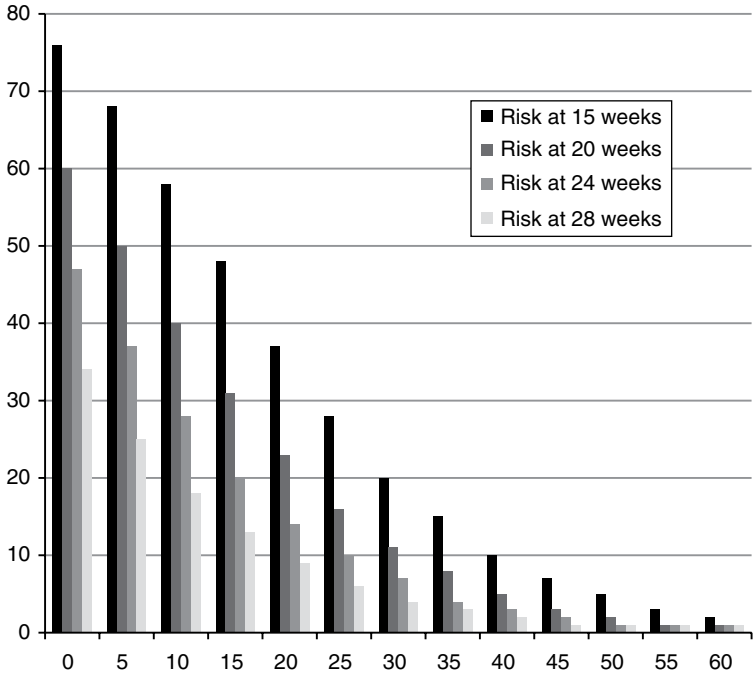

Fig. 28.6 Risk of preterm birth (<32 weeks) by cervical length and gestational age of measurement. *Source:* adapted using data from Iams JD, Berghella V. Care for women with prior preterm birth. *Am J Obstet Gynecol* 2010;203:89–100.

15 mm or less at 20–24 weeks predicts a risk of preterm delivery prior to 34 weeks' gestation of approximately 50% in a low-risk population. It is absolute cervical length rather than the presence or absence of funnelling which is the principal predictor of spontaneous preterm birth (although clearly the presence of funnelling will lead to a shorter cervical length).

It has been suggested that the introduction of routine measurement of cervical length at the time of the second-trimester anomaly ultrasound scan would enable screening of low-risk populations. This concept is greatly predicated on the assumption that an effective intervention is available (see section on progesterone and cervical cerclage). The value of routine measurement of cervical length also depends on the prevalence of a short cervix and the incidence of preterm birth in the background population. In UK populations this approach will only detect about 15% of all preterm births, a reflection of the multi-aetiological nature of the syndrome.

Women at high risk of preterm birth may be offered serial measurement of cervical length to assess their risk of preterm labour. This approach appears to be superior to a single measurement in assessing the risk of preterm delivery. It has been widely advocated as an approach for the detection of women who would benefit from progesterone prophylaxis during pregnancy. It is also a particularly useful approach in women with a history of a previous preterm birth or second-trimester pregnancy loss in whom a diagnosis of cervical insufficiency or incompetence is not clear and can be used to reduce the number of unnecessary cervical cerclage procedures performed. In this management strategy, cervical cerclage would be indicated either when cervical length reduces to a fixed cut-off, commonly 25 mm, or falls below the 10th or 3rd centile for cervical length at that gestational age. In continental Europe it is common practice to perform a vaginal assessment of cervical length at each antenatal consultation, although multicentre trials have shown that this policy is of no benefit in predicting the risk of preterm delivery.

Bacterial vaginosis

As alreadt discussed, BV is a risk factor for preterm birth, although most studies have shown that treating BV with antibiotics does not change the risk. Studies of the risk of preterm labour associated with BV have reported widely varying results. However, it seems that, overall, BV approximately doubles the risk of preterm delivery. It also appears that there is a relationship between the gestational age at diagnosis of BV and the risk of preterm delivery, in that if BV is diagnosed earlier in pregnancy this appears to be associated with a higher risk of preterm delivery. Routine screening for BV is not therefore undertaken in low-risk populations. Some obstetricians do include screening for BV in the management of high-risk populations, and this is currently undertaken by non-genetic techniques, although the future introduction

of DNA sequence-based bacteriology may change this situation. Currently, diagnosis of BV can be made on Gram staining of vaginal fluid using either Nugent's or Spiegel's criteria, by gas–liquid chromatography of vaginal fluid (finding a high ratio of succinate to lactate) or on clinical grounds based on a high vaginal pH, a fishy odour in a thin homogeneous vaginal discharge and the presence of clue cells in the discharge on a wet mount. There is no significant difference in the ability of each of these diagnostic tests to predict preterm birth.

Although there is reasonably good evidence that BV is a risk factor for preterm delivery, it is less clear that treating it with antibiotics is beneficial. This may be in part because various studies of BV have used different antibiotics in different regimens and at different times, but it may also reflect the fact that antibiotics may not necessarily result in the re-establishment of normal bacterial flora. The two antibiotics commonly used in the treatment of BV are metronidazole administered orally or clindamycin, which may be given either orally or vaginally. Clindamycin may have advantages over metronidazole since it has better activity against anaerobic bacteria and *Mycoplasma hominis* and *Ureaplasma urealyticum* which are often associated with BV. While screening of pregnant women who are at high risk for preterm delivery based on their past obstetric history or other factors might be justified, there is currently no strong evidence to recommend the routine screening and treatment of the general obstetric population.

Summary box 28.4

Preterm labour may be predicted by:

- transvaginal sonographic measurement of cervical length in the second trimester;
- measurement of fetal fibronectin in cervical vaginal fluid in the second trimester.

Fetal fibronectin

Fetal fibronectin is a glycoprotein variant of the fibronectin family present in amniotic fluid, placenta and the extracellular substance of the decidua. Its synthesis and release is increased by the mechanical and inflammatory events which occur prior to the onset of labour. Fibronectin is often described as 'leaking' from disruption to the fetal membranes and decidua in the lower pole of the uterus associated with the early biochemical events of parturition. However, it is also an inflammatory response gene, and therefore concentrations of fibronectin in vaginal fluid can be considered to also be a marker of inflammation (which may be pathological or a normal part of the onset of labour at term).

Fetal fibronectin may normally be detected in vaginal secretions at levels in excess of 50 ng/mL up to 20 weeks' gestation and again after 36 weeks' gestation. Detection up to 20 weeks is possible because the amniochorion is not fully fused with the decidua until that time. Detection closer to term is a feature of the normal mechanical and biochemical events leading to normal term labour. The presence of fibronectin in vaginal secretions at levels above 50 ng/mL between 20 and 36 weeks is therefore not normal and may be used to predict a risk of preterm labour [13,14]. When originally introduced as a commercial test, fibronectin analysis was principally intended to be used in women who present with preterm contractions to differentiate those with a risk of imminent delivery. However, it is now being increasingly used to predict risk in women who are asymptomatic but at risk for other reasons, in particular cervical shortening. The currently available bedside testing kits allow quantification of the concentration of fibronectin in the vaginal fluid, which has improved the predictive performance of the test. So, for example, women with a cervical length below 25 mm between 22 and 28 weeks, but with a fetal fibronectin concentration of less than 10 ng/mL, will have a risk of preterm birth before 34 weeks of less than 10%; this rises to over 50% if the fibronectin concentration is greater than 200 ng/mL.

Predictive algorithms (e.g. QUIPP, Apple Store) have now become available that combine the information of past obstetric history, gestational age, cervical length and fibronectin concentration to produce an estimate of risk delivery within a defined time period (e.g. 7 days) or prior to a defined gestational age (e.g. 34 weeks). These algorithms have been developed based on populations who had interventions if they were identified as being at high risk and therefore their general applicability, particularly to low-risk populations, is uncertain. Nevertheless, they act as a useful guide to enable clinicians to take into account all the risk factors for preterm birth and to direct therapy and counsel patients about the risks and benefits of interventions.

Prevention of preterm labour

In primigravid women with no other significant risk factors for preterm delivery there is currently no effective method for the prediction of preterm labour and therefore management can only be instituted at the time of acute presentation with contractions. However, it is possible to identify a group of women in the antenatal period who are at risk of preterm delivery based on their past obstetric history, the presence of abnormalities of the genital tract, and use of screening tests such as transvaginal ultrasonic measurement of cervical length and detection of fetal fibronectin in vaginal secretions [15].

A continuing problem in the direction of therapies intended to reduce the risk of preterm birth is a lack of suitable tools to stratify women at risk into different aetiological groups. Most studies of interventions have either had no classification or have selected subgroups of women, for example those with a multiple pregnancy or those with a short cervix. Even in those subgroups, however, the underlying aetiology may be different. So, for example, it is possible that damage to the cervix caused by an excisional treatment for CIN, may result in both cervical incompetence and a physically shorter cervix. Such women may benefit from cervical cerclage. However, the cervix may have its structural integrity compromised without necessarily being rendered any shorter and would nevertheless still benefit from cerclage. Cervical shortening may be due to activation of inflammation within the vagina and cervix, in which case cerclage might be detrimental. It is possible that some of the dramatic differences in the effectiveness of interventions that are seen in different clinical trials may arise from enrolment of women whose underlying aetiology of their risks of preterm birth are different, despite the apparent presentation, for example with a short cervix, being similar.

At present, no prophylactic therapy has been demonstrated to be unequivocally beneficial in preventing the onset of preterm labour in a high-risk population. Commonly used therapies include cervical cerclage and progesterone. Previously, non-steroidal anti-inflammatory drugs and oral beta-sympathomimetics have been used. Vaginal pessaries are being studied.

Cervical cerclage

The objective of the MRC/RCOG multicentre randomized trial of cervical cerclage, published in 1993, was to assess whether cervical cerclage in women deemed to be at increased risk of cervical incompetence prolongs pregnancy and thereby improves fetal and neonatal outcome. However, women were randomized only if their obstetrician was uncertain whether to recommend cervical cerclage. Therefore cervical cerclage was compared with a policy of withholding the operation unless it was considered to be clearly indicated. In this study, the largest ever conducted of this question, the overall preterm delivery rate was 28% and there were fewer deliveries before 33 weeks in the cerclage group (13% vs. 17%). This difference was reported to be reflected in deliveries characterized by features of cervical incompetence: painless cervical dilatation and pre-labour rupture of the membranes. The use of cervical cerclage was associated with a doubling of the risk of puerperal pyrexia.

Based largely on these data, current UK guidelines suggest that history-indicated cerclage should be offered to women with three or more previous preterm births and/or second-trimester losses [16,17]. Various tests, including assessment of cervical resistance index, hysterography or insertion of cervical dilators, have been found to have no benefit in predicting cervical weakness. Nevertheless a clinical examination of the cervix of a woman considered at risk is beneficial. It will highlight any congenital or acquired abnormalities and will identify the women in whom cerclage may be a more challenging procedure than expected before discovery on the operating table.

Many obstetricians currently use transvaginal ultrasound measurement of cervical length to assess risk of preterm birth and target intervention by cervical cerclage in women where there is uncertainty about the possible benefit. If ultrasound-indicated cervical cerclage is to be used, the appropriate threshold has not yet been universally agreed, although a length below 25 mm is a commonly used cut-off. The presence of visible fetal membranes at the time of cervical cerclage is a strong prognostic indicator for the risk of preterm delivery. Visible fetal membranes are never seen at a cervical length greater than 15 mm.

An individual patient data meta-analysis of four large studies of targeted cervical cerclage in women with a short cervix taken from a general obstetric population with no increased background risk of preterm birth showed that cervical cerclage was not beneficial. It has therefore generally been concluded that cervical cerclage is of no benefit in a woman with a short cervix but no other risk factors for preterm labour. However, in the analysis the selected cut-off cervical length for cerclage varied between less than 15 mm and less than 25 mm, and the ultrasound examinations were performed relatively late in pregnancy at 22–24 weeks. The results of this meta-analysis also stands in stark contrast to a much smaller earlier study which showed a marked benefit of cervical cerclage undertaken by a single senior skilled obstetrician. As discussed later, there are various aspects of the technical performance of the operation that will affect the outcome. It is possible that the failure to demonstrate benefit of cervical cerclage in a large general population of women with short cervix is partly due to the short cervical length cut-off, late gestational age at screening, variable skill and experience of the operators and technique of the procedure. It is also probably the case that a population of women at risk of preterm birth with a short cervix at the end of the second trimester of pregnancy represents a mixture of women with genuine mechanical cervical problems, who would probably benefit from cervical cerclage, and women whose cervix is short for other reasons, who would probably not benefit and may even be harmed (see discussion on effects of suture material).

Whilst the current evidence is that cervical cerclage is not beneficial in women whose only risk of preterm birth is a short cervix in the late second trimester, there is good evidence to suggest that women with a history of spontaneous second-trimester loss or preterm delivery who have cervical shortening are at an increased risk of subsequent second-trimester loss/preterm birth and may benefit from ultrasound-indicated cerclage while those whose cervix remains long are at low risk. A meta-analysis of four randomized controlled trials of cervical length-indicated cerclage in women with a prior second-trimester loss or birth before 36 weeks showed an almost 50% reduction in deliveries prior to 35 weeks in the cerclage group. Women with a prior LLETZ represent another group who may benefit from cervical cerclage and are becoming an increasingly large cohort in the obstetric population. This group is now often managed in a similar way, with a cut-off cervical length of 25 mm being used to indicate cervical cerclage. Although there are no randomized controlled trials in this group of patients, current observational data suggest that this policy reduces their risk of preterm birth to that of the background population. A cervical length of 38 mm at 12 weeks or 36 mm at 16 weeks can be used as a screen to discharge women in this cohort from further surveillance.

Cervical cerclage technique

Various different techniques have been described for cervical cerclage. The operation was originally popularized in the 1950s by Shirodkar as a transvaginal pursestring suture placed following bladder mobilization and posterior dissection to allow insertion at the level of the internal os. In the 1960s the simpler McDonald procedure of a transvaginal pursestring suture without bladder mobilization become popular. Some exponents of the McDonald procedure deliberately place the suture midway along the cervix to reduce the risk of bladder injury and to facilitate removal. It is now clear that the success of cervical cerclage depends on placing the suture as close to the internal os as possible. In my experience this will require dissection of the bladder off the cervix in more than 50% of cases.

Cervical cerclage is most commonly performed using a braided Mersilene tape suture with needles on each end. However, there is evidence that use of Mersilene may be associated with higher rates of pregnancy loss and preterm birth than use of the more inert material nylon. Mersilene, when used for cervical cerclage and in other forms of surgery, may encourage bacterial biofilm formation, and has a detrimental effect on the vaginal microbiota leading to activation of vaginal/cervical inflammation [18]. Some operators who use Mersilene tape completely bury the suture. This is associated with better outcomes but with much greater difficulty in removing the stitch at the end of the pregnancy. Similarly, leaving large amounts of Mersilene tape in the vagina after cerclage to facilitate removal probably increases the risk of adverse outcome. The use of Mersilene tape for cervical cerclage may explain the higher puerperal sepsis rates seen in the large trials, but also the dramatically improved outcomes seen in women who undergo abdominal cerclage, in which accurate placement of the stitch at the isthmus is made easier, whilst the stitch itself is in an anatomical location unexposed to the vaginal microbiota.

The current evidence, although based on small numbers, is that insertion of a cervical cerclage where the only risk of preterm birth is multiple pregnancy is not beneficial; indeed it may be associated with an increase in the risk of preterm delivery and pregnancy loss. Similarly, cerclage does not appear to be of benefit in women with multiple pregnancy and a short cervix but no other risk factors for preterm birth. This underlines the aetiological differences in the risk of preterm birth between singleton and multiple pregnancy. There are no large studies of the role of cerclage in women with twins who have a past history of second-trimester pregnancy loss or preterm delivery. However, it would be illogical to deny a woman who had previously benefited from cervical cerclage, a cerclage in a subsequent pregnancy because she was carrying twins.

Emergency 'rescue' cerclage

Rescue cervical cerclage may be performed when a woman is admitted with silent cervical dilatation and bulging of the membranes into the vagina but without the onset of uterine contractions. Characteristically, such women present with slight vaginal bleeding, a watery vaginal discharge, or vague pelvic or vaginal pain. The available literature, mostly composed of case reports and small case series, suggests that rescue cerclage may delay delivery by a further 5–7 weeks on average compared with expectant management/bed rest alone, associated with a twofold reduction in the risk of delivery before 34 weeks. However, there are concerns that emergency or rescue cerclage might convert a second-trimester pregnancy loss into an early preterm delivery with its associated handicap risk, particulary in the context of chorioamnionitis. Adverse features which should contraindicate rescue cervical cerclage include evidence of chorioamnionitis: maternal pyrexia, abdominal pain, contractions, raised white blood cell count or C reactive protein levels. Whether antibiotics are beneficial in such cases has not been established.

Non-steroidal anti-inflammatory drugs

The central role for prostaglandins and inflammatory cytokines in the onset of labour at term and in the aetiology of preterm labour suggests that non-steroidal

anti-inflammatory drugs (NSAIDs) may be beneficial in preventing preterm delivery. NSAIDs work largely by inhibition of the cyclooxygenase enzymes which catalyse the synthesis of prostaglandins. However, various NSAIDs also have other mechanisms of action, including effects on intracellular signalling pathways and on inflammatory transcription factors such as NF-κB and AP-1. Whilst there are several studies of the use of NSAIDs in the acute management of preterm labour, there are few good randomized trials of their use as prophylaxis. NSAIDs are associated with significant fetal side effects, in particular oligohydramnios and constriction of the ductus arteriosus. Oligohydramnios occurs in up to 30% of fetuses exposed to indometacin. The effect is dose dependent and may occur with both short-term and long-term exposure. Discontinuation of therapy usually results in a rapid return of normal fetal urine output and resolution of the oligohydramnios.

Constriction of the ductus arteriosus occurs in up to 50% of fetuses exposed to indometacin at gestational ages greater than 32 weeks. There is a relationship between dose and duration of therapy and gestational age. Ductal constriction is seen less commonly below 32 weeks and rarely below 28 weeks. Long-term indometacin therapy, particularly after 32 weeks, is therefore associated with a significant risk of persistent pulmonary hypertension. More detailed ultrasound studies have shown that administration of indometacin is associated with a rapid reduction in hourly fetal urine production but that oligohydramnios may develop more slowly and become significant at between 15 and 28 days.

There are two major isoforms of the cyclooxygenase enzyme, COX1 and COX2. COX1 is constitutively expressed in the majority of cells whereas COX2 is inducible and catalyses the synthesis of prostaglandins at the sites of inflammation. Since it is probable that it is COX1 whose function is important for fetal renal function and ductal patency, it was hoped that the use of NSAIDs selective or specific for COX2 might be associated with a lower risk of fetal side effects. However, nimesulide, which is approximately 100-fold more effective in inhibition of COX2 than COX1, is associated with an incidence of fetal oligohydramnios similar to that seen in fetuses exposed to indometacin and there have been isolated case reports of fatal fetal renal failure. Prophylactic use of the COX2-specific rofecoxib, although associated with weaker effects on both fetal renal function and the ductus arteriosus than indometacin or nimesulide, is associated with an increased rate of preterm delivery. The reasons for this are unclear but probably represent an effect on anti-inflammatory as well as proinflammatory prostaglandins [19].

At present therefore there is no good evidence that NSAIDs confer benefit when used as prophylaxis for preterm labour. They are associated with a significant risk of potentially life-threatening side effects. If NSAIDs such as indometacin are to be used, perhaps as short-term therapies in association with cervical cerclage, and particularly for more than a few days after 28 weeks, then it is essential that there should be ultrasound surveillance of fetal urine production or amniotic fluid index and of the ductus arteriosus and that therapy should be stopped when fetal side effects become evident.

Progesterone

Progesterone is probably the most widely used intervention to prevent preterm labour worldwide. Currently, two different progestin preparations are in common use. The synthetic 17α-hydroxyprogesterone caproate, which is chemically similar to testosterone and is not a natural progesterone metabolite, has been shown to reduce the risk of preterm birth in women at high risk based on past history but who do not have a short cervix. Current evidence suggests that 17α-hydroxyprogesterone caproate is not effective in the group of women whose risk of preterm birth is predicted by a short cervix, nor is it effective in women at risk of preterm birth because of multiple pregnancy.

The mechanism of action of 17α-hydroxyprogesterone caproate is unclear. Concentrations of progesterone in the circulation during normal pregnancy are substantially above the K_d for the progesterone receptor. As discussed, unlike in other species, in the human progesterone concentrations in the circulation do not fall at the time of either term or preterm labour. There is no evidence for lower progesterone concentrations either in the circulation or in tissues in women at risk of preterm birth. The relative binding affinity of 17α-hydroxyprogesterone caproate for nuclear progesterone receptors is only about 30% that of natural progesterone. 17α-hydroxyprogesterone caproate does not inhibit myometrial contractions *in vitro*.

Several large randomized trials in multiple gestations have identified harm related to exposure to 17α-hydroxyprogesterone caproate, and the synthetic drug is therefore contraindicated in this population. In addition, 17α-hydroxyprogesterone caproate is given as a weekly intramuscular injection, which itself is very painful and therefore patient compliance may not be good. For these reasons 17α-hydroxyprogesterone caproate has not found great popularity outside the USA.

Probably the most widely used progesterone for prevention of preterm birth is natural progesterone administered as a vaginal pessary. Vaginal progesterone appears to be principally effective in patients identified as at risk of preterm labour because of a short cervix. It is not effective in women at risk who have a normal cervical

length, nor has it been proven to be of benefit in multiple pregnancy, although there is some evidence that it may be beneficial in women with twins who also have a short cervix. Unlike 17α-hydroxyprogesterone caproate, natural progesterone has not been associated with any harm to either mother or fetus.

Both an individual patient data meta-analysis of five randomized controlled trials and a systematic review of 36 randomized controlled trials support the use of vaginal progesterone to reduce preterm birth in women with singleton pregnancies at risk of preterm birth associated with a short cervix. The results of both systematic reviews are mainly driven by the 2011 international PREGNANT trial, a randomized controlled trial in which pregnant women at low risk for preterm birth were screened for cervical length with transvaginal ultrasound and progesterone given if the cervix measured 10–20 mm [20]. Overall, the study showed a clear benefit for progesterone in reducing risk of preterm birth in this group, although the trial also showed substantial heterogeneity across study sites. Progesterone appeared to be highly effective in several studies outside the USA, but to have no significant effect on preterm birth rates in US populations. Vaginal progesterone was declined FDA approval for use in the USA partly because of a lack of significant effect on preterm birth rates in the US study centres. The largest randomized controlled trial of vaginal progesterone, OPPTIMUM, was undertaken in the UK and published in 2016 [21,22]. This included women at risk of preterm birth for a variety of reasons and was powered to include three primary outcomes: preterm birth, a composite of neonatal death or severe morbidity, or childhood neurodevelopment. It showed that vaginal progesterone did not reduce any of the primary outcomes but that there was no harm associated with progesterone use. The study did show a non-statistically significant reduction in the risk of preterm birth in women randomized to progesterone because of a short cervix and has been criticized because of a lower compliance rate than seen in other studies, and because the study was not powered to specifically study the patient with a short cervix. A meta-analysis performed after publication of OPPTIMUM continues to show a significant benefit of vaginal progesterone in women with a short cervix.

The potential mechanism of action of natural progesterone is also unclear. The concentrations of progesterone in the circulation during normal pregnancy are substantially above the K_d for the nuclear progesterone receptor. There is no evidence for lower progesterone concentrations in the circulation of women at risk of preterm birth, and administration of vaginal progesterone to women at risk does not elevate circulating progesterone concentrations. It seems likely that the mechanism of action of natural progesterone is local rather than systemic, and it is possible that it may act both through the parent hormone and through metabolites. Progesterone may act to increase the volume and quality of cervical mucus, hence improving physical and biochemical barriers to ascending infection. One widely excepted hypothesis is that progesterone may act as an anti-inflammatory. In cell culture model studies, progesterone inhibits cytokine- or lipopolysaccharide-stimulated activation of inflammatory transcription factors, prostaglandin synthetic enzymes, and the synthesis of prostaglandins and cytokines. However, clinical studies have shown that progesterone does not inhibit cervical–vaginal inflammatory mediators, nor does it have any effect on the vaginal microbiota.

Summary box 28.5

- Current evidence shows that cervical cerclage is not beneficial in women whose only risk of preterm birth is a short cervix in the late second trimester.
- There is good evidence that women with a history of spontaneous second-trimester loss or preterm delivery who have cervical shortening will benefit from ultrasound-indicated cerclage.
- A cervical cerclage should be placed as near to the internal as as possible.
- Vaginally administered progesterone does not reduce the risk of preterm birth in women at risk because of their past history who have a normal cervical length. It may reduce the risk in women with a short cervix in the second trimester.

Preterm pre-labour rupture of membranes

Preterm pre-labour rupture of membranes (PPROM) occurs in approximately 2% of all pregnancies and accounts for up to one-third of preterm deliveries. The most frequent consequence of PPROM is preterm delivery, with some 50% of cases delivering within a week, 75% within 2 weeks and 85% within a month. There is an inverse relationship between gestational age and latency, with a shorter interval between membrane rupture and preterm labour at later gestational ages. As with preterm labour, postnatal survival following PPROM is directly related to gestational age at delivery and birthweight. However, there is the additional complication that where PPROM occurs prior to 23 weeks' gestation there may be neonatal pulmonary hyperplasia leading to an increased risk of neonatal death, even if delivery occurs at gestational ages at which the outcome would usually be good.

The risk of pulmonary hyperplasia following PPROM is approximately 50% at 19 weeks falling to about 10% at 25 weeks. The retention of amniotic fluid within the uterus is associated with better outcome. A pool of amniotic fluid greater than 2 cm is associated with a low incidence of pulmonary hypoplasia.

Although many women with preterm rupture of the fetal membranes go into labour fairly quickly thereafter, those women who do not establish in preterm labour shortly after PPROM are at risk of chorioamnionitis. This may represent infection ascending into the uterine cavity, although in some cases PPROM may follow established chorioamnionitis. In either case such infection can be harmful and potentially fatal to both mother and baby and so PPROM requires careful clinical monitoring to allow early detection and treatment of *in utero* infection and chorioamnionitis.

Accurate diagnosis of PPROM is therefore important. This may be based on history, identification of a pool of liquor in the vagina and of oligohydramnios on ultrasound. Biochemical tests of PPROM are available that depend on detection of nitrazine (pH), placental α-microglobulin (PAMG)-1 or insulin-like growth factor binding protein (IGFBP)-1 in vaginal fluid. Nitrazine (pH) testing does not appear to be useful in diagnosis of PPROM, having a clinically useless positive predictive value. Tests for PAMG-1 or IGFBP-1 have clinically useful positive predictive values and so could be used where clinical assessment of PPROM is equivocal but if clear pooling of amniotic fluid is seen are probably unnecessary.

Once PPROM has been confirmed the management is a balance between the risks of prematurity if delivery is encouraged versus the risks of maternal and fetal infection if there is conservative management. It is important to recognize, especially in the context of PPROM, that increasing gestational age at delivery by increasing the latency period is not necessarily associated with improvements in neonatal and childhood outcomes. The links between chorioamnionitis, and particularly funisitis, and lung disease and cerebral palsy imply that to deliberately retain the fetus in an adverse uterine environment could potentially worsen early neonatal outcomes and thus the risk of cerebral palsy.

The ORACLE II study [23] from 2001 showed that prophylactic use of erythromycin improves neonatal morbidity, reduces the risk of sepsis and is associated with a longer latency period, whereas co-amoxiclav increases the risk of necrotizing enterocolitis and should therefore be avoided. Antibiotics of any type, given prophylactically, do not reduce the incidence of perinatal death or neonatal encephalopathy and do not affect the rates of maternal sepsis or maternal death. These findings have been confirmed by meta-analysis of subsequent studies [24,25]. Follow-up of the babies in the ORACLE I study showed no differences in serious childhood morbidity at 7 years, and in particular no differences in cerebral palsy rates between babies whose mothers were or were not given antibiotics following PPROM. Erythromycin has a number of potential advantages over other antibiotics in PPROM. It can be administered orally and is effective against group B *Streptococcus*, other streptococcal and staphylococcal infections and *Mycoplasma*, all of which may be implicated in chorioamnionitis. Its use is therefore currently recommended in the UK as prophylaxis for up to 10 days following a diagnosis of PPROM. However, this is not based on any stratification of the causes of PPROM. Recent studies have demonstrated that there is a more complex relationship between the vaginal microbiota, PPROM and erythromycin. In cases where the vaginal microbiota is largely *Lactobacillus* dominated, erythromycin may lead to the elimination of potentially protective *Lactobacillus* and allow a dysbiotic BV-like microbiota to become established. A dysbiotic vaginal microbiota correlates with the development of chorioamnionitis and funisitis and is therefore a risk factor for later neurodevelopmental problems. It is probable that the role of erythromycin will need to be re-evaluated when diagnostic tools to assess the vaginal microbiota within clinically useful time scales become available.

Management of PPROM continues to be controversial. There is currently no consensus on how to manage women whose membranes rupture between 34 and 37 weeks' gestation. Most obstetricians will institute conservative management in uncomplicated PPROM before 34 weeks and many would induce labour relatively early in women whose membrane rupture occurs subsequent to 37 weeks. In any woman labour should be induced if there is good evidence of infection, although making a diagnosis of chorioamnionitis may be challenging (discussed below).

A large randomized controlled trial from the Netherlands, PRROMEXIL (PPROM Expectant Management versus Induction of Labor) published in 2012 compared immediate induction of labour or expectant management in women with PPROM between 34 and 37 weeks' gestation [26]. This found that the risk of chorioamnionitis was slightly reduced in the induction of labour group compared with the expectant management group but there were no differences in rates of neonatal sepsis, RDS or caesarean section. Because fewer babies than expected born to the women in the expectant management group developed neonatal sepsis, the trial was underpowered for this outcome; however, a subsequent meta-analysis of eight trials confirmed all

these findings. In 2016, the PPROMT trial, a multicentre randomized controlled trial performed at 65 centres across 11 countries, showed that expectant management does not increase the risk of neonatal sepsis whilst early delivery was associated with increased risk of RDS [27]. Mothers in the expectant management group were more likely to have evidence of sepsis at the time of delivery, but less likely to require caesarean section. From these studies it is reasonable to conclude that, in the absence of signs of infection or fetal compromise, a policy of expectant management with appropriate surveillance of maternal and fetal well-being should be followed in pregnant women who present with PPROM up to 37 weeks. It is probably the case that the later the PPROM, the lower should be the index of suspicion for chorioamnionitis leading to induction of labour.

Lower genital tract swabs are routinely taken in women with PPROM. Positive cultures for potential pathogens do not correlate well with the risk, or development, of chorioamnionitis; however, they are useful in determining the causative organisms once chorioamnionitis develops and in directing antibiotic therapy for both the mother and the preterm neonate. Conservative management should include clinical surveillance for signs of chorioamnionitis, including regular recording of maternal temperature and maternal and fetal heart rate. The roles of white cell count (WCC) and C-reactive protein (CRP) are frequently misunderstood. Neither WCC or CRP are highly specific for chorioamnionitis. There is wide overlap, at the lower ends of the value ranges, between cases with and without histologically proven chorioamnionitis. Chorioamnionitis is often associated with a 'normal' WCC or CRP value. WCC may be normally elevated in pregnancy, will rise in response to antenatal corticosteroid therapy and has a relatively narrow range, rarely being less than 10×10^6/L and rarely exceeding 20×10^6/L,whether there is chorioamnionitis or not. CRP is a better indicator of chorioamnionitis, but is not good for screening for the development of chorioamnionitis because of its low specificity at the cut-off values needed to give high sensitivity, and its inability to 'predict' chorioamnionitis (in other words CRP remains low until chorioamnionitis actually develops) [28]. Most studies have used CRP cut-off values of 5, 12 or 20 mg/L. Where low cut-off values are used the sensitivity improves (i.e. most true cases of chorioamnionitis are correctly identified) but this is at the expense of specificity (i.e. many women who test positive do not in fact have chorioamnionitis). As cut-off values are increased the number of false positives is reduced but at the expense of failing to identify many genuine cases of chorioamnionitis. When upper limits of CRP are set at 30, 35 or 40 mg/L, the last CRP before delivery is 90, 95 and 100% specific for chorioamnionitis. Therefore whilst a low CRP value is not reassuring, a high value (>50 mg/mL) has a very high association with chorioamnionitis, particularly if it has risen rapidly. Chorioamnionitis should therefore be strongly suspected if there is clinical evidence (tenderness, pyrexia, maternal and/or fetal tachycardia), if there is a rapid rise in CRP values, or if a single CRP value is very high in the absence of any other clinical explanation such as pneumonia, pyelonephritis, deep vein thrombosis or pulmonary embolism. The absence of fetal movements or fetal breathing movements is also an adverse sign.

The use of ultrasound measurement of cervical length in women with PPROM is uncertain. Some studies have shown that cervical length is predictive of latency, others have not. Ultrasound assessment is probably preferable to digital assessment since it appears to be associated with little risk of the introduction of infection. However, at present the technique is not generally used in the management of PPROM.

The current evidence is that tocolytic therapy for women with preterm contractions following PPROM leads to an increase in maternal chorioamnionitis without significant benefits to the infant. The potential benefits of tocolytic drugs do not apply in the majority of cases of PPROM since there is usually time for administration of corticosteroids and *in utero* transfer before the onset of preterm labour itself. The dilemma about when to induce labour in cases of PPROM often does not materialize since 50% of women being managed conservatively will deliver within 7 days. The development of chorioamnionitis will stimulate the mechanisms leading to the onset of labour. Labour itself is therefore a marker of potential chorioamnionitis and so should not be inhibited.

Summary box 28.6

- PPROM occurs in 2% of all pregnancies and accounts for up to one-third of preterm deliveries.
- Preterm delivery follows PPROM within a week in 50% of cases.
- Management of PPROM is a balance between the risks of prematurity and the risks of maternal and fetal infection.
- Increasing gestational age at delivery by increasing the latency period is not necessarily associated with improvements in neonatal and childhood outcomes in the context of chorioamnionitis.
- In the absence of chorioamnionitis, current evidence supports conservative management up to 37 weeks.

Management of symptomatic preterm labour

Prediction of delivery risk in symptomatic preterm labour

Of women who present to hospital with preterm contractions and are thought to be in threatened preterm labour, over 70% will remain pregnant for the following 14 days or more. As discussed in more detail later, there is little evidence to suggest that use of tocolytics, namely drugs intended to suppress uterine contractions, confer any significant benefit in cases of preterm labour. The improvement in neonatal morbidity and mortality seen with advancing gestational age is often used as an argument for the potential benefit of delaying preterm labour using tocolytic agents. However, there is no evidence that tocolytic drugs confer this benefit and there is a real risk that to deliberately prolong a pregnancy, particularly in the context of chorioamnionitis, might lead to harm through retaining the fetus in an adverse intrauterine environment.

There are clear benefits to the timely administration of magnesium sulfate ($MgSO_4$) and corticosteroids to reduce the risk of neonatal morbidity (see below), and to *in utero* transfer to a perinatal centre with suitable neonatal intensive care facilities. Inappropriate administration of multiple courses of corticosteroids is associated with harm to the fetus, whilst unnecessary *in utero* transfer is expensive and blocks both obstetric beds and neonatology intensive care cots, to the detriment of other mothers and babies who might benefit from transfer. There is therefore a clear need for predictive tests that can determine which women who present with preterm contractions are genuinely at risk of delivery within the next 7 days and which are not. As with prediction in asymptomatic women, at present the two modalities in common use are transvaginal measurement of cervical length and fetal fibronectin concentrations in the vaginal fluid.

Ultrasound measurement of cervical length

The use of ultrasound measurement of cervical length in women symptomatic of threatened preterm labour varies geographically. In the USA almost all obstetric residents are skilled in ultrasound measurement of cervical length and suitable ultrasound machines are available in the delivery suites. In the UK and most of the rest of world, most delivery suites do not have ultrasound machines equipped with suitable transvaginal probes, and most obstetric registrars do not have the necessary skills. Studies have used various cervical length cut-off values to define risk, commonly 15, 20 or 25 mm. The negative predictive value is generally stable at each defined length whilst the positive predictive value improves at 15 mm. A cervical length of 15 mm, in a woman symptomatic of preterm labour, has positive predictive values of 28 and 44% for delivery within 48 hours or 7 days with negative predictive values of 97 and 94%, respectively. A cervical length of 15 mm could therefore be reasonably used as a cut-off value at which to offer corticosteroids and *in utero* transfer. Studies in the USA have shown that using this strategy no babies in the group considered to be at low risk of preterm birth are born prematurely without a full course of antenatal corticosteroid therapy, and overall babies in this group had significantly lower rates of exposure to steroids and tocolytics.

Biomarkers: fetal fibronectin, phosphorylated IGFBP-1 and PAMG-1

In the UK, the lack of availability of transvaginal ultrasound machines on labour wards and of an appropriately qualified or experienced clinician to perform the ultrasound, together with the ready availability of bedside testing, means that vaginal biomarker testing is probably the optimal diagnostic test at present. Of the three available methods, detection of fetal fibronectin is the most studied and probably most widely used test (Table 28.2). When first introduced these tests were established as being 'test positive' at a concentration that conferred a high negative predictive value at the expense of the positive predictive value. In other words, if the test was 'negative' the risk of preterm delivery within the next 48 hours or 7–14 days was sufficiently low that in most cases it would be reasonable to withhold steroids or *in utero* transfer. The commonly used 'qualitative' fetal fibronectin test uses a 'test-positive' cut-off of 50 ng/mL. Here, a positive fibronectin test in a symptomatic woman predicts a risk of preterm delivery within the next 7 days of approximately 40%, but a negative fetal fibronectin test reduces the risk to less than 1%. Quantitative fetal fibronectin testing has now become available and this has improved the test. Test results can now be interpreted either by using a range of different cut-off values or by direct interpretation of the quantified results. So, for example, as screen-positive cut-off values are increased from the original 50 ng/mL to 200 and 500 ng/mL, the positive predictive value for delivery within 14 days increases from 20% to 37% and 46%, respectively, whilst the negative predictive value only decreases from 98% to 97% and 96%. Using a lower cut-off of 10 ng/mL decreases the positive predictive value to 10% with no effect on the negative predictive value.

It is possible to combine the results of transvaginal measurement of cervical length and vaginal fluid fibronectin concentrations to improve risk stratification, provided that facilities for both tests are available. It is essential that the fibronectin test be performed before transvaginal ultrasound examination. Most studies have

Table 28.2 Performance of quantitative fetal fibronectin test in predicting preterm birth in symptomatic women.

Fetal fibronectin concentration (ng/mL)	No. of subjects	Delivery within 7 days (%)	Delivery within 14 days (%)	Delivery by 34 weeks (%)
<10	170 (57%)	1	1.8	1.5
10–49	62 (21%)	0	1.6	8.2
50–199	41 (14%)	0	7.7	11.5
200–499	14 (5%)	14	29	33
>499	13 (4%)	38	46	75

Source: adapted from Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. *Am J Obstet Gynecol* 2013;208:122.e1–6.

combined measures of cervical length with catagoric fibronectin results based on a cut-off of 50 ng/mL and have demonstrated higher sensitivity and positive predictive value while maintaining high negative predictive value. Where qualitative fibronectin testing is used, it appears that a high fibronectin concentration has a better predictive value than a short cervical length alone. So, for example, a women with a cervical length below 10 mm but a fibronectin concentration of 10 ng/mL has a very low risk of delivery within 7 days, whereas a woman with a cervical length of 30 mm but a fibronectin concentration above 500 ng/mL is at very high risk. However, either of these two scenarios is likely to be quite rare. The improved predictive value of quantitative fibronectin compared with cervical length is probably a reflection of where on the biochemical pathway to preterm labour the individual woman is. In most cases cervical shortening will precede release of fibronectin into vaginal fluid by several weeks. Fibronectin testing is therefore most useful in identifying the woman at imminent risk of preterm delivery. Measurement of cervical length is probably of better value in identifying women whose risk is more remote. Some studies of interventions to prevent preterm birth which have recruited patients based on fibronectin positivity have been, probably justifiably, criticized for enrolling patients who are too late in the processes of parturition to be helped by the intervention. The development of computed algorithms (e.g. QUIPP, Apple Store) is now allowing fetal fibronetcin concentrations to be interpreted as a continuous variable and to provide individualized risk assessment taking into account the patient's history and cervical length measurements if available.

Acute tocolysis [29]

Sympathomimetics

The maximum benefit to the preterm neonate from antenatal corticosteroid administration is from 24 hours to 7 days after the first dose of the course. *In utero* transfer has also been shown to improve neonatal morbidity and mortality and clearly time would be required to move a mother in preterm labour from one hospital to another. Suppression of uterine contractions has therefore been seen as an obvious solution to the problem of preterm labour. The use of tocolytic drugs intended to inhibit uterine contractions began with the introduction of alcohol and then beta-sympathomimetics into obstetric practice in the 1970s. Early clinical trials suggested that beta-sympathomimetics had great efficacy in inhibiting preterm contractions; there was widespread advertising by the manufacturers and most obstetricians developed the impression that tocolysis (specifically with beta-sympathomimetic drugs such as ritodrine and salbutamol) was an effective therapy for acute preterm labour. This impression was strengthened because of the very high placebo response rate, which implied mistakenly that the drug was being effective. More modern studies have shown that ritodrine will delay preterm delivery in a minority of patients for 24 and 48 hours but that its use is not associated with any improvement in any marker of neonatal morbidity or in neonatal mortality rates. Ritodrine and salbutamol are associated with significant, potentially life-threatening maternal side effects (particularly if given in combination with corticosteroids) that include fluid overload, pulmonary oedema, myocardial ischaemia, hyperglycaemia and hypocalcaemia. Numerous maternal deaths have been reported in which tocolysis using beta-sympathomimetic drugs has played a role. Beta-sympathomimetics as tocolytics are therefore now rarely used in the context of preterm labour, since safer, though not necessarily more efficacious, tocolytic drugs are now available, and their use should probably be completely abandoned. Beta-sympathomimetics continue to have a role in the suppression of excessively frequent or strong contractions stimulated by prostaglandins in the context of induction of labour at term, where short-term use poses few risks.

Non-steroidal anti-inflammatory drugs

The NSAID most widely studied as an acute tocolytic is indometacin. Earlier relatively small randomized placebo-controlled studies suggested that indometacin may delay preterm delivery in the short term but the total number of women enrolled in these trials was small. As discussed in previous sections, indometacin has a major effect on fetal renal function and on the fetal cardiovascular system, in particular on the fetal ductus arteriosus. Use of indometacin for tocolysis has also been associated with higher incidences of necrotizing enterocolitis, intraventricular haemorrhage and abnormalities in neonatal haemostasis. A series of later studies have all generally been small and of low overall quality. In some network meta-analyses and indirect comparisons indometacin has appeared to have some benefit in postponement of birth compared with placebo and beta-mimetics and in maternal adverse effects compared with beta-mimetics and $MgSO_4$. However, these types of indirect comparisons (e.g. where indometacin is compared with salbutamol, salbutamol is compared with $MgSO_4$ and therefore indometacin can be indirectly compared with $MgSO_4$) are heavily affected by the entry criteria and high placebo response rates in the original studies. There is a lack of longer-term childhood outcomes, limitations of small numbers, and minimal data on safety. At present there is no evidence that indometacin or any other NSAID has any advantage as a first-line tocolytic over calcium channel blockers or oxytocin antagonists, each of which has a much better maternal and fetal side-effect profile.

Oxytocin antagonists

Although there is no good evidence for an increase in circulating concentrations of oxytocin in either term or preterm labour, both term and preterm labour are associated with an increase in the expression of the oxytocin receptor in the myometrium and oxytocin is synthesized within the uterus itself, in the myometrium and the decidua. This has led to the exploration of drugs which antagonize the oxytocin receptor as tocolytics. At present no specific oxytocin antagonists are available for clinical use, although atosiban, a mixed arginine vasopressin (AVP) and oxytocin receptor antagonist, has a European Medicines Agency licence for the treatment of preterm labour. Atosiban has been the subject of both placebo comparison trials and comparisons with beta-sympathomimetic drugs. The 2000 placebo-controlled trial undertaken in the USA [30] was, to a certain extent, flawed in that randomization at early gestational ages was skewed, resulting in an increase in neonatal deaths amongst very preterm babies whose mothers were treated with atosiban when compared with placebo (Figure 28.7). Atosiban crosses the placenta, but the drug does not accumulate in the fetus with longer infusion rates. Despite its action at the AVP receptor, atosiban does not affect maternal or fetal cardiovascular parameters or fetal oxygenation. The majority of the infant deaths associated with exposure to atosiban were newborns with birthweights below 650 g, suggesting that extreme prematurity not an effect of atosiban was the cause.

The primary outcome of the placebo-controlled trial (i.e. the time between the initiation of treatment and therapeutic failure, defined as either preterm delivery or need for an alternate tocolytic) showed that atosiban was no different to placebo. For this reason, and because of failure to show overall morbidity or mortality benefit, an FDA licence was denied. There were statistically significant differences in the number of women who remained undelivered and did not require an alternative tocolytic at the specific 24- and 48-hour and 7-day time points, although this applied only in women who were beyond 28 weeks' gestation. As with all previous trials of tocolytic drugs, this trial was complicated by a very high placebo response rate. Analysis of the data shows that, for example, at 48 hours post randomization, although 70% of women randomized to receive atosiban appeared to respond to it, in reality the majority of these represented placebo responders. It can be calculated that only 11% had a genuine clinical response. This represents one-quarter of those women who were genuinely in preterm labour and had potential for a genuine clinical response.

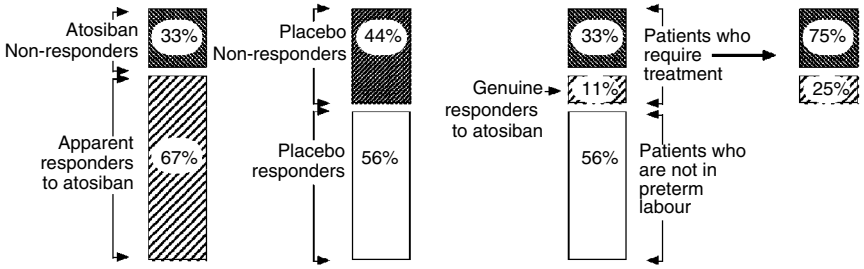

Fig. 28.7 Analysis of the 48-hour outcome data from the placebo-controlled trial of atosiban. Of all patients allocated to atosiban treatment, only 11% showed a genuine clinical response (rather than a placebo response) which represents one-quarter of those with the potential to benefit. This effect applied only in women at 28 weeks' gestational age or greater. *Source:* Romero *et al.* [30].

The trials comparing atosiban with beta-sympathomimetic drugs showed that atosiban was clinically of equal efficacy to beta-sympathomimetics but with a dramatically improved maternal side-effect profile. However, the clinical response rate to either atosiban or beta-sympathomimetic drugs in these trials was so high (>90%) that it is probable that the majority of patients enrolled in the study were not genuinely in preterm labour. Neither the placebo-controlled trial nor the beta-sympathomimetic comparison trials demonstrated any improvement in any aspect of neonatal morbidity or neonatal mortality associated with the use of atosiban.

More recently, it has been found that oxytocin mediates at least two pathways through its receptor, one to stimulate contractions, the other to activate inflammatory pathways and to increase prostaglandin and cytokine synthesis. Atosiban acts as an inhibitor of contractions but as a partial activator of inflammation. A proinflammatory action in a tocolytic is not ideal and may explain the limited efficacy of atosiban. At present, second-generation oxytocin receptor antagonists are in development that are specific to the oxytocin receptor and which do not activate inflammation.

Calcium channel blockers

The central role of calcium in the biochemistry of myometrial contractions led to the exploration of the use of calcium channel blockers, specifically nifedipine, as a tocolytic drug. Because there has been no interest from the pharmaceutical industry in promoting nifedipine for this indication, most of the randomized controlled studies have been comparison trials of nifedipine versus sympathomimetics and other tocolytics. Two small trials comparing nifedipine with placebo or no treatment showed a significant reduction in the risk of birth within 48 hours associated with an increase in maternal adverse effects.

The largest number of trials compare nifedipine with beta-mimetics. Meta-analysis of these trials shows that there were fewer maternal adverse effects, an increase in the interval between trial entry and birth, and a decrease in rates of preterm and very preterm birth, RDS, necrotizing enterocolitis, intraventricular haemorrhage, neonatal jaundice and admissions to neonatal intensive care unit.

There have been three small and one substantial (APOSTEL III) randomized trials comparing nifedipine with atosiban. The three small trials showed contradictory results. Unlike earlier trials of tocolytic agents, APOSTEL III took advantage of cervical length and fibronectin to better define a population in threatened preterm labour. The study showed that tocolysis for 48 hours with nifedipine or atosiban resulted in similar prolongation of pregnancy and perinatal outcome rates. Discontinuation of either nifedipine or atosiban because of side effects was rare, but rates of discontinuation were no different between the two drugs.

At present, the obstetrician (other than in the USA where $MgSO_4$ is still used for its tocolytic action despite evidence that it is ineffecive) has a choice between atosiban or nifedipine and it is probably reasonable, in our current state of knowledge, not to use tocolytic therapy at all. More specific oxytocin antagonists are in development, as are drugs which target other receptors, such as prostaglandin receptors. It is probable that the disappointing results of tocolytics in most trials to date is because of poor trial design and, in particular, the high placebo response rates when contractions alone have been used to diagnose preterm labour. In future trials which are able to target tocolytic drugs more specifically at women genuinely in preterm labour, for example by taking advantage of cervical length measurement or fetal fibronectin testing, may more properly define the potential value of tocolytic therapy.

Antenatal corticosteroid therapy

The potential for antenatally administered corticosteroids to accelerate lung maturity was discovered by Professor Sir Graham ('Mont') Liggins in experiments in which sheep were induced into preterm labour by injection of corticosteroids. Unlike preterm sheep delivered by caesarean section, the sheep in these experiments did not develop fatal RDS. A large number of (human) randomized trials took place during the 1970s and 1980s which, taken together, have shown that a single course of either betamethasone or dexamethasone administered to pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days has a beneficial significant effect on neonatal morbidity and mortality. Although the paediatric use of surfactant has had a major impact on the incidence and consequence of RDS, nevertheless antenatal corticosteroid therapy is still associated with a reduction in neonatal mortality, principally due to a significant reduction in rates of RDS and intraventricular haemorrhage. Antenatal corticosteroids have a receptor-mediated effect on all the components of the surfactant system in type 2 pneumocytes. They also have effects on the structural development of the lungs, lead to accelerated maturation of the fetal intestine and have effects on the myocardium and on catecholamine responsiveness, which may explain the reduced incidence of necrotizing entocolitis and intraventricular haemorrhage seen in extremely preterm infants that appear to be independent of the effect on RDS (Table 28.3).

Women who are considered to be at risk of preterm delivery at between 24 and 35 weeks of gestation should

Table 28.3 Effects of antenatal corticosteroids on neonatal outcomes (World Health Organization analysis).

Interval	Death	RDS	CV haemorrhage
<24 hours	RR 0.6 (0.39–0.94)	RR 0.87 (0.66–1.15) Not significant	
<48 hours	RR 0.59 (0.41–0.86)	RR 0.67 (0.49–0.93)	RR 0.26 (0.09–0.75)
1–7 days	RR 0.81 (0.6–1.09) Not significant	0.46 (0.35–0.6)	
>7 days	RR 1.42 (0.91–2.23) Not significant	0.82 (0.53–1.28) Not significant	

CV, cerebroventricular; RDS, respiratory distress syndrome; RR, relative risk.
Source: World Health Organization. *WHO recommendations on interventions to improve preterm birth outcomes*. Geneva: WHO, 2015.

be targeted for a single course of antenatal corticosteroids. Antenatal corticosteroids should also be considered for women from 23 weeks onwards, based on estimated fetal weight and parental wishes. Whilst antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver from 24 hours and up to 7 days after administration of the second dose of antenatal corticosteroids, there is an effect on neonatal death rates even if delivery is within the first 24 hours so steroid should still be given even if delivery is expected in less than 24 hours.

A single course of corticosteroids does not appear to be associated with any short-term maternal or fetal adverse effects, with the exception of the destabilization of blood sugar control in diabetics or impaired glucose tolerance in pregnancy. Diabetes mellitus should not be considered a contraindication to antenatal corticosteroid treatment for fetal lung maturation, particularly because RDS is more common in the babies of diabetic mothers. Women with impaired glucose tolerance or diabetes who are receiving steroids should have additional insulin according to an agreed protocol and be closely monitored.

The dramatic effects of a single course of corticosteroids unfortunately led to the routine prescription of multiple courses of steroids, often at weekly intervals, in women deemed to be at risk of preterm delivery, especially those with multiple pregnancies. Concerns about the long-term consequences of recurrent exposure to high-dose steroids, namely the adverse effects on development and behaviour, has generally led to an abandonment of this policy. Although one or more repeat courses of corticosteroids is associated with reduced severe lung disease and serious infant morbidity, repeated courses of steroid are associated with an increased risk of intrauterine growth restriction. The challenge for the obstetrician is therefore to use a combination of the clinical history, markers of infection or inflammation, the results of cervical length measurements and fetal fibronectin or other biomarkers to refine the estimate of risk of preterm delivery in any individual woman to correctly target a course of corticosteroids prior to delivery, and to reduce the number of repeat courses ideally to one or none.

Both dexamethasone and betamethasone have been explored in randomized trials, with each having similar effects on RDS rates. Studies in France suggested that betamethasone reduced the incidence of periventricular leucomalacia whereas dexamethasone had no such protective effect; however, this may be explained by the presence of sulfating agents used as preservatives in French preparations of dexamethasone. A historical cohort study used multivariate logistic regression analysis to compare the two steroid-treated groups with each other, finding that the risk of neonatal death was lower with betamethasone than with dexamethasone. In other studies dexamethasone has been associated with a decreased incidence of intraventricular haemorrhage compared with betamethasone. At present, there is no clear evidence of benefit of dexamethasone over betamethasone or vice versa. Therefore either betamethasone 12 mg i.m. in two doses or dexamethasone 6 mg i.m. in four doses are the steroids of choice to enhance lung maturation.

Magnesium sulfate

Prior to the 1980s, $MgSO_4$ was widely used in the USA in the intrapartum management of pre-eclampsia and eclampsia and the clinical impression that $MgSO_4$ made induction of labour more difficult led to its evaluation as a tocolytic agent. With the withdrawal of beta-sympathomimetic drugs from the American market and the failure of atosiban to obtain FDA approval, there are no licensed tocolytic drugs available for the American obstetrician to use and $MgSO_4$ is therefore in common use. However, randomized placebo-controlled trials of $MgSO_4$ show no significant short-term delay of delivery, increase in birthweight or difference in perinatal mortality when compared with placebo. $MgSO_4$ is

ineffective at delaying birth or preventing preterm birth, and has no apparent advantages for neonatal and maternal outcomes when used as a tocolytic agent [31]. However, studies where $MgSO_4$ has been compared with sympathomimetics or indometacin have suggested equal efficacy. These two apparently contradictory findings can probably be explained by the lack of power of the studies to detect a significant difference between drugs with little or no efficacy but a high placebo response rate.

In the late 1990s it began to become apparent that infants born to mothers given $MgSO_4$ either to prevent eclampsia or for tocolysis appeared to have a reduced risk of cystic periventricular leucomalacia and cerebral palsy. Since that time a series of randomized controlled trials has been conducted which confirm that the risks of both cerebral palsy and substantial gross motor dysfunction are reduced in the infants of women given $MgSO_4$ just prior to preterm delivery [32]. The beneficial effects of $MgSO_4$ appear to be greatest in women at early gestations, particularly between 24 and 30 weeks. There is probably little or no effect in women beyond 34 weeks. Every effort should therefore be made to offer intravenous $MgSO_4$ to women at risk of preterm delivery before 30 weeks, and if possible to those up to 32 weeks.

The mechanism of action of $MgSO_4$ in the neonatal brain is not clearly established. It may act by blocking *N*-methyl-D-aspartate (NMDA) receptors which mediate glial injury processes in hypoxia–ischaemia. $MgSO_4$ may also act to block calcium influx into damaged cells, to inhibit vasoconstriction, to reduce cytokine-mediated cell damage, and to interact with a wide range of cellular functions through its complex with ATP. $MgSO_4$ has the advantage over corticosteroids of being effective when administered close to the time of preterm delivery. As with its use in the context of pre-eclampisa, $MgSO_4$ has the potential for toxicity in the mother, leading to nausea and vomiting, lethargy, cardiac dysrhythmia, hypotension, urine retention, and respiratory and cardiac arrest. It is therefore essential that the same safeguards are put in place when it is used for cerebral palsy prophylaxis.

The optimal dosing regimen for $MgSO_4$ has not been determined. Different studies have used different protocols, although these were commonly based on the protocols that would be used in pre-eclampsia, or where the drug is used as a tocolytic. A typical protocol would be a 4-g bolus followed by 1 g/hour i.v.

Antibiotics

Analysis of the use of antibiotics in symptomatic preterm labour with intact membranes in women with no clinically defined infection is dominated by the 2001 ORACLE I trial [33]. This showed that administration of antibiotics to women in spontaneous preterm labour with intact membranes does not delay delivery or improve any aspect of neonatal morbidity or mortality. The only short-term positive health benefit is a reduction in maternal infection rates. However, a follow-up study which examined the effect of antibiotics given during pregnancy to mothers in threatened preterm labour on childhood outcomes at 7 years showed an increase in the risk of cerebral palsy associated with antibiotic use. Surprisingly, this was principally in babies who were actually born at term. Taken together these data show that antibiotics should not be prescribed to women in uncomplicated preterm labour with no evidence of infection. However, it is important to emphasize that there are associations between preterm labour, chorioamnionitis, pneumonia, pyelonephritis and lower urinary tract infection. Care needs to be taken to exclude these diagnoses which do require antibiotic therapy to reduce the risk of complications of puerperal sepsis.

Summary box 28.7

- Of women who present to hospital with preterm contractions, 70% will remain pregnant for the next 14 days or more.
- Risk of preterm delivery in women with symptoms can be assessed using either fetal fibronectin or ultrasound measurement of cervical length, but low fibronectin concentration has a better negative predictive value.
- The is little evidence for the benefit of tocolysis.
- Tocolysis may have value in allowing *in utero* transfer and/or steroid therapy, but this is unproven.
- At present the obstetrician (other than in the USA where $MgSO_4$ is still used for its tocolytic action despite evidence that it is ineffecive) has a choice between atosiban or nifedipine. In our current state of knowledge, it is probably reasonable not to use tocolytic therapy at all.
- Women who are considered to be at risk of preterm delivery at 24–35 weeks of gestation should be targeted for a single course of antenatal corticosteroids.
- Every effort should be made to offer intravenous $MgSO_4$ to women at risk of preterm delivery before 30 weeks, and if possible to those up to 32 weeks.
- Antibiotics should not be prescribed to women in uncomplicated preterm labour with no evidence of infection.

Management of inevitable preterm delivery

Rates of neonatal morbidity and mortality are higher in babies transferred *ex utero* to neonatal intensive care units compared with those born in the tertiary referral

centre. Every effort should therefore be made to transfer a woman to an obstetric unit linked to a neonatal intensive care unit prior to a preterm delivery. The introduction of fetal fibronectin testing has reduced the numbers of unnecessary *in utero* transfers.

Cardiotocography monitoring

Except at the extremes of prematurity (perhaps below 26 weeks) there should be continuous electronic fetal heart rate monitoring once preterm labour is clearly established in most cases. The value of cardiotocography (CTG) in preterm labour is less well established than at term. Physiological control of fetal heart rate differs in the preterm fetus compared with the fetus at term, making CTG interpretation difficult. The fetal heart rate baseline is higher, averaging 155 bpm before 24 weeks compared with 140 bpm in a term fetus. Prematurity may normally be associated with a reduction in fetal heart rate baseline variability and be decreased secondary to the effect of fetal tachycardia but without significant hypoxia. The normal sleep–wake cycles seen at term may be absent or less common. Before 30 weeks the frequency and amplitude of accelerations are reduced, whereas fetal heart rate decelerations without contractions often occur in the healthy preterm fetus between 20 and 30 weeks' gestation. Fetal monitoring in labour should be individualized, taking into account the context of preterm delivery, gestational age and estimated fetal weight, the likelihood of chorioamnionitis and any other complications, the overall prognosis for the neonate, and the wishes of the parents. Modern ultrasound-based CTG machines have rendered the use of fetal scalp electrodes largely redundant but they should particularly be avoided in babies below 34 weeks' gestational age.

Vaginal or caesarean section delivery

There is no evidence of benefit for routine delivery by caesarean section where the presentation is cephalic. However, hypoxia is a major risk factor for the development of cerebral damage and there should therefore be a relatively low threshold for delivery by caesarean section in the presence of abnormal fetal heart rate patterns. Nevertheless, preterm labour is usually rapid. The fetal head will be small, and therefore there will be a complete absence of the relative cephalopelvic disproportion seen at term, meaning that there is no need for moulding of the fetal head. In many cases the cervix is already ripe and effaced before the onset of contractions.

The preterm delivery of a breech continues to be an obstetric dilemma. Although it is now established that elective caesarean section is preferable for the term breech, it has proved impossible to undertake randomized trials of caesarean section for the preterm breech. One potential disadvantage of planning to deliver the preterm breech (or indeed cephalic presentation preterm) by elective caesarean section is the high incidence of 'threatened' preterm labour which does not lead to preterm delivery. An aggressive policy of delivering preterm babies by caesarean section has the potential to lead to iatrogenic preterm deliveries. At the other end of the spectrum, caesarean section before term where the breech is already in the vagina may be more traumatic than a vaginal delivery. At present, until further evidence becomes available the mode of delivery of the preterm breech will need to be made on a case-by-case basis by the obstetrician at the time. There is no evidence of benefit from the old practice of elective forceps delivery to protect the fetal head during preterm delivery and episiotomy is rarely required. If instrumental delivery is required for the preterm infant below 34 weeks, ventouse should be avoided. It is usually easy to rotate a preterm fetal head to an occipito-anterior position manually, or it can be done using Kielland's forceps by those who still have the skill. There is now good evidence for the benefit of delayed cord clamping and in waiting at least 30 seconds but no longer than 3 min if the mother and baby are stable. If the preterm baby needs to be resuscitated or there is significant maternal bleeding, the umbilical cord can be briefly milked in the direction of the neonate and then clamped more quickly. If delivery by caesarean section is required, there may be a need to perform a classical caesarean section through a vertical incision in the uterus, particularly at very preterm gestational ages when the lower segment of the uterus is poorly formed. Occasionally, an incision initially made in the lower segment proves to be insufficient for delivery. In these cases the incision can be converted to a J-shaped incision. Particularly at the limits of viability, delivery should be performed has atraumatically as possible, ideally delivering the baby *en caul* in intact membranes. This greatly minimizes the risk of fetal trauma, and nautical folklore has it that a child born *en caul* will never drown at sea.

Summary box 28.8

- There is no evidence of benefit for routine delivery in preterm labour by caesarean section where the presentation is cephalic.
- Except at the extremes of prematurity, there should be continuous electronic fetal heart rate monitoring once preterm labour is clearly established.

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29

Stillbirth

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Stillbirth is defined in the UK as the birth of a baby on or after 24 weeks of gestation who does not show any signs of life [1]. The definition recommended by the World Health Organization (WHO) for international comparison is a baby born with no signs of life at or after 28 weeks' gestation. [2] Stillbirth may be further divided into antepartum and intrapartum. In the UK, *antepartum stillbirth* is defined as the birth of baby on or after 24 weeks of gestational age, showing no signs of life and known to have died before the onset of labour. *Intrapartum stillbirth* is defined in the UK as a baby born at or after 24 weeks of gestational age, showing no signs of life and known to be alive at the onset of labour.

The incidence of stillbirth varies between countries but in the UK affects up to 1 in 200 pregnancies [3]. Despite the many advances in women's health over the past decades, there has been no significant change in the UK incidence of stillbirth, nor has the worldwide incidence of stillbirth changed [4]. The stillbirth rate does vary appreciably between regions. As no one factor leads to stillbirth, the stillbirth rate is considered to be a measure of the general health of women as well as the quality of the provision of antenatal and intrapartum care and as such it has been used as a regional comparator [5].

Stillbirth is a devastating pregnancy outcome. Each stillbirth is a tragedy and brings with it enormous distress and grief, not only for the parents and their extended family and friends but for all the health professionals who care for them. Late-gestation stillbirths are particularly poignant, particularly if not associated with a significant congenital abnormality and if delivery at an earlier gestation would not have been associated with a prohibitive infant mortality or morbidity.

Stillbirth rates

The UK rate of stillbirth is 4.16 per 1000 total births [6]. This mortality rate is higher than that reported by other high-income countries, where worldwide estimates show an average stillbirth rate (at 28 weeks' gestation) of 3.5 per 1000 births (Fig. 29.1). There are 2.6 million stillbirths globally, with more than 7178 deaths daily [2]. The majority of deaths occur in developing countries, with 98% occurring in low- and middle-income countries.

Significant regional differences in the stillbirth rate have been noted [7]. The variation in stillbirth rates may primarily reflect multicultural differences, with women in lower socioeconomic groups having twice the stillbirth risk compared with women from higher socioeconomic groups. Unfortunately, there are significant variations in data collection, definitions (especially gestational age cut-offs) and research methodology that make direct comparisons between countries difficult. Furthermore, variations in access to termination of pregnancy services impact on stillbirth rates that is difficult to account for. Regions with the highest stillbirth rates have some of the most significant limitations in data quality [8]. The number of stillbirths has reduced more slowly than has maternal mortality or mortality in children younger than 5 years, which were explicitly targeted in the Millennium Development Goals [9, 10].

The fact that regional and national differences in stillbirth rate exist and appear to be related to wider factors impacting on women's health suggests that reduction in the rate of stillbirth is possible and potentially a useful indicator of improving socioeconomic and healthcare systems. This is published as the annual rate of reduction,

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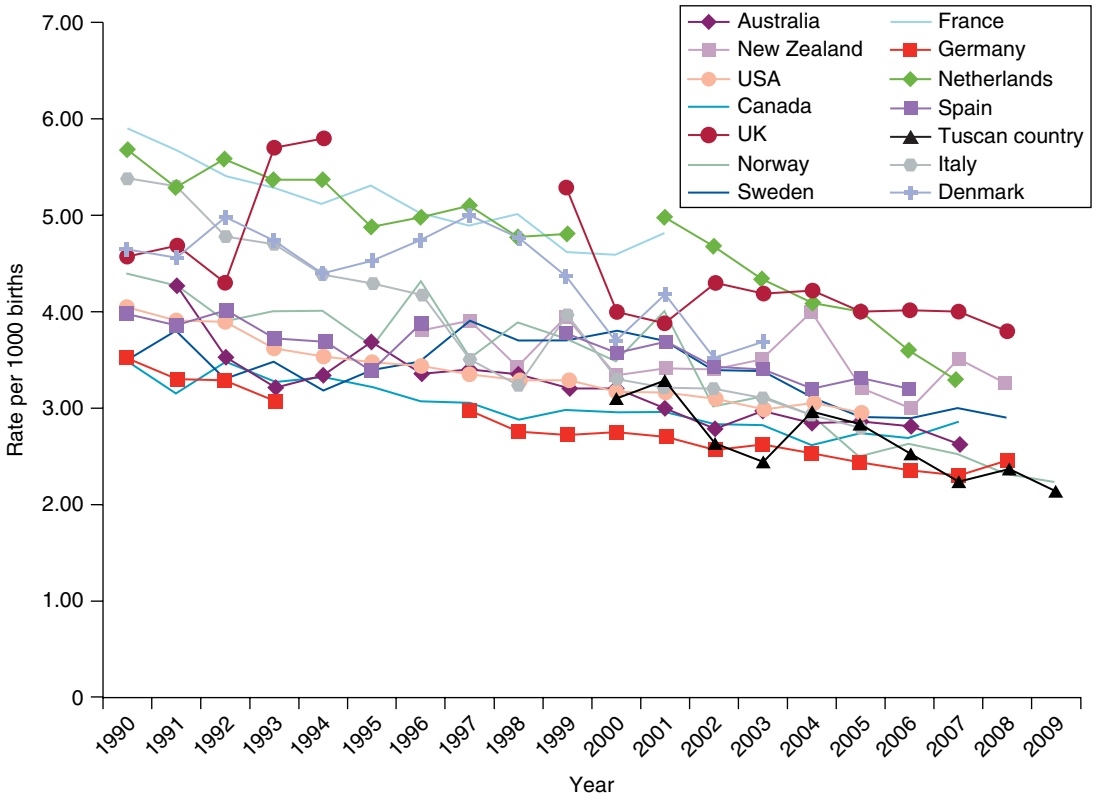

Fig. 29.1 Stillbirth rates and reductions since 1990 in high-income countries. *Source:* Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ* 2005;331:1113–1117. Reproduced with permission of the BMJ Publishing Group Ltd.

and allows comparison over time of the stillbirth rate within one region or country.

Classification of stillbirth

Broadly, stillbirths may be divided into those associated with intrapartum or antepartum death, with further stratification by gestational age. Globally, about half of all stillbirths occur in the intrapartum period, representing the greatest time of risk. The estimated proportion of stillbirths that are intrapartum varies from 10% in developed regions to 59% in South Asia [2,11].

The aetiology of stillbirth is multifactorial and despite intensive investigation of potential causes, many cases remain unexplained. Another complicating factor is that often more than one condition may contribute to stillbirth in an individual case (e.g. preterm rupture of membranes with infection in a fetus with polyhydramnios secondary to gastrointestinal obstruction). Additionally, conditions may be associated with stillbirth without directly causing them (well-controlled gestational diabetes and a cord event).

Several classification systems for causes of stillbirth have been developed. No single classification system is universally accepted as each has its own strengths and weaknesses. There are additional sources of confusion when considering the challenge of classification. First, the definition of stillbirth varies among investigators, countries, health organizations and classification schemes. Second, many systems are designed to classify perinatal mortality and therefore by definition include both stillbirths and neonatal deaths. It is likely that stillbirth and neonatal death have many similar, overlapping but distinct sets of disease states. However, aetiologies for neonatal death may not be relevant to intrauterine fetal demise, for example at 20 weeks of gestation. Additionally, classification systems can include a single aetiology, which is problematic given the complexity of stillbirth, and means that a single distinct cause cannot be attributed to the majority of cases.

A recent systematic review identified 81 systems for classification of causes of stillbirth [12]. Many of these different systems have been developed for different purposes, for example to attribute the most likely cause as part of counselling for grief and future pregnancies, or to assist clinicians in defining best practice, or to develop strategies for the prevention of

stillbirth through health service organizational changes. Consequently, the different classification systems prioritize information in different ways, which means they are not directly comparable.

There are national and international drivers to reduce the stillbirth rate. One of the key factors that has been highlighted is the importance for healthcare systems of understanding the changes and measures that need to take place to improve stillbirth rates, by studying attributable causes over time. To facilitate this, a uniform system of classification is required. The perfect system does not exist given the complexity of the aetiology of stillbirth. The UK has recently adopted the Frøen–Codac 2009 classification system [13] for use in national perinatal mortality surveillance. This classification system has been shown to record the primary cause of 46–47% of all stillbirths as 'unknown' [14, 15]. This system is designed to be applicable to high and low socioeconomic nations and involves detailed recording and sub-analysis.

Alternative classification systems include Wigglesworth [16] (66.2% of stillbirths remain unexplained) and relevant condition at death or ReCoDe [17] (Table 29.1). The latter classification mentions the coding of primary and secondary 'causes' of stillbirth, the goal being to identify the relevant conditions present at the time of death *in utero*. It is a hierarchical classification where the hierarchy starts from the conditions directly affecting the fetus and moves 'outward' in anatomical groups. These authors emphasize the important contribution of fetal growth restriction, with approximately 50% of stillbirths associated with fetal growth restriction. The ReCoDe classification may be able to assign a cause for 85% of cases of stillbirth.

Aetiology

Stillbirth has multiple associated maternal and fetal risk factors (Table 29.2). In two-thirds of pregnancies that result in stillbirth, more than one factor is known to be associated with stillbirth and so it is often unclear what the actual cause of death is.

Several risk factors for stillbirth are present prior to pregnancy, including parity, ethnicity, socioeconomic status and mental health problems. Interestingly, the risk for stillbirth and parity is bimodal, with both nulliparity and a parity of three or higher being risk factors for stillbirth. It is likely that the root cause of stillbirth with parity is different in the nulliparous and multiparous woman and that different strategies will be required to address them [18]. In the UK, mothers of African, African-Caribbean and South Asian ethnic origins have been shown to have a higher risk of stillbirth than women of Caucasian origin. First-generation migrants, regardless of ethnic origin, also have a higher risk of stillbirth than women born in and brought up in the UK. Maternal age appears to have a bimodal distribution, with pregnancies in women younger than 25 and older than 35 years of age being at greater risk for stillbirth.

Table 29.1 Classification system according to relevant condition at death (ReCoDe).

Group A: Fetus
1) Lethal congenital anomaly
2) Infection
   2.1) Chronic
   2.2) Acute
3) Non-immune hydrops
4) Isoimmunization
5) Fetomaternal haemorrhage
6) Twin-twin transfusion
7) Fetal growth restriction*

Group B: Umbilical cord
1) Prolapse
2) Constricting loop or knot†
3) Velamentous insertion
4) Other

Group C: Placenta
1) Abruptio
2) Praevia
3) Vasa praevia
4) Other 'placental insufficiency'‡
5) Other

Group D: Amniotic fluid
1) Chorioamnionitis
2) Oligohydramnios†
3) Polyhydramnios†
4) Other

Group E: Uterus
1) Rupture
2) Uterine anomalies
3) Other

Group F: Mother
1) Diabetes
2) Thyroid diseases
3) Essential hypertension
4) Hypertensive diseases in pregnancy
5) Lupus or antiphospholipid syndrome
6) Cholestasis
7) Drug misuse
8) Other

Group G: Intrapartum
1) Asphyxia
2) Birth trauma

Group H: Trauma
1) External
2) Iatrogenic

(*Continued*)

Table 29.1 (Continued)

Group I: Unclassified
1) No relevant condition identified
2) No information available

* <10th customized weight for gestational age centile.
† If severe enough to be considered relevant.
‡ Histological diagnosis.
Source: Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ* 2005;331:1113–1117. Reproduced with permission of the BMJ Publishing Group Ltd.

Table 29.2 Conditions associated with stillbirth.

Infection
Severe maternal illness
Placental infection leading to hypoxaemia
Fetal infection leading to congenital deformity
Fetal infection leading to damage of a vital organ
Precipitating preterm labour with the fetus dying in labour
Maternal medical conditions
Hypertensive disorders
Diabetes mellitus
Thyroid disease
Renal disease
Liver disease
Connective tissue disease (systemic lupus erythematosus)
Cholestasis
Antiphospholipid syndrome
Heritable thrombophilias
Red cell alloimmunization
Platelet alloimmunization
Congenital anomaly and malformations
Chromosomal abnormalities including confined placental mosaicism
Fetomaternal haemorrhage
Fetal growth restriction
Placental abnormalities including vasa praevia and placental abruption
Umbilical cord pathology including velamentous insertion, prolapse, occlusion and entanglement
Multifetal gestation including twin–twin transfusion syndrome and twin reverse arterial perfusion
Amniotic band sequence
Central nervous system lesions

Source: Reddy UM, Goldenberg R, Silver R *et al.* Stillbirth classification: developing an international consensus for research. Executive summary of a National Institute of Child Health and Human Development Workshop. *Obstet Gynecol* 2009;114:901–914. Reproduced with permission of Wolters Kluwer Health, Inc.

One of the main risks for stillbirth is presumed placental dysfunction, which commonly results in impaired fetal growth [3] Very low birthweight (less than 3rd centile) is associated with a 10-fold increased risk of stillbirth [19]. Although placental dysfunction is not currently modifiable, recognition of the association between fetal growth rates and stillbirth allows risk stratification of pregnancies, with greater surveillance of pregnancies with intrauterine growth retardation and consideration of elective delivery timed to allow an appropriate balance between the risk of stillbirth and infant mortality [20].

Specific population attributable risk (PAR) factors for stillbirth have also been defined. The PAR factor score indicates the relative increase in risk of stillbirth associated with specific risk factors when applied to women in higher income countries. PAR factors are particularly important as many of them are potentially modifiable and the score indicates the increased risk of stillbirth related to the risk factor [10] (Fig. 29.1). Key risks include maternal infection, hypertension, diabetes mellitus, underlying chronic diseases as well as nutrition, obesity and smoking. Cigarette smoking is strongly associated with increased risk of stillbirth, with a PAR factor score of 7%. Smoking is known to result in fetal growth restriction, and although the mechanism is uncertain it may be due to an impact on placental function. Cessation of smoking during early pregnancy has been demonstrated to reduce the incidence of intrauterine growth restriction, premature birth and stillbirth [21]. Early pregnancy smoking cessation programmes are therefore important for the health of both mother and child.

Maternal obesity is a particularly important modifiable risk factor. Obesity is associated with a PAR score of 8–18%. Conversely, maternal age over 35 and maternal smoking both had PAR scores of around 7%. The risk of stillbirth is doubled among women with the highest body mass index (BMI) category (2.19, 2.03–2.36) compared with women with a normal BMI. Several pregnancy complications associated with maternal obesity, notably gestational diabetes and pre-eclampsia, have been implicated in fetal death and stillbirth [22]. The method by which obesity leads to stillbirth is unclear, although there are a number of potential mechanisms and it is likely that obesity has its effects via multiple pathways simultaneously [23]. It is well described that obesity during pregnancy increases the risk of gestational diabetes mellitus as well as hypertensive disorders, both pre-existing and gestational. Both gestational diabetes and hypertension are established risk factors for stillbirth [24]. A recent publication from MBRRACE suggests that some cases of stillbirth could have been avoided if gestational diabetes had been diagnosed early at the screening stage and managed appropriately. In some cases of stillbirth, had the pregnancy been screened adequately for gestational

diabetes, the stillbirth might have been avoided [15]. Obesity also increases the risk of hyperlipidaemia during pregnancy. Hyperlipidaemia reduces prostacyclin secretion and enhances peroxidase production. This in turn results in vasoconstriction and platelet aggregation and may contribute to pre-eclampsia through this mechanism [24]. Other conditions such as sleep apnoea are more common in obesity and obese pregnant women have more extended periods of snoring, more apnoea–hypoxia events, and more episodes of oxygen desaturation during sleep than non-obese pregnant women. It is possible that this greater tendency towards sleep apnoea and its consequent hypoxia reduces oxygen delivery to the fetus, thereby increasing the risk of stillbirth [25]. Women with obesity may be less able to perceive changes in fetal movement than women with a normal BMI and it has been suggested that this may lead to delayed presentation with a fetus at risk of antepartum death. Obese women may also experience more difficulty with labour and delivery, and monitoring during labour can be technically challenging in obese women.

Socioeconomic factors are also important in the aetiology of stillbirth. In the UK, pregnancies in women living in areas with the highest levels of social deprivation are over 50% more likely to end in stillbirth or neonatal death compared with births from the least deprived areas [5]. For women who are first-generation immigrants living in socially deprived conditions, the risk of stillbirth is more than twice the rate of stillbirth in women born in the UK, even from the same socioeconomic class and ethnic background [26]. The reasons for this difference are likely multifactorial. There is a greater incidence of obesity, poor nutrition and smoking in the population of women from deprived economic backgrounds and women who are socially disadvantaged are less likely to receive adequate antenatal care. A common factor underlying many stillbirths – the absence or low quality of antepartum and intrapartum care – means that referral for increased supervision is less likely to occur [27].

Finally, domestic abuse is an important aetiological factor. The mechanisms by which domestic abuse contributes to increased perinatal mortality are not fully understood. One possible pathway is a direct effect of blunt physical trauma causing disruption to the placenta and fetal death. A second possible mechanism is elevated maternal stress levels and poor nutrition, both of which are associated with low birthweight or preterm delivery and are well-known risk factors for perinatal and infant mortality. Thirdly, and probably most importantly, a woman who is experiencing domestic abuse may have particular difficulties accessing and using antenatal care services. Ensuring that women who suffer from domestic abuse are able to access antenatal care is a key consideration when designing antenatal care pathways [28].

Diagnosis of intrauterine fetal demise and antepartum stillbirth

Women with intrapartum stillbirth may present with diminished sensation of fetal movements, although it is more common for women to present with a condition associated with intrapartum stillbirth such as pre-eclampsia, chorioamnionitis and placental abruption. Diagnosis of intrapartum fetal death cannot be made clinically or on the basis of cardiotocography. The diagnosis of intrapartum fetal death should only be made by real-time ultrasonography. Ultrasound is required to demonstrate absent fetal cardiac activity [29]. Ultrasound may additionally demonstrate Spalding's sign (collapse of the fetal skull with overlapping bones) or fetal hydrops. Ultrasound is less reliable at detection of occult placental abruption.

Once the diagnosis has been confirmed, the parents can be told prior to delivery, which allows them to be prepared for the stillbirth. It is important to acknowledge emotional responses for all the caregivers following a diagnosis of stillbirth [30]. Telling parents about the diagnosis must be made in a clear and empathic manner. The manner in which the diagnosis is communicated remains with parents and affects the subsequent grief response. One large systematic review demonstrated that responses from parents and staff were often related: the behaviours and actions of staff have a memorable impact on parents while staff described emotional, knowledge and system-based barriers to providing effective care [31].

Management of antepartum stillbirth

In the absence of issues regarding maternal well-being, the choice of induced delivery or waiting for spontaneous labour must be given to couples following the diagnosis of intrauterine fetal demise. Waiting for spontaneous labour carries risks, including maternal disseminated intravascular coagulation (DIC) and chorioamnionitis. The risk of DIC is 10% if the intrauterine death occurred within 4 weeks and rises to 30% after 4 weeks. Maternal haematology, including platelet count, fibrinogen and coagulation studies, should be regularly monitored for the development of DIC [32].

Because of the risk of complications, women should be counselled that induction of labour is generally the safest option and that vaginal delivery is likely the best option for those planning subsequent pregnancies. Induction of labour using mifepristone has been shown to reduce the time from the start of induction until delivery for women in the third trimester. For women with a second-trimester intrauterine fetal death and an unripe cervix, vaginal misoprostol has been shown to be more effective than intravenous oxytocin at inducing labour [33]. However, it is important to note that misoprostol remains unlicensed in the UK for the induction of labour for second-trimester intrauterine death. For women with a previous caesarean section, or uterine scar from other surgery, there is limited evidence to help guide the management of induction of labour. Although most of the evidence of significant risks of induction of labour in women with previous uterine surgery relate to adverse fetal outcomes rather than adverse maternal outcomes, induction of labour following fetal demise using prostaglandin is considered reasonable [34]. Although misoprostol is associated with increased risk of uterine rupture, using lower doses (25–50 μg) will reduce this [35]. An alternative to pharmacological induction of labour is mechanical cervical ripening. This may reduce the risk of uterine rupture from pharmacological agents but the risk of infection and subsequent maternal morbidity may increase [36,37].

Legal considerations following stillbirth

The current law on stillbirth registration is set out in the Births and Deaths Registration Act 1953, amended by the Still-Birth (Definition) Act 1992. The legal definition of stillbirth is 'any child expelled or issued forth from its mother after the 24th week of pregnancy that did not breathe or show any other signs of life'.

A fully registered doctor or midwife must medically certify stillbirth; the doctor or midwife must have been present at the birth or examined the baby after birth. HM Coroner must be contacted if there is doubt about the status of a birth and the police should be contacted if there is suspicion of deliberate action to cause stillbirth. In the UK referrals to the coroner should also occur for an apparently fresh stillbirth not attended by a healthcare professional or should there be any concern regarding potential for criminal act, such as common assault.

Fetal deaths delivered later than 24 weeks that had clearly occurred before the end of the 24th week do not have to be certified or registered. The baby can be registered as indeterminate sex awaiting further tests.

Within the UK, the mother (or father if the couple were married at the time of birth) is responsible for registering the stillbirth, normally within 42 days (21 days in Scotland) but with a final limit of 3 months for exceptional circumstances. Routine birth and parental information is required to register the birth and the birth is entered onto the Stillbirth Register, which is separate from the standard Register of Births. The parents are then issued with a Certificate of Stillbirth and the documentation for burial or cremation. A certificate for cremation cannot be issued before the registration.

Stillbirths are currently not routinely covered by coronial law, except in Northern Ireland. There are examples of parents who have petitioned for the circumstances surrounding the death of their baby to be referred to the coroner (or procurator fiscal in Scotland) when parents have felt that local hospital reviews were inadequate. In some such cases, the coronial reports have highlighted vital gaps in quality of care [38].

Lactation suppression

Suppression of lactation is of psychological importance for some women following the loss of their baby. Simple measures such as a supportive bra, ice packs and analgesics can be used, but up to one-third of women using these measures will experience severe breast pain [39]. It is important to ascertain the mother's wishes: many women desire to suppress lactation, while some women wish to make altruistic donations to breast milk banks.

A single dose of cabergoline (1 mg) seems to be as effective as bromocriptine (2.5 mg twice daily) for 14 days [40] for lactation suppression. Dopamine antagonists may cause transient hypertension and therefore may be contraindicated in patients with hypertension [41].

Psychological aspects

The death of a baby is a profound loss [42]. The grief following the death of a baby may be different from other types of bereavement. From the moment that the pregnancy has been confirmed, the parents envision an entire lifetime for themselves and their baby. These expectations develop during the pregnancy and with the death of their baby, parents lose an entire future [43]. It is important to acknowledge the necessary grief of families and offer appropriate individualized support [44, 45].

There is considerable interpersonal variation in grief and mourning. This is true for different family members and issues can arise between partners when they cannot synchronize their grief and this subsequently may be a source of interpersonal and relationship stress.

Ultimately, this results in a significantly increased risk of relationship breakdown between the parents following stillbirth [46, 47].

Bereavement is also a significant risk factor for development of psychiatric illness. Among mothers, the relative risk of being hospitalized for any psychiatric disorder is highest during the first year after the death of the child but remains significantly elevated 5 years or more after the death [48].

Multiple pregnancy with loss of one of the babies presents particular emotional challenges for families. Parental attachment to surviving babies is often difficult and approximately one-third of couples experience difficulties coping at home following the birth [49]. Informal and formal support for bereaved couples should be offered [50].

Follow-up investigations

Understanding how or why their baby has died can help the parents in their grieving process. Any findings can be used to inform the parents if there is a risk to future pregnancies and the level of this risk and can help identify any additional treatment or surveillance in any future pregnancy. All parents should be offered investigations to help determine the cause of the stillbirth whilst respecting their wishes.

The Royal College of Obstetricians and Gynaecologists (RCOG) has a suggested list of investigations [29].

- Serological investigations include maternal haematological studies and routine biochemistry (may help diagnose and manage pre-eclampsia and its complications, sepsis and intrahepatic cholestasis of pregnancy and identify diabetes), Kleihauer test (fetal–maternal haemorrhage in addition to dose of anti-RhD gammaglobulin), and maternal infection screen (parvovirus B19, rubella, cytomegalovirus, herpes simplex and *Toxoplasma gondii* and others as indicated). Thrombophilia and antiphospholipid screening is currently recommended, although the association between inherited thrombophilias and intrauterine fetal demise is uncertain.
- Antibody screening and anti-Ro and anti-La antibodies will be indicated if there is concern regarding fetal anaemia or hydrops. Parental screening for fetal/neonatal alloimmune thrombocytopenia will be indicated if there is evidence of otherwise unexplained fetal bleeding.
- Cytogenetic analysis should be offered (especially if there is evidence of dysmorphic features or a congenital anomaly) either from samples taken at the time of postmortem or from the placenta or cord at delivery [51].
- Histopathological examination of the placenta is recommended in all cases of stillbirth. Although some reports find causal or contributory placental abnormalities in up to 60% of stillbirths, the significance of such findings in many cases remains uncertain [52].

Parents should be offered full post-mortem examination to help explain the cause of an intrauterine fetal demise as this can provide more information than other (less invasive) tests and can sometimes be crucial to the management of future pregnancies [53]. Post-mortem may not be acceptable to parents because of individual, cultural or religious beliefs and their decision must be respected. Alternative options to invasive post-mortem may be considered, including post-mortem MRI and tissue diagnostics [54,55]. Written consent must be obtained for any invasive procedure on the baby, including tissues taken for genetic analysis. Consent should be sought or directly supervised by an obstetrician or midwife trained in special consent issues and the nature of perinatal post-mortem.

Large-scale studies involving health economics are needed to determine which investigations are most appropriate after stillbirth [56].

Management of a future pregnancy and prevention

There is limited evidence to help guide the timing of subsequent pregnancy. Historical data suggested that pregnancies occurring within 6 months of a stillbirth were associated with increased risks of preterm birth, low birthweight and small-for-gestational-age babies and outcome. However, couples should be reassured that the absolute risk remains low [29, 57–59].

Two interventions may assist in reducing stillbirth: firstly, smoking cessation advice should be offered if indicated and, secondly, overweight women (BMI >30 kg/m^2) should be advised to lose weight [60, 61]. Further advice on adequate nutrition and a healthy lifestyle may also reduce subsequent stillbirth. Global strategies that have been advocated in addition to the above include screening and treatment of syphilis, presumptive treatment for malaria, insecticide-treated mosquito nets, birth preparedness, access to emergency obstetric care, caesarean section for breech presentation, and elective induction for post-term delivery [62].

In a future pregnancy, couples should be offered pregnancy care in a specialist unit with access to obstetrician-led care. Management of the pregnancy will depend on the history of the loss, for example reducing risk of pre-eclampsia by low-dose aspirin, serial growth scans to assess fetal growth in cases of suspected growth restriction

and/or pre-eclampsia, and cervical length assessment and possible cervical cerclage in cases of preterm labour.

Early term induction of labour may be offered especially in cases of previous pre-eclampsia and where there are placental issues including placental abruption, while acknowledging the limited evidence base for this practice [63].

The management of the subsequent pregnancy is important as there is an increased recurrence risk of pre-eclampsia and placental abruption following a stillbirth [64,65]. Additional psychological support is often required [50]. There may also be a delayed grief reaction and an effect on mother–baby bonding [66].

Internationally, there is a focus on reducing the stillbirth rate. The Every Newborn Action Plan has the target of 12 or fewer stillbirths per 1000 births in every country by 2030; 94 mainly high-income countries and upper middle-income countries have already met this target, although with noticeable disparities [9, 67].

Whilst the social and societal benefits in reduction of stillbirth are obvious, the cost–benefit analysis also shows that there may be a significant return on investment for interventions to reduce the number of stillbirths. Improvements in maternal, newborn and child health services could generate as much as 10-fold to 25-fold returns in economic and social benefits [68]. A *Lancet* series makes the case for a more than triple return on investment for prevention of stillbirths, in reducing maternal deaths, newborn deaths and stillbirths. The economic and social benefits associated with reductions in stillbirths compared with the cost of the interventions to achieve this reduction make a powerful case for healthcare investment into this aspect of maternity care [69].

Summary box 29.1

- Stillbirth rates in the UK have not changed significantly over the past 20 years, although national and international agendas have been set to reduce the rates.
- Many stillbirths have been considered 'unexplained' and therefore unavoidable. In many cases, however, risk factors such as obesity, smoking and fetal growth restriction are found and therefore the risks are potentially modifiable.
- Fetal growth restriction is commonly not detected antenatally and strategies to improve detection are needed.

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30

Analgesia, Anaesthesia and Resuscitation

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In consultant-led units more than 70% of obstetric patients require anaesthetic input. This includes labour analgesia, anaesthesia for caesarean delivery and other surgical interventions, input into management of patients requiring critical care, and resuscitation. Because the role of the anaesthetist has expanded, current guidelines suggest that as a minimum there should be dedicated consultant anaesthetic input during the working week, and that elective obstetric work should be separately staffed [1].

Pain

The International Association for the Study of Pain defines pain as 'an unpleasant, subjective, sensory and emotional experience associated with real or potential tissue damage, or described in terms of such damage'. In simple terms, pain is what hurts. More than 95% of women report pain of varying intensity in labour. Melzack [2] measured pain in parturients using the McGill Pain Questionnaire and showed that although scores ranged from mild to excruciating, only pain associated with digit amputation and causalgia was equal to or greater than labour pain, which outscored cancer, post-herpetic neuralgia and pain of fracture.

Although pain may be considered the physiological consequence of normal labour, it may also be the harbinger of pathological processes, such as obstructed labour, fetal malposition, uterine hyperstimulation, uterine rupture or extant pathology such as fibromas or other tumours, haemorrhoids, and adhesions or scarring from previous surgery.

Severe pain stimulates a sympathetic autonomic response the magnitude of which reflects the severity of pain, and is exacerbated by dehydration and exhaustion. It is characterized by hyperventilation, tachycardia, hypertension, increased oxygen and glucose consumption, and vasoconstriction with decreased blood flow across the placenta. Maternal plasma adrenaline and noradrenaline concentrations increase 200% and 600%, respectively, during labour without analgesia. Increased maternal catecholamine levels can be associated with dysfunctional labour [3]. In the presence of maternal disease and/or fetal compromise, such effects are undesirable and under some circumstances may even be life-threatening.

Summary box 30.1

Severe and prolonged pain is associated with sympathetic automomic hyperactivity, increased maternal heart rate and blood pressure, vasoconstriction, increased oxygen consumption and reduced fetal oxygenation.

Non-regional analgesia for labour

Non-pharmacological methods of pain relief include antenatal education, aromatherapy, hypnotherapy ('hypno-birthing'), acupuncture, water injection, water immersion, massage and other relaxation techniques (this list is not exhaustive). A recent review suggests that continous support by a trained support person or 'doula' reduces analgesic requirements, shortens labour, increases satisfaction and improves outcome for the neonate. The effect is greatest if the support is provided by someone who is neither part of the woman's social network nor part of the hospital staff. It is worth noting that the effect is greatest in units where neuraxial analgesia is not routinely available [4]. This bears out the clinical experience that neuraxial analgesia is often requested when one-to-one care is not available. The evidence for other techniques is generally of poor quality, although

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

some, such as water immersion (birthing pools), are very popular and may reduce analgesia requirements.

Entonox (50% N_2O in oxygen) is widely used in the UK. Although 80% of women who use it would do so again, and there is evidence it is effective, it is associated with side effects such as nausea, vomiting and dizziness [5]. Although the use of sevoflurane and other inhalation anaesthetics has been studied, currently they are not part of mainstream clinical practice. Systemic opioids (pethidine and diamorphine) are almost universally available in birthing units in the UK, although evidence suggests that their effect is sedative [6] and that they have no analgesic effect in labour compared with placebo [5]. When offered this form of medication women should be informed of this. Diamorphine may be slightly more effective and may have less effect on the neonate than pethidine and is slowly replacing pethidine in some units in the UK.

Patient-controlled intravenous analgesia (PCA) is an alternative if regional analgesia is contraindicated. The ultrashort-acting opioid remifentanil has theoretical advantages over other opioids owing to its short latency and rapid metabolism. However, respiratory depression occurs in over 30% of women and cases of hypoxic cardiac arrest have been reported. The evidence for analgesic efficacy is modest [7]. If remifentanil PCA is used for labour, pulse oximetry and the continuous presence of trained personnel is mandatory and it should only be used in units where staff are experienced in and regularly care for women with this type of analgesia [1].

Regional analgesia

There is no question that neuraxial blockade (epidural or intrathecal) provides the most effective form of pain relief in labour, and very few women cannot benefit from this form of analgesia (Table 30.1). Based on data from 70% of obstetric units in the UK in 2011, the Obstetric Anaesthetists' Association (www.oaa-anaes.ac.uk) estimated that the average regional analgesia rate in 2007 was 22.7%, although this varied in units that offered the service from 4.1 to 37.6%. Modern regional techniques aim to provide pain relief whilst preserving sensation, minimizing motor blockade (muscle weakness) and reducing the effects on labour. The basis for achieving this is to reduce the dose of local anaesthetic used. Such techniques are frequently referred to as 'low-dose' or 'mobile' epidurals. In 2008, 80% of UK units were using low-dose techniques [8]. Guidance from the National Institute for Health and Care Excellence (NICE) published in 2014 states categorically that low-dose regimens should be used for the initiation and maintainence of analgesia [9]. Methods for reducing local anaesthetic consumption include combining the local anaesthetic with an opioid to achieve a synergistic effect (commonly fentanyl), avoiding conventional test doses (usually high concentrations of local anaesthetics) and using a combined spinal–epidural technique. The latter involves injection of the initial dose into the intrathecal space (a spinal injection) prior to placing an epidural catheter. The intrathecal dose requires one-tenth of the amount of local anaesthetic to be effective and provides almost instantaneous pain relief. The combined spinal–epidural technique is therefore particularly useful in the later stages of labour and in multiparous women in whom rapid labour is anticipated. It may also provide more reliable analgesia throughout labour and the use of combined spinal–epidural analgesia for labour is growing (Table 30.2) [10].

There is growing evidence that the effects of regional analgesia on the progress and outcome of labour are dose related. Systematic review of randomized controlled trials comparing regional and non-regional (opioid) analgesia shows that regional analgesia does not increase the overall risk of caesarean delivery but may be associated with increased caesarean delivery for fetal distress [11]. The effect is the same whether started early or later in labour [12]. Regional analgesia prolongs the second stage of labour (by approximately 15 min) and increases the need for augmentation and the use of instrumental vaginal delivery [11,13]. Evidence from randomized controlled studies suggests that low-dose neuraxial regimens are associated with fewer instrumental deliveries compared with conventional epidural analgesia [14]. Concerns about impaired maternal effort in the second stage of labour have resulted in the widespread habit of discontinuing regional analgesia in late labour [15]. However, a recent review concludes that in the absence of large trials the evidence suggests that all this achieves is poor analgesia in the second stage of labour [16]. Neither is there any evidence to withhold neuraxial analgesia from women in the latent stage of

Table 30.1 Contraindications to regional analgesia.

Absolute
Maternal refusal
Lack of personnel/facilities
Pre-existing coagulopathy
Local infection at insertion site
Raised intracranial pressure (risk of coning)
Drug allergy
Relative
Haemodynamic instability
Anatomical abnormalities
Neurological disorders (medicolegal implications)
Systemic infection

Table 30.2 Single-shot spinal, combined spinal–epidural and epidural techniques.

	Single-shot spinal*	Epidural	Combined spinal–epidural
Onset of action (min)	Fast (1–5)	Slow (10–20)	Fast (1–5)
Median pain score 60–90 min	0	0–3	0
Total drugs dose	Low	High	Low
Observable leg weakness (%)†	100	5–50	0–40
Post-dural puncture headache (%)	1–2	0.3–1.0	0.2–0.7
Hypotension (%)†	20–80	5–10	5–10
Failure (i.e. GA is required) (%)†	1.7–6.0	2–6	0.3–0.7
Pruritus (%)†	50–80	20–80	20–80
Duration (min)	60–240		

*Single-shot spinal anaesthesia dose is two to three times subarachnoid dose of combined spinal–epidural.
†These side effects are dose-dependent with epidural and combined spinal–epidural techniques. High ranges associated with full anaesthesia doses.
Source: Paech M. Newer techniques of labor analgesia. *Anesthesiol Clin North Am* 2003;21:1–17. Reproduced with permission of Elsevier.

labour [9]. Other side effects of regional analgesia include increased use of urinary catheterization, maternal fever (non-infective and believed to be a result of the local anaesthetic) and pruritus due to neuraxial opioids.

Ambulation in labour has not been shown to significantly affect the mode of delivery, However, mobility may decrease analgesic requirements and avoids the risks associated with prolonged recumbency. Mobilizing with regional anaesthesia has been shown to be safe and is viewed positively by women who undertake it [17]. To permit safe ambulation, all delivery unit staff must be appropriately trained and certain conditions must be met (Table 30.3). Motor and proprioceptive block must be excluded. Studies have demonstarated that women themselves can reliably tell if they can ambulate safely [18]. Results are currently awaited from a study comparing upright and recumbent positions in the second stage of labour in nulliparous women with neuraxial analgesia (ISRCTN Registry 35706297).

Summary box 30.2

In the UK, 80% of units now use 'low-dose' epidurals. Reduced doses of local anaesthetics decrease the incidence of motor block, allow ambulation and may diminish the effects on progress of labour and need for assisted vaginal delivery.

There are several obstetric and medical indications for neuraxial block in labour in addition to the need for pain relief (Table 30.4). Cases considered at high risk of requiring intervention for delivery benefit from an indwelling epidural catheter (which has been tested and shown to be effective) that can be rapidly replenished (e.g. in the case of an after-coming twin). Maternal disease in which the effects of pain or the Valsalva manoeuvre associated with pushing may be detrimental will also benefit from regional analgesia in labour. Obesity per se may become a major indication for this type of analgesia, since the whole spectrum of obstetric complications are increased in this group. Difficulties in siting neuraxial blocks make its early use advisable.

Table 30.3 Requirements for safe 'mobile epidurals' in labour.

Cooperative understanding parturient
Presenting part of fetus engaged and well applied to cervix
Minimal or no motor and proprioceptive block
No postural hypotension
Continuous fetal monitoring (cardiotocography) when indicated
Suitable conditions
Good epidural catheter fixation
Attending midwife
Disconnection of intravenous line (bung inserted)
No shoes
Safe, even floor without cables, steps or mats

Table 30.5 lists serious complications of regional blockade. A national survey in the UK carried out by the Royal College of Anaesthetists found that serious complications associated with death or permenent sequelae were rarer than previously estimated [19]. Although approximately 50% of all blocks performed are in the obstetric population, the incidence in this population was low compared with other patient populations possibly due to the general level of good health of obstetric patients. There were no deaths. Overall the incidence of

Table 30.4 Indications for regional analgesia for labour.

Pain relief
Avoid the deleterious effects of pain (maternal exhaustion, raised catecholamines, maternal and fetal acidosis)
Reduce premature urge to push
Anaesthesia for manual removal of placenta
Reduce need for emergency general anaesthesia
Multiple pregnancy (rapid anaesthesia for delivery of after-coming twin if required)
Breech
Suspected cephalopelvic disproportion/macrosomia
? Previous caesarean section
? Obesity
Improve uteroplacental flow/fetal condition
Pre-eclampsia
Preterm labour
Impaired uteroplacental function (poor Doppler/non-reassuring CTG)
Improve maternal condition
Reduces oxygen demand, (especially women with cardiac/respiratory disease)
Reduces circulating catecholamines (especially maternal fixed cardiac output states)
Decreases urge to push (Valsalva manoeuvre) in second stage

Table 30.5 Serious complications of regional blockade.

Complication	Incidence
Cardiovascular collapse	Very rare
High total spinal (relative/absolute overdose of local anaesthetic)	
Local anaesthetic toxicity (inadvertent intravenous administration)	
Infection (epidural abscess)	1 in 145 000
Meningitis	
Epidural haematoma	1 in 168 000
Trauma (direct damage to spinal cord/nerve root damage)	
Permanent	1 in 240 000
Transient	1 in 6700

Source: Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *Anesthesiology* 2006;105:394–399. Reproduced with permission of Wolters Kluwer Health, Inc.

permenent harm in the obstetric population resulting from neuraxial blockade was between 0.3 and 1.24 per 100 000; combined spinal–epidural analgesia was associated with the highest incidence (3.9 per 100 000) and epidurals with the lowest (0.62 per 100 000).

Anaesthesia for caesarean section

The increased use of regional anaesthesia for caesarean section has contributed to the fall in anaesthetic-related maternal mortality. The great majority of anaesthetic-related maternal deaths are due to general anaesthesia, particularly in the emergency situation. General anaesthesia is particularly hazardous in obstetrics because of changes associated with pregnancy that increase the risk of difficult or failed intubation, of hypoxia and of aspiration. General anaesthesia is frequently reserved for the extremely urgent section when the anaesthetist, who may not have previously met the patient, has very little time for assessment. There are concerns that as general anaesthesia is used less and less in obstetrics, skills will dwindle increasing the risks of this type of obstetric anaesthesia. The Royal College of Anaesthetists suggests that more than 95% of elective and more than 85% of emergency cases should be performed under regional anaesthesia [20]. However, in the most urgent cases, up to a 15% rate of conversion to general anaesthesia may be expected. In 2013, only 10% of caesarean sections in the UK were performed under general anaesthesia [21].

The four-grade classification of urgency of caesarean section, endorsed by the Royal College of Obstetricians and Gynaecologists and the Royal College of Anaesthetists and used in the National Sentinel Audit of caesarean sections, should be universally adopted to improve communication especially in the emergency situation [22]. Prior to scheduled surgery, regardless of the type of anaesthetic planned, patients should be fasted (6 hours for solids, 2 hours for clear fluids) and given premedication (oral ranitidine and metoclopramide). Labouring women at risk of caesarean section should be limited to sips of water and given oral ranitidine 150 mg 8-hourly throughout labour. Intravenous ranitidine 50 mg may be given within 30 min of induction whereas sodium citrate, which is only effective for 15–30 min, should be given immediately before induction of general anaesthesia. In the emergency situation, intrauterine resuscitation of the fetus (Table 30.6) should be undertaken during preparation for anaesthesia [23]. Oxygen therapy in the presence of profound fetal distress is still recommended, although the evidence is not compelling [24].

Table 30.6 Intrauterine resuscitation.

Relieve aortocaval compression: left lateral position ≥15° tilt, uterine displacement
Ensure effective analgesia: top up epidural (decreases maternal catecholamine levels and improves uteroplacental blood flow)
Rapid intravenous infusion (transiently decreases uterine activity)
Stop Syntocinon infusion (often overlooked)
Tocolysis (terbutaline/glyceryl trinitrate)
High-flow maternal oxygen (optimize oxygen delivery

Regional anaesthesia is recommended in severe pre-eclampsia as haemodynamic stability is better maintained than in the normotensive patient and because the risks of general anaesthesia are further increased in pre-eclampsia. Abnormal placentation is no longer seen as an absolute indication for general anaesthesia. A combination of general and neuraxial anaesthesia allows the mother to be awake for delivery, after which general anaesthesia can be induced for caesarean hysterectomy or other complicated surgery. Similarly for fetal surgery, or other surgery during pregnancy, combined general anaesthesia and regional blockade is frequently used. The combined spinal–epidural technique allows effective anaesthesia to be prolonged as long as required and the epidural component can be used to provide postoperative analgesia.

Summary box 30.3

The great majority of direct anaesthetic-related maternal deaths are associated with emergency general anaesthesia. The Royal College of Anaesthetists recommends that more than 85% of emergency and more than 95% of elective caesarean sections should be performed under regional anaesthesia.

Cardiopulmonary resuscitation and critical care

Cardiac arrest during pregnancy is rare. The commonly quoted incidence is 1 in 30 000 pregnancies. A recent survey from the USA found the incidence of cardiac arrests during hospitalization for delivery to be much higher than this (1 in 12 000). Nearly 60% of cases survived to hospital discharge [25]. The most common conditions associated with cardiac arrest were mainly obstetric: haemorrhage, amniotic fluid embolism, thromboembolism and sepsis. In a recently completed study in the UK, the single most common cause of cardiac arrest leading to peri-mortem caesarean section was anaesthetic catastrophe (Virginia Beckett, personal communication). The majority of fatal cardiac arrests in the UK are caused by 'indirect' causes, the leading one being cardiac disease. Although the overall maternal mortality in the UK has declined, there has been no change in that from indirect deaths since 2003 [26]. In the obstetric patient, pulseless electrical activity/asystole is more common than ventricular fibrillation arrest. Hypovolaemia due to haemorrhage is probably the commonest cause. Pulmonary embolism is another cause of pulseless electrical activity. Amniotic fluid embolism appears to be causing an increasing number of maternal deaths in the UK, and typically presents with sudden cardiovascular collapse often associated with profound hypoxia. Local anaesthetic toxicity and magnesium overdose also occur in this population. Lack of knowledge of resuscitation (both basic and advanced) among healthcare professionals caring for maternity patients has repeatedly been highlighted [27]. In consecutive reports on maternal mortality in the UK, resuscitation skills were judged to be poor in a significant number of cases. One of the 'top ten' recommendations of the 2003–2005 report was that 'All staff must undertake regular, written, and audited training for the improvement of basic, immediate and advanced life support skills'. A growing number of courses are available. Training should be supplemented by regular team practice of cardiac arrest drills to ensure appropriate care is delivered [28].

Resuscitation in pregnancy is different from resuscitation in the non-pregnant adult. Cardiopulmonary resuscitation is both more difficult to perform and less effective in the obstetric patient. Occlusion of the inferior vena cava is the norm in the supine position at term and results in a more than 60% reduction in venous return. In order to reduce aortocaval compression, uterine displacement or pelvic tilt is required. Because of the importance of uninterrupted cardiac compressions and because effective cardiac compression becomes progressively more difficult the more the patient is tilted, uterine displacement is the preferred method [29]. Hypoxia develops more quickly due to increased oxygen requirements and decreased oxygen reserves. Artificial ventilation becomes more difficult due to enlarged breasts and decreased lung compliance resulting from the enlarging uterus. Reduced lower oesophageal sphincter tone increases the risk of regurgitation, requiring endotracheal intubation as early as possible.

Speed of response is crucial to the outcome for both the woman and her child [30]. Minimizing aortocaval compression, airway protection, normal hand position for cardiac compressions (modified hand position now not recommended by the Resuscitation Council) and early uterine evacuation form the basis for resuscitation of the pregnant patient at term (Table 30.7). It is now

Table 30.7 Cardiopulmonary resuscitation in the pregnant patient.

Basic life support
Left uterine displacement (manual displacement/tilt/wedge)
Hands higher on sternum
Cricoid pressure to prevent regurgitation*
Advanced life support
Secure airway early
Early evacuation of uterus (within 5 min of cardiac arrest)
Remove fetal monitors prior to defibrillation
Avoid lower limb intravenous access
(Drug doses should not be altered)

*Cricoid pressure is recommended by UK authorities but not by those in the USA [29,30].

Table 30.8 Indications for transfer to an intensive care facility.

General
Lack of trained staff/facilities on delivery suite
Cardiovascular
Use of inotropes
Management of pulmonary oedema
Respiratory
Mechanical ventilation
Airway protection
Tracheal toilet
Renal
Renal replacement therapy
Neurological
Significantly depressed conscious level
Miscellaneous
Multiorgan failure
Uncorrected severe acidosis
Hypothermia

recommended that early (within 5 min) evacuation of the uterus should be considered, regardless of fetal viability, to improve chances of successful resuscitation, from about 20 weeks [29]. Uterine evacuation in this situation will not require haemostasis until circulation is restored. The delay caused by aseptic precautions may itself be fatal. A scalpel and a pair of forceps plus gloves for the operator's protection may be all that is required [29,30]. A midline incision has been recommended as it is helped by the separation of the recti abdomini muscles that occurs in later pregnancy; however, if staff involved are more familiar with a Pfannenstiel incision, then this should be used.

A report on obstetric admissions to intensive care indicates that the majority of obstetric admissions are post partum (>80%). Of these, much the most common cause was haemorrhage (>30%). In contrast, among antenatal admissions, non-obstetric conditions predominated, with pneumonia being the single most common cause [31]. The early provision of critical care to the sick parturient can reduce morbidity and mortality. The anaesthetist on the delivery suite must identify as early as possible when transfer to intensive care is required (Table 30.8).

The limits to what care can be safely provided on the delivery suite will be determined by local resources. The effects of intensive care management on the fetus must be considered [32]. Maternal oxygen-carrying capacity should be optimized, the effects of pharmacological agents on uteroplacental blood flow considered, adequate maternal nutrition ensured and radiological investigations minimized. Post partum there are obvious advantages to keeping the mother and infant together. Recommendations on the standards for critical care on delivery suites have been defined [32]. The role of the obstetric anaesthetist in neonatal resuscitation is poorly defined. There is general agreement that the first responsibility is to the mother [33,34]. However, since up to one-third of cases where neonatal resuscitation is required occur apparently without warning, there is also consensus that all those likely to be present at delivery, including the obstetric anaesthetist, should have undergone training in neonatal resuscitation.

Summary box 30.4

During cardiopulmonary resuscitation in the pregnant patient, aortocaval compression must be minimized using uterine displacement, the airway protected from aspiration by intubation, and the uterus emptied within 5 min of cessation of circulation to maximize chances of maternal and fetal survival.

Summary

The majority of parturients require anaesthetic input. Regional analgesia has been modified to reduce adverse effects on the progress and outcome of labour. By increasing consultant anaesthetic presence on the delivery suite and by minimizing the use of general anaesthesia for emergencies, anaesthetic-related maternal mortality and morbidity has been reduced. At-risk parturients should be identified and referred for antenatal anaesthetic input. The anaesthetist plays a key role in the provision of critical care for the obstetric patient.

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Part 6

Postnatal Care

31

Puerperium and Lactation

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The puerperium is the period from delivery of the placenta until 6 weeks after delivery. It is a time of enormous importance to the mother and her baby and yet it is an aspect of maternity care that has received relatively less attention than pregnancy and delivery. During the puerperium the pelvic organs return to the non-gravid state, the metabolic changes of pregnancy are reversed and lactation is established. In the absence of breastfeeding, the reproductive cycle will recommence within a few weeks. The puerperium is a time steeped in myth, cultural dogma and rituals, and indeed many of the medical recommendations about the puerperium have developed as adaptations of socially acceptable traditions rather than science.

The puerperium is also a time of psychological adjustment. While most mothers' elation following the arrival of a newborn baby is obvious, the transition to becoming a responsible parent and anxiety about the child's welfare will influence the mother's ability to cope. These anxieties may be compounded if she has had a difficult labour or if she has any medical complications. However, the majority of women are subject to another problem that new mothers find very difficult to cope with and this is the plethora of well-meaning but conflicting advice from doctors, midwives, relatives and friends. These cultural influences may be in conflict with the mother's own beliefs and so whilst it is understandable that these individuals wish to support the mother, it is extremely important that an atmosphere be created whereby a mother can learn to handle her baby with confidence in her own way. Midwifery and obstetric staff play an important role in supporting this philosophy. In caring for a woman during the early puerperium, the role of the obstetrician and midwife is to monitor the physiological changes of the puerperium, to diagnose and treat any postnatal complications, to establish infant feeding, to give the mother emotional support and to advise about contraception and other measures that will contribute to her continuing health. It is important to bear in mind that maternal morbidity and mortality are an ongoing risk in the puerperium and hence its importance cannot be understated.

Physiology of the puerperium

Two major physiological events occur during the puerperium: the establishment of lactation and the return of the physiological changes of pregnancy to the non-pregnant state. Some changes occur quite rapidly (within 2 weeks) whilst others take 6–12 weeks to complete.

The uterus

The crude weight of the pregnant uterus at term is approximately 1000 g while the weight of the non-pregnant uterus is 50–100 g. From a clinical perspective the uterine fundus is no longer palpable abdominally by 10 days after delivery. By 6 weeks after birth, the uterus has returned to its normal size. The cervix is very flaccid after delivery, due to the reduction in collagen content as a result of cervical remodelling prior to labour, but within a few days returns to its original state. The placental site in the first 3 days after delivery is infiltrated with granulocytes and mononuclear cells and this process extends into the endometrium and the superficial myometrium. By the seventh day, there is evidence of regeneration of endometrial glands and by day 16 the endometrium is fully restored. Decidual necrosis begins on the first day and by the seventh day a well-demarcated zone exists between necrotic and viable tissue. The presence of mononuclear cells and lymphocytes persists for about 10 days and it is presumed that this acts as some form of antibacterial barrier. Haemostasis immediately after birth is accomplished by arterial smooth muscle contraction and compression of vessels by the uterine muscle.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

The vessels in the placental site are characterized during the first 8 days by thrombosis, hyalinization and obliterative fibrinoid endarteritis. Immediately after delivery, bleeding lasts for several hours and then rapidly diminishes to a red-brown discharge by the third or fourth day after birth. This vaginal discharge is known as lochia and after the third or fourth day becomes mucopurulent and sometimes malodorous. This is known as the lochia serosa and it has a mean duration of 22–27 days. However, 10–15% of women will have lochia serosa for at least 6 weeks [1]. Not infrequently, there is a sudden but transient increase in uterine bleeding between 7 and 14 days after delivery. This corresponds to the shedding of the slough over the placental site and as myometrial vessels are still at this stage larger than normal, this accounts for the dramatic bleeding that can occur. However, although some women are alarmed by this event, it is self-limiting and subsides within 1–2 hours. The endometrium will proliferate from the basal layers of the decidua but this is influenced by the method of infant feeding. If lactation is suppressed, the uterine cavity may be covered by new endometrium within 3–4 weeks; however, if lactation is established, endometrial growth in the majority of women may be suppressed for as long as breastfeeding continues. This is because lactation suppresses ovarian function and so a physiological hypo-oestrogenic state is created that prevents endometrial cell growth

Ovarian function

Women who breastfeed their infants will be amenorrhoeic for long periods, often until the child is weaned. However, in non-lactating women, ovulation may occur as early as 27 days after delivery, although the mean time is approximately 70–75 days. Among those women who are breastfeeding, the mean time to ovulation is 6 months. Menstruation resumes by 12 weeks after birth in 70% of women who are not lactating and the mean time to first menstruation is 7–9 weeks. The risk of ovulation within the first 6 months after delivery in women exclusively breastfeeding is between 1 and 5% [2]. The hormonal basis of puerperial ovulation suppression in lactating women appears to be the persistence of elevated serum prolactin levels, which may suppress adipoleptin secretion from adipocytes. Prolactin levels fall to the normal range by the third week after birth in non-lactating women but remain elevated to 6 weeks after birth in lactating women. Prolactin is then only elevated during episodes of suckling.

Cardiovascular and coagulation systems

Changes take place in the cardiovascular and coagulation systems that have practical and clinical implications and these are summarized in Table 31.1. Although both heart rate and cardiac output fall in the early puerperium, there may be an early rise in stroke volume and, together with the rise in blood pressure due to increased peripheral resistance, it is a time of high risk for mothers with cardiac disease and these mothers require extra supervision at this time (see Chapter 8). Although by 6 weeks a woman's body has changed physically back to the non-pregnant state, it can be seen from Table 31.1 that cardiac output may remain elevated for up to 24 weeks after birth. During the immediate postnatal period, fibrinolytic activity is increased for 1–4 days before it returns to normal by 1 week. Platelet counts are normal during pregnancy but there is a sharp rise in platelets after delivery, making it a time of high risk for thromboembolic disease [3].

Urinary tract

During the first few days, the bladder and urethra may show evidence of mild trauma sustained at delivery and these changes are usually associated with localized oedema. These are transient and do not remain in evidence for long. The changes that occur in the urinary tract during pregnancy disappear in a similar manner to other involutional changes and within 2–3 weeks the hydroureter and pelvic dilatation in the kidney are almost eliminated and completely return to normal by 6–8 weeks after birth.

Table 31.1 Changes in the cardiovascular and coagulation systems during the puerperium.

	Early puerperium	Late puerperium
Cardiovascular		
Heart rate	Falls: 14% by 48 hours	Normal by 2 weeks
Stroke volume	Rises over 48 hours	Normal by 2 weeks
Cardiac output	Remains elevated and then falls over 48 hours	Normal by 24 weeks
Blood pressure	Rises over 4 days	Normal by 6 weeks
Plasma volume	Initial increase and then falls	Progressive decline in first week
Coagulation		
Fibrinogen	Rises in first week	Normal by 6 weeks
Clotting factors	Most remain elevated	Normal by 3 weeks
Platelet count	Falls and then rises	Normal by 6 weeks
Fibrinolysis	Rapid reversal of pregnancy inhibition of tissue plasminogen activator	Normal by 3 weeks

Weight loss

There is an immediate loss of 4.5–6 kg following birth due to the baby, the placenta, amniotic fluid and blood loss that occurs at delivery. By 6 weeks after delivery, 28% of women will have returned to their pre-pregnancy weight; those women who did not have excessive weight gain in pregnancy should have returned to their normal pre-pregnancy weight by 6 months after delivery. Women with excessive weight gain in pregnancy (>15 kg) are likely to find that at 6 months they still have net gain of 5 kg, which may persist indefinitely [4]. Breastfeeding has no effect on postpartum weight loss unless lactation continues for 6 months [5]. Diet and exercise have no effect on the growth of infants who are being breastfed and women can therefore be encouraged to return to normal activity and to regain their weight even though they are lactating [6].

Thyroid function

Thyroid volume increases by approximately 30% during pregnancy and this returns to normal over a 12-week period. Thyroxine and triiodothyronine return to normal within 4 weeks after birth.

Hair loss

Hair growth slows in the puerperium and women will often experience hair loss as temporarily more hair is lost than regrown. This is a transient phenomenon but it is important for women to realize that this may take between 6 months and a year to return to normal. The low levels of circulating oestrogen are the aetiology of this phenomenon and so it is more common in breastfeeding mothers.

Management of puerperium

The morbidity associated with the puerperium is underestimated and an important review showed that mothers have high levels of postpartum problems. Nearly one-third (31%) of women felt that they had major problems for up to 8 weeks after birth. In trying to reduce the impact of this morbidity, there are a number of principles which need to be applied in planning postnatal care.

1) *Continuity of care*. An ideal pattern of care is one that offers continuity from the antenatal period through childbirth and into the puerperium involving the smallest team of health professionals with which the mother can empathize.
2) *Mother–infant bonding*. It is now well established that mothers and their partners should be able to hold and touch their babies as soon as possible after delivery. Good postnatal facilities that allow rooming-in, privacy and the opportunity for close contact play an important part in helping parents have a good experience of early parenting.
3) *Flexible discharge policies*. The optimum duration of postnatal stay varies with the needs of the individual mother and her baby. Some mothers will elect to have a home confinement, some will elect to have early discharge at 6 hours postnatally and others may have greater needs, particularly those who have had complicated deliveries and those who wish to establish breastfeeding before going home. The current pressure on maternity services in the Western world means that any length of stay in hospital to respond to maternal needs as opposed to medical necessity has curtailed this flexibility. While this has not had an impact on successful breastfeeding, psychological morbidity may have increased.
4) *Emotional and physical support*. Mothers require help and support after childbirth and this may come from partners, relatives and friends. Good professional support is also important and good communication between hospital staff, community midwives, general practitioner (GP) and health visitor is essential.

Routine observations

During the patient's stay in hospital, regular checks are made of her pulse, temperature, blood pressure, fundal height and lochia and any complaints noted. The perineum should be inspected daily if there has been any trauma and the episiotomy or other wounds checked for signs of infection. It is also important that urinary output is satisfactory and that the bladder is being emptied completely. These observations are necessary to give the earliest warning of any possible complications.

Ambulation in the puerperium

It is now well established that early mobilization after childbirth is extremely important. Once the mother has recovered from the physical rigours of her labour, she should be encouraged to mobilize as soon as possible. The physiotherapist has an important role to play in returning the patient to normal health during the puerperium. Leg exercises will be particularly important to encourage venous blood flow in any mother who has been immobilized in bed for any reason. Exercises to the abdominal and pelvic floor muscles are most valuable in restoring normal tone, which may have been lost during pregnancy.

Complications of the puerperium

Serious and sometimes fatal complications may arise during the puerperium. The most serious complications are thromboembolism, infection and haemorrhage, but mental disorders and breast problems occur also.

Thrombosis and embolism

The MBRRACE-UK 2014 report [7] shows that pulmonary embolism is still the major cause of death in the puerperium. The rate of death has remained unchanged for many years and approximately 50% of deaths occur post partum (Table 31.2). The authors suggest that it is unsurprising that there has been little impact on these figures because of the direct association with obesity. Some 49% of women who died of pulmonary embolism were either overweight or obese and this has become a major international issue. Data from the USA suggest that their maternal mortality rate is rising and one accepted factor is obesity. Over 60% of women falling pregnant in the USA are seriously overweight. Other factors are also contributing to the increased risk, including increased maternal age, changing ethnicity, and increasing medical complications of pregnancy.

All pregnant women should be assessed for venous thromboembolism (VTE) during pregnancy and this should be repeated either during or after birth to determine their suitability for thromboprophylaxis. If thromboprophylaxis is deemed appropriate, moderate-risk women should receive this for 10 days and high-risk women for 42 days.

Table 31.2 Deaths from pulmonary embolism reported by MBRRACE-UK.

Triennium	Total deaths	Rate per 100 000	Postnatal	Rate per 100 000
1985–1987	30	1.3	13	0.6
1988–1990	24	1.0	11	0.5
1991–1993	30	1.3	17	0.7
1994–1996	46	2.1	25	1.1
1997–1999	31	1.5	13	0.6
2000–2002	25	1.3	16	0.8
2003–2005	33	1.56	15	0.8
2006–2008	18	0.79		
2010–2012	26	1.08		

Table 31.3 Deaths from puerperal sepsis as reported by MBRRACE-UK.

Triennium	Total deaths	Rate per 100 000	Postnatal	Rate per million
1985–1987	09	0.4	2	0.9
1988–1990	17	0.72	4	1.7
1991–1993	15	0.65	4	1.7
1994–1996	16	0.73	11	5.0
1997–1999	18	0.85	4	1.9
2000–2002	13	0.65	5	2.5
2003–2005	18	0.85	3	1.4
2006–2008	26	1.13		
2010–2012	12	0-5		

Puerperal infection

Puerperal pyrexia, which is potentially fatal, may have several causes but is an important clinical sign that merits careful investigation. Infection may occur in several sites and each needs to be investigated in the presence of elevated temperature.

Genital tract infection

Genital tract infection continues to be a life-threatening problem for women and Table 31.3 shows the risk of puerperal sepsis and maternal death over the last years of maternal death reports. The most virulent organism is β-haemolytic *Streptococcus* but more commonly *Chlamydia*, *Escherichia coli* and other Gram-negative bacteria will be the infective agents. Table 31.4 summarizes the main causes of postnatal pyrexia. Early diagnosis and treatment are imperative if the long-term sequelae are to be avoided. Whilst it is encouraging that rates of death have halved in the last 5 years, they have still not returned to those of 1985. Vigilance with diagnosis and rapid administration of antibiotics are important strategies, as is the involvment of infectious disease consultants, especially when a woman fails to respond to the antibiotic of first choice.

Table 31.4 Causes of postnatal pyrexia.

Urinary tract infection
Genital tract infection
Endometritis
Infected episiotomy
Mastitis
Wound infection following caesarean section
Deep venous thrombosis
Other infection, e.g. chest infection, viral infections

Patients may present more acutely ill with what is now known as a systemic inflammatory response. The presence of any two of new onset of confusion, sustained heart rate of more than 90 bpm, respiratory rate of greater than 20 breaths/min and a temperature of more than 38.3°C or less than 36°C confirms the diagnosis. Immediate administration of antibiotics should be commenced without waiting for investigation results. If any one of the following signs is present, a diagnosis of severe sepsis should be made with consideration of transfer to intensive care:

1) systolic blood pressure less than 90 mmHg;
2) heart rate more than 130 bpm;
3) oxygen saturation less than 91%;
4) respiratory rate more than 25 per min;
5) responds only to pain or unresponsive.

Urinary tract infection

This is a common infection in the puerperium following the not infrequent use of catheterization during labour. Some women will also develop urinary retention and require indwelling catheters. *Escherichia coli* is the commonest pathogen and again early treatment is advised.

Respiratory infection

Chest infections are not normally a serious problem in the puerperium, although recent outbreaks of potentially fatal influenza viruses have increased the level of concern. The infrequent use of general anaesthesia has reduced the risk of chest infection in the immediate postpartum period but any woman who presents with signs of a serious chest infection must have the possibility of an underlying pulmonary embolus excluded.

Other causes

Any surgical wound should be examined for evidence of infection and this is obviously important following caesarean section. Wound infection may manifest itself as a reddened tender area around the incision, with associated swelling and induration. Treatment will depend on the extent and severity of the infection. If the infection is well localized, it may discharge spontaneously but an abscess may require incision and drainage. Broad-spectrum antibiotics will be required and bacteriological specimens should be sent for examination. It is occasionally necessary to re-suture wounds after infection but often wounds will granulate from the base and heal spontaneously. The legs should always be inspected if a puerperal pyrexia is present because of the risk of thrombophlebitis and it may also be a sign of deep venous thrombosis. The breasts should be examined for signs of breast infection, although breast abscess formation is very unusual before 14 days after birth.

Urinary complications

Other than infection, urinary retention is the commonest complication following delivery, especially if there has been any trauma to the urethra and resulting oedema round the bladder neck. A painful episiotomy may make it very difficult for women to spontaneously micturate and retention of urine may occur. Following epidural anaesthesia, there may be temporary interruption of the normal sensory stimuli for bladder function and over-distension of the bladder may occur. It is extremely important that in the immediate postnatal period urinary retention is avoided as over-distension may lead to an atonic bladder, which is then unable to empty spontaneously. If the bladder is distended, it is usually palpable abdominally but if this is not the case or the clinician is uncertain of the abdominal findings, an ultrasound scan should be performed to determine the volume of urine retained in the bladder. The treatment of urinary retention is to leave an indwelling catheter on continuous drainage for 48 hours. The patient can be ambulant during this time. After the bladder has been continuously emptied, the catheter can be removed and then the volumes of urine passed can be monitored. If there is any suspicion that further retention is occurring, then a suprapubic catheter should be inserted so that the bladder can undergo a further period of continuous drainage and then intermittent clamping of the catheter can be instituted until normal bladder function returns.

Incontinence of urine

Urinary incontinence will occur in many women immediately following delivery and approximately 15% of women will have urinary incontinence that persists for 3 months after birth [8]. However, a study by Glazener *et al*. [9] showed that three-quarters of women with urinary incontinence 3 months after childbirth still have this 6 years later. A further follow-up study has shown that this does not improve after 12 years, with 75% still experiencing urinary incontinence [10]. Urinary incontinence is more frequently seen following instrumental delivery and least frequently after elective caesarean section. Urinary fistulae are uncommon in obstetric practice today, although direct injury from obstetric forceps may occasionally occur. Complications to the ureter are most commonly seen after a complicated caesarean section, when ureteric injury may either result in a ureteric fistula or ureteric occlusion. Women with this type of urinary problem should not be managed by obstetricians but should be referred to a urological colleague for surgical management.

Incontinence of faeces

It is now recognized that 35% of women undergoing their first vaginal delivery develop anal sphincter injury

[11,12]. Approximately 10% will still have anal symptoms of urgency or incontinence at 3 months after birth. Again, in the 12-year follow-up study by Glazener *et al.* [10], there was no improvement in this anal incontinence rate over time and at 6 years the faecal incontinence rate actually increased to 13%. The aetiology of this type of anal sphincter trauma is complex in the same way that mechanisms which maintain continence are complex, but include instrumental delivery, prolonged second stage of labour, birthwieght over 4.0 kg, occipito-posterior position and episiotomy. Instrumental delivery is a recognized cause of trauma and randomized trials suggest that the use of vacuum extraction is associated with less perineal trauma than forceps delivery [13,14]. The incidence figures confirm this: forceps delivery is associated with a 32% incidence of anal incontinence compared with a 16% incidence for vacuum extraction. The incidence of third- and fourth-degree tears varies enormously from centre to centre, suggesting that the clinical ability to recognize this type of trauma may vary. In those women who have a recognized anal sphincter rupture, 37% continue to have anal incontinence despite primary sphincter repair [15]. A recent Cochrane review of the role of caesarean section in avoiding anal incontinence concluded that there is insufficient evidence to recommend this [16].

Secondary postpartum haemorrhage

Delayed postpartum bleeding occurs in 1–2% of patients. It occurs most frequently between 8 and 14 days after birth and in the majority of these cases it is due to sloughing of the placental site. However, if this bleeding is not self-limiting, further investigation will be required. Ultrasound examination of the uterine cavity will usually determine whether there is a significant amount of retained products, although it can be difficult to distinguish between blood clot and retained placental tissue. Suction evacuation of the uterus is the treatment of choice and, if this is required, it is imperative that antibiotic cover is given. If curettage is not required immediately to arrest bleeding, it is best to start antibiotics at least 12 hours beforehand. This will reduce the risk of endometritis leading to uterine synechae. A combination of metronidazole and co-amoxiclav can be used in those patients who have endometritis without retained products of conception. In those who do have retained products who require curettage, intravenous antibiotics in the form of metronidazole and a cephalosporin, clindamycin or gentamicin are the antibiotics of choice. Great care must be taken at the time of curettage as the infected uterus is soft and easy to perforate. Rarely, these measures do not result in cessation of bleeding, and in life-threatening circumstances embolization of the uterine arteries may be effective in controlling the bleeding, as may the use of uterine tamponade using a Foley catheter balloon. If these techniques fail, then hysterectomy as a life-saving procedure may be needed.

It is important to remember that choriocarcinoma may present in this manner and, if suspected, can be diagnosed by elevated levels of human chorionic gonadotrophin. Rarely, a patient with a coagulopathy may present with a secondary haemorrhage.

Puerperal psychological disorders

Mild pyschological disturbance and transient depression are extremely common in the few days after birth. This transient state of tearfulness, anxiety, irritation and restlessness has been variously described as the 'blues' and it may occur in up to 70% of women. It usually resolves by day 10 after delivery and is probably associated with disruptive sleep patterns and the adaptation and anxiety of having a newborn baby. The changes in steroid hormone levels that occur immediately following delivery are not correlated with this transient depressive state, and because it is transient no therapy is needed. Postpartum depression and psychosis are dealt with in Chapter 14.

Counselling of patients after perinatal death

See Chapter 29.

Drugs during lactation

Drugs taken by a breastfeeding mother may pass to the child, and it is important to consider whether particular drugs will have any effect on the fetus. This is often a difficult problem and the reader is referred to Schaefer *et al.* [17] for more information.

Infant feeding

The major physiological event of the puerperium is the establishment of lactation. Some mothers in developed countries still reject breastfeeding in favour of artificial feeding but there is increasing evidence of the important short- and long-term benefits of breastfeeding. The World Health Organization (WHO) now recommends exclusive breastfeeding for 6 months.

Advantages of breastfeeding

Nutritional aspects of breast milk

Human milk does not have a uniform composition: colostrum differs from mature milk and the milk of the early puerperium differs from the milk of late lactation. Indeed, the content of milk varies at different stages of

the same feed. Nevertheless, there are substantial differences in the constituent concentrations of human milk and cows' milk (Table 31.5), with human milk having less protein but more fat and lactose. Human milk and milk formulas also differ with respect to a number of specific components, for example the long-chain polyunsaturated fatty acids, and this may have important neurodevelopmental consequences for the baby [18]. There is no doubt that breast milk is the ideal nutrition for the human baby.

Protection against infection

One of the most important secondary functions of breastfeeding is to protect the infant against infection. This is particularly important in developing countries, where it has been estimated that in each year there are 500 million cases of diarrhoea in infants and children and about 20 million of these are fatal. However, the extent to which breastfeeding protects against infection in infants in developed countries has been a matter of dispute. In a study from Dundee, Scotland, it was found that babies who had been breastfed for at least 3 months had greatly reduced incidences of vomiting and diarrhoea compared with babies who were either bottle-fed from birth or completely weaned within a short time of delivery [19]. This study also found that the protection against gastrointestinal illness in breastfed babies persisted beyond the period of breastfeeding itself and, in the developed country setting at least, was not undermined by the early introduction of at least some supplements. There was a smaller protection against respiratory tract infections but not against other illnesses.

A number of mechanisms contribute to the anti-infective properties of breast milk. Breast milk contains lactoferrin which binds iron, and because *E. coli* requires iron for growth, the multiplication of this organism is inhibited. Breastfeeding also encourages colonization of the gut by non-pathogenic flora that competitively inhibit pathogenic strains. In addition, bactericidal enzymes such as lysozyme are present in breast milk that contribute to its protective effect.

Table 31.5 Comparison of the constituents of human and cows' milk.

Constituent	Human milk	Cows' milk
Energy (kcal/100 mL)	75	66
Protein (g/100 mL)	1.1	3.5
Fat (g/100 mL)	4.5	3.7
Lactose (g/100 mL)	6.8	4.9
Sodium (mmol/L)	7	2.2

However, the most specific anti-infective mechanism is an immunological one. If a mother ingests a pathogen that she has previously encountered, the gut-associated lymphoid tissue situated in the Peyer's patches of the small intestine will respond by producing specific IgA, which is transferred to the breast milk via the thoracic duct (Fig. 31.1). This immunoglobulin, which is present in large amounts in breast milk, is not absorbed from the infant's gastrointestinal tract but remains in the gut to attach to the specific offending pathogen against which it is directed. In this way the breastfed infant is given protection from the endemic infections in the environment against which the mother will already have immunity [20]. Breast milk also contains living cells, such as polymorphs, lymphocytes and plasma cells, and although their functions are not yet fully understood they may also be active against invading pathogens.

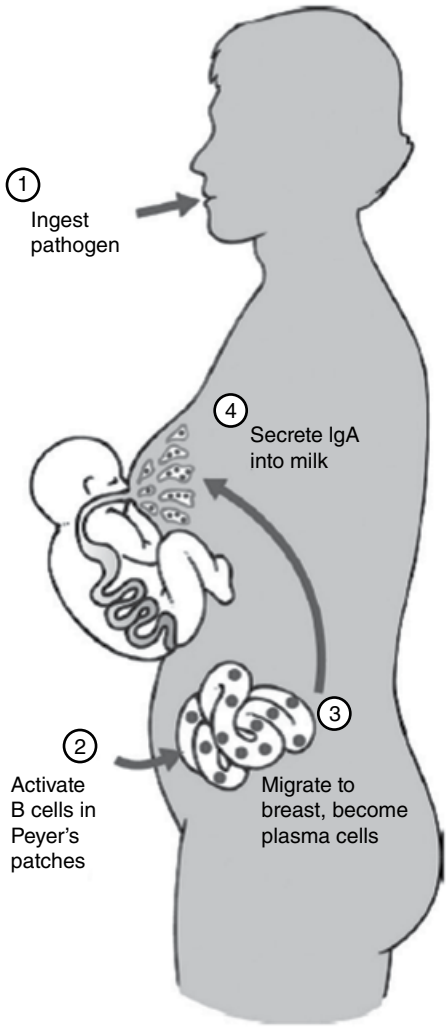

Fig. 31.1 Pathways involved in the secretion of IgA in breast milk by the enteromammary circulation.

Breastfeeding and neurological development

Previous studies have suggested that breastfed infants have a superior neurodevelopmental advantage and for many years this has been part of the campaign to encourage breastfeeding. However, there may not be such a great impact when the confounding variables, including parental IQ and socioeconomic status, are controlled for. In a 10-year follow-up study, Jedrychowski *et al*. [21] suggest that the increase in IQ ranges from 2.1 to 3.8 points depending on the length of breastfeeding. It would seem wise not to overestimate this effect when couselling mothers about the advantages of breastfeeding.

Breastfeeding and atopic illness

There are a number of reports that show a lower incidence of atopic illness, such as eczema and asthma, in breastfed babies. This effect is particularly important when there is a family history of atopic illness [22]. When the atopic illness is present, it is commonly associated with raised levels of IgE, especially to cows' milk protein. Oddy *et al*. [23] suggest that apart from a positive family history, the most important predisposing factor for atopic illness is the early introduction of weaning foods. The protective effect of breastfeeding against atopic illness may therefore be secondary rather than primary, because breastfeeding mothers tend to introduce supplements at a later stage. Nevertheless, mothers with a family history of atopic illness should be informed of the advantages of breastfeeding and of the dangers of introducing supplements too quickly.

Breastfeeding and disease in later life

Breastfeeding may be associated with reduced juvenile-onset diabetes mellitus [24] and neoplastic disease in childhood [25]. It is possible that some of these benefits are related to the avoidance of cows' milk during early life rather than to breastfeeding per se, for example it is possible that early exposure to bovine serum albumin could trigger an autoimmune process leading to juvenile-onset diabetes. Breast milk is a particularly important ingredient in the diet of preterm infants as it appears to help prevent necrotizing enterocolitis among these particularly vulnerable babies.

Breastfeeding and breast cancer

There is an epidemic of breast cancer among women in the developed countries of the Western world. A number of recent studies have shown a reduced risk (~10%) of premenopausal breast cancer among women who have breastfed their babies [26]. Because breastfeeding appears to have no effect on the incidence of postmenopausal breast cancer, its overall protective effect will be relatively small but the protection offered by lactation still represents an important advantage against a much feared and common disease.

Breastfeeding and fertility

The natural contraceptive effect of breastfeeding has received scant attention in the Western world because it is not a reliable method of family planning in all cases. Nevertheless, on a population basis, the antifertility effect of breastfeeding is large and of major importance in the developing world. It has to be remembered that the majority of women in the developing world do not use artificial contraception and rely on natural checks to their fertility. By far the most important of these natural checks is the inhibition of fertility by breastfeeding. In many developing countries, mothers breastfeed for 2 years or more, with the effect that their babies are spaced at intervals of about 3 years. In the developing world, more pregnancies are still prevented by breastfeeding than by all other methods of family planning combined. The current decline in breastfeeding in the developing world is a cause for great concern because, without a sharp rise in contraceptive usage, the loss of its antifertility effect will aggravate the population increase in these countries.

Mechanisms of lactational amenorrhoea

The mechanisms of lactational amenorrhoea are complex and incompletely understood. The key event is a suckling-induced change in the hypothalamic sensitivity to the feedback effects of ovarian steroids. During lactation, the hypothalamus becomes more sensitive to the negative feedback effects and less sensitive to the positive feedback effects of oestrogen. This means that if the pituitary secretes enough follicle-stimulating hormone to initiate the development of an ovarian follicle, the consequent oestrogen and inhibin secretion will inhibit gonadotrophin production and the follicle will fail to mature. During lactation there is inhibition of the normal pulsatile release of luteinizing hormone from the anterior pituitary gland which is consistent with these observations.

From a clinical standpoint, the major factor is the frequency and duration of the suckling stimulus, although other factors such as maternal weight and diet may be important confounding factors. If supplementary food is introduced at an early stage, the suckling stimulus will fall and early ovulation and a return to fertility will be the consequence.

Breastfeeding and obesity

Artificially fed children have twice the risk of childhood obesity compared with breastfed children [27]. Breastfed children also have a significantly reduced blood pressure [28]. These children have a significantly reduced chance

Table 31.6 Prevalence of breastfeeding from birth until 9 months, 1985–2013.

	1985	1990	1995	2000	2005	2013
Birth	63	62	66	69	76	74
6 weeks	41	42	42	42	41	
4 months	26	28	27	28	27	12
6 months	23	22	21	21	22	
9 months	14	14	14	13	12	1

of being obese as adults and dying prematurely from cardiovascular disease. These reports are primarily observational studies, and therefore some caution must be observed as the risks are multifactorial.

Trends in infant feeding in the UK

Because of the many advantages of breastfeeding, it is important that mothers are given accurate information and encouraged to breastfeed successfully whenever possible. Conversely, mothers who choose to bottle-feed should be given proper instructions on best practice and be supported in their decision. In the UK, about 74% of mothers overall start to breastfeed but many discontinue after a short time. The prevalence of breastfeeding in the UK up to 2013 is shown in Table 31.6 and the figures have shown no significant change over the previous 10 years, although a small increase in breastfeeding at birth is noted. Factors associated with a higher breastfeeding prevalence include higher social class, primiparity, older age of mother and place of residence (mothers in the south of the UK have a higher prevalence). In attempting to improve these disappointingly low rates of successful breastfeeding, it is important that health professionals should understand the physiology of lactation.

Physiology of lactation

At puberty, the milk ducts that lead from the nipple to the secretory alveoli are stimulated by oestrogen to sprout, branch and form glandular tissue buds from which milk-secreting glands will develop (Fig. 31.2). During pregnancy, breast tissue is further stimulated so that pre-existing alveolar–lobular structures hypertrophy and new ones are formed. At the same time milk-collecting ducts also undergo branching and proliferation. Both oestrogen and progesterone are necessary for mammary development in pregnancy but prolactin, growth hormone and adrenal steroids may also be involved. During pregnancy only minimal amounts of milk are formed in the breast despite high levels of the

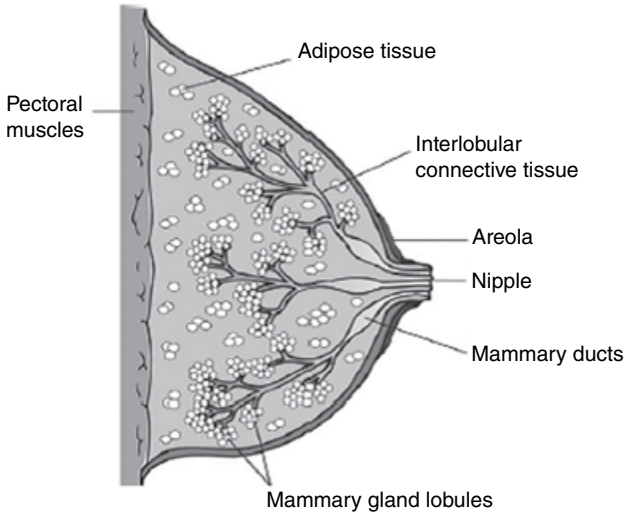

Fig. 31.2 Structure of the lactating breast.

lactogenic hormones prolactin and placental lactogen. This is because the actions of these lactogenic hormones are inhibited by the secretion of high levels of oestrogen and progesterone from the placenta and it is not until after delivery that copious milk production is induced.

Milk production

Two similar but independent mechanisms are involved in the establishment of successful lactation (lactogenesis): the first causes release of prolactin, which acts on the glandular cells of the breast to stimulate milk secretion (Fig. 31.3), and the second induces release of oxytocin, which acts on the myoepithelial cells of the breast to induce the milk ejection reflex (Fig. 31.4). Although these two mechanisms are similar, in that they can both be activated by suckling, they are mediated through two entirely different neuroendocrinological pathways. As can be seen in Figs 31.3 and 31.4, the key event in lactogenesis is suckling and the sensitivity of the breast accommodates itself to this important activity. During pregnancy the skin of the areola is relatively insensitive to tactile stimuli but becomes much more sensitive immediately after delivery. This is an ingenious physiological adaptation which ensures that there is an adequate stream of afferent neurological stimuli from the nipple to the hypothalamus to initiate and maintain the release of prolactin and oxytocin, both of which are required for successful lactation.

Milk ejection reflex

Successful breastfeeding depends as much on effective milk transfer from the breast to the baby as on adequate milk secretion. The milk ejection reflex is mediated by

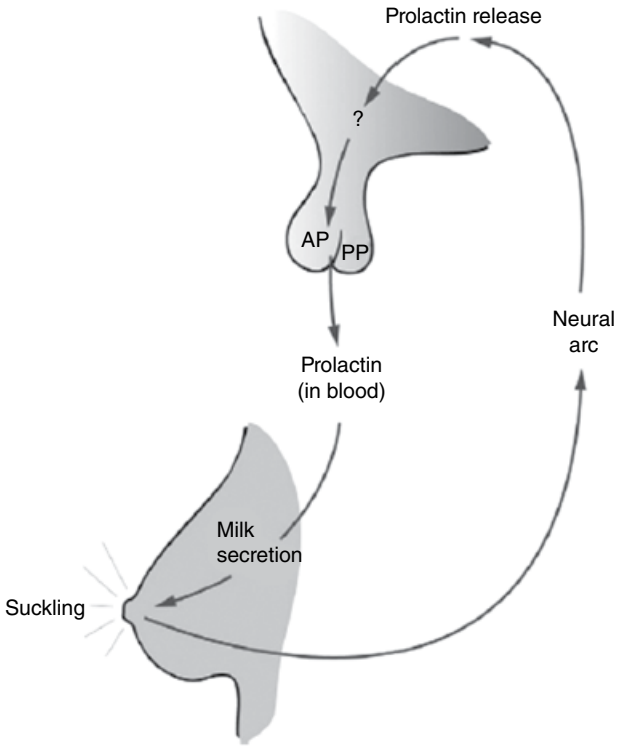

Fig. 31.3 Pathway of prolactin release from the anterior pituitary (AP).

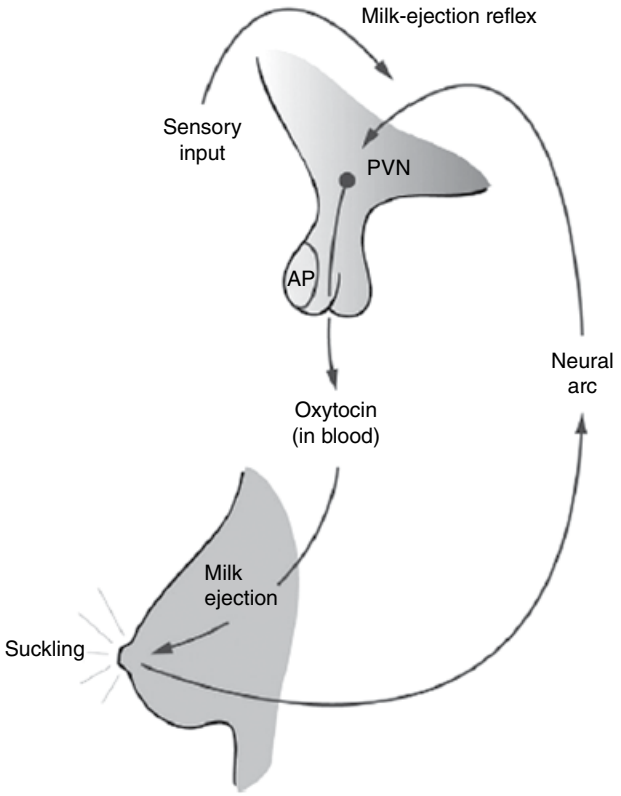

Fig. 31.4 Pathway of oxytocin release from the posterior pituitary. PVN, paraventricular nucleus.

the release of oxytocin from the posterior pituitary gland (see Fig. 31.4). Oxytocin causes contraction of the sensitive myoepithelial cells that are situated around the milk-secreting glands and also dilates the ducts by acting on the muscle cells that lie longitudinally in the duct walls. Contraction of these cells therefore has the dual effect of expelling milk from the glands and of encouraging free flow of milk along dilated ducts. This is recognized by the mother as milk 'let-down' and she may be aware of milk being ejected from the opposite breast from which the baby is suckling. In contrast to prolactin, which is secreted only in response to suckling, oxytocin can be released in response to sensory inputs such as the mother seeing the baby or hearing its cry. Oxytocin has a very short half-life in the circulation and is released from the posterior pituitary in a pulsatile manner. The highest levels of oxytocin may be released prior to suckling in response to the baby's cry, while prolactin is released only after suckling commences. The milk ejection reflex is readily inhibited by emotional stress and this may explain why maternal anxiety frequently leads to failure of lactation. Successful breastfeeding depends on engendering confidence in the mother and ensuring correct fixing and suckling on the nipple.

Another factor is of potential physiological importance as an inhibitor of breast milk: if the milk is not effectively stripped from the breast at each feed, this will inhibit lactopoiesis and lead to a fall in milk production.

Volumes of breast milk

During the first 24 hours of the puerperium the human breast usually secretes small volumes of milk, but with regular suckling milk volumes steadily increase and, by the sixth day of the puerperium, an average volume of 500 mL will be taken by the baby. Once lactation is fully established, an average daily milk volume is about 800 mL. In well-established lactation, it is possible to sustain a baby on breast milk alone for 4–6 months.

Management of breastfeeding

Despite the fact that it is a physiological event, many women experience difficulties in establishing breastfeeding. The greatest asset that a nursing mother can have is the support of an experienced and sympathetic counsellor. This counsellor may be a midwife, a health visitor or a lay person but the creation of a relaxed and confident environment is vital for successful breastfeeding. Babies are individuals, so there is no simple strategy that works in every case; mothers should be

Table 31.7 Ten steps to successful breastfeeding.

1	Have a written breastfeeding policy
2	Train all staff
3	Inform all pregnant women about the benefits and management of breastfeeding
4	Help mothers to initiate breastfeeding within 30 min of birth
5	Show mothers how to breastfeed
6	Foster the establishment of breastfeeding support groups
7	Practice 24-hour rooming-in
8	Encourage breastfeeding on demand
9	Give newborn infants no other food or drink, unless medically indicated
10	Use no artificial teats

encouraged to learn to respond to their own babies but all too often well-meaning but dogmatic and conflicting advice is given. The best approach is to give mothers all the options and let them make their own decisions; they will soon learn by trial and error what is best for their own babies. As an important stimulus to the promotion of effective breastfeeding, the concept of 'baby-friendly' hospitals has been developed, with breastfeeding an important part of that assessment. The Baby-Friendly Initiative has adopted 10 successful steps to breastfeeding as its central strategy and these are outlined in Table 31.7. Support for the breastfeeding mother is both an art and a science and the reader is referred to some of the detailed texts on the subject [29,30].

Suppression of lactation

Those women who do not wish to breastfeed should not be given any medication to suppress lactation routinely. They should be encouraged to use non-pharmacological approaches initially and only if these fail should a pharmacological approach be used. The drug of choice is cabergoline 1 mg stat to prevent lactation or 0.25 mg twice daily for 2 days to suppress established lactation. Bromocriptine is contraindicated due to the risk of heart attack and stroke.

Summary box 31.1

- The physiological changes that occur during pregnancy are reversed after birth and return to their normal pre-pregnancy state over a period that varies from 6 weeks to 6 months.
- Thromboembolism remains a major cause of maternal death, which in the majority of cases is avoidable with prompt and appropriate treatment.
- Puerperal infection remains a major cause of maternal death worldwide and in the majority of cases is avoidable with prompt recognition of the clinical symptoms and signs and subsequent treatment.
- Postpartum monitoring of urinary function is essential to avoid urinary retention and subsequent long-term bladder dysfunction.
- Postnatal suicide is an increasing cause of maternal death and there is therefore a need for antenatal and postnatal vigilance in detecting at-risk mothers and ensuring they receive appropriate psychiatric support.

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32

Neonatal Care for Obstetricians

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Management decisions during pregnancy and labour require knowledge of neonatal care and outcome. The informed obstetrician will thus more confidently deal with prospective parents' questions and be more engaged in the collaborative planning of perinatal care, particularly in high-risk pregnancies or where the fetus is at high risk of neonatal complications. This chapter therefore focuses on the basic neonatal knowledge required by the practising obstetrician but also provides a personal perspective gained from experience of some of the determinants of success and occasional failure of perinatal care. A neonatal reference text should be consulted for more detail on transitional physiology, neonatal resuscitation, neonatal conditions and management to augment the brief notes included later in this chapter.

Anticipation and levels of neonatal care

After birth, 90% of babies are cared for by their mothers and healthcare professionals should aim to facilitate this natural process. Approximately 8–10% of babies require more than normal care and about 2–3% need intensive care (level 3) following delivery; the majority of these may be anticipated because of impending prematurity, fetal abnormalities or concerns about fetal well-being. Care in complex cases requires multidisciplinary involvement, good planning and handover of respective responsibilities and duties of care from obstetrician and midwife to the neonatal team. Anticipating potential problems during the antenatal period facilitates the achievement of excellent care and helps avoid the unexpected becoming an uncontrolled emergency.

Other care categories are special care (level 1) or high-dependency care (level 2). Levels 1–3 are delivered in the neonatal unit. If the baby's condition allows, a level of care sometimes referred to as 'transitional care' is delivered usually on a postnatal ward and aims to avoid separation of mother and baby and to promote breastfeeding. Healthcare professionals support the mother to deliver medical care that may not be safely provided at home. Promotion of and support for breastfeeding is essential at all levels of neonatal care.

Summary box 32.1

Promoting good neonatal outcome in high-risk deliveries

- Anticipation and management of potential problems requiring specialist neonatal care is facilitated by multidisciplinary communication.
- Explicit, detailed and well-documented explanation of anticipated neonatal scenarios after delivery allows clear pathways of care to be agreed with parents before birth.

Antenatal communication and care plans

Anticipation and management of potential problems requiring specialist neonatal care is facilitated by multidisciplinary communication. The essential role of the neonatologist in antenatal discussions is to ensure that a comprehensive plan for delivery (timing, mode and place) and clear plans for resuscitation and stabilization are in place. The possible scenarios following birth need to be clearly discussed with parents to ensure their views and aspirations are fully taken into account when plans are agreed. The neonatal management plan will include the personnel and expertise of staff required at the delivery and the level of resuscitation deemed appropriate.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

The planning of place of delivery is especially important for infants with an antenatal diagnosis of a surgical condition. Antenatally there should be multidisciplinary discussions between parents, neonatolgists and surgeons as well as obstetricians in order to provide information regarding survival and treatment options.

Documentation

The neonatal plan for complex babies should be clearly documented and copies made available in the maternal case record, the hand-held maternal notes and the neonatal service pending file. These plans will involve resuscitation, specialist management (e.g. cardiac or surgical) and likely scenarios that may require different pathways of care. The plans should also detail the mother's feeding intention, particularly if feeding after birth is anticipated to be problematic (e.g. extreme prematurity and some surgical cases). In some cases where only compassionate care is required, detailed plans should include pain relief and comfort feeds and may also include hospice care plans.

Antenatal counselling and late karyotype

Knowledge of the karyotype can reduce uncertainty when considering the longer-term prognosis of the high-risk fetus. Not always considered is the value to the neonatologist of knowing the karyotype for planning the extent of resuscitation even if parents are unwilling to terminate the pregnancy on the basis of an abnormal karyotype. In such cases, a late karyotype specifically to inform early neonatal management is invaluable and may prevent active resuscitation when a more appropriate plan may be to provide compassionate care and support for the family.

Timing of delivery

Consideration of the multidisciplinary management of the baby after elective delivery facilitates team coordination. It is essential to ensure appropriate members, equipment, investigations and theatres are available if these should be required. In addition, anxious parents should not have their expectations and confidence dashed by unrealistic or non-existent perinatal plans.

Resuscitation plan for high-risk deliveries

Formal resuscitation plans are required for certain high-risk deliveries, such as extreme prematurity at the margins of viability, some serious fetal malformations that may require specialist intervention and stabilization, or if there is uncertainty about survival and long-term outcome. Explicit, detailed and well-documented explanation of anticipated neonatal scenarios after delivery allows clear pathways of care to be agreed with parents before birth. A well-meaning reassurance that the paediatrician or neonatologist will be present at delivery is inadequate and unhelpful. Therefore it is essential that engagement and timely communication between professionals involved antenatally (obstetrician, midwife, fetal medicine specialists, clinical geneticists, fetal cardiologists or surgeons) and a senior neonatologist is required in all cases where neonatal resuscitation and early stabilization may be needed before definitive management can be started. Such engagement will provide full and detailed information to the family and permit a written plan to be agreed with the parents and other professionals. The plans help to avoid confusion, especially if spontaneous labour and delivery occurs after-hours or pre-empts planned delivery.

Resuscitation guidelines

Plans for resuscitation need to take into consideration the various resuscitation guidelines that have been produced by international and national bodies, such as the International Liaison Committee on Resuscitation (ILCOR), the Royal Colleges and the British Association for Perinatal Medicine [1]. The ethical and practical issues of starting, withholding or withdrawing (or redirecting) resuscitation and neonatal intensive care should be explicitly considered and discussed with the family [2,3]. Palliative care may be a positive option but needs to be discussed and planned in detail. These discussions help prepare families and staff for the different outcomes following birth.

In the UK the guidelines are heavily reliant on data obtained by the population-based EPICure studies of 1995 [4] and 2006 [5]. There have been significant advances in health service organization and perinatal management, including use of antenatal steroids, surfactant and ventilation techniques. The outcome data of the EPICure 2 showed that survival increased in babies born between 22 and 25 weeks' gestation from 40% in 1995 to 53% in 2006 (P <0.001) [5]. This improvement in survival demonstrates that guidelines need to be continually reviewed in the light of advances in care.

Compassionate and palliative care

Palliative care after birth may be the preferred option for some babies. There is increasing awareness of the need for palliation, improving management and increasing availability of resources for neonatal palliative care. Planning before birth for such a care pathway helps parents establish links with caring staff and plan visits to palliative care centres if needed and avoids delays in hospital.

Communication following neonatal death

In circumstances where neonatal death is the outcome, family support by neonatal staff should include the antenatal team wherever possible. Continuing engagement by the obstetric staff in the postnatal care of the baby and family is especially helpful when the outcome is death or significant early morbidity. This ongoing communication between the antenatal and postnatal teams improves quality of care for the individual family and for all babies in general, as open dialogue fosters respect and support.

Organization of neonatal services

Providing the appropriate level of care for the mother and/or her baby requires careful planning and well-organized and integrated health services.

Managed neonatal clinical networks

Managed health service networks aim to deliver appropriate healthcare to a defined local population in the most effective and efficient manner. Specialized neonatal care is a high-cost, low-volume service that is increasingly delivered in managed networks. In 2009, the UK Department of Health *Toolkit for High-Quality Neonatal Services* [6] set the standards of care that should be provided for preterm or sick infants. Included in these recommendations was the stipulation that neonatal care should be delivered in managed clinical networks.

Within each network, different hospitals provide a range of care as agreed by that network. The level of care provided by each hospital is based on resources, capacity, geography and the availability of appropriately skilled and trained staff. A network consists of at least one neonatal intensive care (level 3) unit providing intensive care facilities, with specialist staff and facilities. The various network hospitals collaborate to ensure that every infant has access to the most appropriate level of care. The development of coterminous maternity networks are also enhancing the organization of perinatal services.

In the UK, neonatal intensive care (level 3) units provide care for extremely preterm babies and the sickest term babies requiring all levels of advanced respiratory support and parenteral nutrition. These units have 24-hour cover from specialized nursing staff and neonatal specialist doctors. Local neonatal (level 2) units provide respiratory support for babies of 28 weeks' gestation or more and special care (level 1) units provide care for babies that do not require respiratory support for prolonged periods (usually 24–48 hours only).

Neonatal transport

Ensuring that babies receive the appropriate level of care ideally requires delivery in the correct place if delivery is predictable and safe antenatal transfer of mother is possible. Postnatal transfer of babies to the correct level of unit after delivery also needs to be available. Specialist neonatal transfer services are evolving that have the expertise and equipment and thus help to avoid depleting specialist staff from the either the referral unit or the specialist centre. A major role of the neonatal networks is to ensure that pregnant women are transferred to the most appropriate setting if it is predicted that their baby will need a higher level of care than that provided by the admitting hospital. In order to facilitate family involvement, it is also expected that the infant should be cared for within the network rather than being transferred great distances.

Birth and postnatal adaptation: neonatal resuscitation

Only 1% of normal birthweight babies require active resuscitation after birth and only 0.2% require advanced resuscitation including endotracheal intubation. Although the need for resuscitation may be predictable based on risk factors, 30% of babies requiring resuscitation are not predicted. Babies who may be at risk of not making a successful adaptation without assistance include those in the following groups: preterm births (usually <36 weeks), those with known fetal complications, infants of diabetic mothers, fetal distress, fresh meconium-stained liquor, malpresentation and breech, multiple pregnancies, caesarean section under general anaesthesia or for fetal distress, risk of fetal infection and instrumental delivery.

In the UK, the Royal College of Paediatrics and Child Health (RCPCH), the Royal College of Obstetricians and Gynaecologists (RCOG) and the Royal College of Midwives (RCM) have published their recommendation that all professionals present at the time of birth are proficient in resuscitation of the newborn [7]. Basic neonatal resuscitation is now a requirement of training for obstetricians and midwives and advanced resuscitation for neonatal paediatricians and practitioners.

Antenatal and newborn screening

Antenatal screening continues after birth with newborn screening programmes. In the UK, antenatal screening includes the National Health Service (NHS) fetal anomaly,

Table 32.1 NHS Newborn Blood Spot Screening Programme.*

	England	Wales	Scotland	Northern Ireland
Congenital hypothyroidism	√	√	√	√
Cystic fibrosis	√	√	√	√
Sickle cell disease	√	√	√	√
Phenylketonuria	√	√	√	√
Medium-chain acyl dehydrogenase deficiency	√	√	√	√
Maple syrup urine disease	√	√	–	–
Isovaleric acidaemia	√	√	–	–
Glutaric aciduria type 1	√	√	–	–
Homocystinuria	√	√	–	–

*Blood sample taken at 5–8 days after birth.

infectious diseases in pregnancy and sickle cell and thalassaemia screening programmes. These results influence antenatal management of mother and fetus and, in some cases, postnatal management of the newborn. The NHS National Screening Committee recommendations for systematic neonatal population screening include the following.

- NHS Newborn and Infant Physical Examination (NIPE) Screening Programme carried out within 72 hours and then repeated at 6–8 weeks. The specific areas included are the detection of congenital cataracts (red reflex), congenital heart disease, developmental dislocation of the hip and cryptorchidism in boys.
- Newborn Hearing Screening Programme (NHSP) carried out within 2 weeks by automated otoacoustic emission (AOAE) in well babies and automated auditory brainstem response (AABR) in babies following neonatal intensive or special care.
- NHS Newborn Blood Spot Screening Programme involves taking a blood sample at 5–8 days after birth in term babies. There are currently differences in the tests included in the different countries within the UK (Table 32.1).

Neonatal outcome

Prematurity

Prematurity is the major determinant of neonatal outcome in developed countries. The preterm birth rate (live births occurring before 37 weeks' gestational age) is 5–9% in Europe and 12–13% in the USA and is increasing. In the USA there has been a 31% increase in prematurity since 1981 [8]. In England and Wales, there were 700 000 liveborn babies in 2013, 7% preterm and 1.0% less than 32 weeks' gestation [9].

The infant mortality rate (deaths at less than 1 year of age) in term infants was 3.8 per 1000 live births compared with 21.1 for preterm infants. Of those born at less than 32 weeks of gestation, 15% resulted in an infant death and this accounted for over half of all infant deaths. Variation may be due to methodological differences such as case ascertainment, selection bias, and varying outcome definitions and follow-up duration. Reports from geographically defined population-based studies show lower survival rates than single-centre selective studies that are subject to bias.

Variation in preterm birth rates (all births) also appears to have a major influence on reported neonatal mortality rates between populations. Compared with other European regions, the delivery rate per 1000 births between 22 and 31^{+6} weeks in two regions in England (Trent: 16.8, 95% CI 15.7–17.9; Northern: 17.1, 95% CI 15.6–18.6) was significantly higher compared with a group mean of 13.2 (95% CI 12.9–13.5) [10]. Live birth rates showed similar trends. When comparisons were made between regions after adjustment for prematurity rates, the variation in survival outcomes was reduced.

Perinatal management policies and differences in perinatal healthcare provision as determinants of survival are inadequately quantified. The extent to which obstetricians use antenatal steroids and actively manage delivery and whether neonatologists perform resuscitation and redirection of care during intensive care, all potentially have effects on reported survival and outcome.

At the extremes of viability, biological variation and ethical considerations are important in determining management policies. Policies based simply on gestation at birth are inadequate and prediction of outcome may be more accurate if gender, exposure to antenatal steroids, single or multiple births and birthweight are considered with gestation.

Survival

Advances in perinatal care have resulted in a significant increase in survival of preterm babies. Survival in late preterm babies (32–36 weeks) is 98–99%. There are limited data on longer-term morbidity in this group but recent reports suggest this neglected area should be studied in greater detail. There are five times more late preterm babies born than babies born before 32 weeks' gestation and therefore as a group require considerable healthcare resources.

Babies born before 28 weeks' gestation have shown the greatest increase in survival since the advent of modern perinatal care. Few babies less than 28 weeks' gestation survived until techniques were developed during the

1960s and 1970s to provide respiratory support. Over the following two decades, the use of antenatal corticosteroids, use of surfactant and improvements in respiratory support have resulted in striking improvements in reported survival.

The EPICure study of all births between 22 and 25 weeks' gestation in the UK and the Republic of Ireland during 1995 provided important population-based information on babies born at the borderline of viability [4,11]. During the study regionalized neonatal care was poorly developed. This study was repeated in the UK during 2006 for babies born between 22 and 26 weeks' gestation in England [5]. Survival overall increased from 40 to 53% as well as at each week of gestation. The development of more regionalized neonatal care delivery in the UK, with increasing use of managed neonatal networks during the period between the two studies, may have contributed to the improvement.

Neonatal mortality and early morbidity

Neonatal death in preterm births is largely due to respiratory complications, periventricular haemorrhage and infection. Antenatal steroids, the use of early surfactant and continuous positive airway pressure are all associated with a reduction in death and morbidity.

Childhood morbidity

Neurodevelopmental sequelae of prematurity present during the first 5 years after birth and include cerebral palsy, poor cognitive performance and sensory impairments (visual and auditory deficits). During later years, academic underachievement and behavioural sequelae may occur. The definitions used for neurodevelopmental impairments and disability between studies are not uniform but more rigorous definitions are evolving. Disability reported in studies usually refers to one or more severe functional impairments, including non-ambulatory cerebral palsy, developmental quotient or IQ of less than −2 or −3 standard deviations from the norm, blindness and hearing impairment not improved with aids.

Neuromotor domain

Although cerebral palsy is the most commonly quoted outcome after very preterm birth, developmental and cognitive impairments are more common. The term refers to static injury to the developing brain that affects motor function. Different patterns are described and most commonly after preterm birth spastic diplegia is found. Of infants born between 22 and 26 weeks' gestation who were evaluated at 3 years of age in EPICure 2, 14% had cerebral palsy with increasing proportions at lower gestation [12] and it is more commonly seen in boys. Overall rates do not appear to be changing significantly as survival increases, but there is concern that the absolute prevalence will increase with increased survival of the most immature babies.

Developmental domain

The most common disability at 3 years is developmental or cognitive impairment, affecting up to 45% of extremely preterm babies [12]. As gestational age increases, the percentage of those with developmental impairment decreases. During the school years this domain of impairment is even more significant.

Sensory and communication domain

The prevalence of severe impairment of hearing and vision in very preterm babies is relatively low (hearing impairment not improved with aids <2%, blindness <3%). Less severe impairments are more common and include squints and refractive errors.

Academic attainment

Cognitive impairment appears to be the major determinant of school performance. At 8–9 years, approximately 20% of very low birthweight babies require special education and for those in regular schools, 25% repeat a year and 11–15% receive special help. At 11 years, the EPICure cohort showed significantly lower academic attainment compared with controls [13]. The proportions requiring special educational support was 62% of the extremely preterm group compared with 11% for the term controls (odds ratio, OR 13.1, 95% CI 7.4–23.3). Statements of Special Educational Needs were issued for 34% of the preterm cohort compared with 0.7% for controls (OR 76, 95% CI 10–552).

Behavioural/psychiatric sequelae

There is an excess of attention deficit hyperactivity disorder (ADHD) among preterm survivors. A meta-analysis of six follow-up studies revealed a relative risk of 2.64 (95% CI 1.85–3.78) among preterm babies. The EPICure study found ADHD in 11.5% of preterm babies and in 2.9% of term controls (OR 4.3, 95% CI 1.5–13) and autism spectrum in 8% compared with 0% in term controls [14].

Outcome in teenage and adult survivors

Various functional limitations occur in 86% of early teenage survivors with birthweight below 750 g. Growth disorders (49%), mental or emotional problems (58%), restrictions on physical activity (32%) and visual impairment (31%) are found and 75% use aids such as spectacles and medication. However, in a study of health-related quality of life in adolescent survivors with birthweight below 1000 g, the proportion that scored within the normal range was similar to normal-birthweight adolescents.

Although fewer adult very low birthweight survivors go on to higher education than their peers, they are less likely to engage in risk-taking behaviour and social integration is not impaired.

Health and social care and educational resource utilization

There is a significant increase in utilization of public health, social and educational services by extremely preterm survivors. During the 11th year of life, the EPICure study estimates of public sector costs were £4007 (SD £2537) for controls and £6484 (SD £2537) for the preterm cohort, a significant mean cost difference of £2477 (95% CI 1605–3360; P <0.001) [15].

Other morbidity

Many preterm survivors experience less severe problems such as clumsiness, visual impairment (e.g. squints, refractive errors), growth disorders and respiratory problems.

Respiratory

More than 50% of extremely low birthweight babies require hospital readmission during the first 12 months after discharge from the neonatal unit. These admissions are usually due to respiratory illness precipitated by lower respiratory infections. Chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD) has been reported in up to 40% of very low birthweight survivors. The rate is higher as birthweight and gestation falls. Significant airflow limitation on lung function tests is found in adolescent survivors.

Growth

Growth failure is common during infancy and early childhood but adult stature within the normal range is achieved. Despite this catch-up, extremely low birthweight babies remain at a height disadvantage to normal birthweight controls. In the longer term, there are concerns that accelerated weight gain may lead to increased risk of hypertension and other cardiovascular diseases as well as type 2 diabetes.

Effect on family

The psychological distress that parents of high-risk preterm babies experience is greatest during the first month after birth and persists for the first 2 years. The greatest effect of stress is found in families of low income and lower parental education and with greater severity of functional disability in the child. By adolescence, despite the preceding years of emotional distress, families report positive interactions with friends and within the family, experience enhanced personal feelings of accomplishment and report both positive and negative effects on the marital relationship.

Summary box 32.2

Neonatal outcome in developed countries

- The majority of deaths before 1 year of age (infant mortality) follow preterm birth (66%).
- Advances in perinatal care have resulted in a significant increase in survival of preterm babies.
- Neurodevelopmental sequelae of prematurity present during the first 5 years after birth and include cerebral palsy, poor cognitive performance, attention deficit disorder and sensory impairments (visual and auditory deficits).

Important clinical conditions in neonatology

The most common reasons for babies to require neonatal management or admission are management of prematurity, respiratory distress and possible infection.

Common problems in neonatal care

Prematurity

Temperature control

Preterm infants are particularly susceptible to hypothermia due to their reduced body fat and energy stores. For this reason, the temperature of the delivery room should be maintained around 25 °C. Also, delivering very preterm infants into a plastic bag significantly increases their temperature on admission to the neonatal unit and improves early survival [16].

Respiratory distress syndrome (surfactant deficiency)

The respiratory distress syndrome caused by inadequate surfactant production is mainly a disease of the preterm infant. However, it can occur in term infants, particularly those of diabetic mothers or after caesarean section without labour. Affected infants may require mechanical ventilation and intensive care. The classical clinical presentation is an infant with tachypnoea, subcostal and intercostal recession and nasal flaring that becomes progressively worse over the first 60 hours after birth, and chest radiography shows a ground-glass appearance with air bronchograms. It can be associated with pneumothorax and intraventricular haemorrhage, although in more mature infants it normally resolves without sequelae. The combined use of antenatal corticosteroids and surfactant modify the illness, improving survival and reducing the rates of complications but have little effect on reducing the incidence of BPD or chronic lung disease, which occurs mainly in preterm babies.

Bronchopulmonary dysplasia or chronic lung disease of prematurity

This is a chronic condition affecting up to 50% of infants born at 26 weeks or less. For infants born at 32 weeks' gestation or less, it is defined as either an oxygen requirement at 36 weeks postmenstural age or at discharge, depending on which comes first [17]. Premature delivery, prenatal and postnatal inflammation and infection, ventilation, oxygen and poor nutrition are among the many factors contributing to the development and persistence of BPD. The underlying problem is an arrest in alveolar and peripheral vascular development. The severity is variable, ranging from the need for supplemental oxygen for several weeks to prolonged respiratory support with a ventilator or continuous positive airways pressure and even death. A small proportion of babies are discharged home on supplemental oxygen; most outgrow the need by 12 months of age. All babies born prematurely have an increased risk of respiratory illness within the first few years of life. This is increased in the group with BPD and respiratory problems may persist into adult life.

Retinopathy of prematurity

Infants who are born prematurely or have intrauterine growth restriction (IUGR) are at risk of developing abnormal retinal blood vessels which can lead to blindness. For this reason, retinal screening must take place in all infants born at less than 32 weeks' gestation and those who have a birthweight of less than 1501 g. Retinopathy of prematurity is associated with high levels of oxygen, although the BOOST II trial demonstrated that targeting lower levels of oxygen saturation was associated with an increase in mortality [18]. Laser therapy with ablation of the abnormal vessels results in improved outcome. Intravitreal injections of anti-VEGF (vascular endothelial growth factor) monoclonal antibodies are also being investigated as an alternative to laser therapy.

Brain injury in preterm babies

Preterm infants are at high risk of cerebral injury and consequent neurodevelopmental impairment. The proportion of preterm babies that have injury and impairment is inversely related to gestational age. There are two major patterns of brain injury.

1) Intraventricular haemorrhage may affect only the germinal layers or ventricles, in which case the prognosis is good. However, haemorrhage into the brain parenchyma is caused by haemorrhagic infarction and is associated with neurodevelopmental impairment.
2) Periventricular leucomalacia reflects loss of white matter, sometimes with cavitation. Whereas haemorrhagic parenchymal infarctions can usually be seen by cerebral ultrasonography, periventricular leucomalacia is difficult to see and is probably under-diagnosed.

Both these conditions seem to be becoming less common than a more subtle loss of cerebral matter. The usefulness of cerebral ultrasonography alone to predict neurological prognosis in extremely preterm infants is therefore limited. The more mature preterm infants with normal ultrasound scans at discharge from intensive care have a very low risk of neurodevelopmental impairment, whereas those with definable loss of brain tissue from whatever cause have a greater than 50% chance of long-term impairment. Early MRI scanning of the preterm brain is increasingly being used to delineate neuronal damage and predict long-term neurological outcomes [19].

Necrotizing enterocolitis

This poorly understood inflammatory disease is primarily a condition of preterm infants and those with congenital heart disease. It presents as an acute abdomen in the days or weeks after birth and varies in severity from mild to fatal. Diagnosis is clinical, aided by characteristic radiographic changes such as air in the bowel wall or biliary tree. Treatment can be conservative, with antibiotics and cessation of enteral feeding, but if there is a perforation of the bowel or medical treatment fails, surgery has to take place. Recent trials have suggested that probiotics might reduce the incidence of necrotizing enterocolitis [20] but this has not been supported by the PiPS trial, which could not demonstrate this finding using *Bifidobacterium breve* [21].

Small for gestational age associated with IUGR

In utero chronic hypoxia can affect many of the organs of the newborn infant with IUGR. In particular, fetal distribution reduces blood flow to the bowel, which can lead to necrotizing enterocolitis. The infants have poor thermoregulation and can become hypothermic or hyperthermic. Hypoglycaemia or hyperglycaemia can also be problematic. Polycythaemia can result in a hypercoagulable state leading to renal vein thrombosis and also jaundice due to the increase in erythrocyte numbers. A fetus with IUGR is more likely to develop birth asphyxia and also respiratory distress syndrome.

Hypoglycaemia

Conditions commonly associated with transient low blood glucose are hypothermia, infection, prematurity, IUGR and maternal diabetes. Some infants develop transient hyperinsulinaemia, particularly infants of diabetic mothers with poor antenatal control or those with severe rhesus disease. Rare causes include

Beckwith–Wiedemann syndrome and metabolic defects such as cortisol deficiency, galactosaemia and other enzyme defects of glycogenolysis, gluconeogenesis or fatty acid oxidation. Preterm infants are much less able to mount a ketotic response and hypoglycaemia should be treated promptly. Treatment is initially to give calories in the form of milk or as intravenous glucose infusion. If hypoglycaemia persists, investigations including insulin and counter-regulatory hormone measurements are required.

Jaundice

Jaundice is the most common clinical condition needing medical attention in newborn babies. It occurs in 60% of term and 80% of preterm babies during the first week. Jaundice beginning in the first 24 hours after birth is always pathological. It is usually unconjugated and the commonest causes are haemolytic anaemia or infection. Jaundice beginning on days 2–5 is commonly physiological, but unconjugated hyperbilirubinaemia may have many causes, including haemolytic disease, ABO incompatibility and glucose 6-phosphate dehydrogenase deficiency.

Phototherapy is the mainstay of treatment where treatment is indicated. Failure to control bilirubin levels with phototherapy may necessitate an exchange blood transfusion to avoid neurotoxicity such as kernicterus and hearing impairment. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines for the screening and management of neonatal jaundice were published in 2010 [22]. Conjugated hyperbilirubinaemia signifies liver disease and requires urgent specialist investigation. These infants may be at risk of complications such as significant bleeding and neurological damage.

Respiratory conditions

Respiratory distress

Respiratory distress is one of the commonest problems encountered in the neonatal period. It is manifest by the clinical signs of tachypnoea (persistently over 60 breaths/min), intercostal recession, grunting, nasal flaring and tachycardia. If the baby becomes hypoxic, then cyanosis, apnoea and bradycardia may result. The presence of any signs of respiratory distress needs further evaluation and investigation. Tachypnoea with recession and nasal flaring is frequently the presentation of respiratory or cardiac disorders, while apnoea may be the presentation of a great many systemic disorders such as septicaemia, meningitis, gastrointestinal obstruction or heart disease.

Congenital pneumonia

Congenital pneumonia is a relatively common problem associated with a variety of microorganisms. The infant presents with respiratory distress and chest radiography shows patchy inconsistent shadowing. Treatment is with antibiotics and intensive care as required.

Meconium aspiration

Inhalation of meconium before or during delivery can be an extremely severe problem if pulmonary hypertension with reduced lung perfusion and severe hypoxaemia develop. Meconium may block large or small airways or both and lead to a ventilatory deficit. Although meconium aspiration may be apparent at birth, severe disease may present an hour or more later and it is important that babies suspected of having aspirated are carefully observed.

Treatment of meconium aspiration and associated pulmonary hypertension requires expert intensive care. Early surfactant administration may be beneficial, while high-frequency oscillatory ventilation and the administration of nitric oxide reduce mortality. When other measures fail, extracorporeal membrane oxygenation (ECMO) should be considered.

Transient tachypnoea of the newborn

Transient tachypnoea of the newborn is due to delayed reabsorption of lung liquid and leads to a moderate degree of intercostal recession and tachypnoea. In the preterm infant this can lead to marked respiratory distress, but in a term baby needing high inspired oxygen concentrations, other causes of respiratory distress should be excluded.

Infections

Newborn infants are particularly prone to perinatal infection. Risk factors include low birthweight, prolonged ruptured of membranes, maternal fever or chorioamnionitis. Indwelling cannulae, central venous lines and invasive mechanical ventilation increase the risk of nosocomial infection in those who require neonatal intensive care. Organisms responsible for later neonatal infection frequently come from the skin or gut. Breastfeeding helps promote normal gut flora and reduces the risk of acquired neonatal infections. Adherence to good hand-washing practices by all staff, parents and visitors can significantly reduce the risk of acquired infection.

Septicaemia

The signs of systemic sepsis are non-specific. Infants may present with apnoea, bradycardia or cyanotic episodes and poor feeding is a common association. They may be lethargic and hypotonic and are hyperthermic or hypothermic. Sepsis frequently presents as a metabolic acidosis or shock and occasionally causes petechial skin rash or severe jaundice.

Organisms that commonly cause infection in the newborn period include group B *Streptococcus* (GBS) and

Gram-negative organisms such as *Escherichia coli* or *Klebsiella*. The prolonged use, or multiple changes, of antibiotics in the antenatal period may increase the risk of infection with resistant organisms. Rapid treatment with antibiotics, immediate resuscitation and, frequently, mechanical ventilation is required. Investigations include chest radiography, blood cultures, urine culture, and examination and culture of the placenta. A lumbar puncture is performed once the baby is stable and will tolerate the procedure. The mortality of infants who develop septicaemia in the neonatal period is high, with a significant number of survivors developing subsequent impairment.

Group B *Streptococcus* infection

Mortality due to maternal colonization by GBS is reduced by antibiotic therapy to the mother during labour and early treatment of infants with evidence of infection. About 2% of infants of colonized mothers develop infections, and 70% of these manifest risk factors at birth such as preterm labour, prolonged rupture of membranes or meconium-stained liquor. Urgent antibiotic therapy is indicated for these infants. Well infants shown by surface cultures to be colonized do not require treatment. Recurrent GBS infection can occur, but more commonly GBS infection occurs later in infancy when meningitis is the presenting problem.

Meningitis

Signs of meningitis in newborn infants are non-specific. Meningitis usually presents as septicaemia and can be complicated by cerebral oedema, cerebral infarction, brain abscess or deafness. Common causal organisms are GBS and *E. coli*. *Listeria monocytogenes* is a rare cause of perinatal infection in the UK.

Eye infection

The majority of sticky eyes are not infected but are due to a blocked nasolacrimal duct. In the absence of conjunctival redness or swelling, investigation for infection and treatment with topical antibiotics is not required. Simple measures such as cleaning with boiled water and lacrimal duct massage suffice, with symptoms usually resolving in 3–6 months. Neonatal conjunctivitis can be caused by organisms such as *Staphylococcus aureus*, *Chlamydia trachomatis*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*. Gonococcal ophthalmia usually presents within 24 hours of delivery with profuse purulent conjunctival discharge, and immediate diagnosis and treatment (systemic and topical) is required to prevent damage to the cornea.

Chlamydial ophthalmia, which is now among the commonest causes of neonatal conjunctivitis, presents between 5 and 12 days postnatal age; some babies infected as neonates will develop chlamydial pneumonia later in infancy. Corneal scarring is rare. Two weeks of systemic and topical treatment is required. The identification of either *N. gonorrhoeae* or *Chlamydia* in the baby requires referral of mother and her sexual partner for investigation and treatment.

Skin infection

Simple hygienic methods such as bathing and handwashing can prevent many skin infections. The infant's skin is vulnerable to infection by staphylococci, which usually leads to small pustules or lesions but which can also cause scalded skin syndrome with severe exfoliation. Staphylococcal infections should therefore be treated with antibiotics after appropriate cultures have been taken. Streptococci can also cause skin infection and both may cause systemic illness.

Infection of the umbilical cord is commonly limited to periumbilical redness with a small amount of discharge. The presence of oedema indicating cellulitis can occasionally lead to complications such as spreading cellulitis of the abdominal wall, fasciitis and septicaemia and requires treatment with systemic antibiotics.

Candidiasis usually presents after the first week with napkin dermatitis with or without oral thrush. Topical and oral treatment is required to prevent the candidiasis returning as the gut is colonized with *Candida*. Maternal nipple candidial infection can occur in breastfeeding mothers.

Tuberculosis

Tuberculosis is a re-emergent disease and many hospitals now offer bacille Calmette–Guérin (BCG) immunization to newborn infants. Infants born to mothers infected with active tuberculosis should be vaccinated with isoniazid-resistant BCG vaccine and kept with the mother while both receive treatment with appropriate drugs. Breastfeeding should be encouraged.

Tetanus

Neonatal tetanus due to infection of the umbilical stump by *Clostridium tetani* is the result of poor hygiene and is a distressing and severe condition with extremely high mortality. Opisthotonus and muscle spasms of the jaw and limbs are presenting features and can appear very rapidly after birth. Prevention centres on maternal vaccination during pregnancy and education to improve hygiene and change of local cultural practices.

Neurological conditions

Neonatal encephalopathy

Neonatal encephalopathy can be caused by hypoxic ischaemia due to birth asphyxia but also by other conditions including metabolic disorders and infections. These conditions should be excluded before a confident diagnosis of hypoxic–ischaemic encephalopathy (HIE) due to birth asphyxia can be accepted.

Hypoxia–ischaemia followed by resuscitation may lead to apparent recovery followed by inexorable deterioration beginning 6–8 hours later and ending in severe cerebral injury. Consequently, it is frequently difficult to determine the prognosis soon after birth on clinical grounds alone. However, if asphyxia is severe or happened some time before delivery, the infant will not develop spontaneous breathing; therefore, if despite advanced life support there is no sign of spontaneous breathing 20 min after birth, the outcome is extremely poor.

HIE is graded clinically and a frequently used grading system was described by Sarnat and Sarnat [23]. Infants with grade 1 encephalopathy have a very good prognosis whereas infants with grade 3 almost all die or are severely impaired. About half the infants with grade 2 have severe neurodevelopmental impairment. Unfortunately, a large number of infants at risk fall into grade 2, limiting the utility of the system.

Moderate hypothermia for perinatal HIE

In therapeutic hypothermia, the infant is cooled to between 33 and 35 °C in order to prevent neuronal loss following an asphyxial injury. Hypothermia can be induced by selectively cooling either the head using a cap or the whole body using a cooling mattress. The publication of studies using therapeutic hypothermia for 72 hours for HIE confirmed a significant reduction in death and disability. The Treatment of Perinatal Asphyxial Encephalopathy (TOBY) study showed that the treated group had a significantly increased survival without neurological abnormality at 18 months (relative risk, RR 1.57, 95% CI 1.16–2.12; $P = 0.003$) [24]. The risk of cerebral palsy in survivors was reduced (RR 0.67, 95% CI 0.47–0.96; $P = 0.03$) and there were significant improvements in both the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of the Bailey Scales of Infant Development 11 and also in the Gross Motor Function Classification System. A meta-analysis of three trials (767 patients) confirmed the significant reduction in death and severe disability at 18 months (risk ratio 0.81, 95% CI 0.71–0.93; $P = 0.002$), with a number needed to treat of 9 (95% CI 5–17) [25]. At 6 years of age, more children in the hypothermia group survived without neurological abnormalities (45%) compared with the control group (28%) (RR 1.6, CI 1.15–2.22) [26].

Therapeutic hypothermia is now accepted by most neonatologists in the UK as the standard of care for perinatal HIE. Research is progressing to find additional interventions to augment the benefit of hypothermia. It is important that eligible babies (36 weeks or more) are considered soon after birth for treatment as cooling should be commenced before 6 hours of age. The British Association of Perinatal Medicine has recently published recommendations for the use of therapeutic hypothermia in the UK [27].

Summary box 32.3

Hypoxic–ischaemic encephalopathy

- Neonatal encephalopathy can be caused by hypoxia–ischaemia due to birth asphyxia but other causes have to be excluded.
- The severity of HIE is graded clinically.
- Therapeutic hypothermia is effective in significantly reducing death and disability following perinatal HIE and is now a standard of care.

Cerebral palsy

Cerebral palsy is an umbrella term that describes the consequences of a non-progressive injury to the developing brain. The clinical manifestations include motor, sensory and cognitive deficits that may not be apparent until after 1 year of age and cannot be confidently diagnosed at birth. Although there is an association between neonatal encephalopathy and cerebral palsy, population-based studies have shown that only about 10% of all cases of moderate to severe neonatal encephalopathy in term babies are associated with intrapartum risk factors. Other risk factors for cerebral palsy are preterm birth or very low birthweight, perinatal infection, congenital malformations or multiple pregnancies [28–30].

Convulsions

Convulsions occurring just after delivery in term infants may be due to HIE, metabolic disorders, infections, hypoglycaemia, hypocalcaemia, and hypomagnesaemia or pyridoxine deficiency. Many otherwise idiopathic fits are caused by focal cerebral infarction, which have a much better prognosis than generalized hypoxic–ischaemic injury but are difficult to diagnose without MRI.

Brachial plexus injury

Brachial plexus injury occurs in 0.4–2.5 per 1000 live births. The commonest type, Erb's palsy, involves C5 and C6 nerve roots. The incidence has not declined over the past few decades but the prognosis for recovery has improved, with full recovery expected in the majority of babies with Erb's palsy. A fracture to the clavicle may also be present. Careful neurological examination is needed to determine the level of the lesion as this affects the prognosis for recovery of function. Associated Horner's syndrome is a bad prognostic sign.

Effects of maternal drug use

Infants of mothers who take drugs such as opiates, cocaine, amphetamines, barbiturates, benzodiazepines

and some other medical drugs may develop a withdrawal syndrome, with irritability, poor feeding, apnoea and fits. The babies of mothers who have high alcohol or nicotine intake may also exhibit withdrawal. Wherever possible the mother and baby should be kept together; in many cases breastfeeding is not contraindicated. If a history of maternal drug abuse was known antenatally, a plan of management can be agreed before birth and referral to the social work team may be appropriate. Management of a baby at risk of drug withdrawal involves careful observation and skilled nursing. If withdrawal is severe, treatment with opiates may be required. Naloxone should never be given to infants at risk of opiate withdrawal as it can provoke convulsions. Many labour wards no longer stock naloxone for fear it will be given inadvertently to an infant of a substance-abusing mother.

Congenital abnormalities

Cardiac

Some form of congenital heart disease affects between 7 and 9 per 1000 live births, of whom approximately one-quarter will present in the newborn period. Fetal anomaly ultrasound can detect many lesions but some are more difficult to diagnose. Neonatal presentation is normally due to cyanosis, heart failure and respiratory distress, and shock. Some conditions present with asymptomatic findings on neonatal examination such as a murmur, absent femoral pulses or tachyarrhythmia.

Cyanosis

Causes of cyanotic heart disease include transposition of the great arteries and conditions that reduce pulmonary blood flow such as tetralogy of Fallot and pulmonary or tricuspid atresia. Pulmonary blood flow in these conditions depends on arterial ductal patency and the degree of blood mixture between heart chambers. For those presenting in the neonatal period, immediate treatment is required to prevent the arterial duct (ductus arterious) from closing (by infusion of prostaglandin E_1) and transfer to a specialist paediatric cardiac centre.

Cardiorespiratory distress and heart failure

Causes of cardiorespiratory distress due to increased pulmonary blood flow or heart failure include left-to-right shunting though septal defects. The commonest causes are large ventricular septal defect and persistent patent ductus arteriosus.

Shock

Neonatal shock is usually due to major sepsis, significant hypovolaemia or blood loss or congenital heart disease. Congenital heart diseases causing shock include major interruption to the systemic circulation such as hypoplastic left heart syndrome, critical aortic stenosis and severe coarctation of the aorta or complex cardiac defects.

The asymptomatic murmur

Murmurs are common in newborn infants and are frequently innocent. A thorough search for other signs of cardiac disease should be made and an expert opinion arranged where appropriate. It is important to remember that the mention of a heart murmur can strike panic into even the calmest of parents and the situation needs to be handled with great tact. Rapid definitive diagnosis by echocardiography is the mainstay of successful management.

Respiratory

Congenital diaphragmatic hernia

Herniation of the abdominal contents into the hemithorax leads to severe respiratory difficulties with persistent pulmonary hypertension and maldevelopment of the pulmonary arteries of all sizes. Most cases are diagnosed antenatally but infants can present unexpectedly with respiratory distress and cyanosis at birth. Essential early management involves the passage of a large-bore nasogastric tube into the stomach to prevent gaseous distension, ventilation and rapid transfer to intensive care. All these infants require tertiary-level intensive care, with access to sophisticated mechanical ventilation and modern vasodilator therapy such as nitric oxide. Surgery is delayed until the infant's respiratory status has been stabilized. Survival depends on the degree of underlying pulmonary hypoplasia and the presence of associated congenital anomalies such as cardiac defects. Overall a survival figure of around 60% is often quoted when counselling parents. ECMO can be carried out on infants with a congenital diaphragmatic hernia where medical therapy has failed although it's use in this situation is controversial. Long-term complications include persistent gastro-oesophageal reflux and respiratory problems; neurodevelopmental problems can develop if neonatal hypoxia was severe and has been shown to be worse in those infants treated with ECMO.

Gastrointestinal and abdominal wall defects

Oesophageal atresia and tracheo-oesophageal fistula

These conditions should be suspected when there is polyhydramnios or excessive mucus from the mouth at birth. The baby may show rapid onset of respiratory distress and cyanosis particularly after the first feed. Radiography after a nasogastric tube has been inserted confirms the diagnosis, showing the nasogastric or orogastric tube curling up in the oesophageal pouch (if atresia is present). Associated congenital anomalies occur in 50% or more of infants. Survival is usually determined by the severity of associated congenital anomalies and not the defect itself.

Abdominal wall defects

Exomphalos, in which part or all of the intestine and abdominal organs are in a peritoneal sac outside the abdomen, should be differentiated from gastroschisis, where a congenital defect of the abdominal wall allows herniation of the abdominal contents without a peritoneal sac. The former is frequently associated with other congenital defects while the latter is not. Urgent surgery is required if the amniotic sac has broken and for gastroschisis; immediate management is to wrap the abdominal contents in a plastic wrapper, taking care not to twist the bowel and disrupt its vascular supply. This should help prevent hypovolaemia due to fluid loss from the exposed bowel. The long-term outcome for most with exomphalos is determined by the presence of associated congenital anomalies. In gastroschisis, 90% or more now survive. However, their postnatal course is often protracted and parenteral nutrition may be required for several weeks with its risks and complications. In addition, bowel atresia and necrotizing enterocolitis may develop.

Intestinal obstruction

High intestinal obstructions usually present with vomiting that may be bile stained, and this ominous sign demands urgent investigation. Plain radiography of the abdomen can confirm the presence of obstruction by showing a lack of air in the lower gut or a sign such as the 'double bubble' of duodenal atresia. An upper gastrointestinal contrast study is required in any infant who presents with bile-stained vomiting in order to exclude malrotation and/or volvulus. Both of these conditions are time critical and infants who have produced bile-stained vomit should arrive in a surgical centre for asessment within 4 hours of the onset of symptoms. Hypertrophic pyloric stenosis does not usually present until 2–6 weeks of age.

Lower intestinal obstruction usually presents as failure to pass meconium within 24 hours followed by abdominal distension with or without vomiting. Causes include Hirschsprung's disease, meconium ileus due to cystic fibrosis, low bowel atresia or hypoplasia, and imperforate anus. A meconium plug can sometimes mimic obstruction especially in preterm infants.

Breastfeeding

The importance of breast milk and nutrition cannot be over-emphasized. Human breast milk is the preferred source of nutrition for both term and preterm babies and is associated with a significant reduction in both morbidity and mortality. Every effort should be made to encourage a mother to breastfeed. Breastfeeding within 30 min of a normal birth and early breast massage and expression within 6 hours of a preterm delivery is essential to establish breastfeeding. All professionals who care for women and their babies need to offer support and expert council to promote successful breastfeeding in challenging conditions of stress and ill health.

There are few genuine contraindications to breastfeeding but include some rare inborn errors of metabolism in the baby such as galactosaemia. It is not the practice in the UK to encourage HIV-positive mothers to breastfeed, but this is not the case in developing countries. Breastfeeding is generally safe for the baby if the mother requires medication; rarely, breastfeeding is absolutely contraindicated. Examples of drugs which require caution are given in Table 32.2. When prescribing for a breastfeeding mother it is wise to check that the drug prescribed is safe. Information can be found in the *British*

Table 32.2 Drugs and breastfeeding.

Breastfeeding contraindicated
Cytotoxics, immunosuppressants, ergotamine, lithium, phenindione, chloramphenicol, tetracyclines
Example of drugs to be used with caution during breastfeeding
Antiarrhythmics: amiodarone
Antibiotics: metronidazole
Anticonvulsants: gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, vigabatrin
Antidepressants: doxepin, selective serotonin reuptake inhibitors (SSRIs)
Antihypertensives: beta-blockers
Anxiolytics: benzodiazepines, buspirone
Radioisotopes

Table 32.3 Frequently asked questions.

Is milk from the newborn infant's breast normal? *Answer*: Normal in boys and girls
Is vaginal bleeding in girls normal? *Answer*: Normal
What causes persistent sticky eye after culture and treatment of infection? *Answer*: Blocked nasolacrimal duct. Will recannulate spontaneously. Does not need probing
How often should a baby feed 'on demand'? *Answer*: Usually about 2–4 hours, but every 6 hours is not uncommon in healthy infants
My baby is squinting. Is this normal? *Answer*: Yes, in the first week after birth
Is my breastfed baby getting enough milk? *Answer*: If the baby is gaining weight properly, yes

National Formulary; if a contraindication, caution or a potential problem is identified, the advice of the local paediatric pharmacist or local drug information centre should be sought. Often alternative drugs can be prescribed and breastfeeding continued. Information is also available via websites such as www.ukmi.nhs.uk.

Many minor alterations in physiology cause alarm to parents. Some common questions and responses to them are outlined in Table 32.3. In the absence of disease, reassurance is all that is required.

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33

Perinatal Epidemiology and Statistics

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Background

John Last in the *Dictionary of Epidemiology* defines epidemiology as the 'The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems'. It does not represent a body of knowledge or a specific organ system such as cardiology or neurology but instead represents methodology focused on improved understanding of the determinants of illness and disease. Modern epidemiology remains a young discipline of science. Although many excellent studies were conducted before, it was in the twentieth century where highly informative epidemiological studies were performed that have significantly informed clinical practice and public health. This includes, amongst others, the Framingham Heart Study, an ambitious cohort study which commenced in 1948 with the primary objective of identifying common factors or characteristics that contribute to cardiovascular disease (CVD) by following its development over a long period of time in a large group of participants, who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. In the original cohort of 5209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, extensive physical examinations and lifestyle interviews were conducted that were used to study the common patterns related to CVD development. From 1948 onwards, the original participants returned at regular intervals for collection of detailed information on medical history, clinical examination and laboratory tests. Subsequent second-generation participants were also recruited and in 2002 the study entered a new phase, the enrolment of a third generation of participants, the grandchildren of the original cohort. In the UK there have also been large-scale cohort studies, including the MRC-funded Richard Doll study in the 1950s, in which a cohort of general practitioners were followed up to study the influence of smoking on health and disease [1]. This pioneering work has had a global impact and was key in understanding the harmful effects of smoking. The UK is also home to a number of large-scale cohort studies, including the longest running birth cohort in the world, the 1946 Birth Cohort, and the Southampton Women's Survey, which recruited women prior to conception. In the MRC Cohort Strategic Review in 2014 it was reported that approximately 3.5% of the UK population are cohort members [2].

Reproductive and perinatal epidemiology is a branch of epidemiology that focuses on diseases and disorders of reproduction and/or events in the perinatal period. Perinatal epidemiology includes the study of both maternal and neonatal events. The interrelated nature of human reproduction and development provides the opportunity to develop well-designed prospective cohort studies with collection of longitudinal data at key periods of development in pregnancy and following birth, to understand the impact of pregnancy and development on long-term maternal and offspring health. The Avon Longitudinal Study of Parents and Children (ALSPAC), also known as Children of the 90s, based at the University of Bristol is a world-leading birth cohort study in which, between April 1991 and December 1992, more than 14 000 pregnant women were recruited. These women and the children of ALSPAC have since been followed up over two decades with annual questionnaires for the mothers, fathers and the children from age 5. Over 1200 publications have been published from data collected in this cohort. Perinatal medicine has also been informed by randomized controlled trials including some large international multicentre studies. These have informed and improved our obstetric practice in many areas, including the management of severe pre-eclampsia (MAGPIE Trial 2002), fetal growth restriction (GRIT Trial 2003, TRUFFLE Trial 2015) and breech delivery (Term Breech Trial 2000).

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

This chapter provides an overview of the different study design and quantitative methodologies available to address many of the key research questions in the discipline. Finally, it also provides an overview of the commonly used definitions, statistical methodology and inferences.

Study design

The premise of any research question or hypothesis is based on the relationship between an exposure and outcome of interest. In epidemiology, *exposures* are potential causal characteristics. It can refer to treatment (pharmacological and non-pharmacological behavioural interventions), behaviour (e.g. smoking, drug use), genotype or trait (e.g sickle cell disease, *BRCA1* gene mutation) or environmental (e.g. dust, pollution). *Outcome* refers to either disease states (e.g stillbirth) or clinical phenotypes that have the potential to increase adverse outcomes (e.g small for gestational age).

Study design is defined as the process in which a researcher or research team translates the hypothesis of interest through a detailed project plan into an operational study. The types of research conducted are broadly divided into observational and interventional research (Fig. 33.1). An observational study is when research is focused on the collection of health and socio-demographic variables related to exposure and outcome. These variables can range from population-based data (e.g census data) to specifically designed health-related questionnaires, clinical examination and collection of biomarker samples. Specifically in observational studies the data available from the subjects in the study are not dependent on an intervention administered by the study investigators. Observational research can further be categorized as descriptive or analytical. Descriptive studies are cross-sectional studies that report the incidence or prevalence of health-related states at a specific time point. They do not attempt to provide an association between the exposure and outcome. Observational studies which are analytical in nature are focused on determining the relationship between exposure and outcome through different study designs. In contrast, interventional studies are studies in which the investigator specifically provides an intervention with the aim of exploring the effect of the intervention on health-related outcomes. The choice of study design adopted by researchers will depend on the type of exposure and outcome being studied. All types of observational and interventional studies are described in detail in the following sections.

Cross-sectional studies

Cross-sectional studies involve observation of a total population, or a random subset of it, at a defined time. They provide information on an entire population under study and can describe absolute risks and not just relative risks. They can also describe the prevalence of disease. National audits of maternal and perinatal deaths are variants of cross-sectional surveys [3].

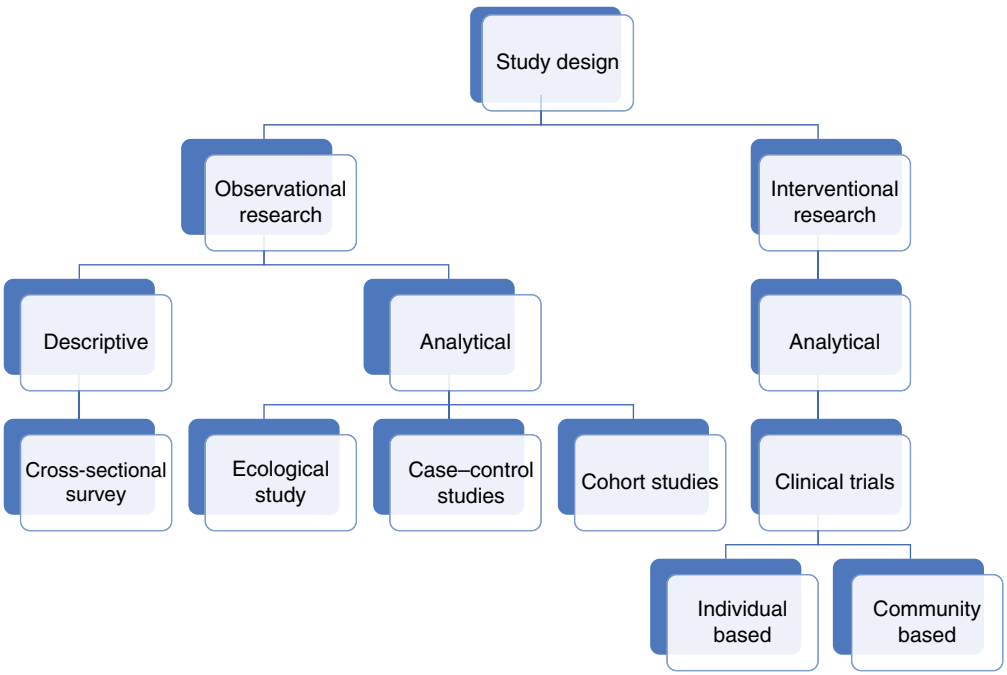


Fig. 33.1 Study design.

Summary box 33.1

Definitions used in maternal death audits

- *Maternal mortality ratio* (MMR): number of maternal deaths per 100 000 live births.
- *Maternal mortality rate*: number of maternal deaths per 100 000 maternities.
- *Total number of maternities*: the number of pregnancies that result in a live birth at any gestation or stillbirths occurring at or after 24 completed weeks of gestation and which are required to be notified by law. Multiple pregnancies are counted only once.
- *Direct maternal death*: the result of a complication of pregnancy, delivery or puerperium from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above.
- *Indirect maternal death*: a pregnancy-related death in a patient with a pre-existing or newly developed health problem that was not the result of direct obstetric causes but which was aggravated by the physiological effects of pregnancy.
- *Coincidental (fortuitous) maternal death*: other fatalities during, but unrelated to, pregnancy or the puerperium.
- *Late maternal death*: a death occurring after 42 days up to 1 year after abortion, miscarriage or delivery that is the result of direct or indirect maternal causes.

Summary box 33.2

Classification of perinatal deaths

- *Stillbirth*: a baby born without signs of life after 23^{+6} weeks of pregnancy. This can be further divided into:
  - Intrapartum stillbirth: a baby known to be alive at the beginning of labour but stillborn.
  - Neonatal death: death of a liveborn baby occurring before 28 completed days after birth. This can be further divided into (i) early (0–6 completed days) and (ii) late (7–27 completed days).
- *Perinatal death*: death of a fetus or a newborn in the perinatal period, which commences at 24 completed weeks' gestation and ends before seven completed days after birth (total of stillbirths and early neonatal death).

Cohort studies

Cohort studies are a form of longitudinal observational study used to analyse risk factors by studying groups of people who do not have the disease either retrospectively or prospectively (the preferred method). These are analytical observational studies in which the comparison of health outcomes between groups is defined by the exposure of interest. Participants in the cohort are defined by exposure and are followed up for a specific period. In pregnancy, examples of cohort studies in recent years include the SCOPE cohort (Screening for Pregnancy Endpoints), a multicentre international prospective cohort study of nulliparous women, and the POPS study (Pregnancy Outcome Predictive Study), also a prospective cohort of low-risk nulliparous women in Cambridge [4,5]. Both cohorts are focused on identifying predictors of preterm birth, pre-eclampsia and small-for-gestational-age (SGA) infants. SCOPE is primarily focused on early pregnancy factors associated with the outcomes of interest, whilst in the POPS study longitudinal clinical data, serum biomarker samples and ultrasound measurements were collected throughout pregnancy which may also provide mechanistic insight to development of disease. The cohort can also be selected by a specific event such as year of birth (a birth cohort). Examples include the 1946 Birth Cohort and the ALPSAC study previously described. The cohort design, which can be either retrospective or prospective, allows the study of multiple outcomes and exposures and specifically rare exposures (e.g. asbestos exposure). It is costly and not appropriate for rare diseases with a long latent period for the development of the outcome of interest.

Case–control studies

Case–control studies can be used for both retrospective and prospective studies. In a case–control study, participants are selected on the basis of the outcome of interest. People with the disease are cases and appropriate controls are selected without the outcome of interest to allow comparisons to be made between exposures of interest. Often controls are matched for characteristics within the group to reduce the bias in the comparison between the groups. For example, in the determinants of factors associated with endometrial cancer in postmenopausal women (cases), healthy controls are matched for age. Data are then collected in both groups and factor(s) that are different between the groups may demonstrate an association with the outcome of interest. Matching in case–control studies precludes the factor in which the groups are matched to be explored as a factor associated with the disease. In the example cited, the effect of age on endometrial cancer cannot be determined. In common with all observational studies, case–control studies do not prove causation but instead demonstrate association. The strength of association, coupled with biological plausibility, are some of the criteria used to suggest association as reported by the Bradford Hill Criteria (Table 33.1) [6].

Table 33.1 Bradford Hill Criteria.

1	Strength of effect size	A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal
2	Consistency	Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect
3	Specificity	Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect, the bigger the probability of a causal relationship
4	Temporality	The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay)
5	Biological gradient	Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence
6	Plausibility	A plausible mechanism between cause and effect is helpful
7	Coherence	Coherence between epidemiological and laboratory findings increases the likelihood of an effect
8	Experiment	Occasionally it is possible to appeal to experimental evidence
9	Analogy	The effect of similar factors may be considered

Inherent within the design of case–control studies, the selection of cases and controls by the investigator precludes any estimation of disease incidence. However, relative risk can be demonstrated between the groups. The control group is a sample of the total population and selected because they do not have the disease. To determine true population risk (incidence of the disease in a population) a larger cross-sectional study or cohort study is required. A variation of this method is the nested case–control study, where cases with a disease in a defined cohort (the nest) are identified and, for each, a specified number of matched controls are selected from the same cohort who have not yet developed the disease. The nested case–control design is easier and less expensive than a full cohort approach. Case–control studies are also particularly useful for rare diseases and diseases with long latency periods. If well designed, this approach will also allow examination of multiple exposures of interest. The temporal sequence of exposure and disease can sometimes be difficult to study in a case–control study and certainly the size of the study will need to be sufficiently large to study rare exposures, which often limits this design in some settings.

A retrospective study is one where the records are studied after all the events and outcomes have already occurred. The data are collected from a given population. Risk factors or disease outcomes are compared between subgroups that have different known outcomes. The study can be designed using a case–control or cohort model. This differs from a prospective study, which is conducted by starting with two groups that are selected by risk factor or randomized and subsequent future outcomes are noted. Retrospective studies have the following benefits: they are cheap, it is easier to collect large numbers and to select cohorts of disease and non-disease, and they are less time-consuming since the main effort required is the collection of data. However, they are limited by incomplete collection of data and recall bias. In contrast, prospective studies follow populations over time to study outcome. In population risk studies, a large number of negative controls will be collected depending on the disease incidence. Although the costs of these studies are significantly higher, they provide an opportunity to specifically tailor data collection.

Issues of confounding and bias limit all observational studies. A well-designed study does have the potential to limit these issues. *Confounding* is defined as the alternative explanation to the association found between exposure and outcomes. A confounder must be associated with both the exposure and the outcome and not be on the causal pathway between the exposure and the outcome. An example of a confounder in the association between coffee drinking and cancer is smoking. It is recognized that coffee drinkers are more likely to smoke and smoking is certainly associated with cancer. Identifying potential confounders allows investigators to design and collect data appropriately, which then has the potential to minimize confounding. At the design stage this includes restricting the study population, matching in case–control studies and randomization in interventional studies. At analysis stratification, standardization and statistical modelling (regression) are methods that can be utilized to minimize confounding. However, this is reliant on the data collected on potential confounders.

Bias is a systematic error that leads to a result which does not represent the truth (e.g. information bias, bias in data collection and reporting, selection of study

participants). Unfortunately, bias cannot be corrected through statistical analysis and can only be minimized by appropriate study design.

Randomized controlled trials

Randomized controlled trials (RCTs) are a type of interventional study design with superior methodology in medical statistical research because they reduce the potential for bias by random selection of participants to one intervention arm or to another intervention, non-intervention or placebo arm. The participants can be patients, health volunteers or communities (randomized cluster trials). This minimizes the possibility that confounding variables will differ between the two groups. However, not all studies are suitable for RCTs and the methodologies mentioned previously may be more suitable. In order to further reduce bias, the randomized trial may be designed as a double-blind RCT, where neither the clinician nor the participant knows which treatment arm the participant is in, or a single-blind RCT, where the clinician knows but the participant does not. In some circumstances an open label trial is carried out, where it is not possible to blind either the clinician or the patient but randomization is performed without bias at time of therapy.

Meta-analysis

Independent trials although well powered and designed at conception, occasionally do not demonstrate an effect of the intervention. Often trials are also repeated with conflicting results. Meta-analysis provides the opportunity to pool results from different studies if sufficiently similar (heterogeneity) with respect to trial population and outcomes of interest. This approach increases the power to detect smaller differences that were not identified in individual studies. It also increases the precision of the effect size observed. The weighted average of the combined effect size is estimated. This is related to the sample size of the individual studies and the effect size observed.

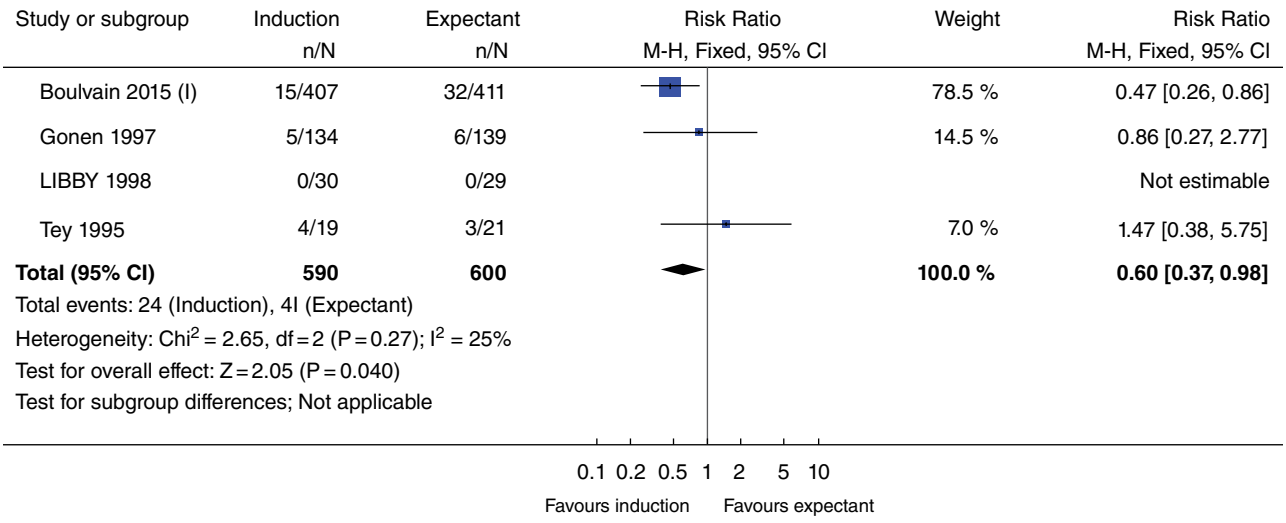
This process of meta-analysis can be part of a systematic review, for example Boulvain *et al.* [7] reported to the Cochrane Collaboration. Figure 33.2 demonstrates the results of a meta-analysis of the effect of induction of labour at 37–40 weeks for suspected fetal macrosomia on the risk of shoulder dystocia. This is a forest (Peto) plot, a graphical display of the relative strength of treatment effects in the different trials. Down the left-hand side are the trials included. The trial quoted above is the last of the four trials listed (first author Boulvain). On the right-hand side is a plot of the risk ratio for each of these studies incorporating confidence intervals represented

Analysis 1.3. Comparison I Induction versus expectant management, Outcome 3 Shoulder dystocia.

Review: Induction of labour at or near term for suspected fetal macrosomia

Comparison: I Induction versus expectant management

Outcome: 3 Shoulder dystocia



(I) Any shoulder dystocia

Fig. 33.2 Summary output from meta-analysis [7].

by horizontal lines. The graph is plotted on a logarithmic scale so that the confidence intervals are symmetrical about the means to prevent apparent exaggeration in ratios greater than 1 when compared with those less than 1. The area of each square is proportional to the study's weight. The overall meta-analysed measure of effect is represented as the diamond on the bottom and the lateral points indicate the confidence intervals. A vertical line is plotted at unity and if the confidence intervals for individual studies or the total effect overlap with this line, then the results are not significant. One study included in this meta-analysis did not study this outcome of interest (LIBBY 1998). Two studies did not reach significance (Gonen 1997, Tey 1995) but the most recent published in 2015 (Boulvain) provided an overall significant result. This is the largest of the four studies. The overall pooled results also suggest a reduction in the risk of shoulder dystocia associated with induction of labour at 37–40 weeks.

Statistics

The primary principle in statistics that is often not well described nor understood is that analysis performed on a study population represents only a sample of the population. Therefore any findings from a study group or comparison between study groups reflect the population from which the study participants are sampled. The robustness of the sampling process will influence the strength of statistical inference which can be applied from the findings in the study population to the underlying population. An example of this is reflected in the size of the study population. If the sample of study population is small compared with the underlying population or in relation to the frequency of outcome, then the uncertainty of the statistical findings will increase, reflected by wider confidence intervals.

Incidence and prevalence

Incidence is a measure of the risk of developing some new condition within a specified period of time. Although sometimes loosely expressed simply as the number of new cases during some time period, it is better expressed as a proportion or a rate within a specific denominator to allow meaningful comparison. Therefore, the incidence (rate) is usually given as the number of new cases per given population in a given time period. In the examples above in pregnancy, the population and time period is self-selecting: the population is pregnant women and the time period is pregnancy and the puerperium. In the non-pregnant population it is more difficult. The time period is usually fixed at a year but the population denominator is more of a problem. In gynaecology, depending on the disease being studied, the at-risk female population may be different. Endometriosis is typically, but not absolutely, seen during the reproductive years; it has been estimated that it affects approximately 10% of all women at some point, but this is lifetime risk not incidence, which is risk of new cases within a risk group over a fixed period of time. Nor is it prevalence.

Prevalence is a measure of the total number of cases of disease in a specific population at any one period of time, rather than the rate of occurrence of new cases. This indicates the burden of the disease on society and is dependent on both the number of new cases and the length of time the disease is present (prevalence = incidence × duration). This equation demonstrates the relationship between prevalence and incidence: when the incidence goes up, prevalence must also rise. Incidence is more useful in understanding disease aetiology as it reflects disease occurrence and also the response to interventions. In the classical example of the cases of puerperal fever described by Semmelweis [8], the higher incidence in one group suggested an aetiological factor related to that group alone and the fall in incidence that followed the hand-washing initiative demonstrated a successful intervention. Therefore, incidence will vary with changes in aetiological factors and prevention. Prevalence is dependent on the duration of disease and the availability of cure. The longer the duration of disease, the higher the prevalence. The prevalence is also dependent on the study population. Using endometriosis as an example, its overall prevalence varies, ranging from 5 to 10%. A study of asymptomatic women undergoing sterilization reported a figure of 6% but this rises to 21% in women with infertility and as high as 60% in those with pelvic pain [9]. Endometriosis is recognized to influence fertility and also cause pelvic pain. This would explain the higher prevalence observed in those subgroups.

The incidence over time can also be studied using Kaplan–Meier plots, which present incidence data as a plot of cumulative incidence over time, taking into account variations in rate of events. This method was used in our recent study exploring the effects of maternal placental syndrome (MPS) in pregnancy on long-term incidence of maternal cardiovascular event (CVE) in women with systemic lupus erythematosus (SLE) (Fig. 33.3) [10]. This plot demonstrates the disease-free incidence over time (probability of CVE-free survival). In all groups this decreases over time. However, in women with a history of MPS in pregnancy, the disease-free incidence decreases further, especially if MPS is

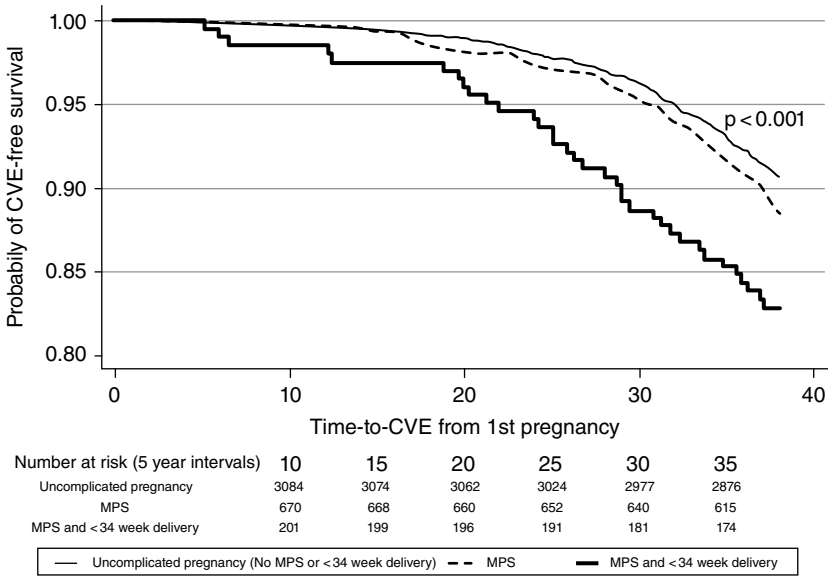


Fig. 33.3 Kaplan–Meier survival estimates for CVE in parous women with SLE [10].

also associated with preterm delivery less than 34 weeks. This may suggest shared etiological pathways leading to MPS in pregnancy and longer-term cardiovascular disease.

Pearl Index

The incidence of a disease or event is often quoted in rate per cent per year, for example the failure rate of contraceptives is quoted using the Pearl Index [11]. The following information is required to calculate the Pearl Index: the number of pregnancies and the total number of months or cycles of exposure of women. The index can then be calculated as follows:

- number of pregnancies in the study divided by the number of months of exposure and then multiplied by 1200;
- number of pregnancies in the study divided by the number of menstrual cycles experienced by the women and then multiplied by 1300; 1300 is used instead of 1200 because the average menstrual cycle is 28 days, giving 13 cycles per year.

These are normally calculated over a trial period of 1–2 years and claims to give the risk of pregnancy in 100 women over 1 year of use or 10 women over 10 years. This assumes that the pregnancy risk is static over the years of use and based on the rate in the first 1–2 years. Again, a Kaplan–Meier plot could be used to test for accumulative pregnancy rates over time when comparing different methods of contraception rather than the Pearl Index alone.

Statistical significance

In studies comparing outcomes between two or more groups, it is important to determine if any observed difference is simply due to chance or is truly different. A result is called statistically significant if it is unlikely to have occurred by chance alone. In the comparison between two groups, investigators are motivated to determine if there is any difference between groups. In the example on the effect of MPS and long-term CVE, are the differences observed between the groups merely due to chance or is there a true difference? It is important to remember that being statistically significant does not mean the result is important or clinically relevant. In large studies small differences can be found to be statistically significant but have little clinical or practical relevance. Tests of correlation may show significant correlations but have no or minor causative relation. Tests of significance should always be accompanied by assessments of relevance and effect-size statistics, which assess the size and thus the practical importance of the difference.

Tested often enough, in theory any result is possible but the likelihood that any given result would have occurred by chance is known as the significance level or *P*-value. In traditional statistical testing, the *P*-value is the probability of observing data similar to that observed by chance alone. If the obtained *P*-value is small, then it can be said that this is unlikely and the results are significantly different. To test whether the results are true or not, they are compared with those expected if the null hypothesis is true or there is no difference. So the basis of comparison of data is testing

whether the null hypothesis is true and the level of significance desired.

The null hypothesis and statistical tests

Statistical convention assumes that the experimental hypothesis (e.g. that one treatment is better than another) is wrong and assumes the *null hypothesis*, or no difference, as correct and that testing will assess whether this is wrong (i.e. that the treatment is better). When the null hypothesis is nullified (not supported within accepted confidence limits), the alternative hypothesis (that one treatment is better than the other) is accepted. Therefore, the null hypothesis is generally a statement that a particular treatment has no effect or benefit or that there is no difference between two particular measured variables in a study.

The result of the statistical test is given as a *P*-value. The size of the *P*-value relates to the likelihood of the result occurring by chance. The lower the *P*-value, the more likely the null hypothesis is nullified and the results are significantly different. A result of $P < 0.05$ means that the probability of this result being due to chance is less than 5% so the results are different to a 95% probability. The nearer to unity the *P*-value, the more likely that the null hypothesis is accepted and that there is no difference, but it should be remembered that 'the null hypothesis is never proved or established, but is possibly disproved'. In other words, if no significant difference is found, the test has not proven that there is no difference but has failed to show difference.

As stated previously, statistical findings are dependent on the population studied. The *P*-value of any test is dependent on the degree of difference in the test results and the number of people or values in the trial. If the trial is not of appropriate size, then two basic statistical errors can be made, type I and type II errors. Type I error, also known as the false positive, occurs when a statistical test falsely rejects a null hypothesis, for example where there is no difference between treatment arms in a trial as stated by the null hypothesis but the test rejects the hypothesis, falsely suggesting that there is benefit of treatment. The rate of type I error is denoted by the Greek letter alpha (α) and equals the significance level of the test, which by convention is usually taken as 0.05 or below. This means that any positive result is correct to a level of 95% probability.

Type II error, also known as the false negative, occurs when the test fails to reject a false null hypothesis, for example where there is a difference between treatment arms in a trial but the null hypothesis states that there is no difference and the test fails to reject the null hypothesis, falsely suggesting that there is no difference. The rate of type II error is denoted by the Greek letter beta (β) and is usually taken as 0.80, i.e. an 80% chance of rejecting a false null hypothesis.

Therefore when designing a trial, two considerations must be assessed:

- to reduce the chance of rejecting a true hypothesis to as low a value as possible;
- to devise the test so that it will reject the hypothesis tested when it is likely to be false.

The ability of a study to achieve this is assessed by the power. The power of a statistical test is calculated on the probability that the test will reject the null hypothesis when the null hypothesis is false and not produce a type II error or a false-negative result. As the power increases, the chance of a type II error occurring decreases as calculated by $\text{power} = 1 - \beta$. Statistical power may depend on a number of factors but, at a minimum, power nearly always depends on the following three factors:

- the statistical difference desired;
- the size of the effect of the treatment or difference between test groups;
- the sample size used to detect the effect.

The statistical difference desired is the chosen maximum *P*-value where the results are accepted as statistically significant, which is usually 0.05 but may be less than this if multiple testing is to be carried out. Once this *P*-value is agreed, power analysis can be used to calculate the minimum sample size required that is likely to detect a specified effect size (or difference). Similarly, the reverse is true and power analysis can be used to calculate the minimum effect size that is likely to be detected in a study using a given sample size. In general, a larger sample size will allow testing for a larger effect size and boost statistical power.

The specificity of the test is equal to $1 - \alpha$ ($1 - 0.05 = 0.95$). Increasing the specificity of the test lowers the probability of false-positive errors, but raises the probability of false-negative errors, which is a reflection on the sensitivity of the test. There are no formal standards for power but it is mostly calculated against the agreed *P*-value of 0.05 (95% specificity) and a 0.80 chance of avoiding a type II error (80% sensitivity). This convention implies a four-to-one trade-off between type II (β) risk and type I (α) risk and can be changed depending on whether a false-positive or false-negative rate is thought to be more important.

Summary box 33.3

Statistical terms

Specificity
Relates to the ability of the test to identify negative results:

True negatives / total condition negatives = $d / b + d$

where *d* is true negatives correctly identified and *b* is false positives. A high specificity implies a high probability that a positive result is positive and there is a low type I (α) error rate.

Sensitivity
Relates to the ability of the test to identify positive results:

True positives / total condition positives = $a / a + c$

where *a* is true positives correctly identified and *c* is false negatives. A high sensitivity implies a high probability that a negative result is negative and there is a low type II (β) error rate.

Power
Relates to the probability that the test will not produce a type II error:

$= 1 - \beta$

Positive predictive value (PPV)
The ratio of positives that are truly positive:

True positives/total test outcome positives = $a/a + c$

A high PPV gives an estimate of the chances that a positive result is truly positive.

Negative predictive value (NPV)
The ratio of negatives that is truly negative:

True negatives/total test outcome negatives = $d/b + d$

A high NPV gives an estimate of the chances that a negative result is truly negative.

Positive likelihood ratio
A measure of the change in the likelihood of a positive result from the prior test likelihood of positivity:

$= \text{Sensitivity} / (1 - \text{specificity}) = \left[a / (a + c)\right] / 1 - \left[d / (b + d)\right]$

It is commonly used in assessments of treatments or predictors of disease. The odds of positivity equals the pre-test odds multiplied by the positive likelihood ratio.

Negative likelihood ratio
A measure of the change in the likelihood of a negative result from the prior test likelihood of negativity:

$= (1 - \text{sensitivity}) / \text{specificity} = 1 - \left[a / (a + c)\right] / \left[d / (b + d)\right]$

It is commonly used in assessments of treatments or predictors of disease. The odds of negativity equals the pre-test odds multiplied by the negative likelihood ratio.

Odds ratio (OR)
A test of effect size as measured by the ratio of the positive odds in one arm against the positive odds in the other arm of the study:

$\text{OR} = (a/b) / (c/d) = ad/bc$

Relative risk (RR)
A test of the probability of an event occurring relative to the risk in the comparative group:

$\text{RR} = \left[a / (a + b)\right] / \left[c / (c + d)\right]$

Terms of significance

The OR is a test of effect size. It has been stated that 'statistics means that we never have to say we are certain'. Statistics is about probability not certainty. This is measured by confidence intervals. Confidence intervals are the range of probability (usually 95%) that if the test is repeated many times the result will always fall within that given range. To observe a true difference between two groups it is important that the confidence intervals do not cross 1 (or unity), meaning that in all cases the direction of difference is the same. The RR is simply the probability of an event occurring relative to the risk in the comparative group. This measure of effect size differs from the OR in that it compares probabilities instead of odds. For small probabilities, the RR and OR are similar.

Prediction testing

Another use for contingency tables is in studies evaluating potentially new tests that screen for disease. Each individual taking the test either does or does not develop the disease. The test can be assessed for its value in predicting the disease.

- True positive: correctly predicts those who will develop the disease.
- False positive: does predict disease but the patient does not get it.
- True negative: does not predict the disease and the patient does not get it.
- False negative: does not predict the disease and the patient does get it.

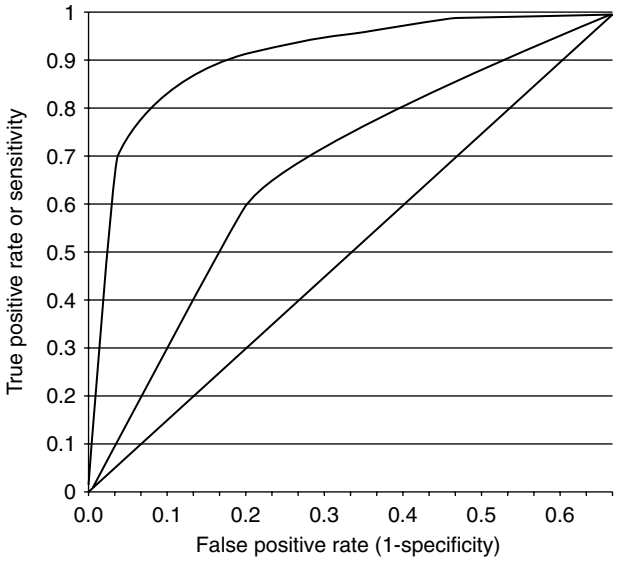


Fig. 33.4 Receiver operating characteristic (ROC) curve. *Source:* Edmonds DK. *Dewhurst's Textbook of Obstetrics and Gynaecology*, 8th edn. Oxford: Wiley-Blackwell, 2012. Reproduced with permission of John Wiley & Sons.

The balance between sensitivity and specificity can be assessed using the receiver operating characteristic (ROC) curve. The ROC curve is a graph of the sensitivity or true positive rate plotted against the false-positive rate (1 – specificity). It is called the ROC curve because it compares the two operating characteristics, the true positive rate and the true negative rate with changing cut-off levels. This allows the optimum cut-off level of a predictive or diagnostic test for any given disease to be determined by finding the optimum sensitivity and specificity for that test (Fig. 33.4).

In Fig. 33.4, the straight line running from zero to 1 is no better than chance alone. Any curve to the left of the line is better than chance. The more to the left, and the nearer the 'perfect' upper left-hand corner, the better the test. In this example the left-hand curve gives the best result for sensitivity 80–90% and specificity 80–90% (false-positive rate = 1 – sensitivity). What cut-off point is used depends to some extent on whether it is better to capture the maximum or miss the fewest in the disease being investigated. As the lines move further left, the more discriminating the test, with a higher sensitivity and low false-positive rate.

Descriptive statistics

Up to now we have discussed the assessment of rates and incidence of a given problem in a population but statistics are also used to describe a population and what values fall outwith the normal range that could be used for diagnostic purposes.

What is normal?

The term 'normal' is one of the most misunderstood terms in medical statistics and epidemiology. In its pure sense, it is the whole population, good and bad, and this should contribute to the normal range. However, in medical testing, normal is often taken as all individuals who are not abnormal, i.e. do not have the disease under study. This produces problems when comparisons are being made or predictors are being assessed, as 'not abnormal' is a post-test value. When using a predictor it is important to test it against the whole population including those who will develop the disease or other diseases as this is how it will function in the real world. Without doing this, the value of most predictive tests is overstated.

Normal distribution

The graph of most 'normal' populations is a bell-shaped curve demonstrating a Gaussian distribution with the mean in the middle and a mirror-image distribution on either side (Fig. 33.5). It is one of the statistical standards and implies that, in most populations, there is an even spread (symmetrical) around the mean or average. The mean is calculated by taking the sum of all the measurements and dividing it by the total number of measurements taken. It is the same as the average. If the dataset were based on a series of observations obtained from a

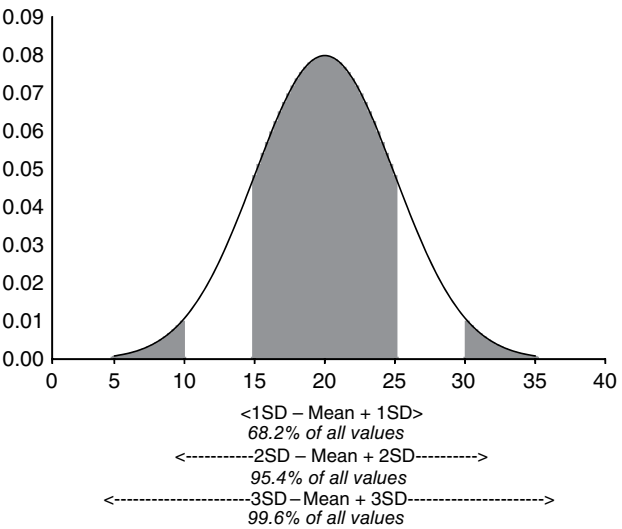


Fig. 33.5 Normal distribution and standard deviation. The mean is 20 and the SD 5. The bands correspond to 1, 2 and 3 SDs from the mean. Mean ±1SD takes in 68.2% of all values; mean ±2SD takes in 95.4% of all values and is equivalent to 95% CI; mean ±3SD takes in 99.6% of all values and is equivalent to the range. *Source:* Edmonds DK. *Dewhurst's Textbook of Obstetrics and Gynaecology*, 8th edn. Oxford: Wiley-Blackwell, 2012. Reproduced with permission of John Wiley & Sons.

sample of the population, it is known as the sample mean, which will relate to, but may not be exactly the same as, the true population mean. Knowing the mean of a population is only the start. Different populations will have different ranges of measurements, some with a far wider range of values making up the population.

The range is calculated by subtracting the smallest measurement (minimum) from the greatest (maximum) and provides an indication of sample spread. It is measured in the same units as the data. For example, if in a given dataset the mean body mass index (BMI) was 29.6, the lowest value 15.2 and the highest 47.3, the range would be 47.3 – 15.2 = 32.1. Because it is calculated from two measurements, the lowest and the highest, it is a weak statistical measure of distribution as it gives no indication of how the measurements are distributed throughout the range. Also, since it is often a measurement of a sample of a larger population, it does not necessarily give the full potential range of the population as a whole.

The measure of variation or spread around the mean can be assessed in many ways but the most common is the standard deviation. The mean and standard deviation describe a sample population and can be used to assess differences with other sample populations. The standard deviation (SD) is the assessment of variability of each individual measurement from the mean and is calculated by taking the average difference of each measurement from the calculated mean. A low SD indicates that the measurements tend to be very close to the mean as the variation is small and the distribution tight, producing a narrow peaked curve, whereas a high SD indicates that the data are spread out over a large range of values, giving a wider flatter curve.

Figure 33.5 shows the graph for a normal distribution and the SD. In a normal distribution, about 68% of the measurements will be within one standard deviation from the mean, while two standard deviations from the mean account for about 95% and three standard deviations for about 99.7%. Therefore, the range of the mean ±1SD will contain the majority of the measurements; the 95% confidence interval of the population will lie within the mean ±2SDs and the mean ±3SDs approximates to the range. This 68/95/99.7 rule holds for all normal distributions irrespective of the size of the range. Therefore, if a sample lies more than 2SDs from the mean of a sample set, it is statistically not part of the set to a level of 95% confidence. Similarly, if two populations are being compared and the means of the populations are further apart than the addition of each population's SD, then the probability is that they are statistically different although more formal testing should be done.

In scientific experimentation, the standard error of the mean (SEM) is sometimes used instead of the SD. The SEM is the SD of the estimated mean of the study sample compared with the true population mean. Therefore, whereas the SD demonstrates the spread or range of the individual sample measurements around the sample mean, the SEM gives the spread or range of the calculated sample mean. The mean ±2SEMs is the 95% confidence range of the sample mean. Therefore if another sample population was studied, the calculated mean will fall within that range 95% of the time. The SEM can be calculated by dividing the SD by the square root of the sample size. Therefore, it is dependent on both the sample range and the sample size.

Comparing sample groups

The most common method of testing two sample populations is Student's *t*-test. The test requires that the populations being compared are normally distributed. It can be used in one of two forms, the unpaired or the paired *t*-test.

The unpaired *t*-test is used when two separate unlinked normal populations are compared. For example, if you are studying two methods of induction of labour and you enrol 100 subjects into your study and randomize half into each treatment group, there are two independent samples to compare the outcomes, in this case the induction to delivery interval. The test used would be the unpaired form of the *t*-test. It does not need to be two randomized groups, just two groups that differ by a single parameter, for example primigravidae and multiparous women, where the same induction agent is used and the results of the primigravidae are compared with those of the multiparous women.

A paired *t*-test consists of matched pairs where a group of patients are tested twice, for example once before an intervention and repeated afterwards. An example would be to test for changes in the Bishop's score after application of vaginal prostaglandin. An unpaired *t*-test can be converted to a dependent *t*-test when the individuals in the two groups are assessed for similarities using measured variables that demonstrate similarities. This could be done in a cohort study looking at the effect of smoking on birthweight and matching each smoker with a matched control, matched for parity, BMI and gestation at delivery.

The *t*-test should be used when the population groups are assumed to be normal in distribution. Normality tests can assess any given dataset for the likelihood that it comes from a normal distribution, allowing the *t*-test to be used. If the data are not normally distributed or are skewed, a non-parametric test should be used. The most common simple tests are the Wilcoxon signed-rank test for paired samples and the Mann–Whitney *U* test for independent populations.

Skewness is a measure of the asymmetry of the population distribution around the mean due to a larger and longer tail on one side or the other. This can be positive or negative, indicating on which side of the mean the skewness lies. A negative skew indicates that the tail on the left side is longer than that on the right side and vice versa. The tail affects the mean, moving it towards the side of the tail and indicating that it is no longer representative of the sample as a whole and thus will overestimate or underestimate the 'average' of the population. The better measure of this is the median.

The median is the value separating the higher half of the population sampled from the lower half. It is calculated by ranging all the sample values from the lowest to the highest and finding the value in the middle. If there is an even number of values, then the median is defined to be the mean of the two middle values. In this case half the population have values less than the median and half have values greater than the median.

In a skewed population, the SD is not an accurate value of the distribution of the population around the median and in this case a better descriptor is the centile range. Just as the median is the value which describes the middle value within the range, the centile describes the percentage of the values contained within a given value range. In this case the median is the 50th centile as it describes the point where 50% of the population lie below and 50% above that value. Similarly, the 90th centile describes the value where 90% of the population are below and 10% above and the 10th centile the value where 10% are below and 90% are above.

It has to be remembered that the normal range statistically is the population range including all values, not a range of those who are designated 'normal' or disease-free. For example, if intrauterine growth restriction is classified as babies less than the 10th centile, then 10% of the normal baby population will fall into that category as well as those who may be truly growth restricted. Further evaluations are required to assess whether the baby is truly growth restricted or just a small normal baby. However, if the 5th centile is used, the baby lies outside the 95% confidence limit of what would be expected; similarly, the 3rd centile would make the baby even more likely to fall into the growth-restricted range as 97% of babies would be expected to be heavier. The 3rd centile is the equivalent of 2SDs from the population mean of a normal distribution. If two skewed or asymmetric populations are to be compared, then non-parametric tests are required.

Comparing asymmetric populations

The Mann–Whitney *U* test (also called Wilcoxon rank sum test) is a non-parametric test for assessing two independent populations. It is a variation of the original Wilcoxon test that is used to study populations of equal size. The Mann–Whitney *U* test is performed by putting all the values from each group into one ranked column from highest to lowest. The sum of the ranks for each group is compared and used to calculate the value *U*. If the samples are different, then one group will have a smaller value of *U*, implying a higher average ranking. This is then used to consult significance tables to assess whether the groups are statistically significant. Most statistical packages will do this automatically.

The Wilcoxon signed-rank test is a paired non-parametric test for assessing two populations which are related, for example a single population tested twice, once before and once after an intervention. It is used as an alternative to the paired Student's *t*-test where the population is not normally distributed. Since this is a paired test, the value from test 2 is subtracted from the value from test 1, giving a value *Z*. These values are ranked similarly to the Mann–Whitney *U* test, rank 1 being given to the smallest absolute value of *Z*. The ranks of the positive values for *Z* and the negative values of *Z* are summed. The smaller of the two rank sums is then used to compare against a table of critical values for a given sample size to assess whether there is a significant difference, with either an increase or decrease after the intervention. This test is powerful as it is less dependent on the size of individual pair changes and is a measure of a population shift, although the problem with this is that the changes could be very small but still statistically significant. As with all statistics, the results must be interpreted with clinical relevance.

Correlation and dependence

All the tests discussed have looked at ways of studying populations if they are different. Other tests look for the correlation between values within the population studied. These tests study the changes between two or more values to see if the changes in these values are linked, for example studies on the effect of maternal BMI on the incidence of caesarean section. In the National Sentinel Caesarean Section Audit, the higher the BMI, the higher the caesarean section rate in those women. Logic tells us that rising BMI affects caesarean section rate and not caesarean section rate affecting BMI. However, the statistics cannot make this assumption and this has to be interpreted by the investigator. Correlations can demonstrate a predictive relationship, for example a rise in BMI of x should be associated with a rise of y% in the caesarean section rate, and this can be used to predict how the BMI of women presenting in pregnancy would affect the caesarean section rate in an institution. Similarly, it may also suggest that a reduction in BMI might reduce the

risk of caesarean section in any given woman. However, just because the values are linked does not mean that they are causative; statistical dependence is not sufficient to demonstrate the presence of such a relationship. The two variables may both be influenced independently by a common third factor.

The result of a test for correlation is given as the correlation coefficient, usually denoted by r, which is a measure of the degree of correlation. The most common test is the Pearson correlation test, which tests for linear correlation. The nearer r is to 1 or −1, the closer the correlation, implying that for each unit rise in one variable there is an equal unit rise ($r = 1$) or fall ($r = -1$) in the other variable. A value P can be given, similar to other statistical tests, stating the confidence that the test is accurate (e.g. 95% confidence if $P < 0.05$), but does not assess how closely correlated the two variables are. The square of the r value gives an approximation of the percentage effect the change of one variable has on the other. Therefore, a test that gives a result of $r = 0.5$ and $P < 0.01$ indicates that there is a statistically valid correlation but only 25% (r^2) of any given change in variable 2 is associated with a change in variable 1. It is only when r is greater than 0.7 that the variable in 1 has over a 50% effect on the variable in 2.

What has been described in the preceding sections is standard statistics and what is seen as statistical significance. It has also been suggested that it is important to assess the results obtained from a clinical viewpoint to assess reality and how the results influence accepted pre-test thinking. This is part of the reasoning behind Bayesian inference.

Bayesian inference

Bayesian inference is the use of a priori belief or probability about a test result to determine the probability that a new test result is true. In other words, knowing what we know from experience or belief, can this new result be true? In day-to-day terms, this is the basis on how we change our beliefs and practices. If a study confirms our preconceived beliefs, we will accept it without question but if it disagrees, then we may struggle to accept it and only change our practice to a degree. However, as more evidence accumulates, the degree of confidence in a test result changes. With enough evidence, the degree of confidence should become either very high or very low. This means that results will naturally be biased due to pre-test prejudices but it allows the changing of that bias with more confirmatory evidence. This is really how we practise in the real world. Many observational studies suggested an increased risk of vaginal breech delivery but many practitioners did not accept these results due to their pre-existing prejudices. The Term Breech Trial, with its large randomized format, convinced those who already believed and some of those who were sceptical but others still found flaws in the study so they did not have to change their beliefs. In a statistical form, Bayesian inference estimates the degree of pre-test belief before any evidence is collected, and then re-estimates the degree of confidence after a set of evidence has been observed by combining the pre-test values with the test results. This process is then repeated whenever additional evidence is obtained, leading to a changing probability that the results are true or false.

Summary box 33.4

Descriptive statistics

- Mean: the sum of all the measurements divided by the total number of measurements taken.
- Range: calculated by subtracting the smallest measurement (minimum) from the greatest (maximum).
- Standard deviation (SD): the assessment of variability of each individual measurement from the mean, calculated by taking the average difference of each measurement from the calculated mean.
- Standard error of the mean (SEM): standard deviation of the estimated mean of the study sample compared with the true population mean.
- Student's *t*-test: used to compare normally distributed populations. The populations can be paired or unpaired.
- Skewness: a measure of the asymmetry of the population distribution around the mean.
- Median: the value separating the higher half of the population sampled from the lower half.
- Centiles: describe the percentage of values contained within a given value range.
- Mann–Whitney *U* test: a non-parametric test for assessing two independent populations.
- Wilcoxon signed-rank test: a paired non-parametric test for assessing two populations which are related.
- Correlation: studies the changes between two or more values within a population to see if the changes in these values are linked.
- Bayesian inference: a method that uses a priori belief or probability about a test result to determine the probability that a new test result is true.

How we use statistics

This chapter has considered examples of how we use statistics. Whatever the results, all are interpreted in the light of our own experience. If we have no preconceived

beliefs, we are open to the results of any trial. If we have a preconceived idea and the trial shows a null result, it confirms to us that what we do is correct, but that is also true of people with a preconceived idea opposite to our own. The Term PROM trial showed no difference between immediate induction of labour or delay in cases of pre-labour rupture of the membranes. This indicates that there is no evidence to support either action. This allowed people to continue to act as they previously did, believing themselves to be correct, but it should have told people that there is no correct answer and that women should be offered a choice of action.

Statistics is a powerful tool in medical research and epidemiology, but it is important to use it at the right time in the right way. If the wrong question is asked, the result is worthless irrespective of the outcome and statistical significance. It is important to think through the problem being addressed carefully and set the correct hypothesis and test it with a study of the appropriate power. Statistics will not cover up for a poorly designed trial with insufficient numbers testing the wrong hypothesis. It is also important to assess the results for clinical relevance and the consequences of changing actions potentially resulting in unforeseen consequences that were not tested for.

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Section 2

Gynaecology

Part 7

Basic Science

34

Clinical Anatomy of the Pelvis and Reproductive Tract

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This chapter aims to summarize important aspects of the anatomy of the abdomen and the pelvis that should be known to the obstetric or gynaecological specialist. Many of the investigations and treatments we order on a daily basis require good anatomical knowledge in order to be properly understood.

Surface anatomy

The anterior abdominal wall can be divided into four quadrants by lines passing horizontally and vertically through the umbilicus (Fig. 34.1). In the upper abdomen is the epigastrium, which is the area just inferior to the xiphisternum, and in the lower abdomen lie the right and left iliac fossae and the hypogastrium.

The cutaneous nerve supply of the anterior abdominal wall arises from the anterior rami of the lower thoracic and lumbar vertebrae. The dermatomes of significant structures on the anterior abdominal wall are T7 (xiphisternum), T10 (umbilicus) and L1 (symphysis pubis).

The blood supply is via the superior epigastric (branch of the internal thoracic artery) and the inferior epigastric (branch of the external iliac artery) vessels. During laparoscopy, the inferior epigastric vessels can be seen between the peritoneum and rectus muscle on the anterior abdominal wall and commence their journey superiorly from approximately two-thirds of the way along the inguinal ligament closer to the symphysis pubis. Care needs to be taken to avoid them while using accessory trocars during laparoscopy and to ensure that they are identified when making a Maylard incision of the abdominal wall.

The anterior abdominal wall

Beneath the skin and the fat of the superficial anterior abdominal wall lies a sheath and combination of muscles including the rectus abdominis, external and internal oblique and tranversalis muscles (Fig. 34.2). Where these muscles coalesce in the midline, the linea alba is formed. Pyramidalis muscle is present in almost all women, originating on the anterior surface of the pubis and inserting into the linea alba. The exact configuration of the muscles encountered by the surgeon depends on exactly where any incision is made.

The umbilicus

The umbilicus is essentially a scar made from the remnants of the umbilical cord. It is situated in the linea alba and in a variable position depending on the obesity of the patient. However, the base of the umbilicus is always the thinnest part of the anterior abdominal wall and is the commonest site of insertion of the primary port in laparoscopy. The urachus is the remains of the allantois from the fetus and runs from the apex of the bladder to the umbilicus. Occasionally this can remain patent in newborns. In early embryological life, the vitelline duct also runs through the umbilicus from the developing midgut. Although the duct is severed long before delivery, a remnant of this structure is found in 2% of the population as a Meckel's diverticulum.

The aorta divides into the common iliac arteries approximately 1–2 cm below the umbilicus in most slim women (Fig. 34.3). The common iliac veins combine to form the inferior vena cava just below this and all these structures are a potential hazard for the laparoscopist inserting ports at the umbilicus.

Epithelium of the genital tract

The anterior abdominal wall including the vulva, vagina and perineal areas are lined with squamous epithelium. The epithelium lining the endocervix and uterine cavity

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

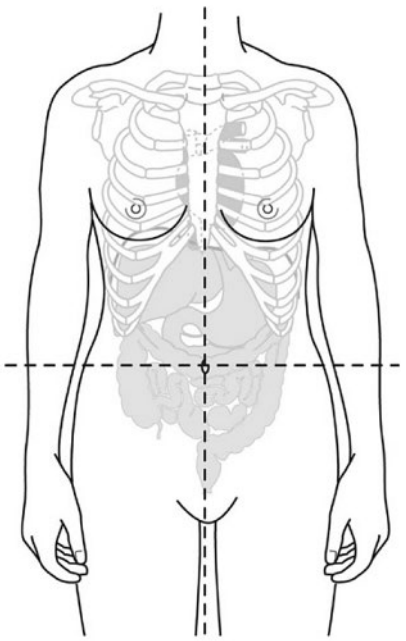


Fig. 34.1 The abdomen can be divided into quadrants.

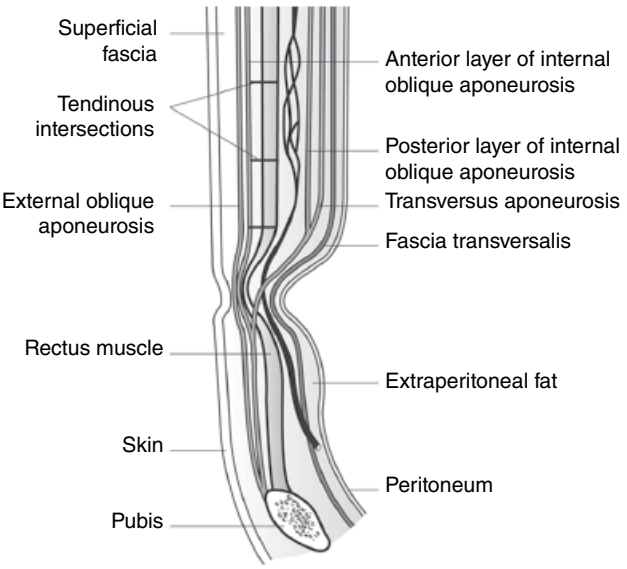


Fig. 34.2 The layers of the anterior abdominal wall in tranverse section.

is columnar and the squamocolumnar junction usually arises at the ectocervix in women of reproductive age. This is an important site as it is the area from which cervical intraepithelial neoplasia (CIN) and eventually cervical malignancy arises. The bladder is lined by transitional epithelium that becomes columnar as it lines the urethra. The anal margin is still squamous epithelium but this changes to columnar immediately inside the anus and into the rectum.

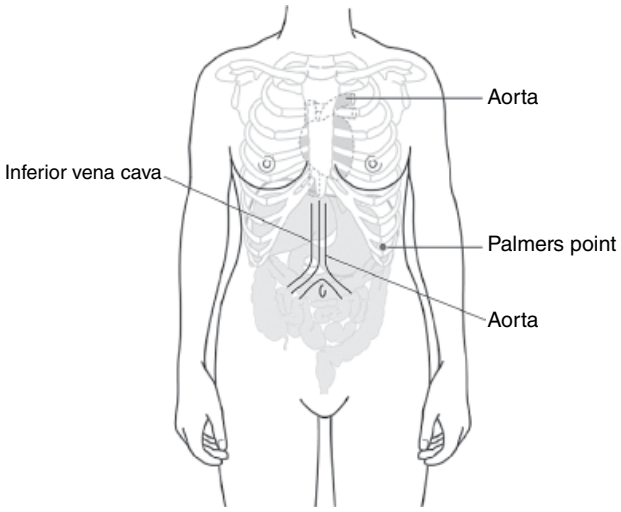


Fig. 34.3 The umbilicus in relation to the underlying vasculature in a thin patient.

The genital tract, from the vagina, through the uterus and out through the fallopian tubes into the peritoneal cavity, is an open passage. This is an essential route for sperm to traverse in the process of fertilization but unfortunately it also allows the transport of pathological organisms that may result in ascending infection.

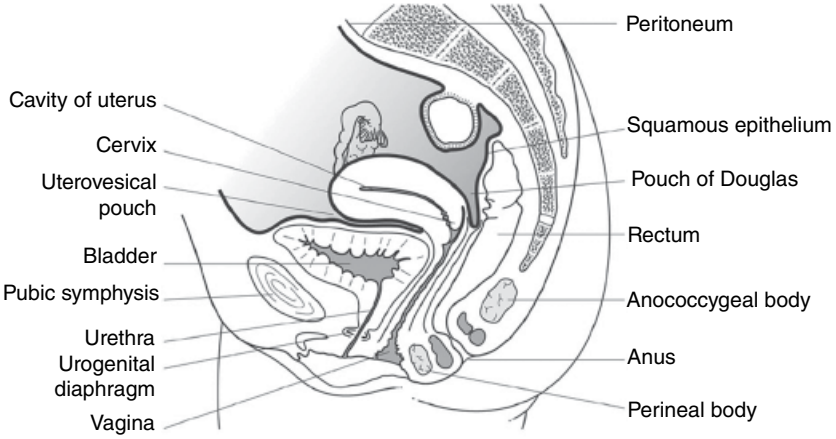
The peritoneum

The peritoneum is a thin serous membrane that lines the inside of the pelvic and abdominal cavities. In simplistic terms, it is probably best to imagine the pelvis containing the bladder, uterus and rectum (Fig. 34.4) and note that the peritoneum is a layer placed over these organs in a single sheet. This complete layer is then pierced by both the fallopian tubes and the ovaries on each side. Posteriorly the rectum also pierces the peritoneum where it connects to the sigmoid colon, and the area between the posterior surface of the uterus and its supporting ligaments and the rectum is called the pouch of Douglas. This particular area is important in gynaecology as the place where gravity-dependent fluid collects. As a result this is where blood is found in ectopic pregnancies, pus in infections and endometriosis caused by retrograde menstruation.

Vulva

The vulva is the area of the perineum comprising the mons pubis, labia majora and minora, and the opening into both the vagina and urethra (Fig. 34.5). The labia majora are areas of skin with underlying fat pads which bound the vagina. Medial to these are the labia minora, which consist of vascular tissue that engorges with blood during sexual

Fig. 34.4 Transverse view of the pelvic organs.



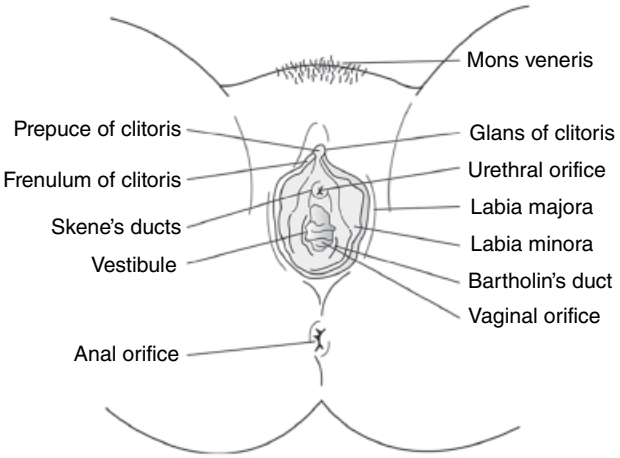


Fig. 34.5 Surface anatomy of the vulva.

arousal. Anteriorly they come together to form the prepuce of the clitoris and posteriorly they form the fourchette. The hymen is a fold of mucosa at the entrance to the vagina. It usually has a small opening in virgins and is only seen as an irregular remnant in sexually active women. To each side of the introitus are the ducts of the vestibular glands commonly known as Bartholin's glands, which produce much of the lubrication during sexual intercourse.

The vulval blood supply comes from the pudendal artery and lymphatic drainage is through the inguinal lymph nodes. The nerve supply comes mostly from the pudendal nerve and pelvic plexus, with branches of the perineal nerves and posterior cutaneous nerve of the thigh important in the posterior region.

The clitoris

The clitoris corresponds to the male penis and consists of the same three masses of erectile tissue (Fig. 34.6). The bulb of the vestibule is attached to the underlying urogenital diaphragm and splits into two because of the presence of the vagina. The right and left crura become the corpora cavernosa and are covered by the ischiocavernosus muscles.

Bony pelvis

The bony pelvis consists of two hip bones (comprising ilium and ischium) that are joined together by the sacrum posteriorly and the symphysis pubis anteriorly (Figs 34.7 and 34.8). In addition, the coccyx lies on the inferior aspect of the sacrum. A plane drawn between the sacral promontory and the superior aspect of the symphysis pubis marks the pelvic inlet and a similar plane drawn from the tip of S5 to the inferior aspect of the symphysis pubis marks the pelvic outlet.

Clinically the ischial spine is important as it can be felt vaginally and progress in labour can be measured using it as a landmark. Additionally, it is an insertion point of the sacrospinous ligament, which also attaches to the lower lateral part of the sacrum. Together with the sacrotuberous ligament and the bony pelvis, it forms the borders of the greater sciatic foramen (through which the sciatic nerve passes) and the lesser sciatic foramen (through which the pudenal nerve enters the pelvis).

The sacrum and ilium are joined by the very strong sacro-iliac joint. This is a synovial joint and is supported by the posterior and interosseous sacro-iliac ligaments. The symphysis pubis is a cartilaginous joint with a fibrocartilaginous disc separating the two bones, which are firmly bound together by the supporting ligaments. There should be virtually no movement of this joint.

Pelvic floor

The obturator internus muscle sits on the medial side of the ischial bone and, together with the body of the pubis, forms a wall that supports the origins of the pelvic floor.

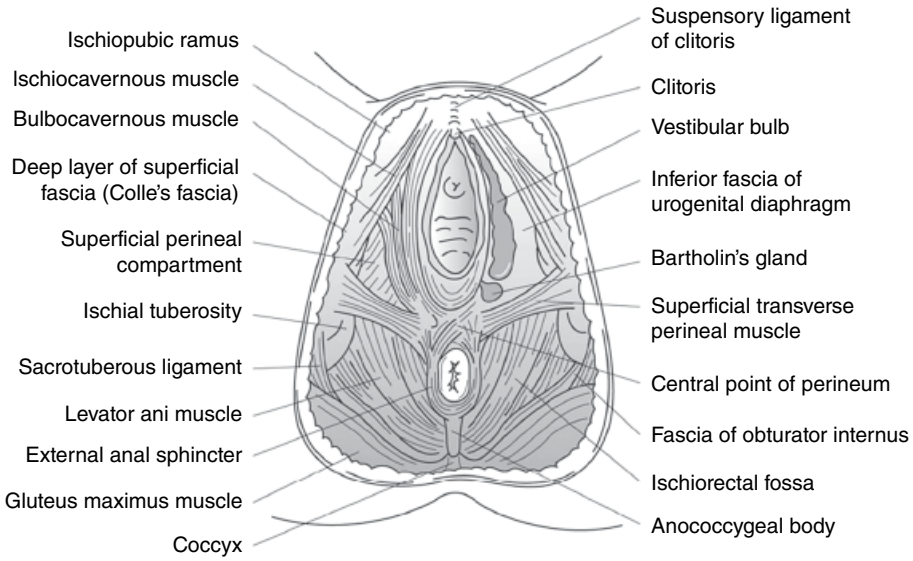


Fig. 34.6 The deeper vulval tissues.

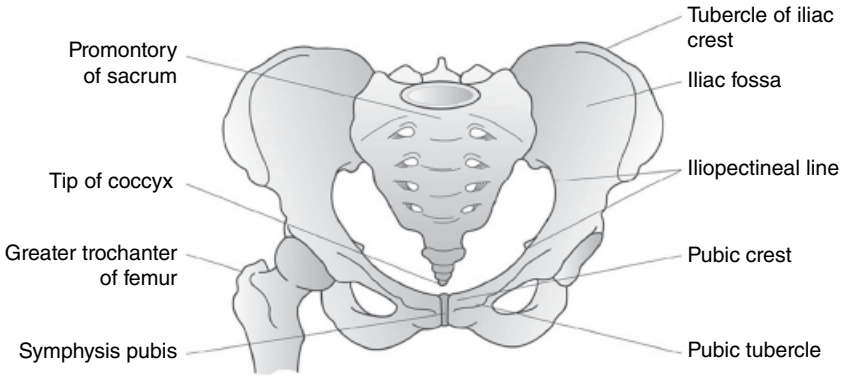


Fig. 34.7 Bony pelvis.

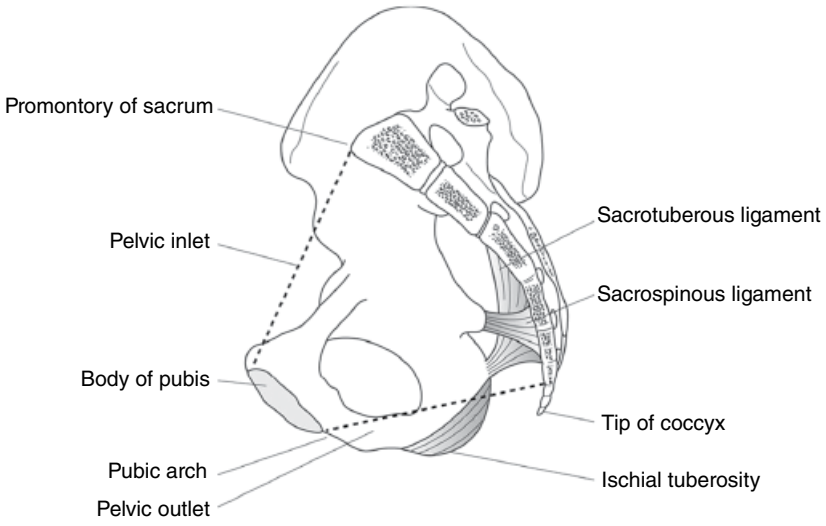


Fig. 34.8 Bony pelvis.

The pelvic floor itself is a sling of various muscles that are pierced by the urethra, the vagina and the anal canal. Posterior to the vagina these muscles form the perineal body. The puborectalis muscle forms a sling around the junction of the anus and rectum and posterior to the anus, and these fibres consist of the pubococcygeus that forms the anococcygeal body in the midline (Fig. 34.9). The collection of muscles is variously referred to as the

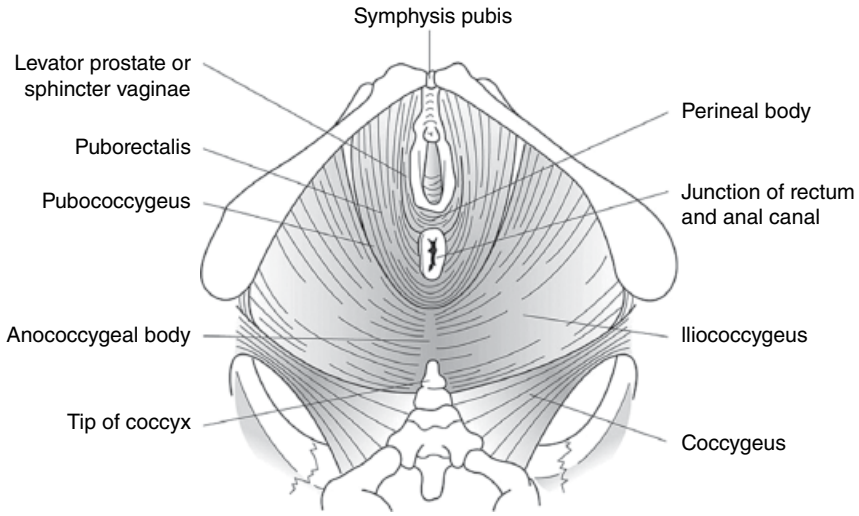


Fig. 34.9 Pelvic floor muscles.

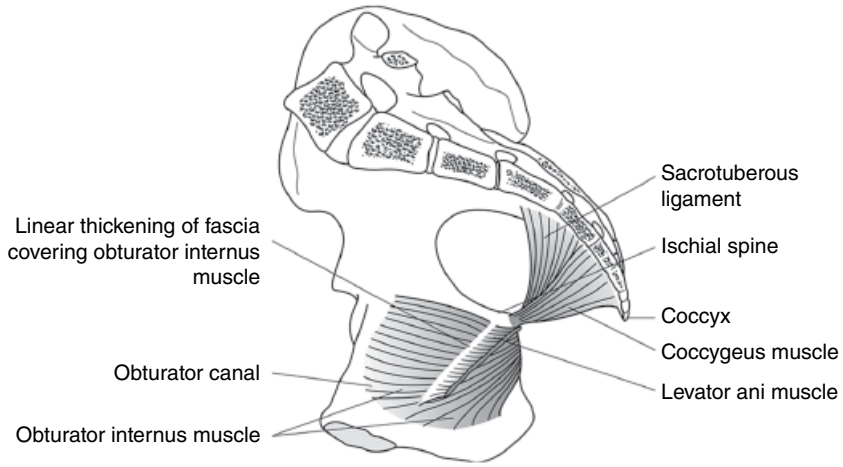


Fig. 34.10 Transverse view of the pelvic floor muscles.

pelvic diaphragm or levator ani muscles (Fig. 34.10). These muscles support the pelvic organs, holding them in position and resisting the forces created when the intraperitoneal pressure is raised as in coughing or straining. The nerve supply is from the fourth sacral nerve and pudendal nerve.

Pelvic organs (Fig. 34.11)

Vagina

The vagina is a distensible muscular tube that passes from the introitus to the cervix. It pierces the pelvic floor and then lies flat on its posterior surface using it as support. It is approximately 8 cm long and the anterior and posterior walls oppose each other. Anatomical textbooks can give a confusing impression when showing this structure as an open tube with a lumen. However, on imaging, the normal vagina should not be distended and does not contain air. Projecting into the top of the vagina is the uterine cervix. The areas of the vagina that border the cervix are referred to as the fornices and are labelled as anterior, posterior, right or left.

The vaginal wall consists of outer and inner circular layers of muscles that cannot be distinguished from each other. The epithelium contains no glands but is rich in glycogen in the premenopausal woman. The normal commensal, *Lactobacillus acidophilus*, breaks down this glycogen to create an acid environment.

Uterus

The uterus is approximately the size and shape of a pear with a central cavity and thick muscular walls (Fig. 34.12). The serosal surface is the closely applied peritoneum, beneath which is the myometrium. The myometrium is smooth muscle supported by connective tissue and comprises three layers of muscle: external, intermediate and internal layers. Clinically this is important as fibroids

leave the layers intact and removal through a superficial incision leaves the three layers intact. The three layers run in complementary directions, encouraging vascular occlusion during contraction, an important aspect of menstrual blood loss and postpartum haemostasis. The mucous membrane overlying the myometrium and which lines the cavity is the endometrium. Glands of the endometrium pierce the myometrium and a single layer of columnar epithelium on the surface changes cyclically in response to the menstrual cycle.

The uterus consists of a fundus superiorly, a body, an isthmus (internal os) and inferiorly the cervix (external os). The cervix is a cylindrical structure that is muscular in its upper portions but comprises fibrous connective tissue in its lower part where it connects with the vagina. The cervix is lined by columnar epithelium that secretes alkaline mucus that neutralizes the effects of vaginal acidity.

The cervix and uterus do not always lie in the same plane and when the uterine body rotates anteriorly it is referred to as 'anteflexed'; when rotated posteriorly, it is referred to as 'retroflexed'. The axis of the entire uterus can be anteverted or retroverted in relation to the axis of the vagina (Fig. 34.13).

The uterus is supported by the muscles of the pelvic floor together with three supporting condensations of connective tissue. The pubocervical ligaments run from the cervix anteriorly to the pubis, the cardinal ligaments

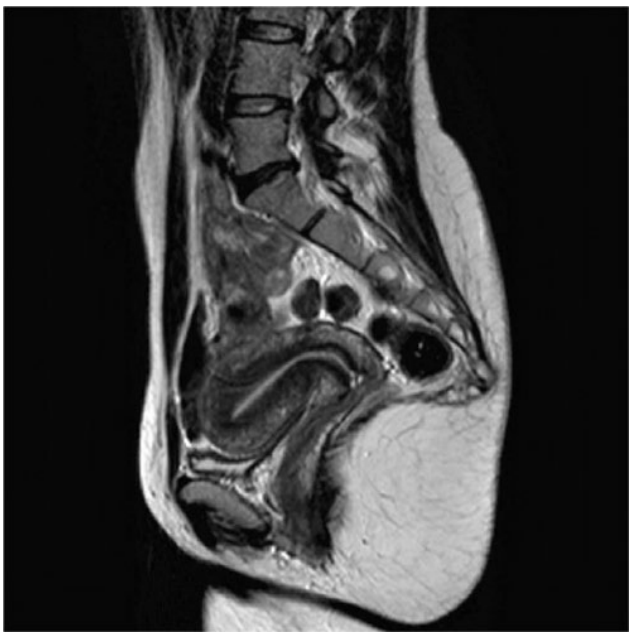


Fig. 34.11 Magnetic resonance image of the pelvis.

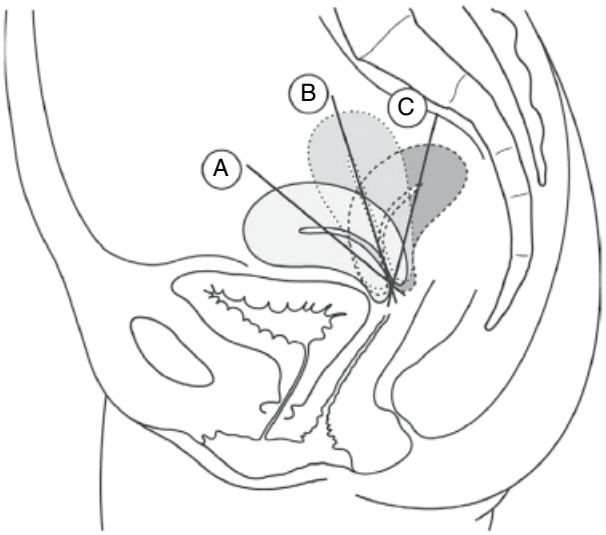


Fig. 34.13 The axis of the uterus in relation to the vagina.

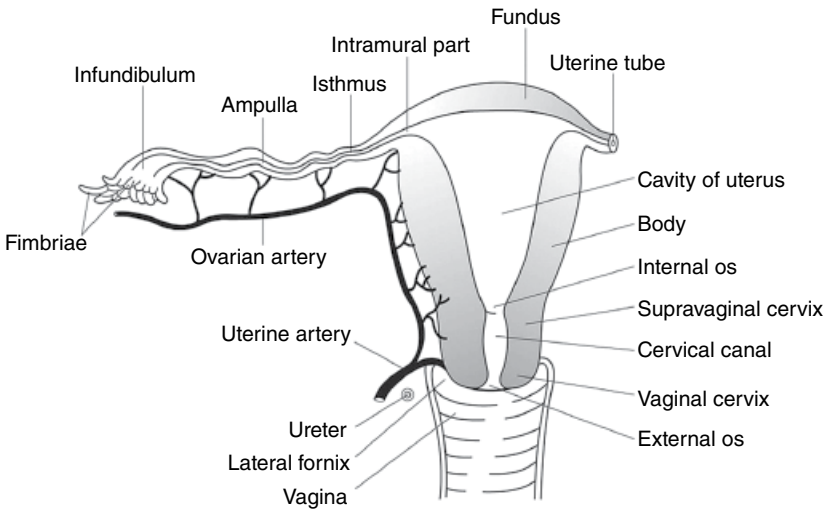


Fig. 34.12 Uterus and fallopian tubes.

pass laterally from the cervix and upper vagina to the lateral pelvic side walls, and the uterosacral ligaments run from the cervix and upper vagina to the sacrum. These uterosacral ligaments can be clearly seen posterior to the uterus in the pouch of Douglas and are a common site for superficial and deep infiltrating endometriosis.

The uterine blood supply is derived mainly from the uterine artery, a branch of the anterior division of the internal iliac artery. An anastomosis occurs with the blood supply delivered through the ovarian ligament and derived direct from the ovarian artery.

The round ligament is the remains of the gubernaculum and extends from the uterus laterally to the pelvic side wall and then into the inguinal canal before passing down into the labia majora. It holds the uterus in anteversion, although it is a highly elastic structure in pregnancy. It is usually the first structure divided at hysterectomy, allowing the surgeon to open the overlying folds of peritoneum known as the broad ligament.

Fallopian tubes

The fallopian tubes are delicate tubular structures that allow transport of the ovum or sperm between the ovary and uterine cavity. The tubes are divided into named regions, most medially the cornu and interstitial portion within the uterine wall, then the isthmus followed by the infundibulum, ampulla and finally fimbrial ends. They are lined by columnar epithelium and cilia which, together with the peristaltic action of the surrounding smooth muscle, propel the fertilized ovum towards the uterine cavity. The blood supply of the fallopian tubes arises from both the uterine and ovarian arteries through the mesosalpinx which is covered by peritoneum.

Ovaries

The ovaries vary in size depending on age and their function. They measure approximately 2×4 cm, with the long axis running vertically, and are attached to the posterior leaf of the broad ligament by the mesovarium. In addition, they are fixed in position by the ovarian ligament (to the uterus medially) and the infundibulopelvic ligament, which contains the ovarian blood supply direct from the aorta. Venous drainage is to the ovarian veins, which drain directly into the inferior vena cava on the right and into the renal vein on the left. The aortic nerve plexus also accompanies the ovary in its descent from around the level of the first lumbar vertebra.

The lateral pelvic side wall is covered by peritoneum that is folded to form the ovarian fossa. Pathological adhesions around the ovary will often cause it to become fixed into the ovarian fossa, causing cyclical pain or dyspareunia. The ovary is not covered by peritoneum but is surrounded by a thin membranous capsule, the tunica albuginea, which in turn is covered by the germinal epithelium.

Bladder

The urinary bladder is situated immediately behind the pubic bone and anterior to the uterine cervix and upper vagina. It has a strong muscular wall consisting of three layers of interlacing fibres, which together are known as the detrusor muscles (Fig. 34.14). The trigone is the only smooth part of the bladder as it is fixed to the underlying muscle. At the superior margins of the trigone lie the ureteric openings and at the inferior aspect the urethra. An inter-ureteric ridge can often be visualized horizontally between the ureters at cystoscopy and is useful for orientation. The rest of the bladder is highly distensible, ensuring that as it is expanded by urine, the pressure of its contents remains the same.

The bladder receives its blood supply from the superior and inferior vesical arteries, which originate from the internal iliac artery. The nerve supply is from the inferior hypogastric plexus. Sympathetic nerves arise in the first and second lumbar ganglia and the parasympathetic supply from the splanchnic nerves of the second, third and fourth sacral nerves.

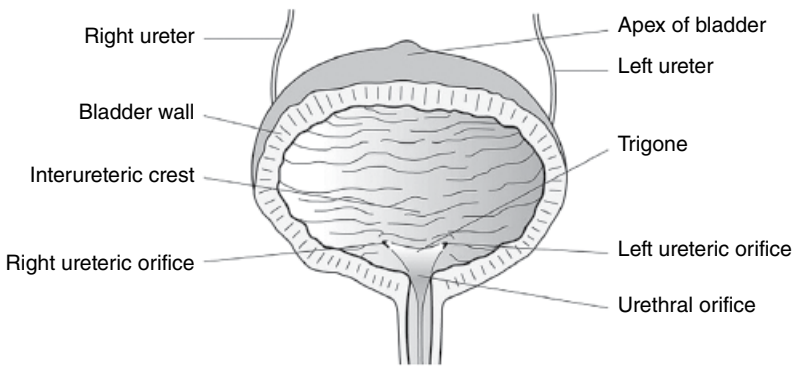


Fig. 34.14 The bladder.

Urethra

The urethra is approximately 4 cm long in the female adult, starting at the internal meatus of the bladder and passing through the pelvic floor to the vestibule. The epithelium is squamous near the external meatus but changes to transitional epithelium approximately 2.5 cm from the meatus. The deeper tissue is muscular and this maintains urethral tone. There are no anatomical sphincters but the muscle fibres of the bladder at the internal meatus act as an 'internal sphincter' and the pelvic floor as a voluntary external sphincter.

Ureters

The ureters run from the renal hilum to the trigone of the bladder and are approximately 30 cm in length. They enter the pelvis by passing over the common iliac bifurcation at the pelvic brim. They then pass along the lateral pelvic side wall before passing anteriorly and medially under the uterine artery as it originates from the internal iliac artery and into the base of the bladder. The ureter comes close to the ovarian artery and vein and can be adherent to these vessels or the overlying ovary in pathological cases. By passing close to the uterine artery it can be mistakenly clamped and divided as a rare complication of hysterectomy.

The ureters are muscular tubes lined by transitional epithelium. The blood supply varies during its course but small vessels along the surface of the ureter require careful preservation when dissecting it free from other structures.

Rectum

The rectum is approximately 12 cm in length and starts at S3 as a continuation of the sigmoid colon. The puborectalis part of the pelvic floor forms a sling around the lower end at the junction with the anal canal. The rectum is commonly depicted in anatomical drawings as being dilated, causing the other pelvic organs to be pushed forward. This is because the original drawings were taken from cadavers but in the live patient the rectum is often empty, allowing the other structures to lie supported on the pelvic floor. The mucosa of the rectum is columnar and this is surrounded by inner circular and outer longitudinal fibres of smooth muscle. The serosal surface is covered by peritoneum.

The blood supply is from the superior rectal artery from the inferior mesenteric artery, and the middle and inferior rectal arteries arise from the posterior division of the internal iliac artery. The nerve supply is from the inferior hypogastric plexus and ensures the rectum is sensitive to stretch only.

Conclusion

A clear knowledge of anatomy is required for many gynaecological diagnoses and certainly for surgery. Many clinicians do not gain a full understanding of pelvic anatomy until they start operating and then rarely refer back to anatomical textbooks. The advent of more sophisticated pelvic floor surgery and especially minimal access surgery has modified the skills required of a gynaecological surgeon, necessitating the need for greater practical anatomical knowledge.

Further reading

Pimal Pictures. The Interactive Pelvis and Perineum: Female. Available at www.primalpictures.com/Male_Female_Pelvis.aspx

Snell RS. *Clinical Anatomy for Medical Students*, 6th edn. Philadelphia: Lippincott, Williams and Wilkins, 2000.

35

Normal and Abnormal Development of the Genital Tract

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Sexual differentiation and its control are vital to the continuation of our species, and for every gynaecologist an understanding of the development of the genital tract is clearly important. Our knowledge of this process has greatly increased in recent years and with it an appreciation of normal and abnormal sexual development. Following fertilization the normal embryo contains 46 chromosomes, including 22 autosomes derived from each parent. The basis of mammalian development is that a 46XY embryo will develop as a male and a 46XX embryo as a female. However, it is the presence or absence of the Y chromosome which determines whether the undifferentiated gonad becomes a testis or an ovary.

Although the sequence of genes required for differentiation of the gonads and development of the genital tract remains to be clearly defined, sex determination equates to gonadal development. This is then followed by a second process known as sex differentiation. Studies of the genetic control of gonadal development are based on animal data. The Y chromosome contains a region known as *SRY* (sex-determining region of the Y chromosome) and it has been shown that the testis-determining factor is on chromosome Yp11.31. In males this gene triggers testis formation from the undifferentiated gonad [1] but *SRY* is only one member of a family of genes that exist within the homeobox known as HMG. These genes, known as *SOX* genes, act in combination to differentiate the gonad to a testis. Mutations of *SRY* cause pure gonadal dysgenesis or hermaphroditism. Ovarian development is also dependent on genes on the short arm of the X chromosome, although the exact mechanism by which these genes invoke ovarian development remains to be defined.

Ovarian differentiation seems to be determined by the presence of two X chromosomes and the ovarian determinant is located on the short arm of the X chromosome; this was discovered by observing that the absence of the short arm results in ovarian agenesis [2]. At present, it is believed that *DAX1* is the gene which determines that the bipotential gonad will become an ovary. Other autosomal loci are certainly involved in ovarian development and development of the Wolffian and Müllerian structures is also under genetic control; this is thought to be a polygenic multifactorial inheritance, although autosomal recessive genes may also be involved [3]. The influence of the differentiated gonad on the development of other genital organs is thus fundamental and the presence of a testis will lead to male genital organ development and its absence means the individual will develop female genital organs whether ovaries are present or not.

Summary box 35.1

Mammalian development depends on the chromosome complement: a 46XY embryo develops as a male but the default state is female if the chromosome complement is anything other than male.

Development of the genital organs

Most embryological accounts agree on the principles of genital tract development, although some different views are held on the development of the vagina. The genital organs and those of the urinary tract arise in the intermediate mesoderm on either side of the root of the mesentery beneath the epithelium of the coelom. The pronephros, a few transient excretory tubules in the cervical region, appears first but quickly degenerates. The duct, which begins in association with the pronephros, persists and extends caudally to open at the cloaca, connecting as it does so with some of the tubules of the mesonephros shortly to appear. The duct is called the mesonephric (Wolffian) duct. The mesonephros itself, the second primitive kidney, develops as a swelling

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

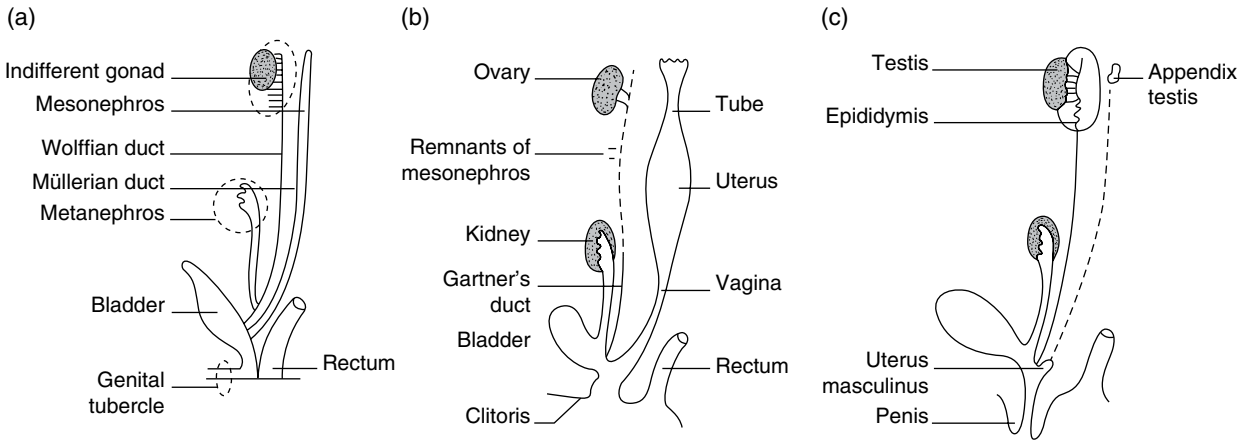

Fig. 35.1 Diagrammatic representation of genital tract development: (a) indifferent stage; (b) female development; (c) male development.

bulging into the dorsal wall of the coelom of the thoracic and upper lumbar regions. The mesonephros in the male persists in part as the excretory portion of the male genital system; in the female only a few vestiges survive (Fig. 35.1). The genital ridge in which the gonad of each sex is to develop is visible as a swelling on the medial aspect of the mesonephros; the paramesonephric (Müllerian) duct from which much of the female genital tract will develop forms as an ingrowth of the coelomic epithelium on its lateral aspect; the ingrowth forms a groove and then a tube and sinks below the surface.

Uterus and fallopian tubes

The two paramesonephric ducts extend caudally until they reach the urogenital sinus at about 9 weeks' gestation. It is important to remember that there is fusion between the caudal tip of the Müllerian and Wolffian ducts during this time The blind ends project into the posterior wall of the sinus to become the Müllerian tubercle (Fig. 35.2). At the beginning of the third month the Müllerian and Wolffian ducts and mesonephric tubules are all present and capable of development. From this point onwards in the female there is degeneration of the Wolffian system and marked growth of the Müllerian system. In the male the opposite occurs as a result of production of anti-Müllerian hormone by the fetal testis. The lower ends of the Müllerian ducts come together in the midline, fuse and develop into the uterus and the cervix. The cephalic ends of the duct remain separate to form the fallopian tubes. The thick muscular walls of the uterus and cervix develop from proliferation of mesenchyme around the fused portion of the ducts.

Vagina

At the point where the paramesonephric ducts protrude their solid tips into the dorsal wall of the urogenital sinus

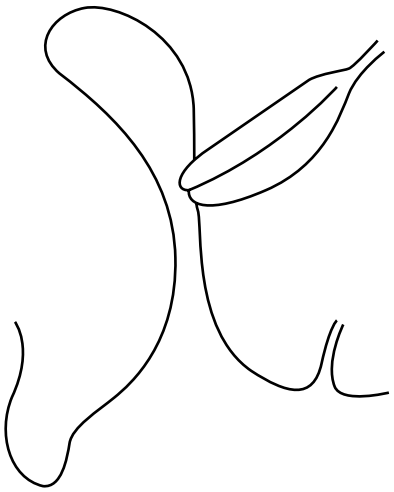

Fig. 35.2 Paired paramesonephric ducts protruding into the urogenital sinus as the Müllerian tubercle at 9 weeks of intrauterine life.

as the Müllerian tubercle, there is marked growth of tissue from which the vagina will form, known as the vaginal plate. This plate grows in all dimensions, greatly increasing the distance between the cervix and the urogenital sinus, and later the central cells of this plate break down to form the vaginal lumen. The complete canalization of the vagina does not usually occur until around weeks 20–24 of pregnancy and failure of complete canalization may lead to a variety of septa, which cause outflow tract obstruction in later years. The embryological development of the vagina has been the subject of debate for many years, but current molecular studies show that the whole vagina is derived from the paramesonephric duct.

External genitalia

The primitive cloaca becomes divided by a transverse septum into an anterior urogenital portion and a posterior

rectal portion. The urogenital portion of the cloacal membrane breaks down shortly after division is complete and this urogenital sinus develops into three portions (Fig. 35.3). There is an external expanded phallic part, a deeper narrow pelvic part between it and the region of the Müllerian tubercle, and a vesico-urethral part connected superiorly to the allantois. Externally in this region the genital tubercle forms a conical projection around the anterior part of the cloacal membrane. Two pairs of swellings, a medial part (genital folds) and a lateral pair (genital swellings), are then formed by proliferation of mesoderm around the end of the urogenital sinus. Development up to this time (10 weeks' gestation) is the same in the male and the female. Differentiation then occurs. The bladder and urethra form from the vesico-urethral portion of the urogenital sinus, and the vestibule from the pelvic and phallic portions. The genital tubercle enlarges only slightly and becomes the clitoris. The genital folds become the labia minora and the genital swellings enlarge to become the labia majora. In the male greater enlargement of the genital tubercle forms the penis and the genital folds fuse over a deep groove formed between them to become the penile part of the male urethra. The genital swellings enlarge, fuse and form the scrotum.

The final stage of development of the clitoris or penis and the formation of the anterior surface of the bladder and anterior abdominal wall up to the umbilicus is the result of the growth of mesoderm, extending ventrally around the body wall on each side to unite in the midline anteriorly.

Gonads

The primitive gonad appears in embryos at around 5 weeks' gestation. At this time coelomic epithelium develops on the medial aspect of the urogenital ridge and following proliferation leads to the establishment of the gonadal ridge. Epithelial cords then grow into the mesenchyme (primary sex cords) and the gonad now possesses an outer cortex and an inner medulla. In embryos with an XX complement, the cortex differentiates to become the ovary and the medulla regresses. The primordial germ cells develop by the fourth week in the endodermal cells of the yolk sac and during the fifth week they migrate along the dorsal mesentery of the hindgut to the gonadal ridges, eventually becoming incorporated into the mesenchyme and the primary sex cords by the end of the sixth gestational week.

The differentiation of the testis is evident at about 7 weeks by the disappearance of germ cells from the peripheral zone and gradual differentiation of remaining cells into fibroblasts, which form the tunica albuginea. The deeper parts of the sex cords give rise to the rete testis and the seminiferous and straight tubules. The first indication that the gonad will become an ovary is failure of these testicular changes to appear. The sex cords below the epithelium develop extensively with many primitive germ cells evident in this active cellular zone (Fig. 35.4). The epithelial cells in this layer are known as pre-granulosa cells. The active growth phase then follows, involving the pre-granulosa cells and germ cells, which are now very much reduced in size. This proliferation

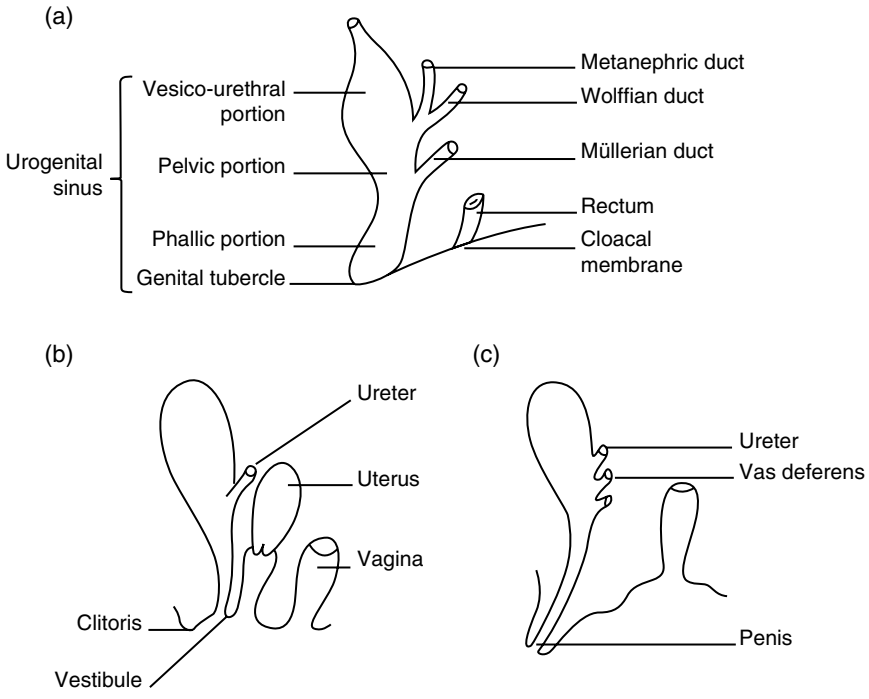

Fig. 35.3 Diagrammatic representation of lower genital tract development: (a) indifferent stage; (b) female development; (c) male development.

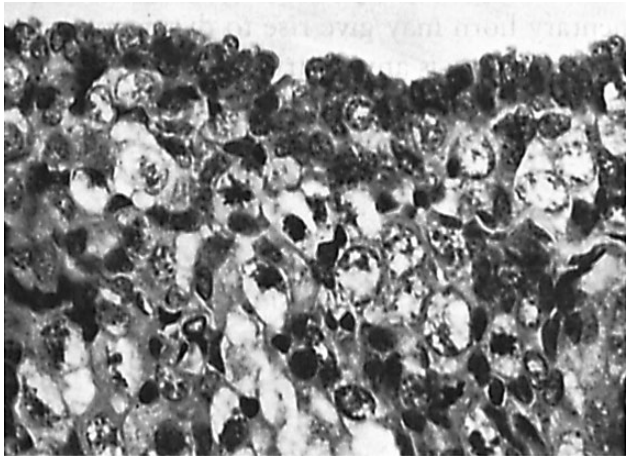

Fig. 35.4 Detail of immature ovary showing small epithelial cells (pre-granulosa cells) and larger germ cells.

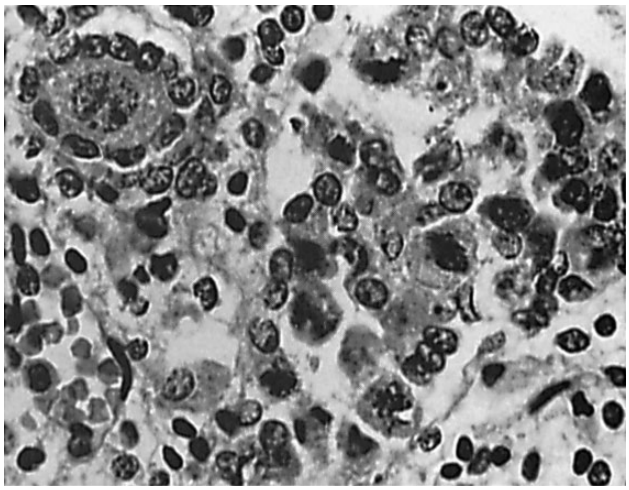

Fig. 35.5 A later ovary (31 weeks) showing a well-formed primary follicle (top left) and a germ cell (centre right) which is not yet completely surrounded by granulosa cells.

greatly enlarges the bulk of the gonad and the next stage (by 20 weeks onwards) shows the primitive germ cells, now known as oocytes, becoming surrounded by a ring of pre-granulosa cells; stromal cells develop from the ovarian mesenchyme later, surround the pre-granulosa cells and become known as granulosa cells and follicle formation is complete (Fig. 35.5). An interesting feature of the formation of follicles and the development of stroma is the disintegration of those oocytes which do not succeed in encircling themselves with a capsule of pre-granulosa cells.

The number of oocytes is greatest during intrauterine life and thereafter declines. Baker [4] found that the total population of germ cells rose from 600 000 at 2 months to a peak of 7 million at 5 months. At birth the number falls to 2 million, of which half are atretic. After 28 weeks

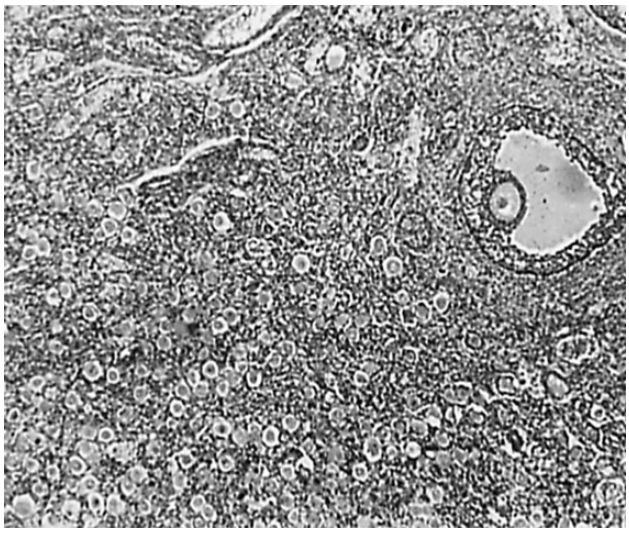

Fig. 35.6 Numerous primary follicles and one showing early development in the ovary of a child stillborn at 38 weeks.

or so of intrauterine life, follicular development can be seen at various stages and various sizes of follicles are also seen (Fig. 35.6).

Disorders of sexual development

Disorders of sexual development (DSD) have been reclassified by Hughes [5] and this has now been adopted as the best way of classifying these disorders (Table 35.1).

Sex chromosome disorders

This group of disorders includes Turner's syndrome (46XO), which is the most important in this group of disorders and the most common. Patients with Turner's syndrome have gonads that contain no oocytes and merely fibrous tissue and as a result of this they have no secondary sexual development (see Chapter 38).

46XY

This group of disorders is divided into three groups.

Disorders of gonadal (testicular) development

The gynaecologist may occasionally come across a case of ovotesticular DSD where both ovarian and testicular tissue exist within the same individual. These patients are rare in Europe and the USA but are notably more common in South Africa. They present with varying degrees of sexual ambiguity, with maleness predominating in some patients while female changes are more apparent in others. In the majority the uterus and vagina are present and the karyotype is usually normal female

Table 35.1 Classification of disorders of sexual development (DSD).

Sex chromosome DSD

A) 47XXY (Klinefelter's syndrome and variants)
B) 45X (Turner's syndrome and variants)
C) 45X/46XY (mixed gonadal dysgenesis)
D) 46XX/46XY (chimerism)

46XY DSD

A) *Disorders of gonadal (testicular) development*
   1) Complete or partial gonadal dysgenesis
   2) Ovotesticular DSD
   3) Testis regression

B) *Disorders of androgen synthesis or action*
   1) Disorders of androgen synthesis
      LH receptor mutations
      Smith–Lemli–Opitz syndrome
      Steroidogenic acute regulatory protein mutations
      Cholesterol side-chain cleavage
      3β-hydroxysteroid dehydrogenase
      17β-hydroxysteroid dehydrogenase
      5α-reductase
   2) Disorders of androgen action
      Androgen insensitivity syndrome
      Drugs and environmental modulators

C) *Other*
   1) Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog, hand–foot–genital, popliteal pterygium)
   2) Persistent Müllerian duct syndrome
   3) Vanishing testis syndrome
   4) Isolated hypospadias
   5) Congenital hypogonadotrophic hypogonadism
   6) Cryptorchidism
   7) Environmental influences

46XX DSD

A) *Disorders of gonadal (ovarian) development*
   1) Gonadal dysgenesis
   2) Ovotesticular DSD
   3) Testicular DSD

B) *Androgen excess*
   1) Fetal
      3β-hydroxysteroid dehydrogenase
      21-hydroxylase
      P450 oxidoreductase
      11β-hydroxylase
      Glucocorticoid receptor mutations
   2) Fetoplacental
      Aromatase deficiency
      Oxidoreductase deficiency
   3) Maternal
      Maternal virilizing tumours (e.g. luteomas)
      Androgenic drugs

C) *Other*
   1) Syndromic associations (e.g. cloacal anomalies
   2) Müllerian agenesis/hypoplasia (e.g. MRKH)
   3) Uterine abnormalities (e.g. MODY5)
   4) Vaginal atresia (e.g. McKusick–Kaufman)
   5) Labial adhesions

(46XX); in the largest series reported, Van Niekerk [6] found that 58% of cases had a normal karyotype, 13% had 46XX/XY, 11% had 46XY and 6% had 46XY/47XXY, with other mosaics accounting for 10%. Gonadal differentiation is interesting in that the commonest combination of ovotestis is for an ovotestis to be on one side and an ovary on the other, with a testis on one side and an ovary on the other being almost as frequent. Ovotestes can be bilateral or combined with a testis but this is much rarer. Diagnosis of true ovotesticular DSD can only be made after gonadal biopsy, and sex of rearing should be determined on the functional capability of the external genitalia after which inappropriate organs should be removed. In some cases it may be possible to identify the ovarian and testicular portions of an ovotestis for certain and to remove only that part that is unwanted. If this is not possible, both must be removed and then the patient needs to be brought up in the gender role for whichever is appropriate and hormone replacement therapy instituted at puberty.

Disorders of androgen synthesis

In group B1 (see Table 35.1), the most commonly seen, though rare, is 5α-reductase deficiency. These patients are genetic males who show ambiguous genitalia at birth and at puberty begin to virilize like normal males. This results in penile enlargement, increased facial hair and muscular hypertrophy but breast development does not occur. The phallus is rather small and a perineal urethral orifice is present. The disorder of androgen synthesis relates to deficiency of 5α-reductase, the enzyme responsible for the conversion of testosterone to dihydrotestosterone, which results in virilization of the external genitalia during embryogenesis. Testosterone is unable to induce virilization during fetal life but at puberty androgen receptors become sensitive to circulating levels of testosterone and therefore a degree of virilization can occur. Management of these patients after puberty can be difficult as they themselves may find sexual orientation difficult and may wish to change their gender role but they must be fully assessed before any permanent decisions are made.

Androgen insensitivity syndromes

In these conditions the individual has a chromosome complement of 46XY but an absence of functional androgen receptors. This is known as complete androgen insensitivity syndrome and during fetal life female external genitalia develop, but as the testis produces Müllerian inhibitor the internal structures of the Müllerian duct regress. However, the Wolffian duct cannot develop as it also lacks androgen receptors. These individuals usually present at puberty with failure of menstruation. They are shown to have bilateral testes and a blind-ending vagina

and they may well feminize at puberty as testicular production of oestrogen induces breast growth. Absence of the androgen receptor means that pubic hair and axillary hair growth is sparse and the diagnosis is often easy to make clinically. The testes are usually normal in size and located either in the abdomen or the inguinal canal and can present as inguinal hernias. These sometimes present in childhood when the diagnosis is made on surgical excision of the mass. Height is slightly increased compared with normal women. Testicular neoplasia is increased though very rare under the age of 30. It is therefore perfectly acceptable to leave the gonads *in situ* until pubertal development has been completed and then to remove them.

Partial androgen insensitivity occurs when the androgen receptor has a mutation and has partial function. At puberty therefore individuals feminize as do patients with complete androgen insensitivity but as they have some function in the androgen receptor, their external genitalia change, with phallic enlargement and partial labioscrotal fusion. Again, bilateral testes are present within the abdominal cavity or the inguinal canal and there are normal circulating levels of testosterone equivalent to a male. At birth phallic enlargement may already be present due to incomplete virilization and the intersex state at birth needs to be assessed and the sex of rearing determined.

Summary box 35.2

- Androgen insensitivity may be complete or partial depending on the defect in the androgen receptor.
- Phenotypic changes depend on the degree of function of the androgen receptor.

46XX

Patients with this group of disorders will most commonly present with congenital adrenal hyperplasia (CAH). Deficiency of 21-hydroxylase is the most common and this leads to elevated levels of androstenedione, 17-hydroxyprogesterone and testosterone. As this is a disorder which is present during fetal life, the elevated levels of androgen lead to virilization of the fetus and therefore clinically female fetuses show clitoral hypertrophy and labioscrotal fusion. The urethral orifice is displaced usually along the dorsal surface of the clitoris and the extent of virilization can vary considerably. Müllerian duct development is normal as are the ovaries. The most severe form at birth is a salt-losing syndrome that can be life-threatening and the administration of mineralocorticoids and sodium are usually needed to correct the hyperkalaemia. Cortisol administration remains necessary throughout life, although requirements may diminish with age.

These patients are diagnosed soon after birth by finding elevated levels of 17-hydroxyprogesterone. Little attention needs to be paid to the anatomy unless there is marked virilization, in which case discussion with the parents about surgical intervention should be considered. However, debate continues about whether or not surgical intervention should occur in infancy or at puberty when the individual can be involved in the decision-making process. Further discussion of this is outside the remit of this chapter.

46XX Müllerian agenesis

The most common of this group of disorders is Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome which is characterized by congenital absence of the uterus and vagina in individuals who are 46XX. These patients usually present with primary amenorrhoea at the age of 12–16 years with normal secondary sexual characteristics as the ovaries are normally developed and functional. The combination of normal secondary sexual characteristics and primary amenorrhoea suggests an anatomical cause. Inspection of the vulva will reveal that this is normal but there is a short vagina which is blind-ending (Fig. 35.7). The diagnosis of an absent vagina can generally be made without difficulty but subsequent ultrasound of the abdomen will define the absence of Müllerian structures. It must be remembered that a very short vagina may also occur in patients with androgen

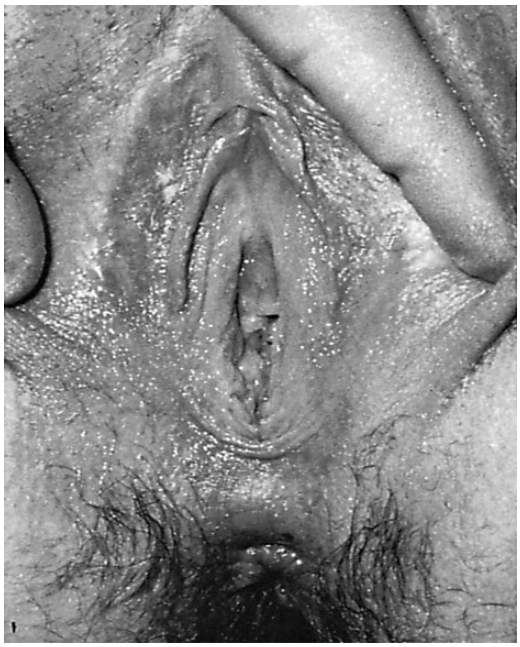

Fig. 35.7 Vulval appearance in a case of absence of the vagina.

insensitivity but assessment of karyotype will differentiate these two groups of patients. In all patients found to have MRKH syndrome, the renal tract should be investigated using ultrasound as some 40% of patients will have renal anomalies, with 15% having an absent kidney. If further investigation is required, intravenous urography can be used to delineate any other renal anomalies [7]. It is extremely rare for laparoscopy to be required to determine the diagnosis but if undertaken must be used with great care as a pelvic kidney may be present. Once the diagnosis is certain, management can be divided into two phases. The first is devoted to the psychological counselling of patients and the second involves the correction of the vaginal anatomy. Some patients may present having already attempted intercourse and this may in fact be entirely satisfactory and therefore no attention needs to be paid to the anatomical side of their management. However, it is important that all patients with MRKH syndrome are assessed with great care so that appropriate therapy can be instigated at the correct time. A full psychological assessment must be carried out before any treatment is commenced or success will be extremely limited.

Psychological counselling of these patients is imperative as they may manifest problems that are devastating and profound. They have feelings of fear and confusion, particularly around their sexual orientation, and may express feelings of rejection and isolation. They have understandable concerns about the ability to embark on heterosexual relationships and of their feeling of inadequacy, as they are infertile. The help of a skilled psychologist in managing these patients and a multidisciplinary approach means that the outcome will be successful in a holistic way, not merely an anatomical success. Until patients are deemed psychologically capable of undergoing the rigours of treatment, all attempts to coerce the clinical team to begin treatment prior to this should be resisted [8,9].

Summary box 35.3

- MRKH syndrome is the second most common cause of primary amenorrhoea.
- Turner's syndrome is the most common.

Non-surgical management

The creation of a vagina should always be attempted by a non-surgical method as the treatment of first choice and only in the rare cases of failure should a surgical solution be considered. This technique was pioneered by Frank [10] and a recent review by Edmonds [7] suggests that success rates in excess of 95% can now be achieved. The principle of the method is that the vaginal dimple should be stretched into a potential space filled with comparatively loose connective tissue and this is capable of considerable indentation. The patient is instructed to use graduated glass dilators (Fig. 35.8) that are placed against the introitus and the blind vagina and gentle pressure is exerted in a posterior direction for approximately 10–20 min twice a day. Gradually the dilator distends the space and then increasing sizes of dilators are used until a neovagina is created. In general it takes between 8 and 10 weeks of repeated use to achieve a satisfactory result. The sexual satisfaction associated with this non-surgical technique far exceeds that of operative vaginoplasty.

Fig. 35.8 Graduated glass dilators.

Summary box 35.4

Vaginal dilator therapy is the therapy of choice for patients with MRKH syndrome.

Surgical techniques

In the few patients who fail a non-surgical technique, vaginoplasty will need to be considered. A large number of techniques have been devised to create a vagina surgically, the most widely used being that of McIndoe and Banister [11]. In this procedure a cavity is created between the bladder and the bowel at the site where the natural vagina would have been and the cavity is then lined by a split-thickness skin graft from the thigh and applied to the space on a plastic mould. The anatomical result can be very successful and remarkably good sexually. A review of 1311 reported cases gave a success rate of 92% [7].

However, there are a number of difficulties and disadvantages of this technique, not least the postoperative period which is painful and somewhat protracted. The graft does not always take well and granulation may form

over part of the cavity giving rise to discharge. Pressure necrosis between the mould and urethra, bladder or rectum may lead to fistula formation but the most important disadvantage is the tendency for the vagina to retract unless a dilator is worn or the vagina used for intercourse regularly. It is therefore best to perform this procedure when sexual intercourse is desired soon afterwards because failure of the patient to maintain the vagina means there will be surgical failure. A further disadvantage of this technique is the graft donor site, which remains visible as evidence of the vaginal problem and most women prefer not to have any external scarring. In order to avoid the use of skin grafts a number of other materials have been used including amnion, although this material is no longer desirable due to the risk of transmission of infection. Other reported techniques include the use of bowel [12] and skin flaps [13] and these have their own individual complications. A procedure known as Vecchietti's operation has been popular in Europe for many years and this involves the use of a small olive placed in the dimple of the absent vagina [14,15]. Laparoscopically, wires are then brought through from the dimple to the anterior abdominal wall and then pressure exerted on a spring device, thereby creating a neovagina in a way that mimics the non-surgical technique of Frank. However, it does not require the woman herself to use the dilators but after 7–9 days the olive is removed and the stretched vaginal skin needs to be further dilated with glass dilators. A recent review of this technique revealed success rates approximating to 90% [7].

Other anatomical anomalies

Fusion anomalies

Fusion anomalies of various kinds are not uncommon (Fig. 35.9) and may present clinically either in association with pregnancy or not. The lesser degrees of fusion defects are quite common, the cornual parts of the uterus remaining separate, giving the organ a heart-shaped appearance known as a bicornuate uterus. There is no evidence that such minor degrees of fusion defect give rise to clinical signs or symptoms. However, the presence of a septum extending down the uterine cavity is likely to give rise to clinical problems. Such a septate or subseptate uterus may be of normal external appearance or of

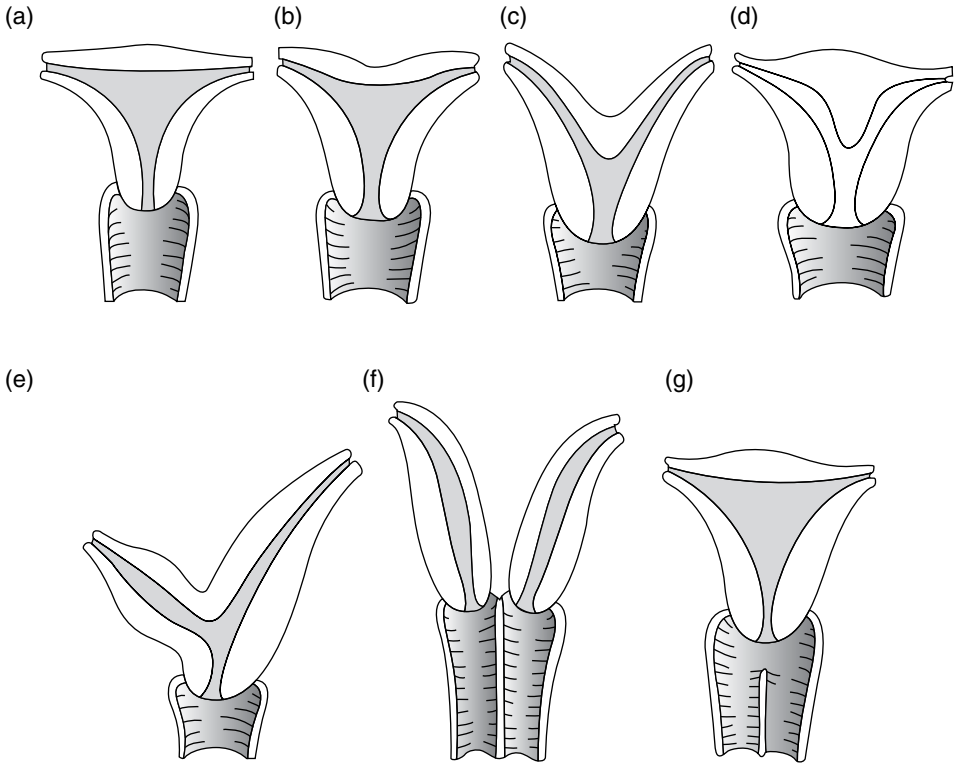

Fig. 35.9 Various fusion abnormalities of the uterus and vagina: (a) normal appearance; (b) arcuate fundus with little effect on the shape of the cavity; (c) bicornuate uterus; (d) subseptate uterus with normal outline; (e) rudimentary horn; (f) uterus didelphys; (g) normal uterus with partial vaginal septum.

bicornuate outline. Clinically, patients may present with recurrent spontaneous miscarriage or malpresentation of the fetus during pregnancy. A persistent transverse lie or breech presentation of the fetus in late pregnancy may suggest a uterine anomaly since the fetus tends to lie with its head in one cornu and the breech in the other.

In more extreme forms of failure of fusion the clinical features may be less, rather than more, marked. Two almost separate uterine cavities with one cervix are probably less likely to be associated with abnormalities than are the lesser degrees of fusion defect. Complete duplication of the uterus and cervix (uterus didelphys) is usually associated with a septate vagina. The septum should be removed before pregnancy.

Rudimentary development of one horn may give rise to a very serious situation if a pregnancy is implanted there. Rupture of the horn with profound bleeding may occur as the pregnancy increases in size. The clinical picture will resemble that of a ruptured ectopic pregnancy, with the difference that the amenorrhoea will probably be measured in months rather than weeks, and shock may be profound. A poorly developed or rudimentary horn may give rise to dysmenorrhoea and pelvic pain if there is any obstruction to communication between the horn and the main uterine cavity or the vagina. Surgical removal of this rudimentary horn is then indicated (see Fig. 35.9).

Transverse vaginal septum/imperforate hymen

An imperforate membrane may exist at the lower end of the vagina, which is loosely referred to as imperforate hymen, although the hymen can usually be distinguished separately (Fig. 35.10). These abnormalities of vertical fusion are seldom recognized clinically until puberty when retention of menstrual flow gives rise to the clinical features of haematocolpos, although rarely they may present in the newborn as hydrocolpos. The features of haematocolpos are predominantly abdominal pain, primary amenorrhoea and occasionally interference with micturition. The patient is usually 14–15 years old but may be older, and a clear history may be given of regular cyclical lower abdominal pain for several months previously. The patient may also present as an acute emergency if urinary obstruction develops. Examination reveals a lower abdominal swelling, and per rectum a large bulging mass in the vagina may be appreciated (Fig. 34.11). Vulval inspection may reveal the imperforate membrane, which may or may not be bluish in colour depending on its thickness. Diagnosis may be more difficult if the vagina is imperforate over some distance in its lower part or if there is obstruction in one-half of a septate vagina.

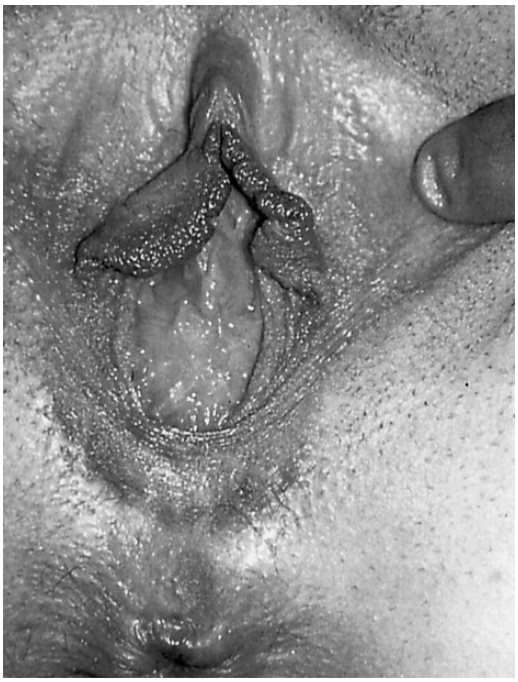

Fig. 35.10 An imperforate membrane occluding the vaginal introitus in a case of haematocolpos. Note the hymen clearly visible immediately distal to the membrane.

Treatment may be relatively simple or rather complex. If the membrane is thin, then simple excision of the membrane and release of the retained blood resolves the problem. Redundant portions of the membrane may be removed but nothing more should be done at this time. Fluid will then drain naturally over some days. Examination a few weeks later is desirable to ensure that no pelvic mass remains that might also suggest haematosalpinx. In fact, haematosalpinx is most uncommon except in cases of very long standing and is associated with retention of blood in the upper vagina. On these rare occasions when a haematosalpinx is discovered, laparoscopy is desirable, the distended tube being removed or preserved as seems best. Haematometra scarcely seems to be a realistic clinical entity, the thick uterine walls permitting comparatively little blood to collect therein. The subsequent menstrual history and fertility of patients who are successfully treated are probably not significantly different from those of unaffected women, although patients who develop endometriosis may have some fertility problems.

When the obstruction is more extensive than a thin membrane and a length of vagina is absent, diagnosis and management are less straightforward and the ultimate interference with fertility is greater. Resection of the absent segment and reconstruction of the vagina may be done by an end-to-end anastomosis of the vagina or by a partial vaginoplasty.

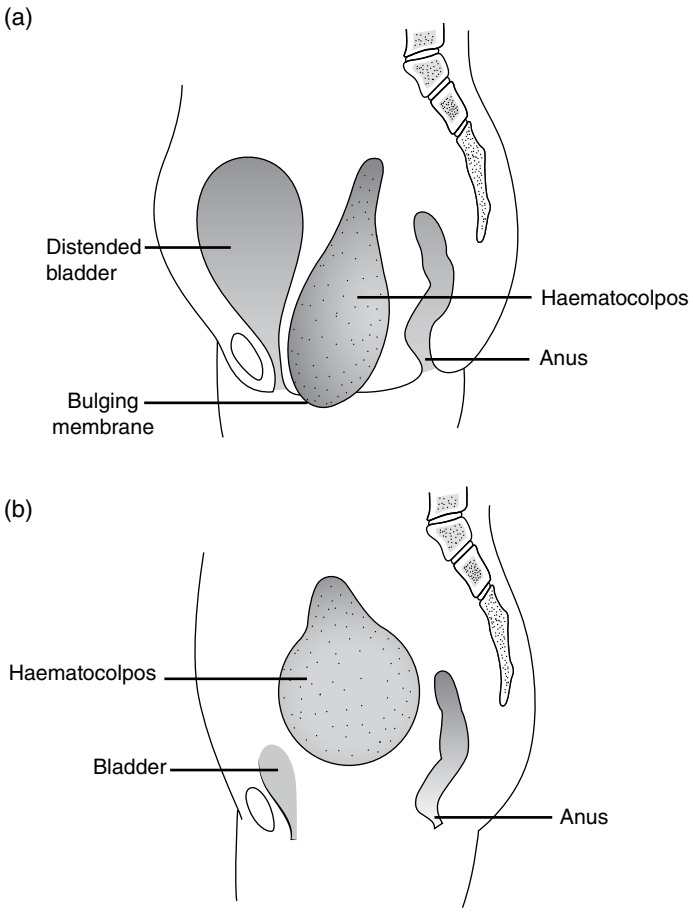

Fig. 35.11 (a) Haematocolpos: note how the blood collecting in the vagina presses against the urethra and bladder base, ultimately causing retention of urine. (b) Haematocolpos associated with absence of the lower portion of the vagina. Note that the retained blood is now above the bladder base and retention of urine is unlikely.

The combination of absence of most of the lower vagina together with a functioning uterus presents a difficult problem. The upper part of the vagina will collect menstrual blood and a clinical picture similar in many ways to haematocolpos will be seen. However, urinary obstruction is rare because the retained blood lies above the level of the bladder base (Fig. 35.11). Diagnosis is more difficult and it may not be at all certain how much of the vagina is absent or how extensive the surgery would need to be to release the retained fluid and recreate the normal anatomy. Imaging may be by ultrasound or MRI, and both these techniques may be successful in determining the exact anatomical relationships prior to surgery being performed. However, in the clinical situation the surgical approach is rarely entirely through the perineum and usually involves a laparotomy to establish finally how best the anatomy can be recreated.

Treatment is difficult and a dissection upwards is made as in the McIndoe–Read procedure. The blood is released, but its discharge for some time later may interfere with the application of a mould and skin graft. If possible, the upper and lower portions of the vagina should be brought together and stitched so that the new vagina with its own skin is created, obviating the risk of contraction. However, the upper fragment tends to retract upwards resulting in a narrow area of constriction some way up the vagina, and this results in subsequent dyspareunia.

Summary box 35.5

- Transverse vaginal septa cause primary amenorrhoea and cyclical abdominal pain.
- The most common septa are low and surgical treatment usually restores total reproductive function.
- High septa have a higher rate of fertility failure.

Longitudinal vaginal septum

A vaginal septum extending throughout all or part of a vagina is not uncommon; such a septum lies in the

sagittal plain in the midline, although if one side of the vagina has been used for coitus the septum may be displaced laterally to such an extent that it may not be obvious at the time of examination. The condition is found in association with a completely double uterus and cervix or with a single uterus and double cervix. In obstetrics this septum may have some importance if vaginal delivery is to be attempted. In these circumstances the narrow hemivagina may be inadequate to allow passage of the fetus and serious tears may occur if the septum is still intact at this time. It is therefore prudent to arrange to remove the vaginal septum as a formal surgical procedure whenever one is discovered, either before or during pregnancy. The septum may occasionally be associated with dyspareunia, when similar management is indicated.

Occasionally, a double vagina may exist in which one side is not patent, and a haematometra and haematocolpos may occur in a single side. Under these circumstances the vaginal septum must be removed to allow drainage of the obstructed genital tract and the results are generally excellent.

Vulval anomalies

Rarely, anomalies in the development of bowel or bladder may give rise to considerable abnormality in the appearance of the vulva. The anus may open immediately adjacent to the vulva or just within it. Bladder exstrophy will give rise to a bifid clitoris and anterior displacement of the vagina, in addition to bladder deformities themselves. Further discussion of these complex problems may be found in Edmonds [16].

Wolffian duct anomalies

Remnants of the lower part of the Wolffian duct may be evident as vaginal cysts, whereas remnants of the upper part are evident as thin-walled cysts lying within the layers of the broad ligament (paraovarian cysts). It is doubtful if a vaginal cyst per se calls for surgical removal, although removal is usually undertaken. The cysts may cause dyspareunia and this is the most likely reason for their discovery and surgical removal. Cysts situated at the upper end of the vagina may be found to burrow deeply into the region of the broad ligament and the base of the bladder and should be approached surgically with considerable caution. A painful and probably paraovarian cyst will require surgery and its precise nature may be unknown until the abdomen is explored laparoscopically. Such cysts are normally easily removed from the broad ligament.

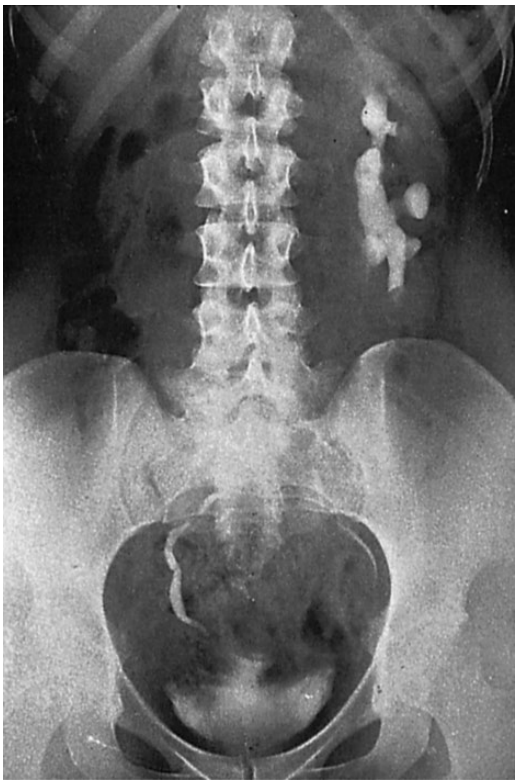

Fig. 35.12 An intravenous pyelogram in a patient with absence of the vagina, showing a single kidney and a gross abnormality of the course of the ureter.

Renal tract abnormalities

The association between congenital malformations of the genital tract and those of the renal tract has already been mentioned. When a malformation of the genital organs of any significant degree presents, some investigation to confirm or exclude a renal tract anomaly would be wise. An ultrasound scan can be performed and will probably be sufficient in the first instance; however, if any doubt arises, an intravenous urogram may be performed. Lesions such as absence of a kidney, a double renal element on both or one side, a double ureter or a pelvic kidney (Fig. 35.12) may not call for immediate treatment but may do so later; moreover, it is as well to be aware of such abnormalities if the abdomen is to be explored or for treatment of the genital tract lesion itself.

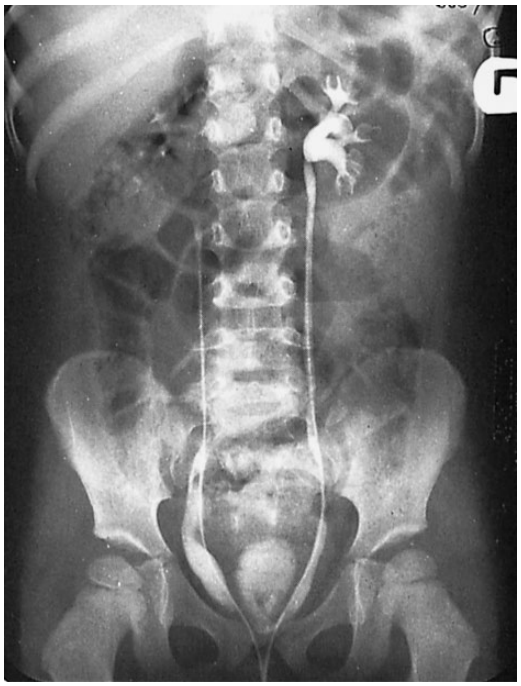

Fig. 35.13 An intravenous pyelogram in a child with an imperforate vagina. Both ureters open ectopically into the posterior urethra.

Ectopic ureter

One abnormality which apparently presents with gynaecological symptoms is the ectopic ureter (Fig. 35.13). A ureter opening abnormally is usually an additional one, although sometimes a single one may be ectopic. The commonest site of the opening is the vestibule, followed closely by the urethra and then the vagina. Other sites are less common. The main symptom is uncontrollable wetness. However, the amount of moisture appearing at the vulva may be small and is sometimes mistaken for a vaginal discharge. This confusion, together with difficulties in confirming the diagnosis of an ectopic ureter, even when one is suspected, may lead to many patients being investigated for years before the condition is recognized. Diagnosis can sometimes be easy but is usually not so. The orifice at the vestibule may be clearly visible but more often careful search is necessary to locate it, if it can be seen at all. Cystoscopy and urethroscopy may be necessary to establish if normal ureteric openings exist in the bladder. Radiological study may be helpful by indicating a double element on one or both sides. Treatment will involve the help of a urological surgeon, and partial nephrectomy and ureterectomy or reimplantation of the ectopic ureter into the bladder may be undertaken.

XY females

Faults in androgen production

In this group of patients androgen production may fail from either anatomical or enzymatic testicular failure.

Anatomical testicular failure

Failure of normal testicular differentiation and development may be the result of a chromosome mosaicism affecting the sex chromosomes or possibly associated with an abnormal isochromosome [17], but usually the sex chromosomes appear normal and the condition is referred to as pure gonadal dysgenesis. Clinically, such cases show variable features depending on how much testicular differentiation is present. Since differentiation is often poor, most patients have mild masculinization or none at all, and the uterus, tubes and vagina are generally present. The presence of the uterus in this condition contrasts with the other forms of XY female described below.

Management of this group of patients is concerned with the reconstruction of the external genitalia in the manner described previously and removal of the streak or rudimentary gonads in view of their raised potential for cancer. The degree of masculinization of such patients is often minimal and if it is limited to a minor degree of clitoral enlargement with little or no fusion of the genital folds, surgery need not be undertaken. The risk of malignancy in the rudimentary testes is probably in the order of 30% and gonadal removal during childhood would be wise. Around the age of puberty replacement oestrogen–progestogen therapy must be started in order to initiate secondary sexual development and menstruation.

Enzymatic testicular failure

Several metabolic steps are necessary for the complete formation of testosterone from cholesterol (Fig. 35.14). A number of biosynthetic defects have been reported at each stage of the process. As a result, clinical features are somewhat varied but since such enzyme defects are generally incomplete there is external genital ambiguity of varying degrees, the uterus, tubes and upper vagina being absent since the production of Müllerian-inhibiting substance by the testes is normal.

The decision on the sex of rearing will depend on the degree of masculinization of the external genitalia but the female role is often the chosen one. Surgical management is as already described. The identification of the precise enzyme defect can be difficult, but may be approached through human chorionic gonadotrophin stimulation of the gonads and measurement of various androgens to determine where the enzyme block occurs.

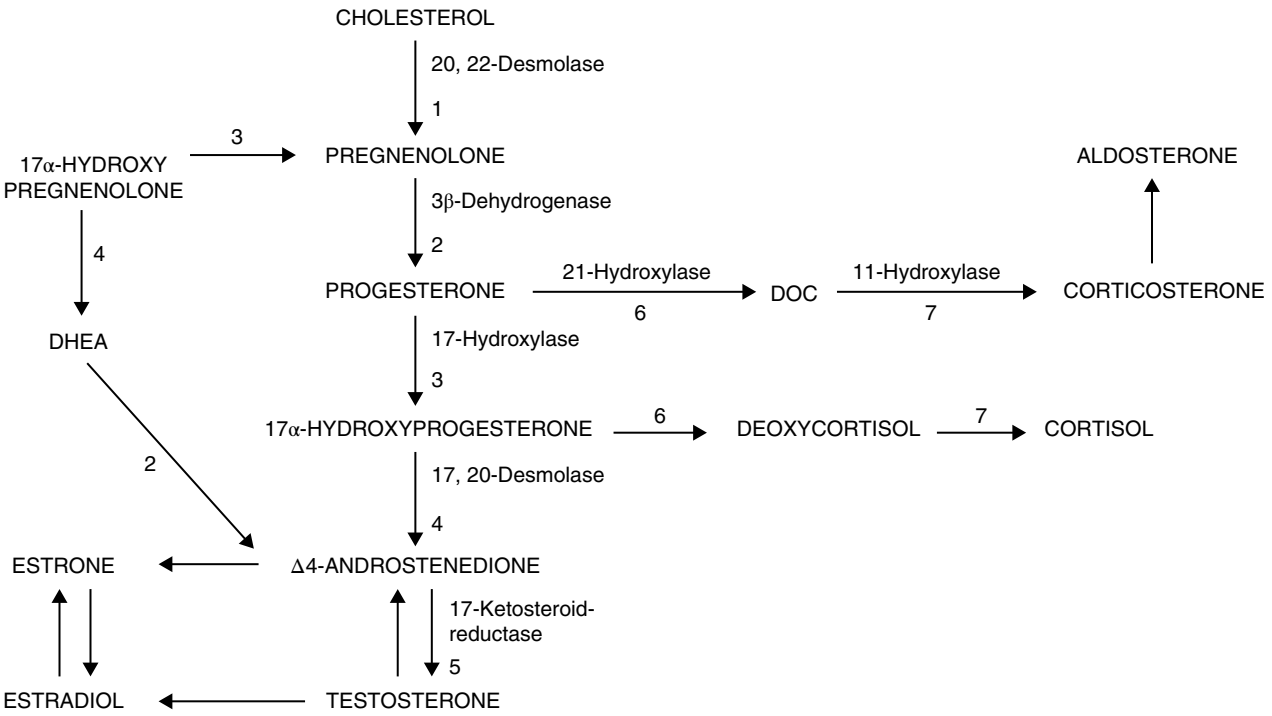

Fig. 35.14 The enzyme steps necessary to convert cholesterol through its various intermediate stages to aldosterone, cortisol and testosterone. Note that 3β-dehydrogenase (labelled 2) is active at two points, as are 17-hydroxylase (labelled 3), 17,20-desmolase (labelled 4), 21-hydroxylase (labelled 6) and 11-hydroxylase (labelled 7). DHEA, dehydroepiandrosterone; DOC, deoxycorticosterone.

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36

Role of Imaging in Gynaecology

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A good medical history-taking and clinical examination are the first steps in the management of a patient presenting with gynaecological symptoms. However, to confirm or exclude a diagnosis suspected on the basis of these, imaging methods are often indicated.

The introduction of ultrasound has changed the approach to many disorders in gynaecology. It has redefined the diagnostic criteria and management of problems in early pregnancy, decreased the need for more invasive procedures in women with abnormal uterine bleeding or infertility, enabled the accurate characterization of pelvic masses and allowed significant advances in the management of patients with pelvic pain. However, as ultrasound assessment might not give a final answer in all cases, second-stage tests such as MRI may be required.

In this chapter, we focus on practical guidance in performing gynaecological ultrasound and discuss the role of different imaging modalities in common clinical conditions encountered in gynaecological practice.

Ultrasound techniques

An ultrasound examination of the pelvis is one of the most common procedures in gynaecology, with most women presenting to a gynaecology department undergoing a scan at some point in their management pathway. Ultrasound is in general readily available, safe, low in cost and less time-consuming compared to other maging modalities. Another important advantage is its possibility for dynamic evaluation, which helps in understanding the origin of lesions and in the detection of adhesions or site-specific tenderness [1]. A potential disadvantage is that the quality of ultrasound imaging, more than in other imaging techniques, not only relies on the equipment but also on its settings as well as on the experience of the ultrasound investigator. Therefore, it is very important to have a good basic knowledge of how the technical features of the machine can be adjusted.

Physical properties and settings

The term 'ultrasound' describes sound waves of such a high frequency that they cannot be heard by humans. The higher the probe frequency, the narrower the beam width. This results in improved resolution, but with the trade-off of poorer penetration. As a result such probes need to be used close to the area of interest. In gynaecology, transabdominal probes tend to range from 3 to 5 MHz and transvaginal probes from 5 to 8 MHz. However, improvements in probe design have led to them being significantly more adaptable than in the past [2]. Besides adjusting the frequency, it is also important to change the focus of the ultrasound beam to optimize the resolution of the image at the depth of interest. Altering the gain is indispensable to acquire proper illumination. Harmonic imaging can further improve image quality, especially in cystic lesions (e.g. ovarian masses). Once the area of interest has been located, the image can be magnified in order to obtain maximum detail.

The use of colour or power Doppler is useful for assessing both the amount of blood flow and the pattern of any blood vessels present. This is helpful in visualizing normal anatomy (e.g. finding the ovaries), defining the origin of structures and, if used in a standardized way, characterizing pathology [1,3–6]. The option of three-dimensional ultrasound is a further advance. This is helpful for the characterization of congenital uterine abnormalities and for the delineation of the endometrial–myometrial junction to assess acquired uterine pathology [7,8].

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Ultrasound approaches

Transvaginal ultrasonography is the method of choice, as it results in the best image quality, due to the proximity of the probe to the gynaecological organs. However, a transabdominal scan may be required to assess the uterus in the presence of large fibroids or to evaluate the adnexa when these are enlarged and extending beyond the level of the pelvis. When a transvaginal scan is considered inappropriate (e.g. virginity, vaginismus or vaginal stenosis due to atrophy, surgery or pelvic irradiation) and if the transabdominal approach is inconclusive, a transrectal ultrasound examination should be considered.

During transvaginal ultrasonography the hand not holding the probe can be used to press on the abdomen and help optimize the image or assess mobility or pain [1]. Although a full bladder can be useful for transabdominal scanning, in many cases it is not required. A good technique is to identify the femoral vessels and follow these upwards to the iliac vessels and finally to the bifurcation of the aorta. An ovarian mass and any lymphadenopathy present can be assessed in this way. A gynaecologist learning to scan should be aware that an examination of the abdomen does not stop in the pelvis and the examiner should be familiar with the normal appearances of the organs of the upper abdomen and the likely sites of metastatic disease in the event of gynaecological malignancy. These might include the peritoneum, lymph nodes around the large vessels, the spleen, liver or the omentum. Ascites may be present in the upper abdomen.

In the event of suspected intra-abdominal blood loss, the presence of fluid above the fundus of the uterus or in the utero-vesical pouch is significant. A further marker of serious intra-abdominal bleeding is the presence of fluid in Morrison's pouch between the liver and the kidney [9].

The uterus should be assessed in the sagittal plane, including detailed evaluation of the cervix, the body of the uterus, the fundus and the endometrial cavity. Views obtained in the transverse plane may help in defining the location of focal pathology. The detection of congenital uterine abnormalities is best achieved using three-dimensional ultrasound whereby the unique coronal view allows most anomalies to be characterized relatively easily [10].

The endometrial thickness, the maximal measurement across the lumen of the endometrial cavity in the sagittal plane including both endometrial layers (double endometrial thickness), is an important assessment. In premenopausal women, endometrial thickness generally varies from 4 to 8 mm in the follicular phase and from 7 to 14 mm in the secretory phase. A sonographic examination in this population should preferably be performed in the early proliferative phase (cycle day 4–6) [3]. Recent consensus documents have outlined proposed terminology to describe the endometrium and myometrium, with any pathology that may be present [3,6].

Difficulties in assessment due to variations in uterine position (particularly when axial) or uterine rotation (endometriosis or adhesions) can be overcome by pressing on the abdomen with the non-scanning hand, or by filling the bladder [3]. The ovaries can be visualized by tracking the vessels in the broad ligament in the transverse plane from the uterus and moving laterally to the pelvic wall nearby the external iliac vessels. It might be useful to apply abdominal pressure to displace superimposed intestines or to use a transabdominal approach if necessary [1].

Sonohysterography

Sonohysterography is the instillation of fluid through a catheter into the uterine cavity to act as a negative contrast agent to outline any focal intra-cavity pathology. Sterile saline or gel may be used [3]. In saline instillation, a neonatal suction catheter may be used, although backflow may necessitate the use of a more expensive balloon catheter to obtain a more stable filling of the uterine cavity. The higher viscosity of gel results in a smaller instillation volume, which makes the procedure better tolerated by patients compared with saline instillation [11]. Moreover, transtubal spillage is less likely to occur and this may be an additional argument for the use of gel instead of saline, as endometrial malignancy is never completely excluded with ultrasonography. A small neonatal suction catheter (2 mm) is sufficient, but it might be helpful to warm the gel to 37 °C to promote flow through the catheter.

It might be prudent in fertile women to advocate contraception during the cycle when the sonohysterography procedure is planned, and some examiners advise that prophylactic antibiotics should be administered prior to the procedure in all potentially fertile women to avoid pelvic inflammatory disease [11,12].

Possible indications for sonohysterography include a thickened or irregular endometrium, poor views of the endometrium (e.g. due to axial position of uterus) and further characterization of focal intra-cavity pathology such as polyps, submucous fibroids and adhesions (Fig. 36.1). There is a large amount of data to suggest that sonohysterography is comparable to hysteroscopy for the assessment of most focal endometrial pathology [13]. Ultrasound without saline instillation is significantly less accurate for this purpose [14]. In the event of uncertainty regarding the endometrial findings, sonohysterography is always a good option to consider. It is also important to

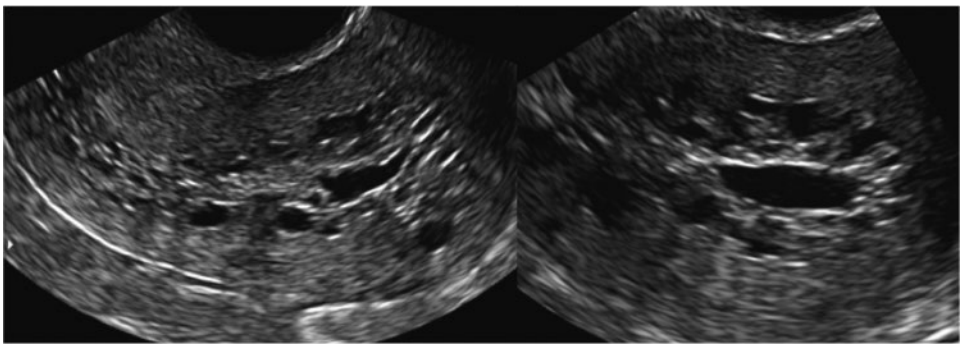


Fig. 36.1 Gel instillation sonohysterography. (*Left*) Unenhanced ultrasound image of the endometrium in a patient using tamoxifen. The endometrial lining is not well assessable. (*Right*) After gel instillation, the endometrium shows a regular lining, besides tamoxifen-induced changes. Focal pathology can be excluded.

remember that the endometrium in premenopausal women is a dynamic structure and so simply repeating a scan after menstruation will often clarify whether there is focal intrauterine pathology or not.

Hysterosalpingo-contrast sonography and hysterosalpingo-foam sonography

The gold standard test to assess tubal patency is laparoscopic chromoperturbation with methylene blue. However, this procedure is associated with the risks of laparoscopy under general anaesthesia. Therefore, as a less invasive radiography technique, X-ray hysterosalpingography has been applied for decades in the diagnostic work-up of the patient presenting with infertility [15]. At present, this exposure to radiation and risk of allergy to the contrast agent can be avoided by tracking the movement of a suspension of air bubbles through the fallopian tubes during hysterosalpingo-contrast sonography [16]. In general, a balloon catheter is used. The contrast media are commercially available, but a cheaper option is to use an alternating injection of water and air in the uterine cavity and to sonographically detect air bubbles around the ovary and free fluid in the pouch of Douglas [17]. More recently, hysterosalpingo-foam sonography was introduced, using 'gel foam', with advantageous physical properties compared with saline [18] (Fig. 36.2). Both hysterosalpingo-contrast sonography and hysterosalpingo-foam sonography are well tolerated by the patient, and show very good agreement in assessing tubal patency compared with laparoscopic chromoperturbation [18–20].

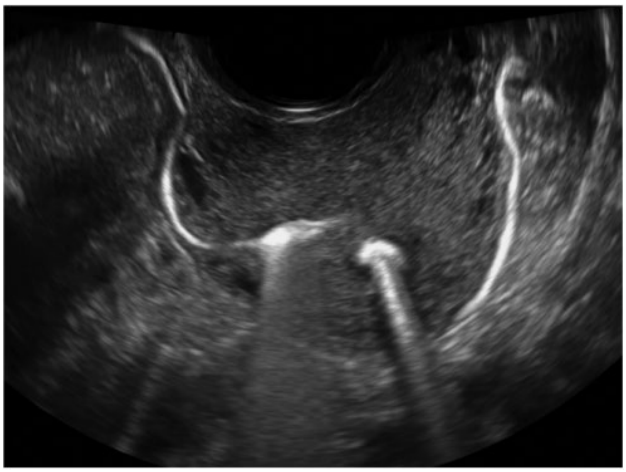


Fig. 36.2 Hysterosalpingo-foam sonography is a dynamic investigation that allows tracking of foam as a hyperechoic suspension through the fallopian tubes. On this image, there is visible bilateral patency through the isthmic and intramural portion of the tubes.

Ultrasound-guided procedures

Ultrasound can guide different invasive procedures in gynaecology. Besides the well-known application in reproductive medicine for oocyte retrieval, there is increasing interest in the field of gynaecological oncology. Ultrasound-guided Tru-cut biopsy has been shown to be an accurate and safe, minimally invasive technique to acquire tissue diagnosis in the management of advanced or recurrent gynaecological tumours or when pelvic metastatic disease from another primary origin is suspected [21,22].

In general, this procedure is performed with a core-cut biopsy needle inserted through a needle guide mounted on the transvaginal probe. Local anaesthesia is not required in a transvaginal approach. A similar approach with an aspiration needle connected to a syringe or vacuum container allows the drainage of symptomatic pelvic cysts, on condition that there is no suspicion of malignancy. Examples are large peritoneal pseudocysts, simple ovarian cysts or tubo-ovarian abscesses in pelvic inflammatory disease [23].

Summary box 36.1

- A good basic knowledge of the technical features of the ultrasound machine is important, as quality of ultrasound imaging relies on the settings of the device.
- Ultrasound assessment and reporting of gynaecological structures, with any pathology that may be present, should be based on international consensuses.
- Transvaginal ultrasound is the method of choice in the assessment of the female pelvis. In certain conditions, a transabdominal or transrectal approach can be considered.
- Pressing on the abdomen with the non-scanning hand can improve the visualization of structures or aid in the evaluation of adhesions or site-specific tenderness.
- Sonohysterography is indicated in the evaluation of a thickened or irregular endometrium, or for further characterization of focal intra-cavity pathology such as polyps, submucous fibroids and adhesions.
- Hysterosalpingo-contrast sonography and hysterosalpingo-foam sonography can replace more invasive and harmful techniques in the assessment of tubal patency.
- Ultrasound-guided biopsy is increasingly being used for diagnosis in the field of gynaecologic oncology.

Imaging in common gynaecological conditions

Abnormal uterine bleeding

Over recent years transvaginal ultrasonography has significantly improved our ability to accurately manage patients with abnormal uterine bleeding. Ultrasound findings are described according to international consensuses [3,6]. Other imaging modalities such as MRI are indicated as second-stage tests in certain circumstances.

Premenopausal bleeding

In 2011, the International Federation of Gynecology and Obstetrics (FIGO) published the PALM-COEIN system (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; not yet classified), which classifies the aetiology of abnormal uterine bleeding [24]. From these causes, imaging methods can only confirm or exclude anatomical abnormalities, i.e. the 'PALM group'. However, these might or might not be the cause of the bleeding problem, as they may also be found in asymptomatic women. In the large majority of premenopausal women, abnormal uterine bleeding is associated with benign lesions such as an endometrial polyp or an intra-cavitary fibroid, whereas endometrial cancer is an uncommon cause. In abnormal uterine bleeding, the usefulness of an ultrasound evaluation of the endometrial thickness to detect pathology is much less obvious in premenopausal women compared with postmenopausal women [25].

Endometrial polyps are a very common finding in women with abnormal uterine bleeding. On ultrasound, they are often hyperechoic and feature a 'bright edge' [3] (Fig. 36.3). In a large proportion of patients, the feeding blood vessels can be visualized on colour Doppler imaging, the so-called 'pedicle artery' sign, which is pathognomonic for focal endometrial pathology [26] (Fig. 36.4). Fluid instillation should be considered if the endometrium is not well visualized on unenhanced ultrasonography, or if within a thickened endometrium no pedicle artery is detectable on colour Doppler examination [27]. MRI is not considered useful in the assessment of endometrial polyps [28].

Fibroids are the most common uterine tumours. Their location is described according to the FIGO leiomyoma

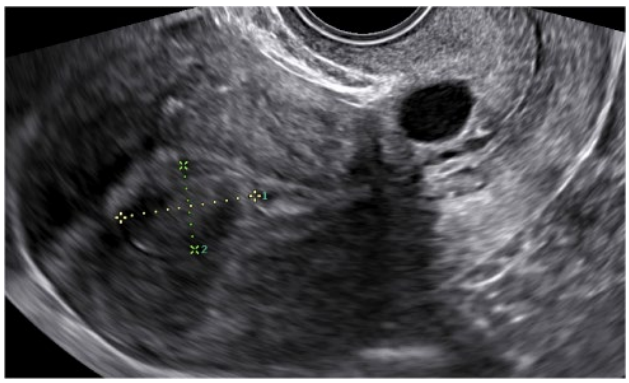


Fig. 36.3 Endometrial polyp with 'bright edge'.

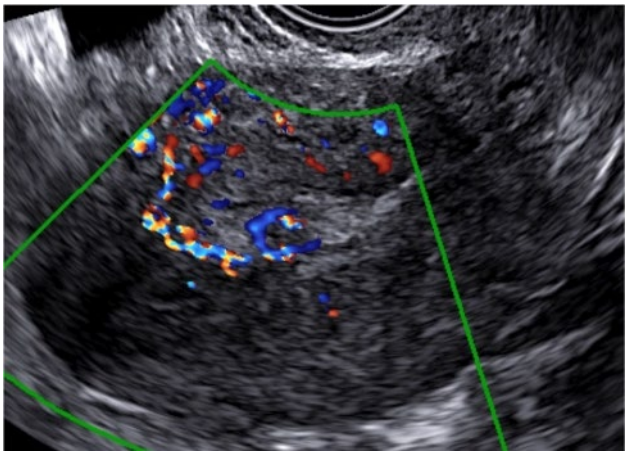


Fig. 36.4 Endometrial polyp with 'pedicle artery' sign on colour Doppler imaging. (*See also colour plate 36.4*)

classification, where the submucosal lesions (i.e. types 0–2) are the most likely to result in abnormal uterine bleeding [24]. Besides the number of fibroids and their size, the relationship to the endometrium is an important factor in choosing the proper surgical strategy should one be needed, and in particular for hysteroscopic or laparoscopic myomectomy. At ultrasonography, fibroids are generally well-circumscribed round lesions within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing due to calcifications. On colour or power Doppler imaging, circumferential flow around the lesion is often visible (Fig. 36.5). However, some fibroids do not exhibit such typical features [6,29]. Three-dimensional ultrasound may help in localizing the fibroid with respect to the uterine cavity. MRI and ultrasound seem to have similar ability to diagnose uterine fibroids, but MRI is superior to ultrasound in determining the exact location of a fibroid, particularly in a large uterus with multiple fibroids [30].

It is often very challenging to discriminate between fibroids and malignant tumours of mesenchymal origin, the so-called leiomyosarcoma. Although several features at ultrasonography and MRI can raise suspicion of a uterine sarcoma, there are no pathognomonic features on any imaging technique [31]. On ultrasound, a sarcoma is generally solitary, large and oval-shaped with heterogeneous echogenicity. There might be irregular anechoic areas due to internal necrosis or haemorrhage. On colour Doppler imaging, a sarcoma is more often highly vascularized, with prominent irregular intralesional vascularity more often seen than in fibroids. The vessels are of unequal size and exhibit irregular branching. Because of their rapid growth, most sarcomas are large at diagnosis. Myometrial lesions with a large diameter (e.g. >8 cm) should be managed with circumspection [6,29] (Fig. 36.6).

Findings in uterine leiomyosarcomas on MRI vary and include a lobulated mass of high-signal intensity on T2-weighted images, a sharply marginated mass of low signal intensity that closely resembles a leiomyoma, or a mass with focally infiltrative margins. Detection of scattered foci of haemorrhage or necrosis can suggest the diagnosis of uterine leiomyosarcoma. A consistent finding in uterine leiomyosarcomas is the absence of calcifications [32]. Presence of these features at imaging should discourage the clinician to select the patient for minimally invasive surgery with tissue morcellation in order to avoid the fragmentation and intra-abdominal spread of malignant disease [29].

Note that computed tomography (CT) is unable to differentiate between different types of uterine pathology. In particular, it has been shown that CT is not able to differentiate between fibroids and sarcomas [31].

Another differential diagnostic difficulty with fibroids relates to their discrimination from adenomyosis. Adenomyosis may be present at one or more sites within the uterine wall or involve most of the myometrium, and may often be dispersed within the myometrium rather than forming a confined lesion, i.e. diffuse adenomyosis. On the other hand, it may be present in only one part of the myometrium, i.e. focal adenomyosis. In rare cases it may present as a large cyst (an adenomyotic cyst or cystic adenomyoma) [6].

The ultrasound features of adenomyosis are myometrial asymmetry, cystic areas within the myometrium, hyperechoic islands, fan-shaped shadowing, echogenic subendometrial lines and buds, and blood vessels passing

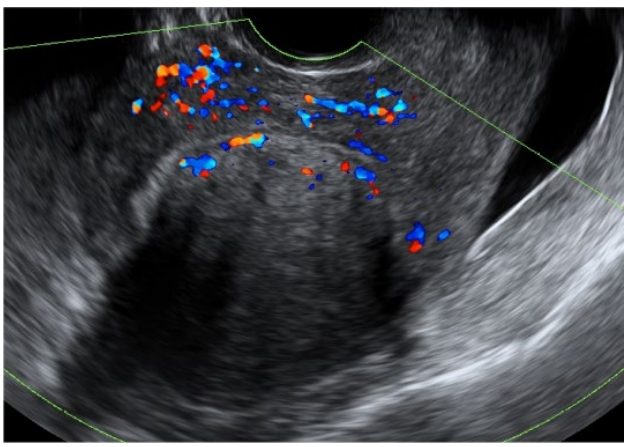


Fig. 36.5 Uterine fibroid with typical features: a well-circumscribed round lesion, presence of acoustic schadowing and limited circumferential vascularization on colour Doppler imaging. (*See also colour plate 36.5*)

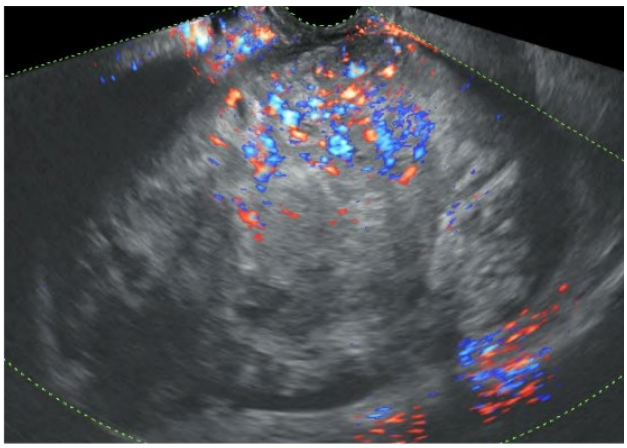


Fig. 36.6 Uterine sarcoma: large oval-shaped lesion with heterogeneous echogenicity and prominent intralesional vascularization on colour Doppler. (*See also colour plate 36.6*)

through the abnormal-looking area as opposed to around the lesion as is seen with fibroids. More recently, the presence of an irregular or interrupted endometrial–myometrial junctional zone imaged using three-dimensional ultrasound in the coronal plane has been reported to have a high diagnostic accuracy for adenomyosis [6,8]. Comparable with ultrasound, MRI can confidently diagnose adenomyosis, and can be used when transvaginal ultrasonography provides indefinite findings or when dealing with difficult cases with coexistence of other abnormalities (e.g. multiple fibroids) [33].

Pedunculated and broad ligament fibroids present their own problems. These principally relate to how confident the examiner is that he or she is not looking at a solid ovarian lesion. This is important given the higher likelihood of malignancy in solid masses thought to be ovarian fibromas [34]. The demonstration of two normal ovaries is the obvious solution to this problem. The use of Doppler to demonstrate that the blood supply originates from the uterus may identify the lesion as uterine in origin and acoustic shadowing is a reassuring sign.

Postmenopausal bleeding

The causes of abnormal premenopausal uterine bleeding, such as polyps and uterine sarcomas, can be found in postmenopausal women as well. However, it is most important that endometrial cancer should be excluded, as this disease will be detected in 10% of patients with postmenopausal bleeding [35]. A simple measurement of endometrial thickness on transvaginal ultrasound examination can reliably discriminate between women who are at low or high risk of endometrial cancer. An endometrial thickness of 4 mm or less decreases the likelihood of endometrial cancer by a factor of ten, regardless of the use of hormone replacement therapy [35]. If the endometrial thickness is 5 mm or more, an evaluation of endometrial morphology and vascularization using grey-scale and Doppler ultrasound imaging with or without fluid instillation can be used to assess for any pathology. If a focal lesion is detected, targeted hysteroscopic resection should be planned. If no focal lesion is visible, blind endometrial sampling is recommended, to exclude pathology and endometrial cancer in particular.

The role of ultrasound in discriminating between benign and malignant pathology in patients with postmenopausal bleeding and a thickened endometrium is the subject of current investigation. Heterogeneous echogenicity and an irregular surface of a focal lesion or of the endometrium in a fluid-filled uterine cavity seem to be useful criteria for predicting malignancy [36] but these and other features need to be confirmed in larger prospective trials [3]. About one in five cases of cancer in women with postmenopausal bleeding do not show a clearly visible endometrium on unenhanced transvaginal ultrasonography. Therefore, if the endometrium is not measurable or not completely visible, it should be considered abnormal until proven otherwise. Sonohysterography should be performed in these circumstances [37].

Other imaging modalities have no role in the primary investigation of women with postmenopausal bleeding, but are used for endometrial cancer staging. MRI using high spatial resolution T2-weighted and contrast-enhanced T1-weighted images provides tumour delineation for the assessment of myometrial invasion with high accuracy. The technique has developed rapidly, especially with the addition of new functional techniques over the past decade, such as diffusion-weighted imaging. Several studies have concluded that ultrasound and MRI can assess the probability of deep stromal invasion and the presence of cervical invasion with similar accuracy.

It has been shown that the grey-scale and vascular sonomorphological appearance of endometrial cancer is significantly associated with endometrial tumour stage, grade and size. High-risk endometrial cancer more often has a mixed or hypoechoic echogenicity, a higher colour score, and multiple vessels with multifocal origin, whereas less-advanced tumours are more often hyperechoic, have no or low colour score, and a single or multiple vessels with a focal origin. Subjective ultrasound assessment of myometrial and cervical invasion has been shown to work better than, or as well as, any objective measurement technique. The best objective measurement technique is tumour–uterine anteroposterior ratio; however, the clinical value and optimal cut-off needs to be established in larger studies. The role of CT and positron emission tomography (PET)-CT is primarily to detect lymph node metastasis and other metastasis [38].

Other possible causes of postmenopausal bleeding should be considered, such as cervical polyps, adnexal pathology and bladder pathology. An advantage of transvaginal ultrasound is that it enables the examiner to investigate the entire pelvis.

Summary box 36.2

- In postmenopausal bleeding, a simple measurement of endometrial thickness on transvaginal ultrasound examination can reliably discriminate between women who are at low or high risk of endometrial cancer.
- Endometrial polyps are a very common finding in women with abnormal uterine bleeding. On ultrasound, the 'pedicle artery' sign is pathognomonic for focal endometrial pathology.

- Fluid instillation should be considered if the endometrium is not well visualized on unenhanced ultrasonography.
- MRI and ultrasonography seem to have a similar ability to diagnose uterine fibroids, but MRI is superior to ultrasound for determining the exact location of a fibroid, particularly in a large uterus with multiple fibroids.
- Although several features at ultrasonography and MRI can raise suspicion of a uterine sarcoma, there are no pathognomonic features using any imaging technique.

Adnexal masses

When ultrasound evaluation of a pelvic mass has excluded non-adnexal pathology (e.g. pedunculated fibroids, see section on premenopausal bleeding), it is very important to discriminate between pathological and functional findings. Since fibroids are only found in premenopausal women, they can be expected to resolve spontaneously and rarely require surgical intervention.

Follicular cysts originate from anovulatory follicles. Usually they appear as unilocular and thin-walled lesions with anechoic contents. They rarely exceed 8–10 cm in diameter and typically resolve spontaneously within 6 weeks [39]. *Corpus luteum cysts* are formed following ovulation. They are thick-walled cysts that often show circumferential blood flow, described on ultrasound as the 'ring of fire'. The cyst content may have a 'spider-web' appearance or contain blood clots, resembling solid components (Fig. 36.7). In these cases, Doppler examination (a clot will have no blood flow) and 'pushing' the lesion with the probe (a clot will have typical jelly-like movement) can be used to help differentiate between clots and solid parts [1]. In most cases, haemorrhagic cysts resolve within 6–12 weeks without intervention [39]. If a lesion does not meet the clinical and ultrasound features of functional changes or persists during follow-up, further investigation is recommended.

Distinguishing between benign and malignant pathology is important both to lessen unnecessary anxiety and to select the optimal patient-tailored management. Depending on the clinical presentation of the patient, benign pathology may be best treated conservatively or in a general gynaecology unit using a minimally invasive approach. On the other hand, masses suspicious for malignancy should be referred to specialized units for appropriate staging and treatment, for example in the case of ovarian cancer where this is known to improve survival [40].

Certain types of ovarian tumours exhibit characteristic ultrasound features which make them very easy to recognize. *Mature teratomas* or *dermoid cysts* are the most frequently encountered non-functional ovarian masses in premenopausal women. Usually they appear as unilocular cysts with mixed echogenicity, due to the presence of different tissue components such as fat, bone, hair and fluid. Acoustic shadowing is typically present and often prevents the cyst being completely visualized ('tip of the iceberg' phenomenon). Different hyperechoic tissues often pack together into a Rokitansky nodule (Fig. 36.8) and the presence of hair is often seen as multiple stripy hyperechoic interfaces ('dermoid mesh'). In general, vascularity is minimal [39]. *Endometriomas* are typically unilocular tumours with echogenic content representing old blood ('ground glass' appearance) and limited vascularity (Fig. 36.9). However, atypical features may be present. Debris within the cyst may give the impression of solid components. It is important to consider the age of the patient when a lesion with the features of an

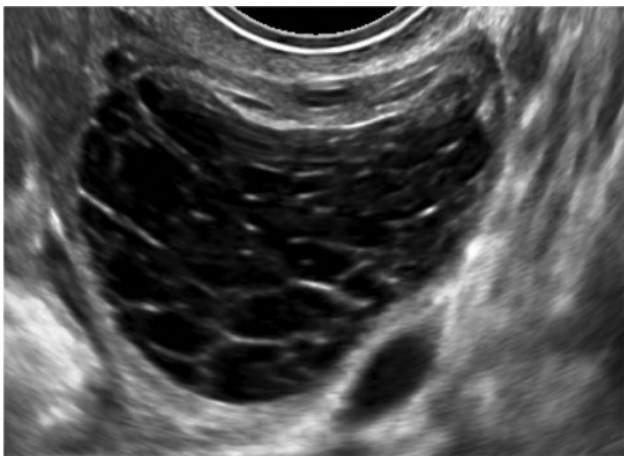


Fig. 36.7 Haemorrhagic corpus luteum cyst with 'spider-web' appearance.

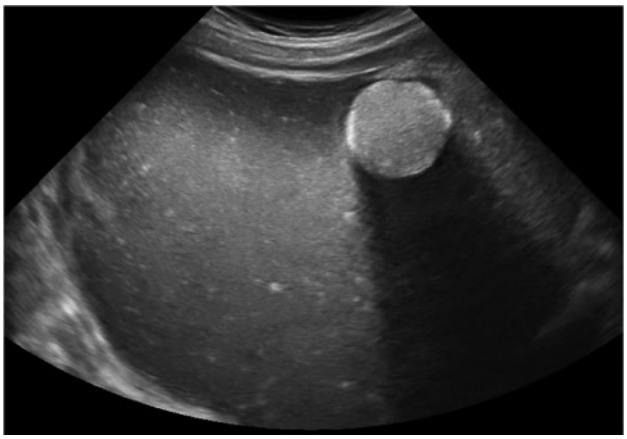


Fig. 36.8 Dermoid cyst with Rokitansky nodule and prominent acoustic shadowing.

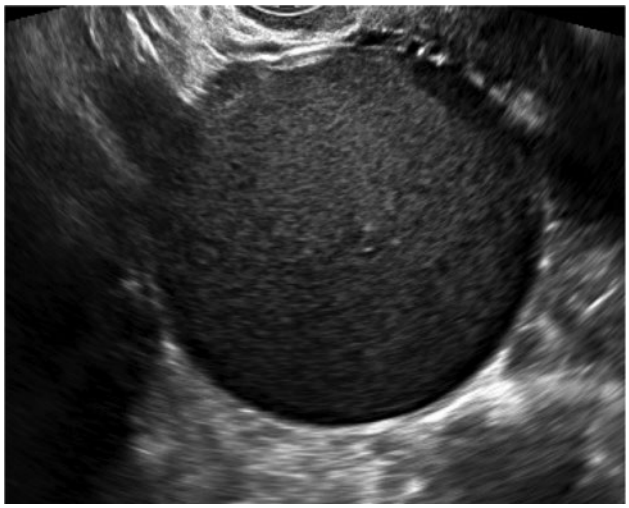


Fig. 36.9 Endometrioma: unilocular tumour with echogenic content representing old blood ('ground glass' appearance).

endometrioma is observed, as in postmenopausal women the risk of malignancy in such lesions is significant [41].

Subjective assessment of the morphology and vascularity, also called 'pattern recognition', by an experienced operator is known to be the best-performing strategy for characterizing adnexal masses. Besides predicting whether a mass is likely to be benign or malignant, in most cases a reasonably accurate evaluation of the likely histological outcome is also possible [42,43]. However, as pattern recognition is very user-dependent [44], more objective methods are needed to allow accurate ultrasound evaluation by less-experienced examiners. The risk of malignancy index (RMI) is one such method that has been in use since the 1990s. It combines ultrasound information with menopausal status and serum CA-125 to produce a numerical score, where a result of 200 or more is usually considered to indicate malignancy [45]. As the RMI score is largely influenced by the serum CA-125 level, it suffers from the inherent problems associated with that marker: a relatively low sensitivity for early-stage and borderline disease, especially in premenopausal women [46]. Despite accumulating evidence in favour of more recent ultrasound-based models, many national guidelines for the management of ovarian masses still advocate the use of RMI.

In 2000, the International Ovarian Tumour Analysis (IOTA) group published a consensus paper in order to standardize the terms, definitions and measurements used to characterize ovarian pathology [5]. With more than 20 000 patients included, this prospective multicentre project aims to develop diagnostic algorithms to classify adnexal masses. In 2008, the IOTA group published the Simple Rules, which are based on five ultrasound features suggestive of a benign lesion (B-features) and five features suggestive of a malignant lesion (M-features) [4]. The Simple Rules have been validated extensively; even in the hands of less-experienced examiners, they retain excellent performance in discriminating between benign and malignant pathology [47].

The IOTA Simple Rules have become very popular because they do not require access to a computer and are perceived to be easy to use. They are incorporated in the guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG) on how to manage premenopausal women with adnexal masses [48]. A weakness of the IOTA Simple Rules is that they cannot classify all adnexal masses as benign or malignant. This means that in about 20% of cases another diagnostic method is needed to classify the 'inconclusive' masses. A reasonable alternative is to consider this group as malignant, as in 40% of these cases this will be proven by histopathology [49]. Table 36.1 shows the ultrasound features of the Simple Rules as a simple tick box system to usefully assess a mass.

In their meta-analysis in 2013, comprising 96 validation studies reporting on 19 different diagnostic ultrasound methods in 26 438 adnexal masses, Kaijser *et al.* [47] showed that IOTA strategies such as the Simple Rules had the best performance in differentiating between the benign and malignant nature of adnexal masses in a preoperative setting. The Simple Rules outperformed

Table 36.1 Simple Rules to identify a benign or malignant adnexal tumour.

Features for predicting a malignant tumour (M-features)	
M1	Irregular solid tumour
M2	Presence of ascites
M3	At least four papillary structures
M4	Irregular multilocular-solid tumour with largest diameter ≥100 mm
M5	Very strong blood flow (colour score 4)
Features for predicting a benign tumour (B-features)	
B1	Unilocular
B2	Presence of solid components where the largest solid component has a largest diameter <7 mm
B3	Presence of acoustic shadows
B4	Smooth multilocular tumour with largest diameter <100 mm
B5	No blood flow (colour score 1)
Simple rules	
If one or more M-features apply in the absence of a B-feature, the mass is classified as malignant	
If one or more B-features apply in the absence of an M-feature, the mass is classified as benign	
If both M-features and B-features apply, the mass cannot be classified	
If no feature applies, the mass cannot be classified	

the RMI, with a sensitivity and specificity of 93% and 81%, respectively, for Simple Rules versus 72% and 92%, respectively, for RMI. In 2016, Meys *et al.* [46] performed a meta-analysis assessing IOTA methods, RMI and subjective assessment by an expert investigator, investigating 47 articles that included 19 674 tumours. They concluded that a two-step approach with Simple Rules as a first step and subjective assessment for inconclusive tumours yielded the best results and matched the test performance of expert ultrasound examiners.

In general, individual features of ovarian masses have not proved useful as predictors of the likely histology. Accordingly, attention turned to mathematical models using multiple variables. The IOTA group has created different prediction models based on logistic regression analysis that give an individual risk of malignancy for the patient [50–52]. Unlike the Simple Rules, risk prediction models require the use of a computer, an application for smartphone or a calculator integrated in the ultrasound device to acquire the result. As a multiclass prediction model, the recent Assessment of Different NEoplasias in the adneXa (ADNEX) model incorporates clinical and ultrasound information not only to calculate the likelihood of malignancy in adnexal masses but also the likelihood that the mass is borderline malignant, stage I primary invasive ovarian cancer, stage II–IV primary invasive ovarian cancer or a metastasis to the ovary from another primary tumour [52]. This is highly relevant given the differences in the clinical management of women with these different tumours.

Adding information on serum CA-125 levels to ultrasound information does not seem to improve earlier mathematical models in discriminating between benign and malignant adnexal masses [53]. Neither does CA-125 in ADNEX, where it is an optional variable. However, in ADNEX the inclusion of CA-125 allows more accurate risk predictions for the different subgroups of malignancy [52]. A two-step approach could be adopted to make clinical use of the predicted risks from ADNEX. First, the risk calculation can be used to discriminate between benign and malignant masses based on the specific risk cut-off value used by individual centres to define malignancy, where the adopted cut-off may depend on local healthcare policy. Second, we can differentiate between the four subgroups of malignant tumours using the predicted risks for these subgroups. In this step, absolute predicted risks as well as the relative change of these risks versus the baseline risks provide clinically useful information to select an appropriate patient-specific management strategy. ADNEX has only recently been developed, but has shown excellent discriminative ability when prospectively validated on IOTA phase 3 data [52] as well as in the first external validation studies [54,55]. ADNEX is freely available online (http://www.iotagroup.org/adnexmodel/) or can be downloaded as an application for smartphone. Figure 36.10 shows the clinical and ultrasound features used in the ADNEX model with the risk calculations for a case example.

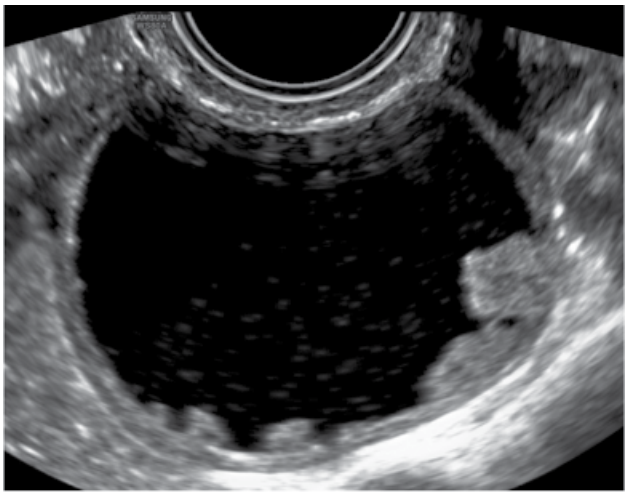
Research is ongoing on how to manage adnexal masses that are unclassifiable by ultrasound, whether using the Simple Rules or subjective assessment by an expert investigator, as evidence shows that 8% of tumours will still be indeterminate even with these methods. In a systematic review and meta-analysis, Anthoulakis *et al.* [56] concluded that pelvic MRI with intravenous contrast administration should be considered the most useful of all diagnostic approaches when investigating adnexal masses that remain unclassified after assessment by ultrasound. This strategy outperformed other imaging modalities including CT.

An extensive description of staging in malignant disease would be beyond the scope of this chapter. Although ultrasound has been shown to be accurate in the assessment of the abdominal spread of gynaecological malignancies in the hands of experienced examiners [57], most centres will use CT for preoperative staging and follow-up [58]. There is also increasing interest in whole-body diffusion-weighted MRI for this purpose, as this technique shows higher accuracy for the evaluation of peritoneal and distant disease compared with CT and PET-CT [59].

Summary box 36.3

- Subjective assessment by an experienced ultrasound operator is known to be best-performing strategy to characterize adnexal masses.
- Certain types of ovarian tumours, such as endometriomas or dermoid cysts, exhibit characteristic ultrasound features that make them easy to recognize.
- IOTA's Simple Rules have been extensively validated and show the best performance of currently available diagnostic tools for discriminating between benign and malignant adnexal pathology, irrespective of the user's level of experience.
- The recent IOTA ADNEX model includes clinical and ultrasound information not only to calculate the likelihood of malignancy in adnexal masses but also the likelihood of four subclasses of malignant tumours.
- Adding information on serum CA-125 levels to ultrasound information does not improve mathematical models for discriminating between benign and malignant adnexal masses.
- Pelvic MRI with intravenous contrast administration can be used as a second-stage test to evaluate adnexal masses that remain unclassified after assessment by ultrasonography.

(a)



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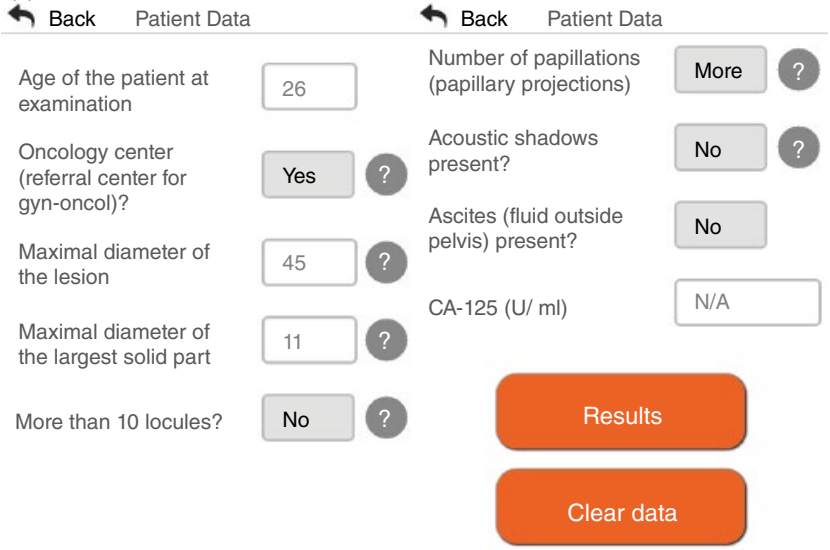

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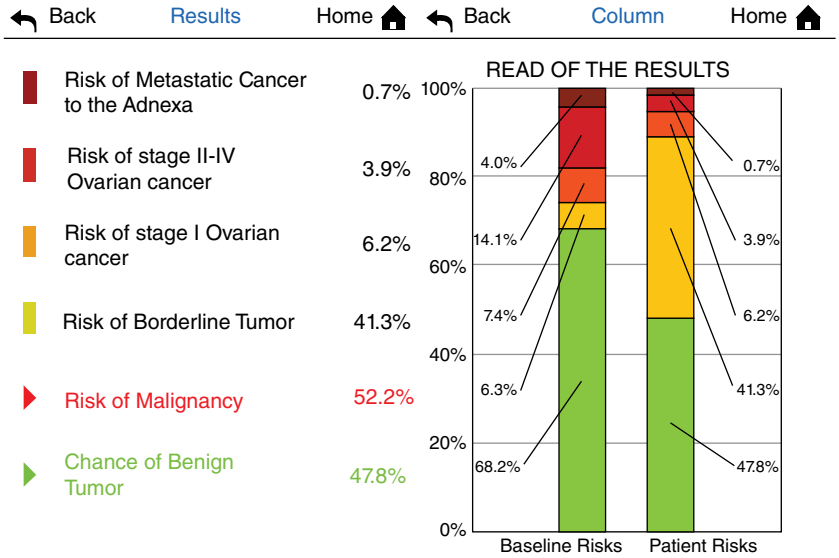

Fig. 36.10 (a) Unilocular-solid ovarian tumour with a maximum diameter of 45 mm detected in a 26-year-old patient. There were four papillary projections, the largest having a maximum diameter of 11 mm. Acoustic shadowing and ascites were absent. (b) Introduction of the clinical and ultrasound variables of this patient in an ADNEX application for smartphone. CA-125 was not available during scanning of the patient. (c) Results of the ADNEX calculation. On the left are the results for the risk of malignancy and the risks of four different subgroups of malignant tumours. On the right is the column chart showing patient risks compared with the baseline risks (general IOTA population). Besides having the highest absolute risk of 41.3%, borderline ovarian tumour has the highest relative risk (6.6). This patient underwent surgery and was shown to have a serous borderline ovarian tumour.

Investigation of pelvic pain in non-pregnant women

It is important to take a history of the nature and location of pelvic pain prior to performing imaging. There are many causes of pelvic pain, many of which may be non-gynaecological, and imaging findings taken in isolation may be misleading. For example, pelvic lesions such as simple ovarian cysts or hydrosalpinges may be an incidental finding, without them being the cause of the pain.

Ultrasound should be considered an extension of the bimanual clinical examination; indeed it is unlikely that a woman with a normal pelvic examination and a negative ultrasound scan has any significant gynaecological pathology. This is true in both the acute and chronic setting. In a study by Haider *et al.* [60] of women attending an acute gynaecology unit, a normal scan was found to be associated with resolution of symptoms in 94.5% of cases. Okaro *et al.* [61] found that for women with chronic pelvic pain and a normal scan, a subsequent laparoscopy was abnormal in only 20% of cases compared with the 58% of cases that would be expected. The commonest pathologies where ultrasound may be of use are cyst accidents, endometriosis and pelvic inflammatory disease. Adenomyosis may also be related to pelvic pain (discussed in the section on abnormal uterine bleeding).

Complications of adnexal masses

An adnexal cyst in isolation may not cause pain and there are few data to tell us what size of cyst is significant in this respect. However, cyst accidents such as haemorrhage, rupture or torsion may lead to varying degrees of acute pelvic pain.

Besides occurring in functional findings such as luteal cysts (see section Adnexal masses), haemorrhage can occur within any ovarian lesion. The enlarged ovary may have a variety of ultrasound features, as the appearance of blood is likely to change from anechoic in the acute stage, to blood clot, retraction and resolution [62]. A haemoperitoneum may be present. Pushing with the probe will provoke pain. Haemorrhage may also present with ground-glass appearance, which is more typical for old blood accumulating over time, as found in an endometrioma (see section Adnexal masses). Here, recent haemorrhage might be visible as a fluid level within the cyst.

Torsion of the adnexae may occur when there is a mass in the ovary, but also in polycystic ovaries after fertility treatment or even in normal ovaries. If an ovarian mass is present, then a mature cystic teratoma is the commonest aetiology. A torted ovary appears congested and oedematous; follicles may be seen at the periphery (Fig. 36.11). Doppler is often misleading as venous flow is lost first with torsion but arterial flow will still be seen [62]. In some cases, the vascular supply may be visualized as a coil (so-called 'whirlpool' sign). Free fluid will be present in about one-third of cases.

In the case of cyst rupture, the ovary may seem either normal or show collapsed cyst walls, in the presence of free fluid in the pouch of Douglas. Pushing with the probe may provoke site-specific tenderness [62]. Rupture of a dermoid cyst may lead to chemical peritonitis.

In most cases, ultrasound is sufficient for the diagnosis of ovarian cyst accidents. However, these patients often present at the emergency department where it is not unusual for them to undergo other imaging techniques as first-line investigations. These conditions may be associated with typical features on CT or MRI [63]. Second-stage imaging with these modalities might be useful in differential diagnostic problems, especially to exclude non-gynaecological pathology.

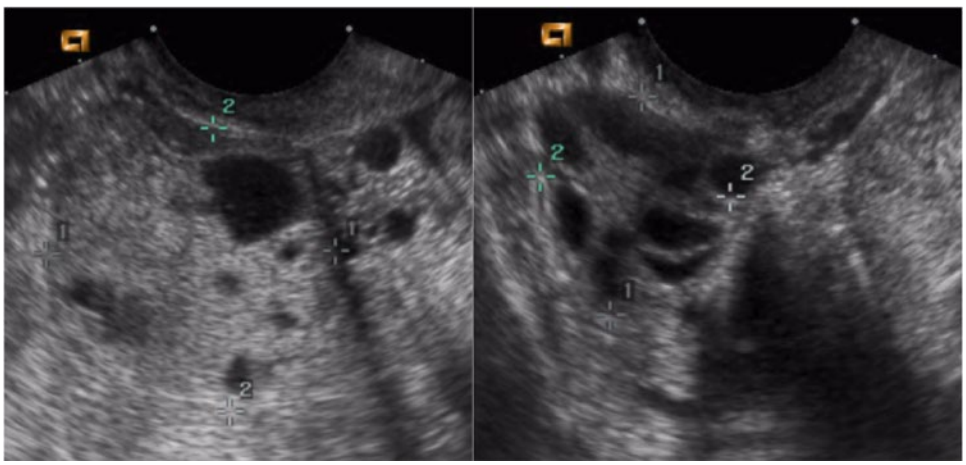

Fig. 36.11 Adnexal torsion. (*Left*) Torted left ovary with congested and oedematous appearance; follicles are seen at the periphery. (*Right*) Normal contralateral right ovary.

Endometriosis

Chronic pelvic pain may be caused by endometriosis. In 2006, Okaro *et al.* [61] introduced the concept that site-specific pelvic tenderness and reduced ovarian mobility (known as 'soft markers') are associated with the presence of endometriosis at laparoscopy. Increasingly, transvaginal ultrasonography is the first-line investigation in the work-up of women with potential underlying endometriosis. The ability of ultrasound to detect ovarian endometriosis and deep infiltrating endometriosis (bowel and non-bowel) is helpful in planning a multidisciplinary surgical approach [64]. Recently, a consensus document was published to ensure that the ultrasound assessment of endometriosis is performed in a standardized manner, with standardized descriptions and measurement techniques [65].

The characteristics of endometriomas within the ovary have been discussed in the section on adnexal masses. Transvaginal ultrasonography has fair performance with high specificity for detecting deep infiltrating endometriosis in the uterosacral ligaments, rectovaginal septum, vagina and bladder [66], whereas it has good performance for detecting deep endometriosis in the rectosigmoid [67]. In the event of negative findings in a patient with symptoms, it is recommended that MRI is used for mapping deep infiltrating endometriosis prior to surgery [68].

Pelvic inflammatory disease

Acute pelvic infection is a clinical diagnosis and should be considered in any sexually active woman with a history of pelvic pain, vaginal discharge or intermenstrual bleeding. In normal circumstances, the fallopian tube may be hard to visualize at ultrasound. In acute salpingitis, however, as the tube becomes inflamed and oedematous with accumulation of pus or exudate, it becomes more prominent. A pyosalpinx has a unilocular and sausage-shaped structure, thick walls, anechoic or low-level echogenic fluid content within the tube and presence of incomplete septa due to folding. In a transverse section it often shows the well-described 'cogwheel' sign, due to central sonolucent fluid surrounded by thickened endosalpingeal folds [69]. Colour or power Doppler examination generally shows significant vascularity. Presence of fluid in the pouch of Douglas is common [39]. The inflamed structures are generally tender on pushing with the ultrasound probe. Adhesions may be visible between different pelvic structures and also on transabdominal scanning in the upper abdomen surrounding the liver, as in Fitz-Hugh–Curtis syndrome due to *Chlamydia trachomatis*. The ovary may or may not be involved in the process. A tubo-ovarian complex represents the involvement of ovarian tissue in the inflammatory process. Normal ovarian parenchyma is visible, but cannot be separated from tubal structures when pushing with the probe. The term 'tubo-ovarian abscess' should be reserved for a later phase in this acute pelvic process, when ovarian tissue is no longer visible, caused by the total breakdown of the normal architecture resulting in loculations of pus and debris [69] (Fig. 36.12). In practice, the clinical features associated with an abscess make the diagnosis relatively straightforward.

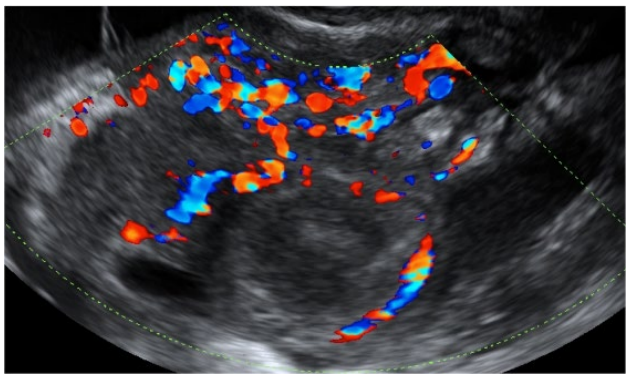

Fig. 36.12 Tubo-ovarian abscess: loculated process with oedematous walls and prominent vascularization on colour Doppler. Normal ovarian stroma is no longer visible. (*See also colour plate 36.12*)

When the acute inflammation stops spontaneously or because of medical treatment, chronic changes may persist. In a hydrosalpinx, the tube appears as an elongated fluid-filled structure, with incomplete septa, but the thickening of the wall is no longer visible. It is characterized by the typical sonographic 'beads on a string' sign, due to 2- to 3-mm-sized hyperechoic structures on the tubal wall, seen on transverse section [69]. Intra-abdominal adhesions may result in peritoneal pseudocysts.

Ultrasound-guided treatment is an important option for tubo-ovarian abscesses. In a study of 302 women, a total of 282 (93.4%) were successfully treated by transvaginal aspiration of purulent fluid, together with antibiotic therapy. In the other 20 women (6.6%), surgery was performed [23].

In circumstances of diagnostic difficulty at ultrasonography, CT or MRI may be considered as second-stage tests, the former often being the first-line examination in an emergency department. These techniques enable discrimination between pelvic inflammatory disease and gastrointestinal or urinary aetiology. It should be mentioned that the visualization of pelvic oedema caused by inflammatory disease of genital origin may be deceptive, since it can induce thickening of adjacent organ walls and suggest an incorrect diagnosis (appendicitis in particular) [70].

Summary box 36.4

- Certain pelvic lesions can be an incidental finding, without being the cause of the patient's symptoms.
- Haemorrhage can occur within any ovarian lesion, but is most common in functional findings such as luteal cysts. Ultrasound features differ depending on the time since the bleeding.
- Adnexal torsion mostly occurs when an adnexal mass is present (e.g. dermoid) but can also occur in normal ovaries. Presence of certain ultrasound features in a patient with pain should raise suspicion.
- The ability of ultrasound to detect ovarian endometriosis and deep infiltrating endometriosis is helpful in planning a multidisciplinary surgical approach.
- In case of negative findings on ultrasound in a patient with symptoms suggestive of the presence of endometriosis, it is recommended that MRI is used for mapping deep infiltrating endometriosis prior to surgery.
- Pelvic inflammatory disease may have different ultrasound characteristics, depending on the stage of the infection. When the acute inflammation stops spontaneously or because of medical treatment, chronic changes may persist (e.g. hydrosalpinx, adhesions).

Investigation of infertility

Transvaginal ultrasound can be used as a screening test for women presenting with subfertility. Strandell *et al.* [71] showed that a simplified ultrasound-based investigation protocol with hysterosalpingo-contrast sonography can replace more expensive and invasive algorithms including hysterosalpingography or laparoscopy. At present, hysterosalpingo-foam sonography is gaining ground in the field of tubal patency testing (see earlier section).

Unenhanced two-dimensional ultrasound is the first-line technique for excluding congenital uterine anomalies in asymptomatic women. The European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) consensus recommends three-dimensional ultrasound in the evaluation of high-risk patients (with symptoms suggestive of the presence of genital anomaly or history of poor reproductive outcome). MRI and endoscopic evaluation are suitable for the subgroup of patients with suspected complex anomalies or in diagnostic dilemmas [7]. The same three-dimensional approach can be used to detect submucosal fibroids, as these are thought to be associated with reproductive dysfunction. More recently, attention has focused on the endometrial–myometrial junction (or junctional zone) and how this may relate to implantation and early pregnancy [8].

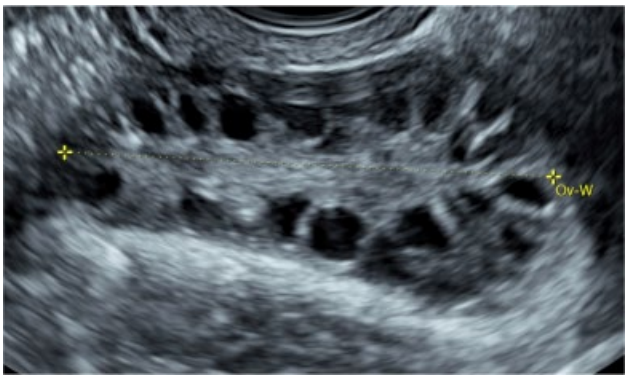

Fig. 36.13 Polycystic ovarian morphology: presence of 12 or more follicles measuring 2–9 mm in at least one ovary and an ovarian volume greater than 10 mL (Rotterdam criteria).

Ultrasound assessment of the ovaries has long been a significant part of the assessment of women with irregular or absent periods. The principal aim is to identify polycystic ovaries (PCO). This morphological finding is defined according to the Rotterdam criteria as the presence of 12 or more follicles measuring 2–9 mm in one or both ovaries and an ovarian volume greater than 10 mL [72] (Fig. 36.13). There is some debate over the clinical relevance of this ultrasound-based definition of PCO, as research has shown that ovaries with this appearance are a common finding in the normal population, especially when assessed with modern ultrasound equipment. Therefore, it has been suggested that the threshold for the number of follicles per ovary used to define PCO be increased to 25 or more [73]. Ultrasound has also become important for the assessment of ovarian reserve, as this is reflected in the number of small (2–6 mm) antral follicles within the ovary [74]. The software that now exists to automatically count follicles has further stimulated interest in this area and seems likely to give us more information about the number and distribution of follicles in various clinical situations [73,75].

Finally, in patients presenting with infertility, ultrasound has an important role in the assessment for the presence of pelvic endometriosis (see section Investigation of pelvic pain in non-pregnant women).

Summary box 36.5

- Ultrasound is the first-line technique in the detection of congenital uterine anomalies. MRI and endoscopic evaluation can be used as second-stage tests.
- Ultrasound features of PCO are defined according to the Rotterdam criteria.

Role of ultrasound in early pregnancy

When a woman presents with symptoms of pain or bleeding in early pregnancy, the main diagnostic options are a currently viable intrauterine pregnancy, a failed (or failing) intrauterine pregnancy and an ectopic pregnancy. The condition where the urinary or serum pregnancy test is positive but neither an intrauterine pregnancy nor ectopic pregnancy can (yet) be visualized on transvaginal ultrasound is described as pregnancy of unknown location (PUL). CT is contraindicated in early pregnancy. MRI can be used but does not play an important role in the management of women with bleeding and pain in early pregnancy because most diagnostic problems can be solved using ultrasound [76].

Normal pregnancy

Transvaginal ultrasonography is the principal diagnostic tool for assessing women in early pregnancy. The sequence of events in early pregnancy follows a nearly fixed pattern. At approximately 5 weeks of gestational age, the gestational sac appears as a small fluid collection with rounded edges and no visible contents, located between the thickened and hyperechoic endometrial layers, the decidua. The yolk sac, a circular structure about 3–5 mm in diameter, makes its appearance at about 5.5 weeks of gestation. Adjacent to the yolk sac, the embryo appears at about 6 weeks, with the heartbeat visible [77].

An early pregnancy can be dated by comparing the crown–rump length of the embryo with established reference curves derived from large numbers of apparently normal pregnancies [78]. It has commonly been thought that the size of an embryo in the first trimester can be translated into a gestational age value with impunity, but the size and growth of the first-trimester embryo are affected by maternal age, ethnicity, chromosomal abnormalities in the embryo and imminent miscarriage [79,80]. Finding a smaller than expected embryo is not necessarily a reflection of inaccurate dating and it is often wise to schedule a follow-up scan in these circumstances in view of the risk of miscarriage.

Sensitive home pregnancy tests inform women they are pregnant before their missed period. The potential impact of this was illustrated by Bottomley *et al.* [81], who showed that the likelihood of a scan showing an intrauterine pregnancy of uncertain viability was 60% at 35–41 days' gestation and 29% at 42–48 days. It is likely that if women attend for an ultrasound scan soon after a positive pregnancy test result, a viable pregnancy will not be confirmed, leaving potential for errors about possible miscarriage [81].

Miscarriage

In diagnosing non-viability of an early pregnancy, a false-positive diagnosis carries much worse consequences than a false-negative diagnosis, as a false-positive diagnosis may lead to a medical or surgical intervention that eliminates or severely damages a viable pregnancy, while a false-negative diagnosis causes a short delay in intervention for a failed pregnancy. Thus, the criteria for diagnosing non-viability in early pregnancy should virtually eliminate false-positive results [77]. When in 2011 several papers showed that previously accepted criteria for ruling out a viable pregnancy were not safe, the Royal College of Obstetricians and Gynaecologists (RCOG), the UK National Institute for Health and Care Excellence (NICE) and the American College of Radiology changed their guidelines for defining miscarriage [82–84]. There is agreement regarding the initial scan criteria, based on measurement of crown–rump length and mean gestational sac diameter. These cut-offs are associated with 100% specificity and narrow confidence intervals [85]:

- empty gestational sac of mean diameter ≥25 mm;
- embryo with a crown–rump length ≥7 mm and no heartbeat.

On the other hand, guidance on repeat scan criteria is not unanimous. Based on expert opinion rather than evidence, Doubilet *et al.* [77] stated that the absence of an embryo with a heartbeat 14 days or more after a scan showing an empty gestational sac or the absence of an embryo heartbeat 11 days or more after a scan showing a gestational sac and yolk sac were both categorically a miscarriage. No current guidelines take into account the influence of gestational age.

It is important for anyone carrying out a scan in early pregnancy to always remember that doctors should do no harm, and so repeating an ultrasound scan after an interval is mandatory if there is any doubt about the outcome.

Ectopic pregnancy

The clinical features of ectopic pregnancy are covered in detail elsewhere in this book, but it is important to emphasize the long-held maxim that every fertile woman has a potential ectopic pregnancy until proved otherwise. At one time the assessment of women with possible ectopic pregnancy was built on the principle of failing to identify an intrauterine pregnancy, in other words a diagnosis of exclusion. In most cases the diagnosis is now based on the positive visualization of the ectopic pregnancy [2].

Transvaginal ultrasonography is the primary diagnostic tool for clinically stable women with a suspected ectopic pregnancy [86]; of these patients, 73.9% are diagnosed on an initial assessment [87] and 94% are diagnosed prior to surgical intervention [88]. This difference is explained by the fact that in a number of cases an early pregnancy is categorized as PUL, before the ectopic pregnancy mass is subsequently seen using ultrasonography. This appears to

be simply a reflection of the gestational age of the pregnancy; at early gestations the ectopic mass may simply be too small to visualize with ultrasound [89]. The most common finding in tubal ectopic pregnancy, seen in around 60% of cases, is an inhomogeneous or a non-cystic adnexal mass sometimes referred to as the 'blob' sign. The mass is generally spherical, but a more tubular appearance may be seen if bleeding creates a haematosalpinx. It may also be possible to visualize an empty extrauterine gestational sac or 'bagel' sign, which may contain a yolk sac and/or an embryonic pole that may or may not have cardiac activity (Fig. 36.14). The term 'viable ectopic' is applied when embryonic cardiac activity is visualized [88,89]. Doppler is not considered to significantly contribute to the diagnosis of ectopic pregnancy.

The morphology of an ectopic pregnancy when imaged with ultrasound is important. The majority are inhomogeneous masses. However, visualizing a yolk sac or fetal embryonic heartbeat has management implications as these cases tend to do badly when treated medically with methotrexate [90]. There is no specific endometrial appearance or thickness that reliably supports a diagnosis of ectopic pregnancy. A collection of fluid may be seen within the endometrial cavity, classically referred to as a 'pseudosac' [9]. The amount of echogenic fluid visualized in the pelvis correlates closely with findings at surgery. As a rule of thumb, if fluid reaches the fundus of the uterus or is present in the utero-vesical pouch, the haemoperitoneum is considered to be significant [2].

About 7% of ectopic pregnancies are located outside the fallopian tube. Diagnostic criteria for these conditions exist but data on their diagnostic performance are scarce, and care must be taken to avoid misdiagnosis. Examples are confusion between a normal intrauterine pregnancy implanted laterally in an arcuate uterus and an interstitial pregnancy, or a gestational sac implanting over a caesarean scar, without extending into it, and a caesarean scar pregnancy. Because correct assessment in these cases is pivotal in selecting the proper management, referral to specialized ultrasound centres is a sensible strategy [9].

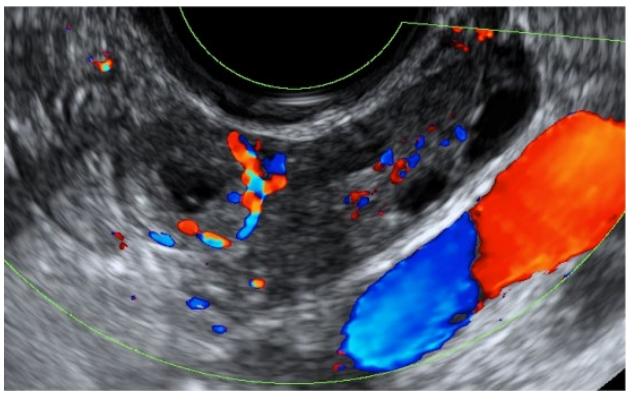

Fig. 36.14 Tubal ectopic pregnancy with 'bagel' sign. Extrauterine gestational sac is visible in a transverse section through the fallopian tube, which could be mobilized from the normal ovary on pushing with the probe. (*See also colour plate 36.14*)

Pregnancy of unknown location

PUL is a common management problem in early pregnancy [81]. It is a clinical scenario defined as a positive urinary or serum pregnancy test but neither an intrauterine pregnancy nor ectopic pregnancy can be visualized on a transvaginal ultrasound scan. Pregnancies classified as PUL include a very early intrauterine pregnancy, an ectopic gestation or a failing pregnancy, whether intrauterine or extrauterine [91]. The incidence of PUL in any given unit is multifactorial and reflects the patient population attending a unit, the ultrasound equipment used and the experience of those carrying out the scans. PUL rates have been reported to be between 8 and 31% [92]. In many cases the inability to locate a pregnancy is simply a reflection of gestational age, and it has been shown in asymptomatic women that restricting scans until 49 days' gestation would optimally reduce the PUL rate without missing ectopic pregnancies [81]. Because of a lack of standardized protocols, the management of PUL varies and may be stressful for women, who are often subjected to repeated blood tests and scans before the final outcome of the pregnancy is known. To some extent the emphasis for the management of PUL has shifted from detection of ectopic pregnancies in the population to selection of pregnancies that are highly likely not to be an ectopic pregnancy in order to reduce follow-up [93].

Clinically, the most commonly used method to predict PUL outcome is the human chorionic gonadotrophin (hCG) ratio (serum hCG at 48 hours/hCG at 0 hours). An hCG ratio of less than 0.87 is associated with a failing PUL and a ratio over 1.66 with a likely viable intrauterine pregnancy. A suboptimal rise between 0.87 and 1.66 indicates an increased risk of ectopic pregnancy [94]. In order to standardize and rationalize PUL management, a number of mathematical models have been developed that have high predictive value for ectopic pregnancy. The most widely evaluated prediction model developed is M4 [95,96], which is based on the initial serum hCG and the hCG ratio. A PUL is classified as 'high risk' (probable ectopic pregnancy) if the predicted risk of ectopic pregnancy is 5% or more. Use of this model has the potential to reduce follow-up in 70% of cases of PUL with a negative predictive value of 97% for the presence of ectopic pregnancy. A recent study investigating the safety of clinical triage with the model showed no serious adverse effects associated with correct use of M4 in over 1000 PULs [92]. If the M4 model depicts a risk of ectopic pregnancy of 5% or more (or if the hCG ratio exceeds 0.87) and the patient is asymptomatic, it is recommended

to repeat serum hCG and ultrasound after 48 hours, as an ectopic pregnancy might become visible at this time. In the case of pain or abnormal bleeding, prompt assessment is required. The M4 model is freely available online (http://www.earlypregnancycare.com/m4triage/index.html).

Summary box 36.6

- The sequence of events in early pregnancy follows a nearly fixed pattern.
- In diagnosing non-viability of an early pregnancy, a false-positive diagnosis carries much worse consequences than a false-negative diagnosis. Therefore, repeating an ultrasound scan after an interval is mandatory if there is any doubt about the outcome.
- Transvaginal ultrasonography is the primary diagnostic tool for clinically stable women with a suspected ectopic pregnancy.
- Ectopic pregnancies located outside the fallopian tube can cause diagnostic difficulties. In these cases, referral to specialized ultrasound centres can be recommended.
- The most commonly used method to predict PUL outcome is the hCG ratio. In order to standardize and rationalize PUL management, a number of mathematical models have been developed that have a high predictive value for ectopic pregnancy.

Conclusion

Ultrasound is now at the centre of many decisions in modern gynaecology. We have seen that in the management of abnormal uterine bleeding, adnexal masses, infertility, pelvic pain, early pregnancy and many other conditions, ultrasound is the first-choice diagnostic tool. In some conditions and in diagnostic dilemmas, other imaging methods such as MRI have proven their value for second-step evaluation. It is important not to be misled by ultrasound findings in isolation, as many lesions may be an incidental finding without being the real cause of the clinical problem. Therefore, attention to clinical history-taking and physical examination is mandatory. If these do not match with ultrasound findings, further investigation is recommended to exclude other (possibly non-gynaecological) pathology.

As ultrasonography is a user-dependent technique, it is important to perform this investigation according to an international consensus, with the use of agreed definitions and measurement techniques. Like all practical skills, becoming proficient at ultrasonography takes time and requires the operator to build up experience based on repetition, feedback and reinforcement for improvement to take place. This requires that clinicians carrying out ultrasound scans know the final outcomes of their patients. The best way to learn to scan is to make the diagnosis and then reinforce the findings by being present at any surgery that then occurs [2].

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37

Ambulatory Gynaecology, Hysteroscopy and Laparoscopy

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Endoscopic surgery is now the default surgical method for most gynaecological procedures, impacting on every area of modern gynaecology from diagnosis to therapy, from reproductive medicine to urogynaecology and oncology. These minimally invasive approaches enhance recovery from the insult of surgery by avoiding large surgical incisions, allowing more rapid discharge from hospital and a quicker return to normal functioning. In previous editions of this textbook, hysteroscopy and laparoscopy were often considered novel interventions, restricted to diagnosis for most practitioners and with therapeutic interventions essentially the preserve of those with a particular interest in minimal access surgery. The complexities of some advanced endoscopic surgical procedures, such as radical cancer surgery, endometriosis excision or resection of large submucous fibroids, are for the 'super-specialized'. However, most day-to-day gynaecological procedures, such as removal of uterine polyps, ectopic pregnancies, ovarian cysts and uteri, can be performed endoscopically and the techniques are within the capabilities of many 'generalists'.

This paradigm shift has arisen primarily as a result of the enthusiasm of surgeons, the expectations of patients and advances in technology. The latter factor is of key importance as visualization, surgical instrumentation and energy modalities have hugely improved the safety and feasibility of endoscopic surgery. Operative hysteroscopy has benefited from the development of new technologies such as bipolar electrosurgery to resect uterine pathologies and tissue removal systems to simultaneously cut and aspirate tissue (overcoming issues over compromised visualization from collected debris and its removal). Advances in instrumentation have not only impacted on the feasibility, safety and effectiveness of existing hysteroscopic procedures, they have also allowed new procedures to be introduced such as hysteroscopic sterilization and global semi-automated endometrial destruction for the treatment of heavy menstrual bleeding. Moreover, the miniaturization and portability of equipment now facilitate ambulatory or outpatient/office-based intervention in traditional hospital or contemporary community-based settings. Ambulatory gynaecology avoids the costs and morbidity of hospital admission, providing safe, acceptable and convenient treatment to women.

In operative laparoscopy, advanced bipolar and ultrasonic instruments have facilitated haemostasis and tissue dissection. Laparoscopic instruments are now smaller and have greater degrees of articulation that facilitate single-port laparoscopy and natural orifice transluminal endoscopic surgery. The enhanced visualization, instrumentation and ergonomics associated with robotic surgery are manifest in many centres but at present the costs are prohibitive for more generalized adoption in the absence of data supporting enhanced effectiveness.

The scientific evidence supporting the adoption of minimal access surgery is expanding, with the publication of diagnostic studies examining the accuracy of endoscopic tests, observational series/registries scrutinizing complications of endoscopic interventions and randomized controlled trials evaluating effectiveness of interventions. The young gynaecologist embarking on training in endoscopy will now find a plethora of evidence produced by organizations such as the Cochrane Collaboration and national evidence-based guidance such as that produced by the National Institute of Health and Care Excellence (NICE) in the UK.

Endoscopic surgery is not confined to the practice of gynaecology. However, as pointed out by a previous author of this chapter, it is worth reminding readers, and especially the new cadre of gynaecologists in training, that laparoscopic surgery was first developed by gynaecologists not general surgeons. Indeed, it was Semm, a gynaecologist, who carried out the first laparoscopic appendicectomy in 1983 [1].

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Equipment common to hysteroscopy and laparoscopy

Light source and light lead

One of the great advantages of endoscopic over open surgery is the visualization of the anatomy and so adequate illumination is vital. Light sources have evolved from the initial platinum wire loop to fibreoptics and the rod-lens system. Illumination is now usually achieved using an incandescent bulb and heat generated is in the form of infrared light. A condensing lens concentrates light from the bulb into a narrow beam at the cable input and the light is then transmitted to the laparoscope via a gel or fibre cable. High-definition cameras require a higher performance light source because they have reduced sensitivity given the smaller pixel size.

Camera and monitor system

The camera system consists of three key components: the camera head, the camera control unit and the monitor to visualize the image. The image is captured as a digital signal from a distal mounted lens and transmitted through a rod-lens system to an ocular mounted lens which magnifies it and the image is visualized on a monitor.

Current three-chip cameras consist of a goal lens, a prism assembly and three sensors for acquiring the primary colours, providing more natural colour reproduction than earlier technologies. Video laparoscopes are now also available where the chips are built into the end of the optic, capturing the image at the tip of the laparoscope and improving image quality and accuracy. Three-dimensional imaging provides greater depth perception [2], although the technology has yet to achieve widespread popularity. A video cable transmits the digital image data between the camera head, camera control unit, and monitor. Flat screens in high definition have superseded earlier monitors and provide a much superior image. Narrow-band imaging is a recent innovation, which uses a specific narrow wavelength to change the normal colour contrasts of the laparoscopic image.

Energy modalities

Electrosurgery, often referred to as diathermy, has been used in surgery for over 100 years and has become an integral component of both hysteroscopic and laparoscopic surgery. Laparoscopic energy modalities are essential for dissection, ligation and haemostasis [3]. Monopolar, bipolar, ultrasonic and advanced bipolar energy sources are currently used. Electrosurgical cutting

Fig. 37.1 Advanced bipolar (LigaSure™). *Source:* Medtronic, USA. Reproduced with permission of Medtronic, USA.

depends on electrical arcing between the electrode and tissue resulting in vaporization and cell explosion, whereas coagulation is achieved with the electrode in contact with tissue causing heating and coagulation.

Monopolar electrosurgery delivers an electrical current via one active electrode that disperses through the patient to an attached passive return electrode. The advantages of monopolar diathermy include the ability to chose pure or mix/blend currents so that cutting and dissection can be achieved while providing haemostasis and coagulation. Disadvantages include (i) unintentional thermal injury due to thermal spread and unintentional visceral contact with active or heated electrodes, (ii) direct or capacitive coupling and (iii) improper placement of the return electrode or contact with volatile substances such as cleaning fluids.

Bipolar electrosurgery differs from monopolar in that the current travels only between the two active prongs of the electrodes. Therefore, the energy travels only through the target tissue and not through the patient. Both electrodes are of equal size, producing similar temperature changes at both ends, allowing for targeted desiccation at lower temperatures. This translates to a lower risk of collateral damage. The advantages of bipolar electrosurgery include a virtually eliminated chance of alternate site burns or direct and capacitative coupling. As no return electrode is required, the risk of a dispersive electrode burn is eradicated. The disadvantage of bipolar electrosurgery is its inability to cut tissue.

Advanced bipolar electrosurgery refers to devices that have been developed to more precisely manage delivery of bipolar electrical energy, providing consistent and rapid tissue and blood vessel sealing. They also incorporate a mechanical cutting blade at the electrode site. This blade is deployed to provide bloodless cutting after very effective desiccation of the tissue (Fig. 37.1).

Ultrasonic energy can also be used to dissect, cut and coagulate tissue, avoiding the potential dangers associated with electrical currents (Fig. 37.2). Mechanical energy is generated from rapid vibrations of a blade or shears at the tip of the instrument, causing water to evaporate from the tissues at a low temperature. This desiccates the tissues and allows precise cutting and dissection. The other mechanism it uses is stretching of the tissue by the blade edge, causing friction and generating heat, cutting the tissue. The advantage of the ultrasonic scalpels compared with electrosurgery is the reduction in tissue charring, desiccation and spread of thermal energy, lowering the risk of inadvertent injury to other structures. Devices are now also available that combine both advanced bipolar electrosurgery with ultrasonic energy.

Advanced bipolar devices and ultrasonic energy appear to provide more rapid and bloodless operating compared with conventional electrosurgery. To date, studies have not demonstrated a significant difference in complication rate between devices but this may be due to a relatively low complication rate in gynaecological procedures [4,5]. However, there is a need for properly designed and powered comparative studies to guide surgeons regarding the most effective and safe modes of energy to use for specific operations.

Fig. 37.2 Harmonic Ace® + 7 curved shears (Ethicon, Somerville, NJ, USA) and generator. Ultrasonic energy is used to dissect and desiccate tissue

Laser energy in minimal access gynaecological surgery has diminished with the advent of the newer, easier to use and cheaper energy modalities described here.

Photo and video documentation

The universal use of video cameras at endoscopic surgery lends itself to recording still images, short excerpts of procedures or even whole procedures. Photographs are clinical records that can be discussed with the patient as well as colleagues if a second opinion is sought. Video recordings are excellent for teaching, and can also be

used for research, to measure performance and to assess new instruments and techniques. Review of recordings can also help with the understanding of operative complications and are increasingly useful with regard to complaints and negligence claims.

Equipment for hysteroscopy

Direct imaging within the uterine cavity utilizing hysteroscopy requires an endoscope, outer sheath(s) for passage of distension media, a light lead and camera relaying to a monitor.

Hysteroscopes

Hysteroscopes can be rigid or flexible. The majority of gynaecologists use rigid hysteroscopes because the image tends to be superior, the equipment is more robust and it can be sterilized. Moreover, operative procedures can be undertaken using rigid hysteroscopes whereas flexible hysteroscopes are restricted to diagnosis. Rigid hysteroscopes generally have a Hopkins rod-lens optical system whereas flexible and very narrow rigid hysteroscopes contain optical fibres.

Rigid hysteroscopes come in different sizes in terms of their outer diameter, 2.7, 2.9 and 4 mm being popular sizes. The distal lens can be straight or oblique, the most frequently used being 0° and 30° angles of view. Oblique lenses have the advantage of a wider field of view, enabling diagnosis and facilitating operative procedures as instrumentation can be visualized under higher magnification. Diagnostic procedures can be performed using a single outer sheath fitted around the optic to allow irrigation of fluid or gas distension media thereby achieving uterine distension. Continuous flow permits simultaneous irrigation/suction and tends to be used for surgery where removal of blood and tissue debris is necessary to maintain visualization within the uterine cavity. To achieve continuous flow, operative hysteroscopes have both inflow and outflow channels (inner sheath for inflow, outer sheath for outflow) in addition to a working channel which can accommodate miniature ancillary instruments. Most diagnostic and operative hysteroscopic set-ups are less than 5.5 mm in outer diameter. Resectoscopes and tissue removal systems can be up to 9 mm in outer diameter.

Uterine distension

The uterine cavity is a potential space and has to be distended at relatively high pressure to afford a panoramic view. To achieve this, gas (CO_2), low-viscosity fluids (e.g. normal saline, 5% dextrose, 1.5% glycine, 3% sorbitol, 5% mannitol) or high-viscosity fluid (e.g. Hyskon, which is 32% dextran 70 in dextrose) can be used. Normal saline is most frequently used for diagnostic hysteroscopy, replacing the use of gaseous CO_2 media. The choice of fluid distension media for operative hysteroscopy depends on the type of instrumentation; physiological media, namely normal saline, should be preferred when using mechanical instruments. Resectoscopic electrosurgery traditionally required the use of electrolyte-free solutions such as glycine, sorbitol or mannitol because they employed monopolar electrical circuits. Bipolar electrosurgery using miniature electrodes or conventionally sized resectoscopes are now widely available and these necessitate the use of electrolyte-containing fluid distension media, i.e. normal saline which is safer as it minimizes the sequelae of inadvertent fluid overload and induced hypo-osmolar hyponatraemia.

The pressure required to provide an adequate view of the uterine cavity depends on a number of factors, but tends to be around 100 mmHg (13.3 kPa). An enlarged non-compliant uterus, leakage of distension medium through the cervix or excessive suction when using a continuous flow system will mean that a higher inflow pressure is required. The desired distension is achieved by using gravity, pressure bags or special hysteroscopic pumps, which can also more accurately monitor fluid balance, thereby reducing the risk of fluid overload.

Mechanical instruments

Miniature flexible or semi-rigid mechanical instruments such as scissors, grasping and biopsy forceps can be used with operating sheaths for minor procedures such as target biopsy or polypectomy. These instruments tend to be fragile because of their size, typically 7 or 5 French gauge (3 Fr = 1 mm), so replacements should be available should they break. On the plus side, they are very unlikely to injure the patient.

Bipolar electrodes

The first miniature bipolar electrodes were introduced in the late 1990s; the Versapoint™ Bipolar Electrosurgery System (Ethicon, Somerville, NJ, USA) allows electrosurgical resection of structural anomalies such that they can be used for polypectomy, removal of small intra-cavity fibroids and metroplasty. The 5 Fr Versapoint electrodes include the spring, twizzle and ball design (Fig. 37.3). Other bipolar electrodes are now available. As these electrodes are bipolar, physiological solutions such as normal saline and Hartmann's solution can be used for uterine distension, but a dedicated electrosurgical

Fig. 37.3 Versapoint Bipolar Electrosurgery System™ (Ethicon, USA). Spring-tip electrode suitable for removing polyps, and grade 0 fibroids) is shown with the electrosurgical generator. A needle-like twizzle-tip electrode is also available (not shown) for removing polyps, septa, and adhesions. *Source:* photos by T. Justin Clark.

generator is required. The flow of electricity is limited to the distal tip of the electrode with current circulating between the distal active and slightly more proximal passive return surfaces. The electrodes are versatile because they can be passed down the 5 Fr working channel of any standard operative hysteroscope.

Resectoscopes

Hysteroscopic resectoscopes are used to resect or ablate the endometrium and excise focal lesions such as polyps and fibroids, remove septa and lyse adhesions. Originally the resectoscopes used a monopolar electrode but advances in technology have led to the development of equally effective bipolar resectoscopes that have the safety advantage of using isotonic distension media with reduced risks of serious complications arising from fluid overload and induced hypervolaemic hyponatraemia.

The modern resectoscope consists of five components: the optic, handle mechanism, inflow and outflow sheaths and an electrode (Fig. 37.4). The handle mechanism can be active or passive in design; for hysteroscopy, a passive handle is preferable as it maintains the electrode inside the sheathing system out of view and out of harms way. A typical resectoscope has an outer diameter of 26 or 27 Fr (8.7–9 mm) and uses a 4-mm oblique view optic. Narrower 'mini' resectoscopes are now also available although they are not established in routine practice [6]. The electrodes themselves come in different designs, but

Fig. 37.4 Bipolar Resectoscope™ (Olympus, Hamburg; Storz, Tuttlingen, Germany). Key components include the optic, handle mechanism, inflow and outflow sheaths, and loop electrode. *Sources:* Storz, Germany and Olympus, USA. Reproduced with permission of Storz, Germany and Olympus, USA.

the cutting loop (for polypectomy, myomectomy and endometrial resection), rollerball or rollerbar (for endometrial ablation or tissue vaporization) and the knife electrode (for metroplasty) are the most popular.

Tissue removal systems

Tissue removal systems are the most recent technological advance in hysteroscopic surgery. They were developed to provide simultaneous mechanical cutting and tissue retrieval thereby maintaining better views during surgical procedures within the uterine cavity and avoiding the use of more hazardous thermal energy. A tissue removal system consists of a bespoke operating 0° hysteroscope with an operating channel that allows the insertion of a disposable cutting handpiece comprising two rotating hollow metal tubes which rotate and shave away the pathology being approximated. Each tube incorporates a small aperture or 'window' distally through which removed tissue is extracted by the application of external suction tubing; the removed tissue is then trapped in a tissue collector. A generator provides the electrical energy to rotate the mechanical tissue removal system. The first of these systems was the TruClear™ (Medtronic, Minneapolis, MN, USA) (Fig. 37.5), which has been followed by similar products from Hologic (Bedford, MA, USA) called Myosure™ and Karl Storz (Tuttlingen, Germany) called Intrauterine BIGATTI Shaver (IBS®). More recently, the Symphion™ (Boston Scientific, Natick, MA, USA) has been produced which combines a tissue removal system with bipolar radiofrequency energy.

Equipment for laparoscopy

Laparoscopes

Laparoscopes are built around a rod-lens system that transmits images to the camera. Fibreoptic microlaparoscopes are also available but are more fragile and provide an inferior image. Laparoscopes come in a range of diameters (3–12 mm) and various angles of view (0–30°). The 10-mm 0° laparoscope is most widely used in gynaecological surgery. The vast majority of gynaecologists prefer a multi-puncture approach with instruments inserted through ancillary ports usually sited to facilitate triangulation and manoeuvrability. Ancillary port sites are usually 5–15 mm depending on the diameter of the instruments to be accommodated. More recently, miniature surgical instruments, typically with diameters of 3 mm or less, can be utilized with less scarring [7].

Veress needle

The Veress needle [8] is a spring-loaded needle used to create a pneumoperitoneum at laparoscopy, most commonly inserted at the umbilicus. The Veress needle is usually inserted transabdominally, but in obese patients can be introduced through the uterine fundus or vagina [9]. It is available in reusable and disposable forms. For patients with suspected periumbilical adhesions or a previous umbilical hernia repair, Palmer's point (left subcostal) entry should be performed. An alternative is open entry (Hassan's technique) where the layers of the anterior abdominal wall are dissected through a small linear incision. This may reduce the incidence of major vessel injury though not bowel injury [10]. Optical entry techniques are also favoured by some surgeons and can be used before or after insufflation. They generally consist of a hollow transparent trocar in which is loaded a 0° laparoscope [11].

Trocars and cannulae

Trocars and cannulae act as conduits for the laparoscope and other instruments. They come in a variety of sizes depending on the diameter of the instrumentation to be accommodated, with 5 mm and 10–12 mm ports being the most commonly used. The older types of trocar are made of steel, are reusable and are sharp-tipped. Now

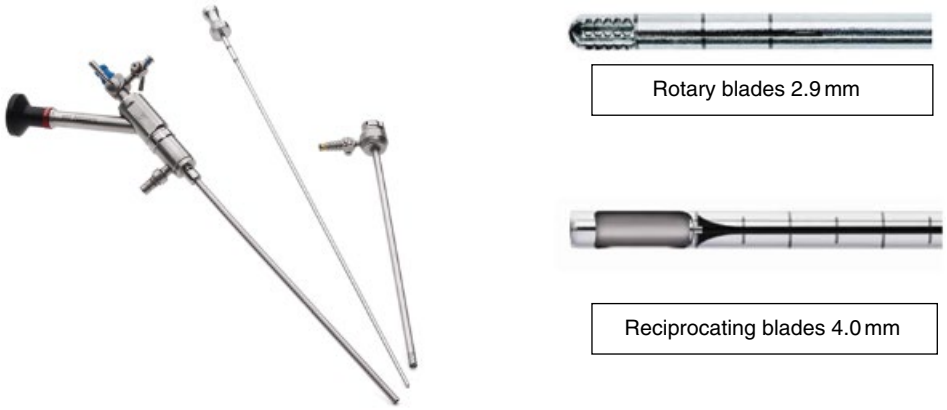

Fig. 37.5 TruClear™ tissue removal system (Medtronic, Dublin, Ireland): operating hysteroscope, outflow sheath, obturator and rotary (polyps) and reciprocating (fibroids) cutting blades. *Source:* Medtronic, USA. Reproduced with permission of Medtronic, USA.

there are a host of disposable trocars and cannulae with modifications to optimize performance. A recent Cochrane review comparing visceral and vascular complications did not show any difference in incidence between trocar types [8]. Mini-laparoscopy is performed through 3.5–5 mm ports and although visualization is not yet comparable to that of standard laparoscopy, it is satisfactory and this approach has the advantage of better cosmetic results and a lower incidence of postoperative pain or incisional hernias.

Laparo-endoscopic single-site surgery

Laparo-endoscopic single-site surgery (LESS) is the term coined for single incision laparoscopic surgery. This technique uses a single umbilical port that is adapted such that not only a laparoscope but additional operating instruments can be passed. Bespoke multi-access ports are available with expandable retractors and even home-made designs with a surgical glove attached to the port and instruments passed through small incisions in the 'fingers', which have been inflated by the CO_2 used to create the pneumoperitoneum. The potential advantages of LESS include a better cosmetic result due to a single scar, decreased risk of wound infection and a reduced risk of herniation. However, a meta-analysis comparing LESS with multi-port laparoscopy has not demonstrated any significant difference in operative outcomes, postoperative recovery, postoperative morbidity and patient satisfaction, operating time or cosmetic results [9].

Robotic laparoscopic surgery

Robotic-assisted laparoscopic surgery has been utilized in gynaecology as an alternative to standard 'straight stick' laparoscopy. The da Vinci® surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) consists of three components: the console, which allows the surgeon to control the robot remotely; the inSite® vision system, which provides a three-dimensional image of the operative field via a 12-mm laparoscope; and the patient side-cart fitted with three to four robotic arms to control Endowrist® instruments. Robotic surgery may offer several advantages in gynaecology, including magnified three-dimensional vision, wristed instruments that aid dexterity and precision, and less fatigue and reduced back and shoulder injuries for surgeons because they can operate sitting down at a console [12]. There remains a lack of robust randomized controlled trial data on robotic surgery compared with standard multi-port laparoscopy and at present, in the absence of compelling evidence of improved effectiveness, the costs associated with robotic surgery for the most part remain prohibitive [13,14].

Laparoscopic insufflator

One of the great advantages of laparoscopy over open surgery is superior visualization of the anatomy. This is achieved by creating a CO_2 pneumoperitoneum. CO_2 is used because it is odourless, non-combustible, cheap, colourless and rapidly eliminated from the systemic circulation. Insufflators control intra-abdominal pressure rather than flow, and this should be set at 12–15 mmHg (1.6–2.0 kPa) during surgery; a higher pressure of up to 25 mmHg (3.3 kPa) is recommended during trocar entry as this has the effect of increasing the distance between any trocar being inserted and bowel or large blood vessels thereby, in theory at least, reducing the risk of injury [15].

Suction/irrigation pump

The provision of suction (negative pressure aspiration) and irrigation (instillation of fluid under pressure) helps maintain visualization within the operative field. A 5- or 10-mm suction/irrigation cannula can be used to aspirate blood and clean the pelvis (and more accurately estimate blood loss during surgery), deflate ovarian cysts and aspirate blood during pelvic procedures such as ruptured ectopic pregnancies.

Ancillary instruments

Mechanical instruments

Typically, 5-mm grasping forceps are used to grip tissue. They can be atraumatic, suitable for holding delicate structures such as fallopian tubes, bladder and bowel, or traumatic to ensure a firm grip of more robust tissue, such as when performing ovarian cystectomies (Fig. 37.6). Sharp curved laparoscopic scissors are the other essential ancillary instrument used to dissect tissues.

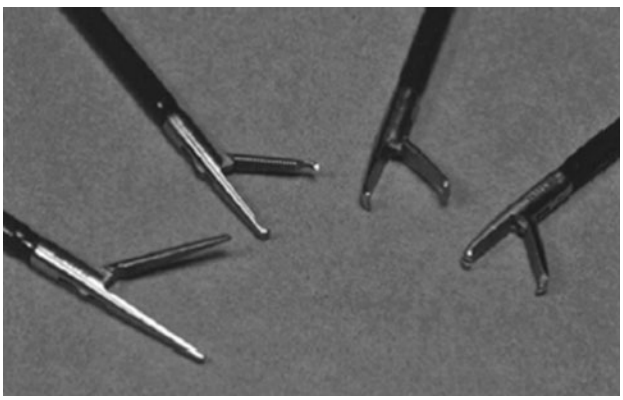

Fig. 37.6 5-mm laparoscopic grasping forceps.

Electrosurgical instruments

Electrosurgical energy encompasses monopolar and bipolar diathermy, as discussed earlier. The basic instruments available consist of scissors or hooks which use monopolar energy to divide or cut tissue. Bipolar forceps can be used to coagulate tissue with less thermal spread than monopolar energy. The tissue can then be divided using passive mechanical or monopolar instruments. Vessel-sealing technologies utilize bipolar energy and optimal mechanical pressure to fuse vessel walls and create a seal. Vessels up to 7 mm in diameter and large tissue bundles can be ligated using these instruments. The LigaSure™ (Medtronic, Fridley, MN, USA) (see Fig. 37.1), Olympus PK™ (Olympus, Southborough, MD, USA) and Enseal™ (Ethicon, Somerville, NJ, USA) systems are examples of these technologies and can reduce operating time and blood loss by securing pedicles more rapidly and effectively than standard bipolar energy combined with suturing. However, they are more costly than standard bipolar diathermy forceps. Ultrasonic scalpels can also be used to dissect, cut and coagulate tissue using energy created through mechanical vibration, avoiding the need for electrical current (see Fig. 37.2).

Sutures

There are many different absorbable and non-absorbable sutures and knot types in laparoscopic surgery. Knots can be tied extracorporeally and intracorporeally and barbed sutures can also be used that retain tension and do not require knot tying, reducing operating times. The types of sutures chosen depend on the type of surgery performed.

Specimen retrieval

Power morcellation

Removal of solid tissue such as ovarian masses, fibroids and the uterus through 'keyhole' port sites can be problematic during laparoscopic surgery. At total hysterectomy, the vagina is opened and the uterus can be removed this way unless it is exceptionally large, in which case mechanical or power morcellation may be required. Power morcellators are inserted through ancillary port sites and consist of a fixed outer tube encapsulating an inner tube with a cutting device. A large grasper is passed through the lumen of the device and tissue drawn up and morcellated within it. They are available in various dimensions and can be reusable or disposable. There has been a recent move towards 'in-bag' morcellation when removing fibroids (leiomyomas) during laparoscopic myomectomy and hysterectomy. This development is in response to the US Food and Administration (FDA) warning regarding the potential risk of tumour spread in cases of undiagnosed leiomyosarcoma during power morcellation (https://www.fda.gov/downloads/MedicalDevices/ ProductsandMedicalProcedures/SurgeryandLifeSupport/UCM584539.pdf).

Culdotomy

Culdotomy (i.e. incision within the posterior fornix of the vagina) can be performed to retrieve specimens, and prior to the advent of retrieval bags was the principal method of specimen removal. However, when the pouch of Douglas is obliterated, such as in the presence of deep infiltrating endometriosis, this is not a safe option.

Retrieval bags

Retrieval bags are now used routinely to remove specimens such as adnexal masses from the pelvis through one of the ancillary abdominal ports. Most specimen bags are 10 or 15 cm in size, the former fitting through a 10-mm port and the latter requiring a 12-mm port. Larger-diameter bags can be passed via a culdotomy. Smaller bags can be used through the umbilical port, avoiding the need for fascial closure; if a larger bag is used, then fascial closure of an ancillary port is required to prevent herniation.

Experimental minimally invasive laparoscopy

*Percutaneous surgical system*s consist of a less than 3-mm laparoscopic shaft percutaneously inserted using a Veress-like needle tip and then an interchangeable 5-mm tool (e.g. scissors, graspers, irrigation systems) is inserted in place of the needle tip [16]. Tools such as monopolar scissors, graspers, hook and irrigation systems can be utilized [17]. *Natural orifice transluminal endoscopic surgery* (NOTES) describes a technique utilizing a natural body orifice for entry into the peritoneal cavity rather than percutaneously. The most common site of entry is the stomach but for gynaecologists the site of entry is the vaginal vault. Laparoscopic surgery can then be performed through this using flexible instruments and the vault can be sutured closed from the vaginal approach [18,19].

Operating theatre organization

Hysteroscopy

While diagnostic hysteroscopy has become an outpatient procedure in most cases, with even minor operative procedures being done under local anaesthesia, more major surgery (e.g. hysteroscopic myomectomy for a sizeable submucous fibroid) usually requires general anaesthesia. It is best to have all the necessary equipment together on a surgical cart, with the monitor at a

comfortable height and position for the operator (and patient if she is awake) (Fig. 37.7).

Laparoscopy

The set-up for laparoscopy is more varied than for hysteroscopy partly because there tends to be more equipment and partly because laparoscopy is not 'solo' surgery but, as is the case with laparotomy, requires the help of assistants. Most gynaecologists prefer to use 0° optics and it is common for one of the assistants to stand on the contralateral side of the patient and control the laparoscope, leaving the lead surgeon free to operate with two hands (Fig. 37.8). However, ergonomically this set-up is not ideal and so where the operating assistant is suitably experienced, the operator or assistant (whether standing adjacent or opposite the operator) can control the laparoscope and ancillary ports to cut, ligate, hold and retract tissue as well as irrigate, suck, suture and retrieve specimens.

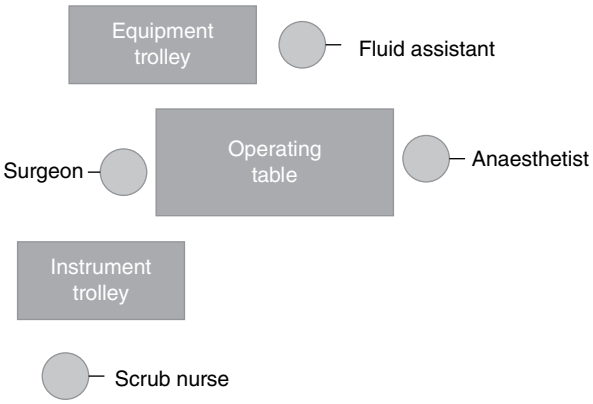

Fig. 37.7 Theatre set-up for hysteroscopic surgery.

Diagnostic hysteroscopy

Diagnostic hysteroscopy is one of the commonest procedures in gynaecology. Technological advances have led to the miniaturization of hysteroscopes and ancillary equipment such that the majority of procedures are feasible in an outpatient setting in conscious women without anaesthesia [20]. Hysteroscopy is highly accurate for the diagnosis of serious endometrial disease [21] and structural uterine anomalies including polyps, fibroids and uterine septa [22]. The indications and contraindications are summarized in Table 37.1.

Transvaginal ultrasound and endometrial biopsy are also useful outpatient tests for evaluating the uterine cavity and can be used as an alternative to, or in conjunction with, hysteroscopy for the diagnostic work-up of women with abnormal uterine bleeding [23] and reproductive problems.

Technique

The patient should positioned in lithotomy with the hips well flexed and the buttocks slightly over the edge of the table to allow unimpeded access irrespective of uterine position (Fig. 37.9). A 'no touch' vaginoscopic approach (Box 37.1) should be adopted as this is associated with reduced pain with no evidence of reduced feasibility or morbidity.

The hysteroscope should be guided into the uterine cavity under direct vision. Routine blind dilatation of the cervix should be avoided to minimize the risk of uterine trauma. When traversing the endocervical canal it is important to have the hysteroscope aligned in the correct relative axis. Light is absorbed along the endocervical canal such that it appears as a dark

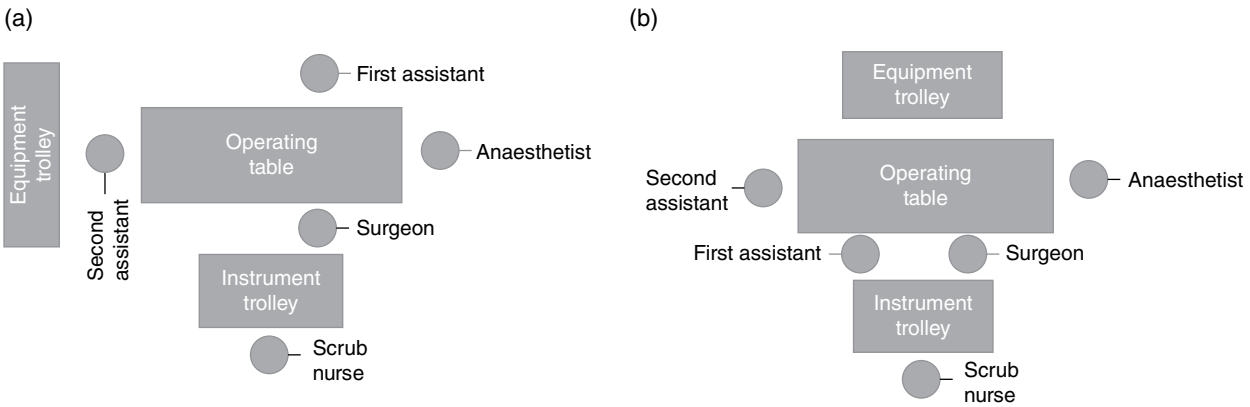

Fig. 37.8 Two schemes for theatre set-up for laparoscopic surgery: (a) first assistant holds camera (better with 0° optic); (b) operating surgeon or assistant holds camera.

Table 37.1 Indications and contraindications for diagnostic hysteroscopy.

Indications
Abnormal uterine bleeding
Heavy menstrual bleeding
Irregular menstrual bleeding
Intermenstrual bleeding (≥3 months)
Postmenopausal bleeding (recurrent or endometrial thickness ≥4 mm/focal anomaly seen on TVS/non-diagnostic EB)
Reproductive failure
Subfertility
Recurrent miscarriage/preterm delivery
Contraindications
Pelvic infection
Pregnancy

EB, endometrial biopsy; TVS, transvaginal ultrasound.

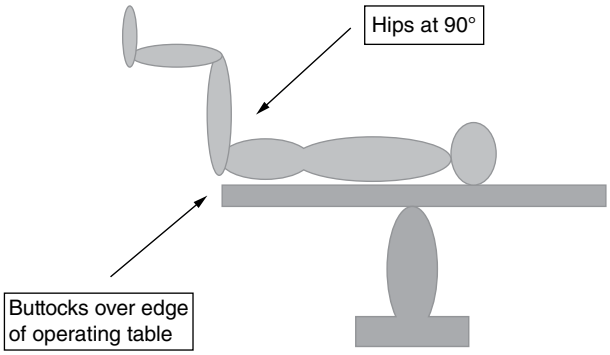

Fig. 37.9 Patient position for hysteroscopy.

ellipse on the monitor; the position of this ellipse can be central or at the 3, 6, 9 or 12 o'clock positions. When using a 0° hysteroscope the cervical canal should appear centrally whereas it should be eccentrically placed when using an oblique-view optic, the exact position depending on the orientation of the hysteroscope (Fig. 37.10).

Once in the uterine cavity, it is simply a matter of systematically inspecting the fundus, cornua and tubal ostia and the four walls of the uterus by a combination of rotating (if using an oblique-view hysteroscope) and moving the hysteroscope up and down and left to right. Panoramic views allow a global appreciation of the cavity shape and size and the presence of structural abnormalities. Magnified views, by approximating the hysteroscope close to the uterine walls, allow a more detailed inspection of the endometrium and surface of focal lesions. Once the uterine cavity has been inspected, the hysteroscope is withdrawn and this is the best time to inspect the endocervical canal. A global biopsy can then be taken, if indicated, using a small curette or a miniature suction biopsy device usually based on the Pipelle™ prototype, H-pipelle, or a change made to an operative sheath for a targeted biopsy.

A Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline has detailed best practice in outpatient diagnostic hysteroscopy aimed at minimizing pain and complications and optimizing patient experience [24]. A summary of the recommendations based on published evidence and expert opinion is provided in Summary box 37.1.

Box 37.1 'No touch' (vaginoscopic) hysteroscopy

This technique is ideally suited to the outpatient clinic as it minimizes patient discomfort by the simple fact that the vagina does not need to be distended by insertion of antiseptic swabs or vaginal specula and tenaculums do not need to be applied to the ectocervix. The approach is also quicker and not associated with loss of feasibility or increased morbidity. The tip of the hysteroscope is introduced into the vaginal introitus, the low-viscosity distension medium is turned on, and as the vagina distends the hysteroscope is guided along the vaginal axis until the external cervical os is identified. As most uteri are anteverted, in practice the external cervical os will be identified in the posterior aspect of the vagina (hands holding the proximal hysteroscope/camera head externally move upwards) and, once approximated, the hysteroscope is angulated anteriorly (hands holding the proximal hysteroscope/camera head externally move downwards) to traverse the cervical canal and thence the uterine cavity. If the cervix is not easily identified, then the hysteroscope should be passed to the posterior vaginal vault and thence withdrawn slowly until the external cervical os comes into view within the distended vagina. The external cervical os can be more difficult to see with small nulliparous external os, long intravaginal cervices or where there is uterine prolapse. This method works in the majority of cases unless there is cervical stenosis, where cervical dilatation after application of local cervical anaesthesia will be required. A large randomized controlled trial is underway evaluating conventional approaches using a vaginal speculum with or without cervical tenaculum/dilatation versus vaginoscopy (https://clinicaltrials.gov/ct2/show/NCT01972945)

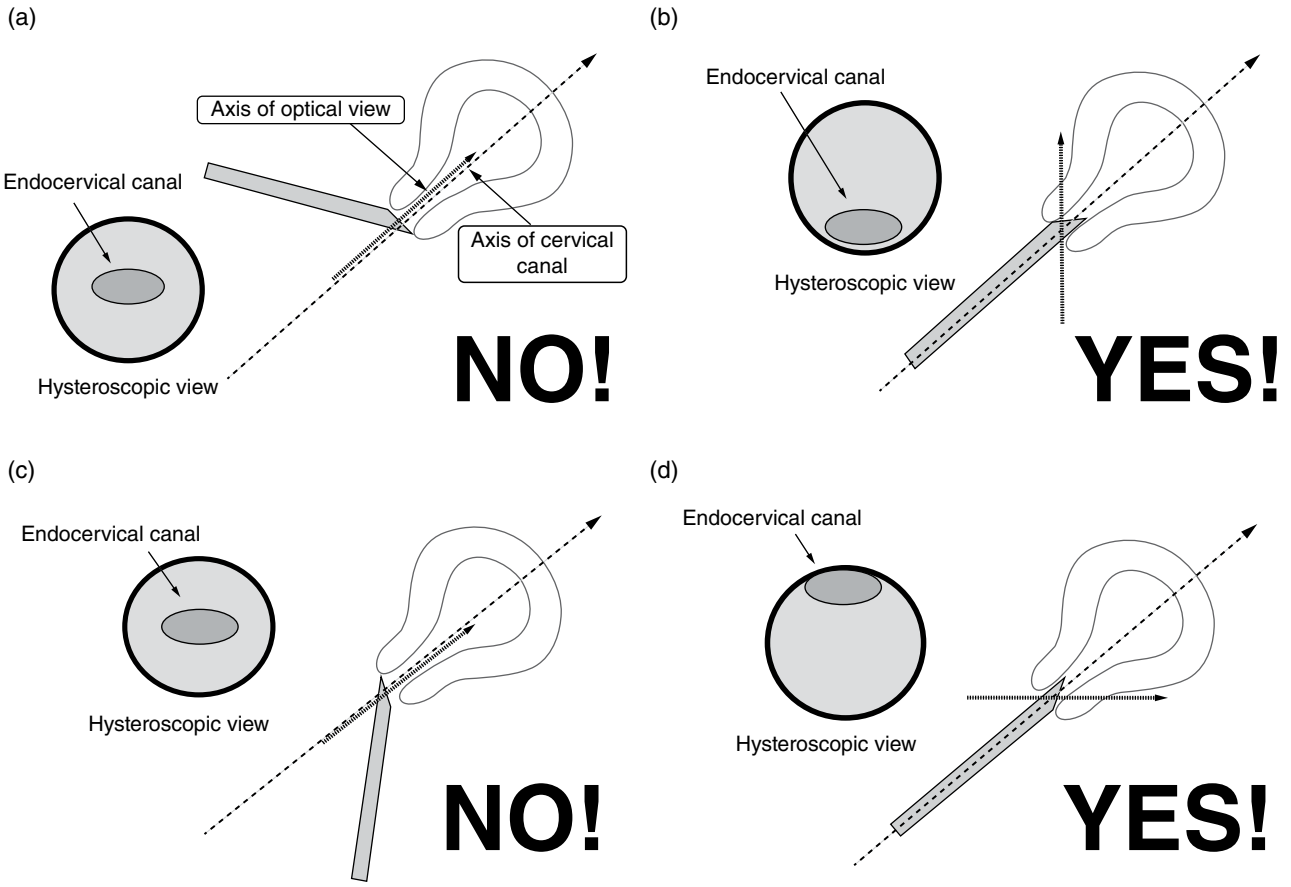

Fig. 37.10 How to insert an oblique-view hysteroscope into the uterus: (a) incorrect insertion with hysteroscope looking upwards; (b) correct insertion with hysteroscope looking upwards; (c) incorrect insertion with hysteroscope looking downwards; (d) correct insertion with hysteroscope looking downwards.

Complications

Diagnostic hysteroscopy is a safe procedure, and complications are uncommon [21]. In a prospective multicentre study of 13 600 women looking at complications of hysteroscopy, diagnostic procedures had significantly fewer complications (0.13%) than operative procedures (0.28%) [25]. The most frequently seen problem with outpatient hysteroscopy is pain when negotiating the cervix or distending the uterine cavity, and vasovagal reactions in response to cervical stimulation. Uterine perforation should not happen if the hysteroscope is introduced under direct vision unless there is extreme cervical stenosis.

Summary box 37.1

Best practice in ambulatory hysteroscopy [24]

- All gynaecology units should provide a dedicated outpatient hysteroscopy service that is appropriately sized, equipped and staffed and located outside the formal operating theatre setting. The healthcare professional(s) should have the necessary skills and expertise to carry out diagnostic and/or therapeutic outpatient hysteroscopy.
- Written patient information should be provided before the appointment and consent for the procedure should be taken.
- Women without contraindications should be advised to consider taking standard doses of non-steroidal anti-inflammatory drugs (NSAIDs) 1 hour before their appointment, but routine use of opiate analgesia should be avoided.
- Routine cervical preparation before outpatient hysteroscopy should not be used unless dilatation beyond Hegar 6 is anticipated.
- Miniature hysteroscopic systems (≤4 mm outer diameter) should be used for diagnostic outpatient hysteroscopy.

Choice of hysteroscope (e.g. flexible or rigid; 0° or fore-oblique distal lenses) should be left to the discretion of the operator.
- Carbon dioxide or normal saline can be used as distension media for diagnostic outpatient hysteroscopy, but normal saline should be used for operative procedures.
- Routine, blind cervical dilatation should be avoided.
- Topical application of local anaesthetic to the ectocervix should be considered where a cervical tenaculum is necessary. Routine administration of intracervical or paracervical local anaesthetic should be used where larger-diameter hysteroscopes are being employed (outer diameter >5 mm) and where the need for cervical dilatation is anticipated (e.g. cervical stenosis). Standard protocols regarding the type, maximum dosage and route of administration of anaesthesia should be implemented.
- Conscious sedation should not be routinely used in outpatient hysteroscopic procedures.
- Vaginoscopy (avoiding the use of a vaginal speculum or cervical instrumentation) should be the standard technique for outpatient hysteroscopy.

Operative hysteroscopy

Hysteroscopic surgery has a number of well-defined indications and these are itemized in Table 37.2.

Polypectomy

The removal of uterine polyps appears to confer benefit in terms of resolving symptoms and obtaining tissue for histological examination [26,27]. Traditional blind removal of polyps (e.g. dilatation and curettage, blind avulsion) risked incomplete removal and uterine perforation. Improvements in hysteroscope design and ancillary instrumentation, coupled with enhanced visualization due to improvements in fibreoptics and digital imaging, has allowed polyps to be removed under direct hysteroscopic vision predominantly in an outpatient setting consigning blind methods to the history books.

Mechanical instruments such as scissors and grasping forceps designed to pass down 5 and 7 Fr operating channels have been used successfully, but their utility is affected by their diminutive size and fragility. The introduction of bipolar intrauterine electrosurgical systems (e.g. Versapoint Bipolar Electrosurgical System) has facilitated rapid resection of focal uterine lesions, all but replacing mechanical approaches. Large observational and randomized trials have demonstrated the feasibility, acceptability and effectiveness of hysteroscopic polypectomy using such approaches [28,29]. However, these studies showed that nearly one in five attempts to remove polyps (detach and retrieve in entirety) failed primarily because of inadequate visualization, patient intolerance or difficulties in retrieval from the uterine cavity down the relatively narrow endocervical canal.

The introduction of tissue removal systems (formerly referred to as hysteroscopic morcellators) with their inherent ability to simultaneously cut and aspirate polyp tissue has overcome these obstacles. A recent randomized controlled trial comparing the TruClear system with the Versapoint Bipolar Electrosurgical System in an outpatient setting demonstrated lower failure rates (<2% vs. 17%) and pain scores along with increased speed of procedure and patient acceptability [30].

Table 37.2 Operative hysteroscopic procedures.

Adhesiolysis
Endometrial ablation/resection
Metroplasty
Myomectomy
Polypectomy
Occlusion of hydrosalpinges before assisted reproductive techniques
Proximal fallopian tube cannulation
Removal of intrauterine contraceptive device
Target biopsy
Treatment of placental remnants
Tubal sterilization

Myomectomy

Submucous fibroid(s) that are entirely within the cavity are classified as type 0. If a portion of the fibroid is intramural, then they are classified as type 1 if less than 50% is intramural and type 2 if more than 50% is intramural [31]. Types 0 and 1 are suitable for hysteroscopic resection and clinical outcomes in terms of perioperative complications, need for further surgery, alleviation of bleeding symptoms [32–34] and optimization of natural and assisted fertility [35] are good. In contrast, removal of type 2 fibroids is more challenging because risks of perioperative bleeding, incomplete removal and uterine trauma are significantly greater. Furthermore, the requirements for repeated hysteroscopic or other surgical interventions are greater to treat ongoing abnormal bleeding symptoms compared with type 0 and 1 fibroids [34].

Whilst most operative hysteroscopic procedures described in this chapter are feasible in an outpatient setting, removal of submucous fibroids generally requires general/regional anaesthesia. The Versapoint electrode can rapidly excise non-fundal grade 0 fibroids although retrieval down the narrow cervical canal, even under general anaesthesia, can be difficult. Moreover, grade 1 and 2 fibroids cannot be resected by point electrodes and for this reason hysteroscopic removal is mostly done with resectoscopes utilizing cutting loop electrodes. Advanced hysteroscopic skills are required and an appropriate caseload to maintain surgical proficiency.

Tissue removal systems are gaining popularity as they are simple to use, avoid the production of 'tissue chips', do not use potentially hazardous thermal energy, are quicker and associated with a reduced learning curve [36]. They are suited to grade 0 and 1 fibroids.

Endometrial ablation/resection

Hysteroscopic endometrial resection and ablation have been subjected to numerous randomized controlled trials and cost–benefit analyses showing that they are effective and useful alternatives to hysterectomy but are no more effective than the newer second-generation techniques [37]. These hysteroscopic first-generation techniques of endometrial destruction have been superseded to some extent by the newer second-generation ablative techniques which are technically easier to perform and associated with comparable clinical outcomes and fewer complications [37].

The development of miniature second-generation, semi-automated ablative technologies has allowed the concept of outpatient local anaesthetic endometrial ablation to progress. The majority of women undergoing the procedure in the outpatient setting find it acceptable [38].

Metroplasty

The most common congenital uterine anomaly amenable to hysteroscopic treatment is the partial or complete uterine septum (septoplasty). The fibroelastic tissue comprising a uterine septum can be divided mechanically using scissors, with electrosurgery (Versapoint electrode or resectoscopic division using a Collins knife electrode) or a combination of mechanical and electrosurgical techniques. Other uteroplastic procedures have been reported including restoration of the shape of a hypoplastic or T-shaped uterus by scoring the myometrium with activated miniature bipolar electrodes in an attempt to increase the uterine capacity [39]. Bipolar electrodes can also be used to create outflow channels in non-communicating rudimentary uterine horns.

Adhesiolysis

Intrauterine adhesions (Asherman's syndrome) occur where there is scar tissue between the uterine walls as a response to infection (endometritis) or trauma from intrauterine surgery, typically vigorous curettage of the endometrium in a recently pregnant or pregnant uterus. Hysteroscopy is the gold standard for accurate diagnosis and assessment of intrauterine adhesions. Hysteroscopic techniques include blunt or sharp adhesiolysis, using mechanical or electrosurgical instruments. In some patients, landmarks remain obscure and entry into the uterus may not be possible by hysteroscopy alone. In these patients it is necessary to perform simultaneous laparoscopy, fluoroscopy or ultrasound to reduce the risk of perforation. Increased uterine cavity size can be achieved by myometrial scoring with scissors or a Collins knife electrode [39].

Proximal fallopian tube cannulation

Tubal catheterization is a technique used to treat a proximal fallopian tube blockage diagnosed following a hysterosalpinogram. Hysteroscopic tubal catheterization is reported to be successful in approximately 50% of patients and 20–40% of these women have been reported to become pregnant either spontaneously or after ovulation induction or intrauterine insemination [40].

Tubal sterilization

The Essure® (Conceptus Inc., Mountain View, CA, USA) permanent birth control system involves placing a micro-insert, consisting of a stainless steel inner coil with polyester fibres and a super-elastic nitinol outer anchoring coil, into the intra-myometrial portion of each fallopian tube. This is done via a fine delivery catheter which is passed down the 5 Fr operating channel of a 30° 5–5.5 mm continuous-flow rigid hysteroscope (Fig. 37.11). The majority of procedures are performed in conscious women in the outpatient setting and most women are discharged home within 30 min following completion of the procedure [41,42]. Occlusion of the narrow tubal lumen occurs over the following 3 months as the polyester fibres cause inflammation and subsequent tissue ingrowth into the micro-insert. Radiology is scheduled at 3 months to confirm the adequacy of sterilization, usually by two-dimensional transvaginal ultrasound to verify satisfactory positioning of devices or hysterosalpingogram to identify tubal occlusion.

Hysteroscopic occlusion of hydrosalpinges

The same Essure technique can be used in women who require tubal occlusion prior to *in vitro* fertilization as treatment for hydrosalpinges. Successful pregnancy

Fig. 37.11 Essure™ permanent birth control system (Bayer, Germany). The expanded micro-insert which is used to occlude the myometrial component of the fallopian tube is shown along with the hand-held operating system. An operating hysteroscope with a 5 Fr working channel is needed [5-mm Storz Bettocchi® hysteroscope (Storz, Tuttlingen, Germany) shown]. *Source:* Storz, Germany. Reproduced with permission of Storz, Germany.

outcomes have been reported and no adverse effects on the fetus or pregnancy are apparent [43].

Treatment of placental remnants

Chronically retained products of conception (RPOC) or 'placental remnants' (i.e. RPOC that have been retained beyond 6 weeks) can be associated with infection, abdominal pain and uterine bleeding and, in the longer term, the formation of intrauterine adhesions affecting subsequent fertility. Chronic RPOC can be mechanically removed using a 'cold' (inactivated) resection loop by entrapment of tissue between the loop and the hysteroscope. More recently, the use of tissue removal systems has been reported and seems well suited to this task as electrosurgical energy is not needed and tissue can be simultaneously cut away and extracted [44].

Ambulatory hysteroscopy

Outpatient hysteroscopy, ambulatory hysteroscopy and office hysteroscopy all describe procedures that are done without general anesthesia and avoid admission to hospital. Advances in equipment, in particular the reduction in size of optics (operative hysteroscopes ≤5.5 mm outer diameter) and the introduction of miniature 5–7 Fr ancillary operative instruments (mechanical tools, electrosurgical snares/electrodes and bespoke tissue removal systems) has allowed first diagnostic and now a range of minor operative procedures to be performed in an outpatient setting [20,45]. These technological advances have initiated the age of efficient, safe and convenient 'see and treat' gynaecology in an ambulatory setting: the patient 'ambulates in' and 'ambulates out'. Women value the convenience of an immediate diagnosis and treatment in what is known as a 'one-stop' service. Not only is outpatient treatment well accepted and convenient, but it has also been shown to be more cost-effective [46,47]. Most uterine operations can be conducted in an outpatient setting in conscious women with or without local anaesthesia (Table 37.3). The exceptions include the majority of fibroid resections, metroplasty procedures and fibrous adhesiolysis, as cutting into the underlying myometrium is necessary and this induces pain.

Recent multicentre randomized controlled trials have demonstrated the safety, feasibility, effectiveness and cost-effectiveness of outpatient hysteroscopic polypectomy [28–30] and endometrial ablation [38]. In addition to the utility of hysteroscopy in facilitating operative procedures, outpatient hysteroscopy is also increasingly fundamental in the management of menstrual disorders – not just making diagnoses but also aiding safe intrauterine instrumentation, for example endometrial biopsy and insertion of levonorgestrel intrauterine system

Table 37.3 Operative hysteroscopic procedures feasible in an ambulatory setting.

Localization and removal of a missed intrauterine contraceptive device
Endometrial polypectomy
Resection of small type 0 submucous fibroid*
Minor adhesiolysis (filmy adhesions)
Endometrial ablation using second-generation devices
Tubal sterilization
Occlusion of hydrosalpinges before assisted reproductive techniques
Proximal fallopian tube cannulation
Treatment of placental remnants
Removal of intrauterine contraceptive device
Target biopsy

*Office Preparation of Partially Intramural Myomas (OPPIuM), mucosal incision [48].

(LNG-IUS), and planning treatment, for example estimating the likely response of symptoms to minimally invasive treatments with LNG-IUS and endometrial ablation, optimizing management of submucous fibroids and determining the most appropriate treatment setting for interventions.

Complications

Although complications are uncommon with operative hysteroscopy [49], anyone carrying out hysteroscopic surgery should be aware of the risks and their prevention and management (Table 37.4). The most serious complications associated with operative procedures relate to uterine trauma and fluid overload.

Uterine perforation is estimated to occur in less than 1% of procedures [25]. Infection and excessive bleeding are rarely seen. The operative procedures associated with most complications are adhesiolysis and resection of type 2 submucous fibroids [25]. If uterine perforation occurs while the cutting or electrical equipment are active, then there is the potential for major intra-abdominal trauma resulting in haemorrhage and viscus injury. A laparoscopy and arguably a laparotomy is mandatory to check the abdominal contents; if there is no injury, hysteroscopic surgery can continue once the perforation has been sutured.

All fluid distension media can cause complications from intravascular absorption of large volumes of fluid into the circulatory system. However, excessive absorption of hypotonic solutions used with monopolar electrosurgery will lead to electrolyte disturbance, lowering serum osmolality and inducing hyponatraemia. Excessive fluid absorption is most likely with prolonged hysteroscopic procedures using larger-diameter endoscopes with continuous irrigation of fluid or where blood vessels within the myometrium are opened. Thus, particular care is required with transcervical resection of the endometrium and hysteroscopic myomectomy (transcervical resection of fibroids, TCRF). Rapid expansion of the extracellular fluid volume ('fluid overload') can lead to acute pulmonary oedema, cerebral oedema and cardiac failure [50]. Therefore, it is important to accurately measure the input and output of fluid during operative hysteroscopy so that significant fluid deficits can be recognized and managed promptly [51,52].

Table 37.4 Complications of operative hysteroscopy.

Early
Uterine perforation
Fluid overload
Haemorrhage
Gas embolism
Infection
Cervical trauma
Electrosurgical burn
Late
Intrauterine adhesions
Uterine rupture in pregnancy (after metroplasty or myomectomy)
Haematometra (after endometrial ablation)
Post-ablation sterilization syndrome (after endometrial ablation)

Intraoperative haemorrhage can accompany uterine perforation but is more often a sign of surgery deep in the myometrium. Air embolism is a rare but devastating complication [53]. It usually happens if air is allowed to enter the distension tubing, typically when bags of irrigant are being changed. Infection is rare after hysteroscopic surgery. There is no evidence for routine use of antibiotics [54], although some surgeons prefer to administer them. The late adverse consequences of endometrial ablation are all relatively rare [55].

Summary box 37.2

Operative hysteroscopy

- Bipolar resectoscopes should be used in preference to monopolar instruments because a more physiological, electrolyte-containing fluid can be used for uterine distension and irrigation. Fluid overload can still occur, but the associated electrolyte disturbances will be less serious.
- TCRF of grade 1/2 fibroids and major uterine adhesiolysis are technically the most challenging operative hysteroscopic procedures. Surgeons undertaking such procedures should have a sufficient caseload to maintain their skills.

- Most operative procedures, with the exception of most fibroid excisions, metroplasty and adhesiolysis, can be undertaken as effectively in the outpatient setting. Women should be offered the choice of treatment setting.
- Proficiency should be attained through structured training programmes including the use of simulation.

Diagnostic laparoscopy

Diagnostic laparoscopy is a basic minimally invasive surgical procedure that is used to diagnose a variety of gynaecological problems but is most commonly used for pelvic pain and subfertility (Table 37.5).

Technique

The vast majority of laparoscopies are performed under general anaesthesia. As with hysteroscopy, it is important to position the patient correctly on the operating table. The buttocks are placed at the edge of the table to allow full uterine anteversion. The legs are placed in leg supports with the thighs at about 45° to the horizontal while ensuring that the hips can be extended sufficiently to bring the thighs in line with the trunk should the need arise for any abdominal surgery.

After washing and draping the bladder is emptied with a catheter. Bimanual examination should be performed to assess the size and mobility of the uterus and to help identify any adnexal masses. The cervix is identified and grasped using a vulsellum forceps and the uterus then sounded and instrumented using a Spackman forceps. This allows uterine manipulation and the option of hydrotubation if tubal patency testing is required.

Table 37.5 Indications and contraindications for diagnostic laparoscopy.

Indications
Acute or chronic pelvic pain
Ectopic pregnancy
Pelvic inflammatory disease (including TB)
Endometriosis
Adnexal torsion
Subfertility
Congenital pelvic abnormality
Abnormal pelvic scan
Unexplained pelvic mass
Staging for ovarian malignancy
Absolute and relative contraindications
Mechanical or paralytic bowel obstruction
Generalized peritonitis
Diaphragmatic hernia
Major intraperitoneal haemorrhage (e.g. shock)
Severe cardiorespiratory disease
Massive obesity
Inflammatory bowel disease
Large abdominal mass
Advanced pregnancy
Multiple abdominal incisions
Irreducible external hernia

Laparoscopic entry

In the UK over 250 000 laparoscopic procedures are performed annually. The overall risk of a major complication is approximately 1 in 1000 [56]. The time of highest risk for injury is during entry to the peritoneal cavity, prior to its visualization. There are various entry techniques, the closed approach being most favoured by gynaecologists. The Royal College of Surgeons favours the open technique. However, there is no evidence to recommend one particular approach over another. A meta-analysis of over 350 000 closed laparoscopic procedures reported a risk of bowel damage of 0.4 per 1000 and of major vessel injury of 0.2 per 1000 [56]. A comparative review of open and closed techniques found a higher risk of bowel injury with the open technique and the risk of vessel injury was so low that no difference was observed [49].

Closed

The closed technique uses the Veress needle for insufflation of CO_2 to distend the abdomen so that the trocar can be inserted safely. A small incision is made vertically from the base of the umbilicus for insertion of the Veress needle. It should be sharp at the tip and the spring-loaded action and patency of the needle tested prior to insertion. A disposable needle is preferable. The operating table should be horizontal for the laparoscopic entry and the Veress needle should be inserted at 90° to the abdominal wall (Fig. 37.12). It should be pushed through the fascia and peritoneum so that two audible clicks are heard. The needle should not be moved laterally during or after insertion. Various tests have been employed to ensure correct placement of the needle but the most reliable one is to check that the initial insufflation pressure is low (e.g. <8 mmHg). Insufflation should be continued until the pressure reaches 20–25 mmHg and then the Veress needle is removed and trocar inserted through the same incision. This again is performed at 90° to the abdominal wall and a two-handed approach with steady pressure should be used. Once the peritoneal cavity is visualized, a 360° inspection of the peritoneal cavity performed and ancillary ports placed, the pressure is reduced to 12–15 mmHg.

Open

The open technique avoids the use of blind needle entry and allows the insertion of a blunt-tipped trocar under direct vision. Once the skin incision is made, the sheath is then opened under vision and a suture placed either side of the incision. These are then pulled into the suture holders on the cannula. On opening the peritoneum, the

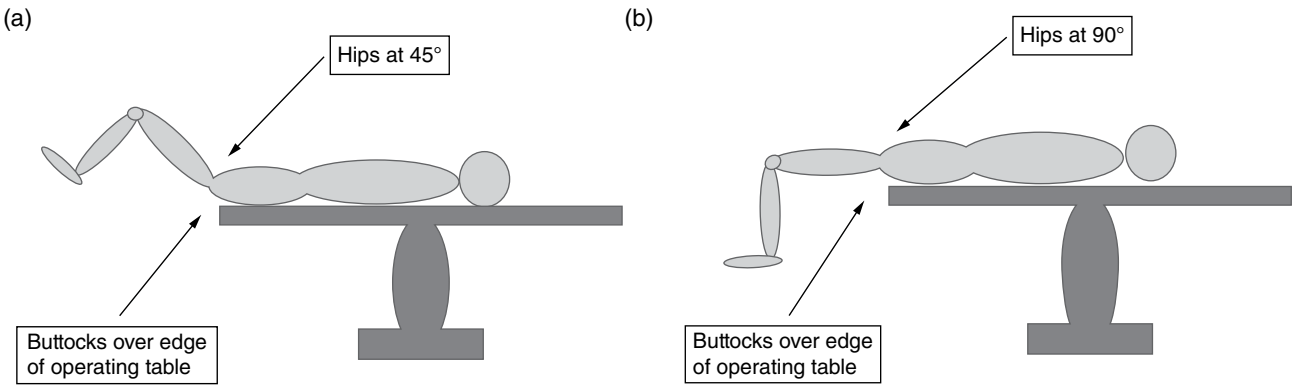

Fig. 37.12 Patient positioning during laparoscopy: (a) position during setting up and diagnostic laparoscopy; (b) position during operative laparoscopy which allows pelvic and abdominal surgery.

cannula is inserted under vision and the sutures then pulled tight to avoid gas leakage. The peritoneal cavity is insufflated and the blunt trocar removed and laparoscope inserted after achieving some abdominal distension. At the end of the procedure after removal of the cannula the sutures are tied together to close the sheath.

Direct entry and optical entry devices

Some practitioners advocate direct entry to the peritoneal cavity using a sharp-tipped trocar without the use of a Veress needle for prior insufflation. While it is not common practice in the UK, meta-analysis comparing it with the closed technique does not demonstrate any significant difference in major complications [57]. Some alternative devices have been developed to improve safety and ease of laparoscopic entry. These include the use of optical trocars, radially expanding trocars and, more recently, optical Veress needles [57–61].

Palmer's entry

Alternative entry sites may be required in patients with a history of previous surgery or a very low body mass index (BMI). Patients with a previous midline laparotomy have a risk of umbilical adhesions of 50% and those with a previous transverse lower abdominal incision have a risk of 23% [62]. Women with a very low BMI have a higher risk of vascular injury as the aorta may be as close as 2.5 cm below the skin surface. Palmer's point provides a safe entry point and is found three fingerbreadths below the left costal margin in the midline. This can be used for all patients except those with a history of surgery in the left upper quadrant or splenomegaly.

Culdoscopy and alternative entry sites

Palmer's point is the safest alternative site of laparoscopic entry for gynaecologists but other sites are often used. Suprapubic insertion can carry the risk of bladder injury and has a higher risk of failed entry [63]. Some gynaecologists use insufflation through the fundus of the uterus but this does increase the risk of ascending pelvic infection. Lastly, culdoscopy can be used but is not advised if there is a history of endometriosis, previous surgery or bowel pathology as the pouch of Douglas may be obliterated and rectal perforation is possible.

Inspecting the pelvis and abdomen

Once the peritoneal cavity is visualized a 360° inspection should be performed before placing the patient in a head-down tilt to displace bowel, allowing better access to the pelvis. Ancillary ports can then be placed under direct vision before lowering the pressure to 12–15 mmHg. For lateral port placement the inferior epigastric arteries should be identified and the ports placed away from these. These can be visualized just lateral to the lateral umbilical ligaments (obliterated hypogastric arteries).

Ending the procedure

Removal of the ports at the end of the procedure should also be done under vision and the sheath closed for any lateral ports over 7 mm or midline ports over 10 mm to avoid an incisional hernia. Gas is released and the peritoneal cavity completely deflated. By keeping the laparoscope inside the cannula as it is being withdrawn, it is possible to check that this port site is not bleeding and has not caught a loop of bowel or omentum. The skin is usually closed with absorbable sutures or glue.

Outcomes and complications

The benefits of laparoscopic surgery over laparotomic surgery include enhanced recovery (i.e. minimizing postoperative pain), quicker mobilization, reduced hospital stay and earlier return to work or normal functioning [64]. Diagnostic laparoscopy is a safe procedure with published complication rates of 2 per 1000 [65]. Most

injuries occur during the laparoscopic entry process (e.g. injury to the inferior epigastric vessels or major retroperitoneal vessels, bowel injury). Therefore care must be taken in planning the most appropriate type and site of entry. Injury to retroperitoneal vessels usually requires immediate laparotomy, whereas it is possible to manage bladder or bowel injury laparoscopically provided the perforation is small.

Operative laparoscopy

Laparoscopy is becoming the preferred route of surgery for an increasing number of conditions traditionally carried out by laparotomy (Table 37.6). This does not mean that laparoscopy is the best option or should be done in all these cases, and there is much debate about the more complex procedures in particular. In fact, only a few procedures have been subjected to prospective randomized comparisons (e.g. ectopic pregnancy, colposuspension, endometriosis, hysterectomy), so in many cases the decision about the route of surgery depends more on the particular skills of the gynaecologist, the presence of contraindications, and the relative risks of complications.

Table 37.6 Classification of laparoscopic procedures.

Basic
Diagnostic laparoscopy
Sterilization
Aspiration of ovarian cyst
Ovarian biopsy
Intermediate
Division of filmy adhesions
Linear salpingotomy or salpingectomy for ectopic pregnancy
Salpingostomy for infertility
Ovarian cystectomy
Excision of endometriomas
Salpingo-oophorectomy
Ovarian drilling with laser or diathermy for polycystic ovaries
Treatment of AFS stage I and II endometriosis
Myomectomy for pedunculated subserous fibroid
Laparoscopic-assisted vaginal hysterectomy without significant associated pathology
Advanced
Division of thick adhesions
Laparoscopic-assisted vaginal hysterectomy with significant associated pathology
Laparoscopic subtotal hysterectomy
Total laparoscopic hysterectomy
Myomectomy for intramural fibroids
Treatment of AFS stage III and IV endometriosis
Pelvic and aortic lymphadenectomy
Pelvic side wall and ureteric dissection
Presacral neurectomy
Incontinence procedures
Prolapse procedures

AFS, American Fertility Society.

Complications

Laparoscopic surgery appears to be inherently safer than conventional surgery [66]. However, although the overall complication rate is generally less, this is not inevitable [67] (Table 37.7). What is definitely true is that (i) major complications such as viscus injury and bleeding from retroperitoneal vessels are more common and (ii) many of the injuries are unfortunately not recognized during the procedure.

The reported rate of complications from major national surveys give an overall figure of 7–12.6 per 1000 procedures, with the more complex procedures having a greater risk of injury [68,69]. Comparing laparoscopic hysterectomy to other methods, there appears to be no significant difference in injury rates except for urinary tract injuries, which are higher [70]. About one-third to half of complications occur during the set-up phase, and one-quarter are not recognized during the surgery, including more than half of bowel and ureteric injuries [71]. The mortality after gynaecological laparoscopy is 4.4 per 100 000, which compares with a mortality of 150 per 100 000 for hysterectomy for benign indications [72].

Summary box 37.3

Laparoscopy

- Palmer's point is the safest entry point if there is concern about adhesions from previous surgery.
- Any instrument which produces heat (e.g. electrosurgery, laser, harmonic scalpel) should be used extremely carefully, if at all, close to vital structures such as bowel and ureter.
- The course of the ureter must be identified when performing any surgery on the pelvic side wall to avoid accidental injury.
- Most ureteric and bowel injuries are not recognized at the time of primary surgery. Excessive postoperative pain should be deemed as secondary to bowel injury unless proven otherwise.

Training in endoscopic surgery

Recognition of the importance of hysteroscopic and laparoscopic surgery to modern gynaecological care, coupled with a wish to improve and structure training in this area, has led surgical colleges such as the RCOG along with specialist societies such as the British Society

Table 37.7 Complications of laparoscopic surgery.

Intraoperative
Bowel injury
Vascular injury
Bladder injury
Ureteric injury
Surgical emphysema
Anaesthetic complications
Postoperative
Unrecognized visceral or vascular injury
Venous thromboembolism
Infection
Port site hernia

for Gynaecological Endoscopy and the American Association of Gynecologic Laparoscopists to provide structured training and accreditation packages for minimal access surgery. Alternatives to training on 'real' patients have been sought through simulation with the aim of enhancing the surgical proficiency of trainees, enabling them to ascend the 'learning curve', ideally prior to them being instructed and supervised on real patients. Basic simulation involves the use of plastic models or box trainers where fundamental surgical skills including dexterity, spatial awareness, hand–eye coordination and familiarity with instrumentation can be gained. Animal tissue or objects such as vegetables can be used to mimic procedures, for example pig bladders are good 'wet' models for hysteroscopic endometrial ablation or potatoes for fibroid resection [73]. Models and computerized simulators are now available to improve performance and virtual reality simulators provide a standardized environment allowing objective assessment of the performance of a trainee.

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Part 8

Childhood and Adolescence

38

Puberty and Its Disorders

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The transition from childhood to adolescence and adulthood is one of the most dynamic changes that occur during the life of a woman. The changes are not only physical, but emotional, psychological, behavioural and sexual, and all these changes encompass the maturation of the female to become reproductively capable. There is enormous variation between individuals in the processes involved in puberty but the five major physical changes are growth, breast development, pubic hair development, axillary hair development and, ultimately, menstruation. Whilst these changes occur temporally at different rates, there may be changes that occur prematurely or in a delayed fashion which alter this process. Finally, some girls may undergo pubertal change without menstruation and others may fail to enter puberty entirely.

Control of the onset of puberty

The age of onset of puberty in girls ranges from 8 to 13 years and the appearance of secondary sexual characteristics before this age is known as precocious puberty; failure of appearance of any secondary sexual characteristics after 13 years in girls is considered delayed puberty. A number of factors are known to play a role in the timing of puberty. Genetics has a clear and dominant role and there is a clear correlation between age at puberty of a woman and that of her daughter. However, there are racial differences, with black females showing an earlier age of pubertal onset compared with white [1]. Furthermore, nutritional status in all ethnic groups seriously influences the age of onset of puberty. Children living in areas of malnutrition have significantly delayed onset of puberty and transfer of these girls to a socioeconomically superior environment reduces the age of onset of puberty significantly [2]. At the other extreme, evidence now exists to suggest that a high body mass index (BMI) is linked to earlier age of maturation, and the relationship between body fat and the onset of puberty is linked to the release of leptin from adipose sites [3]. Leptin and kisspeptin would seem to act as a primary signal to the hypothalamus to allow puberty to commence [4].

The hypothalamus–pituitary–gonadal axis is active during fetal life and quiescent during childhood. It is the reactivation of this axis that leads to sexual maturation, although the mechanism by which this occurs remains unclear. The arcuate nucleus in the basal hypothalamus is responsible for secretion of gonadotrophin-releasing hormone (GnRH) into the hypothalamus–pituitary portal circulation. As puberty commences, the arcuate nucleus begins to secrete GnRH in a pulsatile manner, initially solely at night; however, as time progresses GnRH release adopts a low-frequency low-amplitude pulsatile pattern that starts to induce release of luteinizing hormone (LH) from the pituitary. The low-amplitude pulsatile pattern gradually extends to include daytime secretion and gonadotrophin levels themselves start to increase, reflecting higher pulse amplitude and increasing frequency of GnRH production. As the pattern of follicle-stimulating hormone (FSH) and LH release becomes established, so ovarian activity commences and initially this is disordered as it is uncoordinated. This means that there is follicular growth without coordinated ovulation and although estradiol levels start to rise, there is no evidence of ovulation. The ovary may have appearances that are multicystic due to this chaotic gonadotrophin stimulation and, over time (about 5–10 years), coordinated pulsatile release of GnRH leads to adult frequency of FSH release (approximately every 90 min). At this stage the ovulatory cycle is established.

From age 7, most girls will begin activation of adrenal androgen production, a phenomenon known as adrenarche. As with ovarian estradiol production, androgen production is initially at extremely low levels and increases over time.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Physical changes of puberty

Growth

An increase in vertical growth is the initial physical sign of the onset of puberty. Growth during infancy is relatively rapid until age 3–4 and then it rapidly decelerates when the childhood phase begins. Growth velocity during infancy is approximately 15 cm/year but in middle childhood, until the onset of puberty, slows to 5–6 cm/year. Interestingly, childhood growth rates are usually at their slowest in the 12–18 months immediately preceding puberty and thus if puberty is delayed this effect is exaggerated. At puberty, girls may reach a peak growth velocity of 10 cm/year and will gain approximately 25 cm of growth during puberty. Males in contrast have their growth spurt approximately 2 years later than females but eventually gain approximately 28 cm of added height. Once the final stage of growth velocity decreases, epiphyseal fusion occurs which prevents further growth. During the adolescent growth phase, bone density increases rapidly. Control of the growth spurt is primarily through growth hormone and its major secondary messenger insulin-like growth factor (IGF)-1. Estradiol plays an important role in the increased secretion of growth hormone during puberty, particularly in the early stages. As bone growth and height are maximally achieved, estradiol initiates epiphyseal fusion as it reaches its maximum towards the end of puberty. Thyroid hormone also plays a key role in growth and development as illustrated in severe childhood hypothyroidism, which results in a dramatic decrease in the velocity of growth.

Breast development

Although the growth spurt is usually the first sign of the onset of puberty, in females it is breast change that is usually used as an indicator of development. The initiation of breast development is known as thelarche and Tanner has classified this into five stages [5]. Breast growth is often unequal between the two breasts and Tanner stage 5 represents the mature end stage of breast development. This takes approximately 5 years.

Pubic and axillary hair growth

The adolescent development of female pubic hair occurs in conjunction with androgen release and it is the presence of androgen that determines both pubic and axillary hair growth. In approximately 20% of females, pubic hair growth may precede breast development.

Age of onset of puberty and subsequent health

Early age of menarche is associated with increased risk of breast cancer, cardiovascular disease, depression, behavioural disorders, diabetes and increased early mortality [6].

Summary box 38.1

Development of secondary sexual characteristics is characterized by:

- growth;
- breast development;
- pubic and axillary hair development;
- menstruation.

Precocious puberty

This phenomenon has received increased attention over the last few years with the belief that the age of onset of puberty has been falling. However, in accepting some guidance over age, the appearance of secondary sexual characteristics prior to 8 years should be considered precocious and prompt the clinician to carry out investigations.

Differential diagnosis of early onset of puberty

Premature adrenarche

This is due to the precocious increase in adrenal androgen secretion and is the most common cause of referral for precocious puberty. There seems to be an association between premature adrenarche and increased BMI [7], and in the overweight child referred with precocious puberty it is important not to assume that breast tissue is truly breast development and not adipose tissue. Signs of virilization such as clitoral enlargement, severe acne or increased muscle mass would lead to concerns of a virilizing ovarian or adrenal tumour or late-onset congenital adrenal hyperplasia (CAH). Late-onset CAH can present with pubic hair growth from the age of 1 and should be appropriately investigated.

Premature thelarche

Here, breast growth tends to appear earlier than age 8 and progresses very slowly and usually occurs in isolation of the growth spurt or any other secondary sexual characteristic. The cause of this condition remains unknown and although it is appropriate to exclude an ovarian cyst, these are rarely found.

Central precocious puberty

This refers to progressive breast development prematurely due to early activation of the hypothalamic–pituitary–ovarian axis and is accompanied by the growth spurt; pubic hair is frequently but not always found. This therefore mimics normal onset of puberty but at a very early age. A positive family history of early onset of puberty may be discovered where an *MKRN-3* gene

mutation can be found [6], but in the majority of cases the aetiology is idiopathic. Brain imaging is important, especially in girls with an onset of puberty before the age of 6, where 20% will be found to have a central nervous system (CNS) tumour.

Peripheral precocious puberty

This is far less common than central precocious puberty and is usually induced by excess production of sex steroids. Causes include the following.

- Androgen secretion from a virilizing adrenal tumour.
- Late-onset CAH.
- Oestrogen-secreting tumour causing rapid breast development. If a large ovarian cyst is present, this may be part of McCune–Albright syndrome, with associated classical features of irregular café-au-lait spots and cystic bone lesions called polyostotic fibroid dysplasia.
- Exposure to exogenous hormones, e.g. inadvertent ingestion of birth control pills by children causing excess levels of oestrogens; topical androgen exposure.

Investigations

A number of hormonal studies may be carried out in children with precocious puberty. However, they are of limited value and should be focused on specific clinical entities. LH may be used to distinguish between premature thelarche and central precocious puberty. FSH is of limited value. Estradiol is usually elevated in girls with precocious puberty and very high levels may suggest a tumour. Dehydroepiandrosterone is always elevated in children with premature adrenarche; testosterone when markedly elevated would suggest an androgen-secreting tumour; and in those children who are considered to have late-onset CAH, the diagnosis can be confirmed by measuring 17-hydroxyprogesterone. Radiological studies have somewhat limited value, although pelvic ultrasound may be used if an abdominal tumour is suspected and brain MRI may be used in those children with extreme precocious puberty, where the chances of a positive finding are around 20% and *MKRN-3* gene mutation should be screened for.

Treatment

The majority of girls with central precocious puberty do not require hormonal treatment, because most development is extremely slow and will result in maturity at an age which would be expected even though onset has been early. It is therefore prudent to review children with precocious development of secondary sexual characteristics 6 months later to see whether there has been rapid development of secondary sexual characteristics or not. In these cases, there is a high chance that sexual maturity will be reached by age 9 and therefore suppression of the progress of puberty would be sensible. While it is possible to suppress the pituitary, growth hormone cannot be suppressed and therefore treatment will result in adult height that is significantly greater than would be expected than if the child were left untreated. Children with extremely early puberty are often tall at the time of diagnosis and they tend to finish their growth early but achieve normal adult height. It is appropriate in these young children to suppress the development of secondary sexual characteristics. The standard treatment for central precocious puberty is GnRH analogues, which may be given nasally or by intramuscular injection. Three-monthly preparations are available and therefore four injections a year is all that is required to suppress puberty. GnRH analogues can then be administered until such time as the child reaches approximately age 11, when withdrawal will result in the normal resumption of pubertal changes. Peripheral precocious puberty, when due to an ovarian or adrenal tumour, requires surgical intervention; however, for girls with androgen excess due to CAH, suppression of the adrenal with hydrocortisone will reverse the changes.

Delayed puberty

Delayed puberty is usually considered when girls have no secondary sexual characteristics by age 13.5 years. Delay in puberty occurs in only 2.5% of the population but the identification of those children who do have a significant aetiology for this may be extremely important. It is mandatory to take a detailed history as the presence of chronic medical conditions or excessive athletic participation may be an explanation for delay in the onset of puberty. In females, approximately 50% will have constitutional delay with no explanation and the vast majority will commence the onset of puberty by age 18. A further 40% have been found to have a genetic defect [6]. In the presence of secondary sexual characteristics, menstruation ought to occur within 2 years of the establishment of Tanner stage 2 breast change. However, any child presenting at any stage because of concern over failure to establish either secondary sexual characteristics or menstruation should be investigated at that time. There are often extremely good reasons why a mother will bring her daughter for investigation and this often relates to the fact that a sibling completed her pubertal development at an earlier age or she herself went through puberty at an earlier age. While investigations may not lead to a diagnosis of abnormality, proof of normality is extremely important.

Summary box 38.2

Precocious puberty is usually idiopathic and requires treatment only if changes are accelerated such that completion of puberty will occur prematurely.

Aetiology of primary amenorrhoea

From a clinical point of view it is probably best to classify the aetiologies of primary amenorrhoea based on the presence or absence of secondary sexual characteristics. This is the basis of the classification system shown in Table 38.1. Finally, there is the group of patients in whom there is heterosexual development.

Normal secondary sexual characteristics

Imperforate hymen

The imperforate hymen may present at two stages of development. It may present in early childhood when the infant presents with a bulging hymen behind which is a mucocele, the vagina expanded by vaginal secretions of mucus. This is easily released and does not subsequently cause any problems following hymenectomy. It may also present in later life when a pubertal girl complains of intermittent abdominal pain, which is usually cyclical. The pain is due to dysmenorrhoea associated with the accumulation of menstrual blood within the vagina. The vagina is a very distensible organ and can allow quite large quantities of blood to collect in some cases. This condition is known as haematocolpos. It is very unusual for blood to accumulate within the uterus as the uterus is a muscular organ that is difficult to distend. When some blood does accumulate within the cavity it is known as haematometra. As the vaginal mass enlarges there may be associated difficulty with micturition and defecation. Examination will occasionally reveal an abdominal swelling and observation of the introitus will display a tense bulging bluish membrane, which is the hymen (see Chapter 35).

Transverse vaginal septum

In circumstances where the vagina fails to cannulate, the upper and lower parts of the vagina are separate. These girls present with cyclical abdominal pain due to the development of haematocolpos, but the thickness of the transverse vaginal septum means that the clinical appearance is very different from that of an imperforate hymen. Again, an abdominal mass may be palpable but inspection of the vagina shows that it is blind-ending and although it may be bulging, it is pink not blue. The hymenal remnants are often seen separately. Transverse vaginal septum may occur at three levels, known as a lower, middle or upper third septum. If the space between the upper and lower vagina is considerable, no introital swelling may be visible and rectal examination may disclose a mass. The management is very different from imperforate hymen and very careful assessment must be made before embarking on any management strategy (see Chapter 35).

Table 38.1 Classification of primary amenorrhoea.

Secondary sexual characteristics normal
Imperforate hymen
Transverse vaginal septum
Absent vagina and functioning uterus
Absent vagina and non-functioning uterus
XY DSD: androgen insensitivity
Resistant ovary syndrome
Constitutional delay
Secondary sexual characteristics absent
Normal stature
Hypogonadotrophic hypogonadism
Congenital
Isolated GnRH deficiency
Olfacto-genital syndrome
Acquired
Weight loss/anorexia
Excessive exercise
Hyperprolactinaemia
Hypergonadotrophic hypogonadism
46XX or 46XY DSD
Gonadal agenesis
XX agenesis
XY agenesis
Gonadal dysgenesis
Turner mosaic
Other X deletions or mosaics
XY enzymatic failure
Ovarian failure
Galactosaemia
Short stature
Hypogonadotrophic hypogonadism
Congenital: hydrocephalus
Acquired
Trauma
Empty sella syndrome
Tumours
Hypergonadotrophic hypogonadism
Sex chromosome DSD
Turner's syndrome
Other X deletions or mosaics
Heterosexual development
46 XX DSD
Congenital adrenal hyperplasia
Androgen-secreting tumour
Absent Müllerian inhibitor
46 XY DSD
5α-Reductase deficiency
Partial androgen receptor deficiency
Sex chromosome DSD
True hermaphrodite

DSD, disorders of sexual development.

Absent vagina and a functioning uterus

This is a rare phenomenon when embryologically the uterine body has developed normally but there is failure of development of the cervix. This leads to failure of the development of the upper vagina. The presenting

symptom is again cyclical abdominal pain, but there is no pelvic mass to be found because there is no vagina to be distended. Although a small haematometra may be present, retrograde menstruation occurs leading to the development of endometriosis and in some patients pelvic adhesions. Reconstructive surgery is possible.

Absent vagina and a non-functioning uterus

This is the second most common cause of primary amenorrhoea, second only to Turner's syndrome. Secondary sexual characteristics are normal as would be expected, as ovarian function is unaffected. Examination of the genital area discloses normal female external genitalia but a blind-ending vaginal dimple which is usually not more than 1.5 cm in depth. This is known as Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome and uterine development is usually absent. Often small uterine remnants (anlage) are found on the lateral pelvic side walls. It is important to remember that 40% of these patients have renal anomalies, 15% of which are major, for example an absent kidney, and there are also recognizable skeletal abnormalities associated with this syndrome [8] (see Chapter 35).

46 XY

There are a number of ways in which an individual may have an XY karyotype and a female phenotype, and these include failure of testicular development, enzymatic failure of the testis to produce androgen (particularly testosterone), and androgenic receptor absence or failure of function. In androgen insensitivity there is a structural abnormality of the androgen receptor, due to defects in the androgen receptor gene, which results in a non-functional receptor. This means that the masculinizing effect of testosterone during normal development is prevented and patients are therefore phenotypically female with normal breast development. This occurs because of peripheral conversion of androgen to oestrogen and subsequent stimulation of breast growth. Pubic hair is very scanty in these patients as there is no androgen response in target tissues. The vulva is normal and the vagina is usually short. (see Chapter 35).

Resistant ovary syndrome

This is an extremely rare cause of primary amenorrhoea, but it has been described. There are elevated levels of gonadotrophin in the presence of apparently normal ovarian tissue; patients do have some development of secondary sexual characteristics, but never produce adequate amounts of oestrogen to result in menstruation. It is believed that these women have an absence or malfunction of FSH receptors in the ovarian follicles, and are unable to respond properly to FSH.

Constitutional delay

A number of girls have constitutional delay and normal secondary sexual characteristics, but there is no anatomical anomaly and endocrine investigations are all normal. If serial sampling is carried out over a 24-hour period, these young women are found to have immature pulsatile release of GnRH. This is the sole reason for their constitutional delay. These young women will eventually menstruate spontaneously as the maturation process proceeds.

Summary box 38.3

The management of primary amenorrhoea should be based on the presence or absence of secondary sexual characteristics and treatment appropriately instituted.

Absent secondary sexual characteristics (normal height)

Isolated GnRH deficiency (olfacto-genital syndrome, Kallman's syndrome)

In this condition the hypothalamus lacks the ability to produce GnRH and there is therefore a hypogonadotrophic state. The pituitary gland is normal and stimulation with exogenous GnRH leads to normal release of gonadotrophins. This condition arises due to maldevelopment of neurones in the arcuate nucleus of the hypothalamus. These neurones are derived embryologically from the olfactory bulb and therefore some patients may also have failure of development of the ability to smell (anosmia). When this occurs it is known as Kallman's syndrome. The genetic basis of these two syndromes remains to be clarified. Currently, 24 gene mutations have been described but these only explain 60% of cases [9].

Weight loss/anorexia

Weight loss is more commonly associated with secondary amenorrhoea than primary amenorrhoea, but unfortunately it is increasingly apparent that younger girls may suffer from anorexia nervosa in the prepubertal state. This leads to failure of initiation of puberty and therefore a persistent hypogonadotrophic state exists. The growth spurt is not usually influenced by this, but secondary sexual characteristics are absent.

Excessive exercise

Over recent years it has become increasingly recognized that excessive exercise in pubertal children leads to decreased body fat content, without necessarily affecting body mass. Development of muscle contributes to overall weight, and therefore weight alone cannot be used to

decide whether this is an aetiology for their amenorrhoea via this mechanism. It is essential to obtain an assessment of body fat, which is much more discriminatory. Examples include ballet dancers, athletes and gymnasts and some of these girls may actually develop associated anorexia nervosa.

Hyperprolactinaemia

This is an unusual cause of primary amenorrhoea and is much more commonly seen as a cause of secondary amenorrhoea. There may be a recognizable prolactinoma in the pituitary, but often no apparent reason is seen. A CT scan may reveal evidence of a tumour.

Gonadal agenesis

In this condition there is complete failure of development of the gonad. These girls may be either 46XX or 46XY. The 46XX pure gonadal agenesis is an autosomal recessive disorder and genes other than those located on the X chromosome may be involved. The location of these genes remains unclear and in all these patients their genotype does not affect their phenotype, all of them being female. In 46XY or 45X/46XY, when the absence of testicular determining factor or its receptor is postulated as the cause of the failure of differentiation of the gonad, there is absence of testicular development. These individuals therefore fail to produce any androgen or Müllerian inhibitor. Therefore Wolffian structures regress and Müllerian structures persist and menstruation will occur when oestrogen is administered. The external genitalia reflect the normal female phenotype. Height is normal as the growth spurt occurs at the normal time. However, in those girls who are 46XY, the failure of production of androgen or oestrogen means that their long bones do not undergo epiphyseal closure at the normal time and therefore final height may be above normal.

Ovarian failure

These unfortunate girls have ovarian failure as a result of either chemotherapy or radiotherapy for childhood malignancy.

Galactosaemia

This inborn error of galactose metabolism is due to deficiency of galactose 1-phosphate uridyltransferase. The aetiology of the association between this enzyme and hypogonadotrophic hypogonadism is still to be clarified but patients with galactose 1-phosphate uridyltransferase deficiency have an acute toxic syndrome that causes ovarian cellular destruction thought to be due to the accumulation of galactose metabolites, which may induce programmed cell death (apoptosis).

Gonadal dysgenesis

The gonad is described as dysgenetic if it is abnormal in its formation. This encompasses a spectrum of conditions that vary with the degree of differentiation. The commonest is Turner's syndrome, where there is a single X chromosome giving a 45X karyotype. The missing chromosome may be either X or Y. There are other circumstances in which the gonadal dysgenesis may be associated with mosaicism and here two cell lines exist within one individual, the most common being 45X/46XX. Other structural chromosomal anomalies associated with gonadal dysgenesis involve deletions. If the deletion involves part of the long or short arm of the X chromosome, then loss of this genetic material may affect gonadal development. In Turner's syndrome ovarian development is normal until 20 weeks' gestation and at this stage oocytes are found in the ovaries. However, further maturation is impaired and massive atresia occurs during the latter part of pregnancy. The ovaries in most individuals consist solely of stroma and as there are no oocytes remaining, they are unable to produce oestrogen. There is a normal female phenotype and internal genital development is also normal. The loss of an X chromosome results in short stature as the genes for height are on the short arm of the X chromosome. In mosaicism the proportion of each cell line determines the manifestation of the condition. The higher the percentage of 45X cells, the more likely the features of Turner's syndrome.

In XY individuals, there may be a dysgenetic gonad associated with enzymatic failure and there is failure of testosterone production. This is usually associated with normal production of Müllerian inhibitor and therefore internal development leads to Müllerian atrophy, but the external genitalia fail to masculinize due to the lack of testosterone. Wolffian structures also fail to develop. The external phenotype is therefore female with a short vagina.

Absent secondary sexual characteristics (short stature)

Congenital infection

The most common aetiology in this group is hydrocephalus, as a result of childhood or neonatal infection. It is believed that this damages the hypothalamus and renders the GnRH-secreting neurones functionless, thereby creating a hypogonadotrophic hypogonadic state.

Trauma

Trauma to the skull base may also damage the hypothalamus and prevent GnRH secretion.

Empty sella syndrome

In this unusual condition, the sella turcica is found to be empty and there is congenital absence of the pituitary

gland or at least part of it, leading to failure to produce gonadotrophins. Thus secondary sexual characteristics do not develop.

Tumours

A number of tumours have been described in the pituitary which may lead to destruction of the gland. The most common of these is craniopharyngioma. This is a tumour which usually arises in childhood and results in destruction of the pituitary gland. These children present already on maintenance therapy for other hormonal deficiencies and are hypogonadotrophic.

Turner's syndrome

In pure Turner's syndrome the chromosome complement is 45X and here a syndrome of short stature and ovarian failure leads to the typical features, including growth failure, ovarian failure and cardiovascular abnormalities. These children usually present in infancy or early childhood, but rarely present in the teenage years because of failure of development of secondary sexual characteristics. More commonly, they may be referred from paediatric endocrinology clinics for induction of secondary sexual characteristics. Attempts to improve height have proved difficult to achieve.

Heterosexual development

Congenital adrenal hyperplasia

This occurs as a result of an enzyme deficiency in the steroid pathway of the adrenal gland (see Chapter 35) and children with this condition require steroid replacement [10]. It is imperative that there is good control of CAH at puberty if the children are to develop secondary sexual characteristics at the appropriate time. However, many of these girls fail to comply with their steroid therapy and are therefore uncontrolled. As a result of this, they fail to establish the normal process of puberty. It is therefore quite common to find that puberty is delayed and steroid control needs to be addressed.

Androgen-secreting tumour

This is extremely rare and arises when the ovary contains an arrhenoblastoma. Here excessive production of androgen results in virilization and removal of the tumour resolves the problem.

5α-Reductase deficiency

This form of XY female results from an enzyme deficiency that prevents the conversion of testosterone to 5-hydroxytestosterone, which is a necessary biochemical step in the development of the external genitalia in the male. The cloaca can only respond to this testosterone derivative and not to testosterone itself. The external genitalia are therefore female, but the internal genitalia are normal male as secretion of Müllerian inhibitor leads to Müllerian agenesis. These patients are therefore amenorrhoeic.

True hermaphrodite

In this condition the child has both testicular and ovarian tissue. This may occur either in isolation, such that there is an ovary and a testis in the same individual, or the gonad may contain both ovarian and testicular tissue. This leads to intersex problems at birth (see Chapter 35) and subsequently, if not resolved at birth, amenorrhoea due to androgen production at puberty, thereby preventing the development of the normal menstrual cycle.

Absent Müllerian inhibitor

There is a rare condition in which an XY individual may not produce Müllerian inhibitory substance, which means that the internal genitalia are female with persistence of the Müllerian structures; in addition, because testosterone is produced, the Wolffian structures also persist. In this extremely rare syndrome, there are male and female internal organs.

Evaluation and management

Having understood the classification of these syndromes, it becomes apparent that most of the conditions are rare and constitutional delay is undoubtedly the most common diagnosis. However, as the rest of the diagnoses have serious implications, the diagnosis of constitutional delay should only be made when all other syndromes have been excluded. It is vital to record a full history and examination, including most importantly the development of secondary sexual characteristics and height. Secondary sexual characteristics should be classified according to the staging system of Tanner. Individuals can then be classified according to their secondary sexual characteristics.

Normal secondary sexual characteristics

The presence of normal secondary sexual characteristics should alert the clinician to the presence of outflow tract obstruction. This is the most common cause of primary amenorrhoea in the presence of normal secondary sexual characteristics. It is thus appropriate to carry out investigations to make this diagnosis. It is inappropriate to perform any physical pelvic examination on these young adolescents and imaging techniques should be used. It is simple to arrange a pelvic ultrasound scan to assess the pelvic anatomy, and only in rare circumstances where this cannot be delineated by ultrasound should it be necessary to use MRI. If the uterus is absent, the karyotype should be performed; if this is 46XX, then MRKH

syndrome is the most likely diagnosis. If the chromosome complement is 46XY, the patient is, by definition, an XY female. If the uterus is present on ultrasound, then there may be an associated haematocolpos and haematometra and appropriate reconstructive surgery should be carried out. If the pelvic anatomy is normal, then it is essential to assess gonadotrophin and prolactin levels as this would tend to indicate a hypothalamic cause for the amenorrhoea, so-called constitutional delay. In some conditions the LH to FSH ratio may be elevated (see Table 38.1), and if resistant ovary syndrome is the diagnosis these gonadotrophin levels will be very elevated. Elevation of prolactin levels suggests a prolactinoma.

Management

Patients with an absent uterus require special psychological counselling and their care should be managed in a centre able to offer the complete range of psychological, psychosexual and gynaecological expertise. These young girls will have major problems with future sexual activity and their infertility and require very careful counselling. At the appropriate time a vagina may be created either non-surgically or surgically. In 95% of cases the use of vaginal dilators is successful (see Chapter 35).

In girls found to have an XY karyotype, again careful counselling is necessary about the malignant potential of their gonads, this being reported in around 30%. It is therefore necessary for them to have their gonads removed and this should be performed at a time when counselling is complete. Sharing the information of the karyotype with the patient should be entertained at the time when the relationship between the clinician and the patient warrants it. All patients should be informed of their karyotype when appropriate.

In outflow tract obstruction, surgical management depends on the level of obstruction. The simplest form is an imperforate hymen and in this condition a cruciate incision in the hymen allows drainage of the retained menstrual blood. Transverse vaginal septa are much more difficult to deal with and require specialist reconstruction to create a vagina which is subsequently functional (see Chapter 35) [8].

If investigations suggest that constitutional delay and development of secondary sexual characteristics is complete, there is no need to suggest any treatment other than annual review. These young women very much appreciate the opportunity to return for monitoring until such time as their menstruation commences. In some circumstances it may be useful to promote menstruation using the oral contraceptive pill for one cycle to prove that menstruation can occur and this can be extremely reassuring. If the diagnosis of resistant ovary syndrome is suspected, then diagnosis can really only be made by ovarian biopsy and subsequent histology confirming or illustrating the absence of oocytes. Finally, elevated prolactin levels should provoke the clinician to perform imaging of the pituitary fossa, probably best done by CT, to determine the presence or absence of a microadenoma and management subsequently with bromocriptine.

Absence of secondary sexual characteristics

In this situation, it is extremely important to make an assessment of the patient's height. If the patient is of normal height for age, measurement of gonadotrophin will reveal levels that are either low or high. Low levels of gonadotrophins confirm the diagnosis of hypogonadotrophic hypogonadism, while elevated levels should provoke the clinician to perform a karyotype. The 46XX patient will have premature ovarian failure, resistant ovary syndrome or gonadal agenesis, whereas the XY female will have 46XY gonadal agenesis or testicular enzymatic failure. If stature is short, gonadotrophin levels will either be low (associated with an intracranial lesion) or high (which, following a karyotype, almost certainly indicates Turner's syndrome or a Turner mosaic).

Management

In patients with hypogonadotrophic hypogonadism, treatment should be to manage any acquired problem. Weight-related amenorrhoea may require the input of specialist psychiatrists and psychologists. In isolated GnRH deficiency, seconadary sexual characteristics will need to be induced using hormone replacement therapy. These patients can be informed that they are fertile and that ovulation induction in the future can be performed. Hormone replacement therapy is essential and regimens exist for the induction of secondary sexual characteristics over 3–5 years. Oestrogen should be used alone for about 2 years, and then 2–3 years of gradual introduction of progestogens, thereby establishing normal breast growth over a time frame that is equivalent to normal. Any attempt to accelerate breast growth by using higher doses of oestrogen will result in abnormal breast growth and this should be avoided at all costs. Controversy currently exists over the choice of oestrogen, and the mode of administration. Increasing evidence would suggest that transdermal estradiol is the preferred medication, but compliance in teenagers is an issue. It is likely that both oral and transdermal regimens will continue for some time.

Patients with Turner's syndrome are a special group. Turner's syndrome occurs in 1 in 2500 female births and is the commonest cause of primary amenorrhoea. After the diagnosis is made, paediatric endocrinologists will use growth hormone as early as possible to improve final adult height attainment, and recent studies suggest this can be very successful [11]. Previous recommendations

to delay the induction of puberty until age 15 to maximize height attainment would seem unjustified. Induction of puberty should begin at age 12 and is associated with improved cognitive function. Recent studies have shown that patient's with Turner's syndrome have increased risk of thrombosis, and transdermal estradiol has been shown to be safer and to improve overall body composition [10]. Patients with an XY dysgenesis or enzymatic failure should have gonadectomies performed to avoid malignancy.

It must always be remembered that any chronic medical illness which prevents normal growth will result in delayed onset of puberty and these causes must be considered in any patient presenting in this way.

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39

Gynaecological Disorders of Childhood and Adolescence

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Gynaecological problems in the child and at adolescence can create anxiety in parents particularly, but fortunately very few of these disorders could be considered common or serious. However, when they do present, it is important that the clinician has an appropriate understanding of the various conditions so that the correct advice may be given to the patient. Management is frequently through simple means, with education and a sympathetic approach being essential. The disorders fall into two groups: those related to pre-puberty and those of adolescence.

Summary box 39.1

- Vulvovaginitis is usually due to non-specific bacterial contamination.
- Child sexual abuse should always be borne in mind.
- Treatment is usually through hygiene techniques.

Prepubertal child

Examination of the prepubertal child requires cooperation from both the patient and the mother and requires extreme sensitivity if a successful examination is to be carried out. Positioning the child for examination may require considerable time in order to gain the confidence of the child to allow examination. External examination should be performed with minimal handling of the vulva and, in order to expose the vaginal orifice, gentle traction on the buttocks to expose the vaginal opening can be performed. This can often be more effectively achieved by the mother rather than the physician. Specimens can be obtained using syringes with flexible catheters or occasionally a swab may be inserted if the hymenal orifice allows. In adolescents, vaginal examination should be avoided unless there is good evidence that it is absolutely necessary in order to make a diagnosis. Imaging is the preferred investigation if further information is required.

Vulvovaginitis

This is the only gynaecological disorder of childhood which can be thought of as common. Its aetiology is based on opportunistic bacteria colonizing the lower vagina and inducing an inflammatory response. At birth the vulva and vagina are well oestrogenized due to the intrauterine exposure of the fetus to placental oestrogen. This oestrogenization causes thickening of the vaginal epithelium, which is entirely protective against any bacterial invasion. However, within 2–3 weeks of delivery the resultant hypo-oestrogenic state leads to changes in the vulval skin, which becomes thinner, and the vaginal epithelium also becomes much thinner. The vulval fat pad disappears and the vaginal entrance becomes unprotected. The vulval skin is thin, sensitive and easily traumatized by injury, irritation, infection or any allergic reaction that may ensue. The lack of labial protection and the close apposition of the anus mean that the vulva and lower vagina are constantly exposed to faecal bacterial contamination. The hypo-oestrogenic state in the vagina means that there are no lactobacilli and therefore the vagina has a resulting pH of 7, making it an ideal culture medium for low-virulence organisms.

The complaint is usually of discharge which may be offensive, yellow or green in colour and parents often bring stained underwear as evidence of the condition. It occurs most commonly between the ages of 2 and 7 years. Examination of the vulva reveals inflammation and occasionally excoriation. Children also have the habit of exploring their genitalia and in some cases masturbating. This chronic habit may lead to vulvovaginitis, which can prove extremely difficult to treat. Vulvovaginitis may also occur in childhood in those who have an impaired

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Table 39.1 Causes of vulvovaginitis in children.

Bacterial
Non-specific (common)
Specific (rare)
Fungal (rare)
Candida of vulva only
Pinworms
Viral (rare)
Dermatitis
Atopic
Lichen sclerosus
Contact
Sexual abuse
Enuresis
Foreign body

local host defence deficiency due to the lack of an innate local protective response from neutrophils.

The causes of vulvovaginitis in children are shown in Table 39.1. The vast majority of cases are due to non-specific bacterial contamination, which in the majority of cases is due to poor hygiene. If a specific pathogen is isolated, for example *Streptococcus pneumoniae*, *Staphylococcus aureus* or *Haemophilus influenzae*, antibiotics can be considered. *Escherichia coli* is a contaminant from poor hygiene.

Candidal infection in children is extremely rare, although as a common cause of vulvovaginitis in the adult, it is a common misdiagnosis in children. *Candida* in children is usually associated with diabetes mellitus or immunodeficiency and almost entirely related to these two medical disorders. The presence of viral infections, for example herpes simplex or condylomata acuminata, should alert the clinician to the possibility of sexual abuse.

Vulval skin disease is not uncommon in children, particularly atopic dermatitis in those children who also have eczema. Referral to a dermatologist is appropriate in these circumstances. Lichen sclerosus is also seen in children and may cause persistent vulval itching. The skin undergoes atrophy and fissuring and is very susceptible to secondary infection.

Sexual abuse in children may present with vaginal discharge. Any child who has recurrent attacks of vaginal discharge should alert the clinician to this possibility. However, as non-specific bacterial infection is a common problem in children, the clinician must proceed with considerable caution in raising the possibility of sexual abuse. Only those bacterial infections related to venereal disease, for example gonorrhoea, may be cited as diagnostic of sexual abuse.

It is important that the clinician remembers that many girls suffer from urinary incontinence, particularly at night, and this creates a moist vulva allowing secondary infection by bacteria leading to vulvovaginitis.

Diagnostic procedures

There are two aspects of the diagnosis in this condition in children. The first is inspection of the vulva and vagina. It is imperative that the clinician has good illumination, particularly if there is a history of a vaginal foreign body. It is usually possible to examine the vagina through the hymen using an otoscope. This may well allow the diagnosis of a foreign body to be made.

The second aspect of diagnosis involves the taking of bacteriological specimens. This can be extremely difficult in a small child, as it is unlikely that the child will be cooperative. Any object which touches the vulva causes distress. The best way to take a bacteriological specimen is to use a pipette, which is much less irritating than a cottonwool swab. The pipette allows 1–2 mL of normal saline to be expelled into the lower part of the vagina, the tip of the pipette having been passed through the hymenal orifice. The fluid is then aspirated and sent for bacteriology. If a diagnosis of pinworms is to be excluded, then a piece of sticky tape over the anus early in the morning before the child gets out of bed will reveal the presence of eggs on microscopy.

Treatment

The vast majority of children do not have a pathological organism. The primary treatment in this group is advice about perineal hygiene. All parents of children with chronic vaginal disease are extremely worried that this may cause long-term detrimental effects to their daughters, particularly the fear of sexual dysfunction or subsequent infertility. There is no evidence that this is the case and therefore parents should be reassured that this is a local problem only. Management of these children is directed towards diligent hygiene of the perineum. The child must be taught to clean her vulva, particularly after defecation, from front to back, as this avoids the transfer of enterobacteria to the vulval area. After micturition the mother and child should be instructed to clean the vulva completely and not to leave the vulval skin wet, as this damp warm environment is an ideal culture surface for bacteria that cause vulvovaginitis. The mother must also be informed that vulval hygiene through daily washing should be performed, but that the soap should be gentle and not scented. Excessive washing of the vulva must be avoided as this leads to recurrent exfoliation and vulval dermatitis. During acute attacks of non-specific recurrent vulvovaginitis, children often complain of burning during micturition due to the passage of urine across the inflamed vulva. The use of barrier creams in these circumstances may be very useful. There is no evidence that topical oestrogen and antibiotic creams are of any benefit and should not be prescribed.

Foreign body

Foreign bodies are occasionally found in the vagina and may lead to vaginal discharge. In patients who have persistent vaginal discharge despite treatment, an ultrasound scan may detect a foreign body or, if a history of a foreign body is forthcoming, it is probably best to carry out an examination under anaesthetic and remove any foreign body at that time.

Vaginal bleeding

Vaginal bleeding in childhood is extremely rare and should always be treated with suspicion. The causes of genital bleeding in childhood include a vaginal foreign body, trauma, a neoplasm, premature menarche or urethral prolapse and the diagnosis can almost always be made on clinical inspection. Treatment should be appropriate but if trauma is suspected, sexual abuse must always be considered with referral to the appropriate team.

Labial adhesions

Labial adhesions are usually an innocent finding and a trivial problem, but its importance is that it is frequently misdiagnosed as congenital absence of the vagina. They occur most frequently in children aged between 3 months and 3 years, with a prevalence of about 3%. The physical signs of labial adhesions are easily recognized. It is believed that labial adhesions result from vulvar inflammation in a hypo-oestrogenic environment. The labia minora stick together in the midline, usually from posterior to anterior until only a small opening is left through which urine is passed. Similar adhesions sometimes bind down the clitoris. It may be difficult to distinguish the opening at all. The vulva has the appearance of being flat, and there are no normal tissues beyond the clitoris evident. However, a translucent, dark, vertical line in the midline where the adhesions are thinnest can usually be seen, and these appearances are quite different from congenital absence of the vagina. There are usually no symptoms associated with this condition, although older children may complain that there is some spraying when they pass urine. As late childhood ensues and ovarian activity begins, there is spontaneous resolution of the problem in 80% of children. In the majority of cases no treatment is required and the parents should be reassured that their daughters are entirely normal. In those children in whom there are some clinical problems, local oestrogen cream can be applied for about 2 weeks. There is complete resolution of the labial adhesions in 90% of cases. In the case of failure of oestrogen treatment, topical betamethasone 0.05% may be used and success in this group is about 70%. In the small minority of unresolved cases, surgical separation may be needed but this is extremely rare and should be avoided if possible as recurrence rates are high. Application of a bland barrier cream at this stage may help to prevent further adhesion formation. Finally, in taking a history it is important to establish that there has not been any trauma to the vulva, as very rarely labial adhesions may be the result of sexual abuse.

Summary box 39.2

- Labial adhesions are frequently misdiagnosed as congenital abnormalities.
- Treatment is advice about vulval hygiene.
- Topical oestrogen may be required.

Adolescence

The adolescent gynaecological patient usually presents with one of three disorders: (i) problems associated with the menstrual cycle and menstrual dysfunction, (ii) primary amenorrhoea (see Chapter 38); and (iii) teenage hirsutism.

Menstrual problems

As can be seen in the description of puberty (Chapter 38), menstrual cycles are rarely established as normal ovulatory cycles from the beginning of puberty. It is usual for cycles to be irregular and bleeding sometimes prolonged initially, and it can take some girls several years to achieve a regular menstrual cycle. It is extremely important that the gynaecologist understands this phenomenon, as the management of these cases is usually not active treatment but support and explanation to the mother and daughter.

Heavy menstruation

Trying to establish a history of heavy menstrual bleeding can be challenging in this age group. The patients have little experience and may well not understand normality. Expectation from maternal influence is also a contributory factor and so efforts should be made to interview the daughter alone if possible. Normal menstrual loss should not exceed 80 mL during a period, although in 5% of individuals it is heavier than this and causes no trouble. Getting some idea from frequency of pad change or bleeding in excess of 7 days is helpful. If a history of prolonged bleeding during surgical or dental procedures is obtained, screening for a coagulopathy is appropriate. Some reports suggest that 2–33% of these patients will have an underlying bleeding disorder [1].

The clinician is faced with attempting to assess whether the child truly has menstrual loss that is medically serious or menstrual loss that is irritating and distressing without being medically harmful. The best way to establish which of these is the case is by measuring the haemoglobin. If the haemoglobin level is normal (i.e. >120 g/L), then an explanation should be given to the mother and child of the normal physiology of menstrual establishment, that the manifestation of the menstrual loss is normal and that it may take some time for the cycle to be established. This condition requires no active treatment. However, it is imperative that the child is followed up at 6-monthly intervals until the pattern of menstruation is established, as reassurance is the most important part of the management process of these girls.

In those girls with haemoglobin levels between 100 and 120 g/L, menstrual loss is significantly more than normal. Again, an explanation is required so that the mother and daughter understand the cause of the problem and the child should be administered iron therapy to correct what will be mild iron deficiency anaemia. In terms of management, menstrual loss needs to be reduced and this may be achieved by using either progestogens cyclically for 21 days in every 28-day cycle or the combined oral contraceptive pill. It would be unusual for either of these therapies to be unsuccessful in controlling the menstrual loss. If these therapies are used, they should be stopped on an annual basis so that assessment may be made about whether or not the normal pattern of menstruation has been established by maturation of the hypothalamic–pituitary–ovarian axis. Thereafter, the child requires no further medication. Again, follow-up is essential if reassurance is to be given appropriately.

Finally, in the child with a haemoglobin of less than 100 g/L, it is obvious that serious anaemia has resulted from menstrual loss. This again requires an explanation but more urgent attention from a medical point of view. Blood transfusion should be given if clinically indicated. Progestogens are very much less likely to be effective in this group and the oral contraceptive pill is by far the treatment of choice. It may be given continuously for a short period of time so that the anaemia can be corrected using oral iron and then the pill may be used in the normal way so that menstrual loss occurs monthly, if desired.

Any girl who continues to have menstrual loss which is reported to be uncontrolled by these management strategies should have an ultrasound scan performed to exclude uterine pathology.

Menstrual suppression

Some girls will require menstrual suppression as a means of controlling their blood loss whilst hypothalamic maturity is attained. The most widely used is depot medroxyprogesterone acetate administered every 12 weeks. Amenorrhoea rates of 60% at 1 year and 70% at 2 years can be achieved. The newer alternative is the levonorgestrel intrauterine system which has similar rates of amenorrhoea. It requires a skilled physician to fit and in some cases this may require sedation. The newer, smaller device is not recommended, as amenorrhoea rates at 1 year are at best 12%. Oral progestogens are seldom used for long-term use and have significantly higher side-effect rates. Progesterone-only pills and etonorgestrel implants are not used, as menstrual suppression is not reliably achieved. The combined oral contraceptive pill is also used and the 30-μg pills are best. Continuous use can achieve amenorrhoea rates of 30–50%, although breakthrough bleeding is a common problem.

Summary box 39.3

- Menstrual disorders in adolescents are usually a reflection of normal physiology.
- Treatment should only be instigated if the adolescent is found to be anaemic.
- Treatments should be as simple as possible.

Primary dysmenorrhoea

Primary dysmenorrhoea is defined as pain which begins in association with menstrual bleeding. The management of dysmenorrhoea in the teenager is no different from that in the adult (see Chapter 34). The use of both non-steroidal anti-inflammatory drugs and the oral contraceptive pill is pertinent in teenagers, but again failure of these medications to control dysmenorrhoea should alert the clinician to the possibility of uterine anomaly and ultrasound imaging of the uterus should be performed to establish whether an anomaly exists.

Premenstrual syndrome

This is a difficult problem in adolescence as the psychological changes that are occurring during this time in a woman's life are often complex and stressful. It has been established that premenstrual syndrome is a stress-related disorder. Therefore in teenage girls undergoing puberty the stresses and emotional turbulence associated with this may, not surprisingly, lead to premenstrual problems. These are very difficult to manage and are usually not medically treated but addressed through the help of psychologists, if reassurance from the gynaecologist and an understanding of the process to the mother is not successful.

Hirsutism

Hair follicles cover the entire body and different types of hair are found in different sites. Androgens affect some

areas of the human body and increase hair growth rate and also the thickness of terminal hairs. Androgens are also involved in sebum production and may cause this to be excessive. In some women excessive hair growth may occur on the arms, legs, abdomen, breasts and back such that it constitutes the problem of hirsutism. This may also be associated with acne, which may occur not only on the face but also on the chest and back.

Differential diagnosis

Four major groups of disorders may cause hirsutism in adolescence (Table 39.2). Androgenic causes include congenital adrenal hyperplasia and its late-onset variant and also androgen-secreting tumours. The commonest group constitutes women with polycystic ovarian syndrome and while this is sometimes a difficult diagnosis to make in adolescents, it constitutes by far the greatest problem group. The diagnosis of XY gonadal dysgenesis is something that should be borne in mind when considering a child with hirsutism but a large percentage of patients have idiopathic hirsutism. It is important to remember that some girls will have a constitutional basis for their hirsutism and familial body hair patterns should be borne in mind when considering whether a young patient does in fact have hirsutism. Treatment for hirsutism is the same as in the adult and is covered in Chapter 47. In adolescence the mainstay in the treatment of androgen excess has been the oral contraceptive pill and without doubt this remains the main form of therapy. As the majority of these girls have some ovarian dysfunction, be that polycystic ovarian syndrome or an undefined problem, suppression of ovarian activity is very effective at lowering circulating androgens. If this is insufficient to gain control of hair growth, then the use of cyproterone acetate or spironolactone may be considered.

Table 39.2 Causes of hirsutism in adolescents.

Androgenic causes
Congenital adrenal hyperplasia
Classic
Late onset
Androgen-secreting tumours
Polycystic ovarian syndrome
Idiopathic
XY gonadal dysgenesis

In those patients who are not considered to have hirsutism due to a medical disorder, drug therapies may be ineffective and supportive measures may be necessary for cosmetic benefit. These include hair removal by shaving, waxing or electrolysis of those areas which are particularly cosmetically sensitive and also the use of bleaches to change hair colour, thereby gaining cosmetic benefit.

Summary box 39.4

- Hirsutism in adolescents is often idiopathic or cultural.
- Treatment, as in the adult, is by cosmetic means or endocrine manipulation.

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Further reading

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Part 9

Early Pregnancy Problems

40

Spontaneous Miscarriage

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Spontaneous miscarriage is responsible for considerable emotional and psychological trauma for patients. Recognizing and addressing this issue allows doctors to improve patient care. In the UK this has led to the development of early pregnancy units providing dedicated care for these women. These units also improve clinical care from a diagnostic and management standpoint.

In the UK, early pregnancy complications rarely result in maternal death. The triennial report (2005–2007) reported one maternal death from spontaneous miscarriage, although there were 18 direct deaths from maternal sepsis including deaths in early pregnancy [1].

With the advent of commercially available, sensitive and affordable pregnancy tests, women present at increasingly earlier points in pregnancy looking for reassurance and confirmation of viability. It is important that while their anxiety is recognized, we proceed along safe and accepted diagnostic pathways to avoid misdiagnosis. It is also important to recognize that pregnancy is a dynamic process and that a diagnosis of viability early on in the first trimester does not necessarily signify that the pregnancy will continue, although if a fetal heart pulsation is detected at 6 weeks, there is a 90% chance that the pregnancy will continue beyond the first trimester [2].

The rate of miscarriage varies depending on the gestation of pregnancy and maternal age (Fig. 40.1). Up to 50% of early pregnancies will fail within 4 weeks from the last menstrual period (LMP), so-called biochemical pregnancies. By 6 weeks' gestation, the rate is one in five pregnancies and by the second trimester that has fallen to 1 in 40 [3]. Simple scoring systems and models exist that can help advise women on the likely viability of their pregnancy using both clinical and ultrasound information [4].

Definition

Spontaneous miscarriage is defined as the spontaneous loss of a pregnancy prior to viability, taken legally in the UK as 23 weeks and 6 days of gestation. Beyond this gestation, fetal demise is classified as a stillbirth. The majority of first-trimester miscarriages occur below 12 weeks' gestation with an overall rate of around 20%. Second-trimester miscarriages are less common, accounting for 1–4% of all miscarriages [5]. While some second-trimester miscarriages can be explained as first-trimester losses where the diagnosis is only made in the second trimester, it seems likely that the causes are different.

Terminology has moved away from the word 'abortion', which is firmly associated with therapeutic abortion among the general public. The importance of accurately defining the different types of miscarriage is that it provides the bedrock upon which comparative research can be built, to better understand the relative benefits and outcomes of treatment options (Table 40.1).

The definitions can be seen to be a mixture of clinical and ultrasound-based diagnoses and are often suggested prospectively and confirmed retrospectively. Care must be taken when relying solely on a clinical diagnosis because this is often refuted by ultrasound. For example, in cases where the clinical picture suggests complete miscarriage, there will be ultrasound evidence of retained products in 45% of patients [6].

Aetiology

Although the causes of miscarriage in the first and second trimester appear different, there is inevitably some overlap, in addition to the occasional situation where

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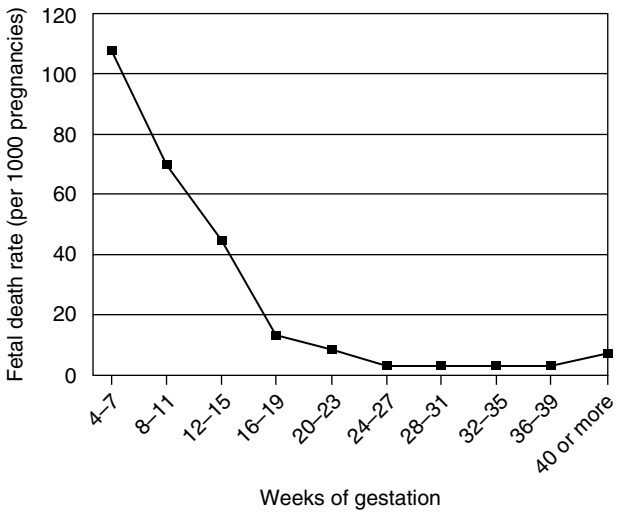

Fig. 40.1 Estimated rates of fetal mortality by weeks of gestation [1].

diagnosis of a first-trimester miscarriage is delayed until the second trimester.

First-trimester miscarriage

Evidence suggests that a significant proportion of miscarriages result from chromosomal and genetic abnormalities. It is likely that abnormal implantation has a role to play in some cases and this is an area of current research. It is thought that up to 95% of chromosomally abnormal embryos result in miscarriage [7]. The following chromosomal abnormalities are associated with miscarriage.

- Trisomies: 68%, mainly trisomy 16, 21 and 22.
- Triploidy: 17.1%.
- Monosomy: 9.8% (XO Turner's syndrome).

Other causes implicated in first-trimester miscarriage include the following.

- Maternal disease: antiphospholipid syndrome, diabetes, thyroid disease.
- Drugs: methotrexate, some antiepileptic drugs.

Table 40.1 Definitions of terms in common usage.

Term	Definition
Threatened miscarriage	Vaginal bleeding in the presence of a viable pregnancy
Inevitable miscarriage	Vaginal bleeding in the presence of an open cervical os and pregnancy-associated tissue still present*
Incomplete miscarriage	Vaginal bleeding that is ongoing where pregnancy tissue has already been passed but ultrasound suggests the presence of further tissue within the uterine cavity
Complete miscarriage	Clinical definition: cessation of bleeding and a closed cervix following miscarriage Ultrasound definition: an empty uterus with a falling hCG where an intrauterine pregnancy was previously confirmed
Missed miscarriage/early fetal demise	Miscarriage occurring in the absence of symptoms or minimal symptoms, where the empty gestation sac or non-viable embryo is still visible within the uterus
Recurrent miscarriage	Three or more consecutive early pregnancy losses
Biochemical pregnancy loss	Pregnancy not located on scan where there is/has been a positive pregnancy test which subsequently becomes negative
Empty sac	A gestation sac with absent or minimal structures
Pregnancy of unknown location (PUL)	Positive pregnancy test where the location of the pregnancy is not currently identifiable using transvaginal ultrasonography†
Pregnancy of unknown viability (PUV)	The presence of intrauterine structures confirming the location of the pregnancy, but where no embryo heartbeat has been seen to confirm its viability. By definition the measurements of the embryo or gestation sac do not meet the criteria for the diagnosis of a missed miscarriage. In this circumstance a repeat scan at an interval is required to confirm viability (see section on ultrasound diagnosis)

*Extreme caution needs to be taken before making this diagnosis as it can be easy to mistake a parous os (external os open as a result of previous vaginal delivery) and the open cervix of inevitable miscarriage. It is a term probably best avoided.
†This is an ultrasound-based classification and not a diagnosis in itself. Further investigations may reveal an intrauterine pregnancy, an ectopic pregnancy or a miscarriage.

- Uterine abnormalities: the role of fibroids is uncertain but they may be implicated [5].
- Infection: varicella, rubella and other viral illnesses.

Second-trimester miscarriage

- Cervix: cervical injury from surgery, cone biopsy and large loop excision of the transformation zone [8].
- Infection: may occur with or without ruptured membranes. May be local to the genital tract or systemic.
- Thrombophilias.
- Uterine abnormalities: submucous fibroids and congenital distortion of the cavity (uterine septa) may be implicated.
- Chromosomal abnormalities: these too may not become apparent until the second trimester.

Summary box 40.1

It is important to recognize that pregnancy is a dynamic process and although at any point viability of a pregnancy can be confirmed, it does not necessarily imply that the pregnancy will continue.

Diagnosis

Diagnosis is based on appropriate history-taking, examination and suitably directed diagnostic tests.History-taking

- LMP: remember to confirm length of cycle, regularity, use of contraception around time of conception, any of which can alter the presumed timing of ovulation (assumed as 15 days after LMP for the purpose of calculating gestation) and hence result in overestimation or underestimation of gestational age.
- Symptoms: pain and/or bleeding. It used to be taught that the presentation of one before the other helped differentiate between ectopic and intrauterine pregnancy but it is clear that this is not the case. The location and nature of the pain is also a poor prognostic indicator. Urinary frequency or diarrhoea can be subtle signs of peritoneal irritation due to intraperitoneal bleeding, associated with ectopic pregnancy.
- Past obstetric and gynaecological history may provide evidence for risk factors for other non-pregnancy related causes of bleeding or indicate risk factors for ectopic pregnancy such as sexually transmitted infection or pelvic inflammatory disease. It is important to ascertain the last smear date and any history of cervical abnormality/colposcopic treatment.
- Past medical history: poorly controlled diabetes mellitus is known to be associated with miscarriage and other chronic illnesses may also be implicated, although these tend to be associated with reduced fertility (capacity to conceive) rather than fecundity (capacity to maintain a pregnancy).
- Medication: prescribed, non-prescribed and recreational.

Examination

General examination to assess the immediate well-being of the patient is mandatory. Young women can mask blood loss and significant decompensation is a late sign and therefore attention should be given to more than just blood pressure, for example tachycardia and/or a raised respiratory rate. Pallor, a reduced conscious level or reduced capillary return are all important. It is useful to note that peritoneal distension may also result in bradycardia.

Abdominal palpation

- Determine the fundal height: the uterus generally becomes palpable above the pelvic brim at 12 weeks' gestation, though this will be affected by multiple pregnancy and the presence of uterine fibroids.
- Evidence of other pelvic masses which may explain the presence of pain, for example ovarian torsion, degenerating fibroids.
- Evidence of intra-abdominal bleeding: generalized tender distension of the abdomen.
- Confirm location of pain.

Vaginal examination

Vaginal examination will reveal whether the cervix is open or if products of conception are identifiable at the cervical os. If so, the relevant tissue should be removed and sent for histopathological diagnosis, as on rare occasions a decidual cast (in the presence of an ectopic pregnancy) can mimic products of conception. Products of conception cannot be confirmed on macroscopic inspection unless fetal parts are seen. Where there is a history of complete miscarriage, 45% of patients will show ultrasound evidence of retained products and up to 6% will have an ectopic pregnancy [9].

Speculum examination of the vagina is also a good opportunity to inspect the cervix and vagina to exclude local causes of blood loss in addition to the quantity of loss at presentation, as patient description can be misleading.

Differential diagnosis (Table 40.2)

Hydatidiform mole is a relatively rare but important complication of pregnancy which should be considered

Table 40.2 Differential diagnosis.

	Uterine size*	Cervix	Blood loss	Pain
Threatened miscarriage	Equivalent to dates	Closed	Any	Variable
Incomplete miscarriage	Smaller than dates	Open	Usually heavy	Present
Complete miscarriage	Smaller than dates	Closed	Previously heavy, now settling	Previously present, now absent
Missed miscarriage	Variable	Closed	Variable	Variable

*Remember that the presence of fibroids may give a distorted assessment of uterine size or large body habitus may make this difficult to accurately assess.

in all cases of miscarriage and, where possible, tissue sent for histological confirmation of products of conception and appropriate follow-up arranged. It is clear, however, that in the presence of spontaneous miscarriage at home that this is not possible. It is likely that in these cases, where there is clinically significant molar change, women will present with ongoing bleeding and the diagnosis considered at this stage. There is no evidence that delay in the diagnosis of molar pregnancy increases the likelihood of molar invasion.

Diagnostic tools

Ultrasound

Ultrasound has progressed enormously since its first use in pregnancy in 1967. It has a pivotal role in the diagnosis of miscarriage. Transvaginal ultrasound has helped identify the early ultrasonographic features seen in a normal early intrauterine pregnancy (Fig. 40.2). The ultrasound landmarks visible on transvaginal scan are as follows.

- Week 5: visible gestation sac.
- Week 6: visible yolk sac.
- Week 6: visible embryo.
- Week 7: visible amnion.

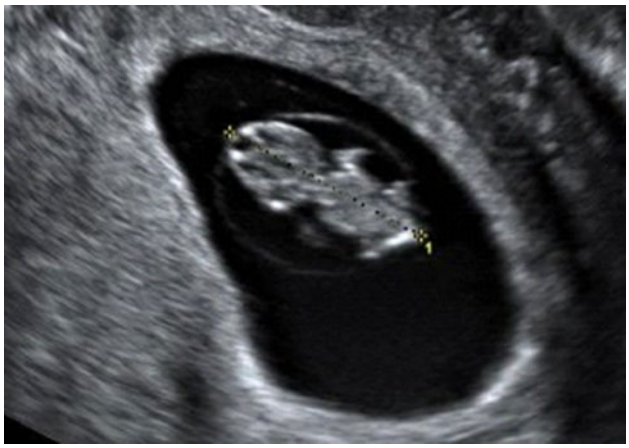

Fig. 40.2 A viable fetus of 7 weeks' gestation with amniotic sac clearly visible.

Failure to identify these landmarks at the presumed gestational age may not necessarily indicate a miscarriage. Dating in early pregnancy is taken from the first day of the LMP and conception presumed to have taken place on day 15. Clearly this leaves a large window for inaccuracy due to varying cycle lengths, delayed ovulation, variability in the ovulation–implantation window and inaccurate recall of menstrual dates.

In the current climate of sensitive urinary pregnancy tests where women are presenting at increasingly earlier gestations with the expectation of reassurance of a viable intrauterine pregnancy, it is imperative that care is given to obtain the correct diagnosis. In these scenarios it may be a number of weeks before a viable pregnancy can be visualized due to natural variation in the appearance of structures and the inevitable uncertainty that surrounds dating.

In 2011, new research demonstrated that previously used criteria for the ultrasound diagnosis of missed miscarriage were unsafe, resulting in an unacceptably high false-positive rate. This implied that a number of pregnancies were being incorrectly diagnosed as missed miscarriages with the potential for the termination of wanted intrauterine pregnancies [10]. Following this, a conference of the Society of Radiologists in Ultrasound in the USA resulted in a consensus paper in the *New England Journal of Medicine* [11] that proposed sensible guidelines for the diagnosis of pregnancy failure based on the 2011 paper by Abdallah *et al.* [10].

Subsequently, the UK National Institute for Health and Care Excellence (NICE) [12], the Royal College of Obstetricians and Gynaecologists (RCOG) [13] and the American College of Radiology [14] have all changed their ultrasound criteria for the diagnosis of miscarriage, which are now based on:

- an empty gestational sac of mean sac diameter (MSD) ≥25 mm; *or*
- an embryo with a crown–rump length (CRL) ≥7 mm and no heartbeat (Fig. 40.3).

Where neither of these criteria has been satisfied on the initial ultrasound scan, the pregnancy should be

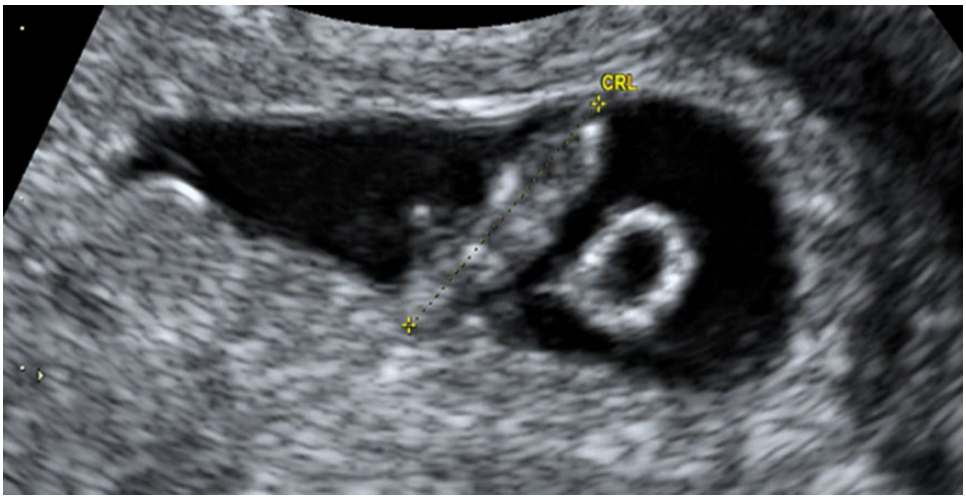

Fig. 40.3 Ultrasound diagnosis of miscarriage must be based on either a mean sac diameter of ≥ 25mm or an embryo with crown-rump length (CRL) of ≥ 7mm.

classified as a pregnancy of unknown viability (PUV) and an ultrasound scan then performed at an interval in order to definitively comment on viability. When considering the optimal interval between ultrasound scans for the diagnosis of miscarriage to be made with certainty, in the study by Preisler *et al.* [15] a minimal time interval of 7 days was 100% specific for miscarriage where the initial scan identified a pregnancy with an embryo of less than 7 mm with no heart activity or a pregnancy with no embryo and an empty gestational sac with an MSD of 12 mm or more.

Where the initial scan identified an empty gestational sac with an MSD of less than 12 mm, a minimal time interval of 14 days was 100% specific for miscarriage if sac size had not doubled. Although the data for these criteria were scanty, this paper also showed that initial scans demonstrating an embryo with a CRL of 3 mm or more with no heartbeat or an MSD of 18 mm or more at 70 days (10 weeks) or older of gestational age was very highly predictive of a missed miscarriage. This has been suggested as a possible new additional criterion to the guidelines for the definitive diagnosis of missed miscarriage [15].

Summary box 40.2

New ultrasound criteria for the diagnosis of miscarriage on initial scan

- An empty gestational sac of MSD ≥25 mm, *or*
- An embryo with a CRL ≥7 mm and no heartbeat.

These findings should be confirmed with a second opinion or repeat scan performed 7 days after the initial scan.

Where scan measurements lie close to the cut-off points, it is prudent to err on the side of caution as there is evidence of significant intra- and inter-observer error even in the case of experienced sonographers [16].

Serum β-human chorionic gonadotrophin

There is little evidence to support the role of β-human chorionic gonadotrophin (β-hCG) in determining viability after the visualization of an intrauterine gestation sac and yolk sac, as considerable variation exists in the normal increase in β-hCG and occasionally falls are identified in the presence of subsequently viable pregnancy. Furthermore, the effect of twin pregnancy on the rise in β-hCG is uncertain. However, serum measurements of β-hCG do have a role in managing pregnancy of unknown location (PUL): a rise of 66% over 48 hours is associated with a viable intrauterine pregnancy; levels between a 65% increase and a 13% decrease are associated with a possible ectopic pregnancy; and a decrease of more than 13% is associated with a failing pregnancy [17]. Furthermore, it is important to recognize that tests are rarely exactly 48 hours apart due to timing of presentation and this will determine interpretation as well. Mathematical prediction models have also been developed that assign PUL as either a high or low risk of complications [18].

Progesterone

The main role of progesterone lies in the assistance it provides in determining the likely outcome of PUL rather than in diagnosing miscarriage. A meta-analysis of cohort studies into the accuracy of single progesterone measurement to predict early pregnancy outcome in symptomatic women revealed that a progesterone level

equal to or below 10 ng/mL predicted a non-viable pregnancy in 96.8% of cases [19].

Management

Management options fall into three groups, medical, surgical or expectant. Factors to be taken into account when discussing these options with patients include the following.

- Type of miscarriage.
- Gestation at which miscarriage is diagnosed: care needs to be taken where miscarriage is diagnosed at later gestations. At 11 weeks and above where there is a missed miscarriage and an embryo measuring significantly less than expected, these patients are at risk of heavier bleeding compared with earlier gestations and should be warned of such. Surgical evacuation may be preferable as the first line of treatment. If the preference is for medical evacuation, then this may be more appropriately carried out in an inpatient setting.
- Facilities available at individual units: out-of-hours access to emergency care and advice in case of heavy bleeding with medical or expectant management; capacity of units to offer inpatient medical management.
- Medical history, for example cardiac disease and sickle cell anaemia. The risks are increased in the presence of haemorrhage and so generally among these patients, surgical evacuation, being associated with less blood loss, is the most appropriate choice. The same applies if there is evidence of infection.
- Patient choice.
- Cost.
- NICE guidance [20].

Expectant management

Historically, women have been offered surgical management as the mainstay of miscarriage treatment. However, the recognition of potentially serious risks associated with curettage has resulted in a move away from intervention and a wider choice of options being offered to women. Up to 85% of miscarriages will resolve spontaneously within 3 weeks of the diagnosis. The rate of success in part depends on the length of delay in intervention. There is also debate as to how to confirm the diagnosis of complete miscarriage, whether by ultrasound or symptoms. It seems likely that the best course to take involves both rather than relying solely on a defined thickness of endometrium. Furthermore, the regularity and vascularity of the contents of the endometrial cavity are probably more important than the thickness alone. Again, the lack of agreement in defining completeness of a miscarriage hampers efforts to assess effectiveness of treatment options.

Patient satisfaction with expectant management depends on appropriate patient selection (earlier gestation/singleton pregnancy/social circumstances) and counselling. Patients should be made aware of what to anticipate (pain and bleeding) and given advice regarding analgesia and what to do with the tissue passed. The advice should be backed up with written information and contact details in case of concern or complications. The recent NICE guidance advocates that all women should be offered expectant management as first line unless there are extenuating circumstances. However, this has been criticized as reducing patient choice [21] and most clinicians would take the view that when the clinical circumstances permit, the management will largely be a matter of patient preference.

Surgical management

Surgical management involves evacuation of the uterus by dilation and suction curettage. 'Surgical management of miscarriage' or SMM is the term in general usage in the UK, having replaced 'evacuation of retained products of conception'. The procedure can be performed under general or local anaesthesia depending on local experience. Cervical dilation can be assisted by cervical priming with prostaglandin or misoprostol a minimum of 1 hour prior to the procedure and is strongly recommended where the woman has not had a previous vaginal delivery [1]. This is believed to reduce the pressure required to dilate the cervix and hence risk of failure of the procedure, retained products and uterine perforation. Curettage is usually safe but it is important to counsel women about the associated risks. These include the risk of general anaesthesia (if relevant), the risk of infection or retained products (3–5%) and the potential bleeding in association with this, and the 0.5% risk of uterine perforation which could lead to other organ damage and the need to progress to laparoscopy or laparotomy in those circumstances. Patients should be reassured that in the presence of a uterine perforation and the absence of additional complications, the implications for future fertility are negligible. Asherman's syndrome, where intrauterine synechiae develop and interfere with conception, used to be said to arise from over-vigorous curettage. However, there is little supporting evidence for this. Manual vacuum aspiration is an alternative option for surgical management of miscarriage. The procedure uses a vacuum aspirator to gently empty the contents of the uterus, using local anaesthesia. Used frequently in developing settings, it has started to gain favour universally for the management of retained products, where patients wish to avoid

the risks associated with medical management and a general anaesthetic.

Medical management

Medical management of miscarriage involves using uterotonic therapy alone or in conjunction with anti-hormone therapy to achieve evacuation of the uterine cavity.

Available uterotonic agents include gemeprost and misoprostol, which are both prostaglandin (PG)E_1 analogues. Gemeprost is licensed for use in the management of uterine evacuation. It requires refrigeration and is more expensive than misoprostol. Misoprostol is not licensed for use, can be stored at room temperature and costs significantly less. It can also be given orally as well as per vagina or rectum. Side effects include nausea, vomiting and diarrhoea, which can be problematic. PGE_1 analogues can be used in conjunction with anti-hormone therapy. Mifepristone, an anti-progesterone, was previously used to sensitize the uterus to the effects of uterotonics and improve complete evacuation rates, but recent NICE guidance does not support its use [20]. There is no evidence to support the use of other uterotonics such as ergometrine, oxytocin or other prostaglandins in this situation.

Overall, the success rate of medical management (72–93%) is similar to that of expectant management (75–85%) [22] but medical management has the advantage that patients can control the course of events by timing medication to allow miscarriage to take place. However, these success rates are dependent on how much time has elapsed following treatment: the longer the wait, the higher the success rate.

When compared with surgical management, there is significantly more associated blood loss but no increased requirement for blood transfusion [23,24]. Reassuringly, differing rates of infection between the three options are not statistically significant.

Summary box 40.3

- Expectant, medical and surgical management of miscarriage are all viable options for the management of first-trimester miscarriage and choice should be based on patient wishes as well as the clinical situation.
- The incidence of infection is not significantly higher in any management group.
- Blood loss is heaviest in medical and expectant management compared with surgical, though with no increased risk of blood transfusion, and this should be taken into account when counselling certain groups, for example patients with sickle cell anaemia, in whom blood loss should be kept to a minimum.

Rhesus status

Despite the absence of antigens on the surface of embryonic red blood cells until 12 weeks' gestation, there is concern regarding the possibility of sensitization of rhesus-negative women from early pregnancy events. Current guidelines from the British Blood Transfusion Society and the RCOG are quoted here.

Spontaneous miscarriage

Anti-D immunoglobulin should be given to all non-sensitized RhD-negative women who have a spontaneous miscarriage after 12 weeks of pregnancy. Published data on which to base recommendations in earlier miscarriages are scant. There is evidence that significant fetomaternal haemorrhage only occurs after curettage to remove products of conception but does not occur after complete spontaneous miscarriage [25,26]. Anti-D immunoglobulin should therefore be given when there has been an intervention to evacuate the uterus. On the other hand, the risk of immunization by spontaneous miscarriage before 12 weeks' gestation is negligible when there has been no instrumentation to evacuate the products of conception and anti-D immunoglobulin is not required in these circumstances. Anti-D immunoglobulin is also recommended in cases of ectopic or molar pregnancies and in cases of uterine bleeding where this is repeated, heavy or associated with abdominal pain.

NICE guidance recommends anti-D prophylaxis of 250 IU for women with early pregnancy loss undergoing surgical procedures. It recommends that women should not be offered prophylaxis for:

- medical management for ectopic pregnancy or miscarriage;
- threatened miscarriage;
- complete miscarriage;
- PUL.

There is no need to perform a Kleihauer test to assess the volume of fetomaternal haemorrhage prior to prophylaxis.

Threatened miscarriage

Anti-D immunoglobulin should be given to all non-sensitized RhD-negative women with a threatened miscarriage after 12 weeks of pregnancy. Where bleeding continues intermittently after 12 weeks' gestation, anti-D immunoglobulin should be given at 6-weekly intervals. Evidence that women are sensitized after uterine bleeding in the first 12 weeks of pregnancy where the fetus is viable and the pregnancy continues is scant [27], although there are very rare examples. Against this background,

routine administration of anti-D immunoglobulin cannot be recommended. However, it may be prudent to administer anti-D immunoglobulin where bleeding is heavy or repeated or where there is associated abdominal pain, particularly if these events occur as gestation approaches 12 weeks.

It is recommended that a Kleihauer test be performed to assess the quantity of fetomaternal haemorrhage after 20 weeks.

Summary box 40.4

Anti-D immunoglobulin is required in the following circumstances for non-sensitized RhD-negative women.

- Spontaneous miscarriage at 12 weeks' gestation and beyond.
- Miscarriage at any gestation where there has been surgical intervention or, if spontaneous, where the bleeding has been heavy or repeated.
- Threatened miscarriage at 12 weeks and beyond. If repeat episodes, repeat anti-D at 6-week intervals.

Psychology and counselling

Pregnancy loss at any gestation is an emotional time for women and it is important that counselling reflects that. Recent data have confirmed high levels of depression and anxiety in women following a miscarriage or ectopic pregnancy. It has also shown that a significant proportion (28%) of women 3 months after such an event screened positive for post-traumatic stress disorder [28]. The language used should be sensitive, avoiding terms such as pregnancy failure or abortion, which in layman's terms implies therapeutic abortion and has no place in the terminology relating to miscarriage. Where possible, all information given should be supported by written material as, again, it is recognized that while as doctors we believe our counselling to have been comprehensive, in reality a distressed patient may absorb very little. It is quite possible that any information given will need to be repeated before it is fully understood. Early pregnancy services should allow for the provision of counselling and psychological treatment when required.

Conclusion

Miscarriage is unfortunately a frequent outcome of pregnancy. Guidelines have been refined to ensure that the use of ultrasound to make a diagnosis of miscarriage based on measurements of the gestation sac or embryo are safe. Patient management should be focused on making the experience as bearable as possible by taking time to explain and discuss options, thus allowing patients to feel supported and in control. Within the framework described, patients should be allowed to make choices best suited to them. Information should be reinforced with a written explanation for patients to read, using a format that is easy to understand. Psychological sequelae to miscarriage are not uncommon and clinicians should be alert to the fact that depression, anxiety and post-traumatic stress disorder may occur in these women.

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41

Recurrent Miscarriage

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Definition

Recurrent miscarriage has several definitions. The Royal College of Obstetricians and Gynaecologists (RCOG) defines recurrent miscarriage as the loss of three or more consecutive pregnancies before viability [1]. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. However, advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation. Hence some late second-trimester miscarriages can also be considered as extreme preterm labour. At the other end of the spectrum is the issue of biochemical pregnancy losses. The European Society of Human Reproduction and Embryology defines biochemical losses as a transient positive pregnancy test without ultrasonic visualization of the pregnancy [2]. Miscarriage can be further classified, on ultrasound findings, into loss of an empty gestation sac (loss of pregnancy before 10 weeks' gestation) or loss of fetus (loss of a pregnancy after visualization of fetal heart activity) [2] (Table 41.1).

Despite attempts at standardization of definitions, some investigators consider two consecutive losses as a recurrent miscarriage, as two losses have been found to increase the chance of a subsequent pregnancy ending in miscarriage [3].

Epidemiology

Approximately 15% of all pregnancies that can be visualized on ultrasound end in pregnancy loss [4]. Three or more losses affect 1–2% of women of reproductive age and two or more losses affect around 5% [4]. Despite extensive investigation of women with three or more miscarriages, the cause of recurrent pregnancy loss remains unknown in the majority of cases [5].

Advancing maternal age is associated with miscarriage. Age-related miscarriage rates are as follows: 12–19 years, 13%; 20–24 years, 11%; 25–29 years, 12%; 30–34 years, 15%; 35–39 years, 25%; 40–44 years, 51%; and 45 or more years, 93% [6]. This is because with increasing maternal age there is a decline in both the number and quality of the remaining oocytes. Paternal age over 40 also increases the risk.

An increasing number of previous miscarriages also adversely affects the risk of future miscarriage [5]. A history of a live birth followed by consecutive miscarriages does not reduce the risk of further miscarriage substantially [5]. Being both underweight and obese has been associated with recurrent miscarriage [7]. A body mass index (BMI) over 30 kg/m^2 is an independent variable with significant increase in miscarriage risk (odds ratio of 1.7–3.5).

Summary box 41.1

- Recurrent miscarriage is defined as three consecutive pregnancy losses.
- Miscarriages should be further classified on the basis of ultrasound findings into biochemical, empty gestation sac, fetal or second trimester.
- In women with recurrent miscarriage, poor prognostic factors for further miscarriage include number of previous losses, maternal age and obesity.

Other associated factors and their management

Factors that have been associated with early recurrent miscarriage include parental and fetal chromosomal abnormalities [8,9], structural uterine abnormalities [10],

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Table 41.1 Classification of miscarriage.

Type of miscarriage	Gestation range (weeks)	Fetal heart activity	Ultrasound findings
First trimester			
Biochemical	0–6	Never	Not visualized
Empty gestation sac	4–10	Never	Empty gestation sac or large sac with minimal structures without fetal heart activity
Fetal	6–12	Lost	Crown–rump length and fetal heart activity previously identified
Second trimester	12–24	Lost	Fetus identified of size equivalent to 12–24 weeks' gestation

antiphospholipid syndrome [11], some thrombophilias [12], autoimmune disease, and endocrinological disorders such as polycystic ovarian syndrome and untreated diabetes [13]. It is important to realize that many of these associations are weak and there are only a very few published observational studies that give prognostic implications for positive tests for conditions associated with recurrent miscarriage. Hence the evidence that many of the associated factors are causative is poor. There are even fewer high-quality, large-scale, randomized controlled trials showing that a treatment for women with recurrent miscarriage is effective at preventing a subsequent miscarriage. Ideally, evaluation of a couple with recurrent miscarriage would achieve the aim of guiding management options by finding contributory factors to the pregnancy losses, providing prognostic value in the subsequent pregnancy and directing treatment of proven benefit to improve live birth rates. This ideal has not been achieved by current research.

Structural genetic factors

Fetal chromosomal abnormality

Chromosomal abnormality in the miscarried pregnancy is the most common cause of early pregnancy loss, especially in older women. This accounts for up to 70% of early pregnancy losses, falling to only 20% when the pregnancy loss is between 13 and 20 weeks' gestation [8]. Defects are commonly trisomy, polyploidy or monosomy. Ideally, products of conception should be sent for karyotyping, as an abnormal fetal karyotype is diagnostic for the cause of miscarriage and is an important prognostic factor, suggesting a successful outcome of more than 75% in the next pregnancy [8]. However, this investigation is not perceived to be cost-effective.

Parental chromosomal abnormalities

Parental chromosomal abnormalities are found in about 2% of women with recurrent pregnancy loss, with the most common being a balanced reciprocal translocation [14]. Couples with balanced translocations are at risk of conceiving future children with unbalanced translocations. However, a large case series of couples with recurrent miscarriage and balanced translocation have found the risk of unbalanced translocation in offspring to be less than 1% [15]. This 1% miscarriage rate is close to the miscarriage rate of normal pregnancies after invasive prenatal diagnosis. Observational studies of couples with recurrent miscarriage and balanced translocations have found live birth rates of over 70% in the subsequent pregnancy [15]. This 70% live birth rate is similar to that in couples with recurrent miscarriage without chromosomal abnormalities [4]. Thus, the cost-effectiveness of investigating parental karyotype has been questioned [14]. If balanced translocation is detected, supportive care with the option of invasive prenatal diagnosis is appropriate [1]. A significant number of candidate genes have been studied to try to demonstrate a genetic basis for recurrent miscarriage but no conclusive results have emerged [16].

There was hope that pre-implantation genetic diagnosis (PGD) and assisted reproductive techniques (ART) would improve the live birth rate for women with recurrent miscarriage and balanced translocations. However, in practice PGD-ART has a series of disadvantages. Not all the cells in a four- or eight-cell embryo are genetically identical, so PGD is not a reliable measure of the pregnancy karyotype. The pregnancy rate and live birth rate from PGD-ART is lower than from natural conception [17]. Furthermore, natural conception involves the selection of normal oocytes, then the selection of normal pregnancy, allowing genetically abnormal pregnancies to miscarry. These natural selection steps are circumvented in PGD-ART, creating large numbers of abnormal embryos. Consideration can be

given to PGD where women have subfertility and recurrent miscarriage and a balanced translocation, as observational studies show that PGD-ART has better pregnancy outcomes, despite lower rates of embryo transfer and shorter time to a successful pregnancy [17]. However, a recent study comparing natural conception and PGD-ART in patients with a balanced translocation failed to demonstrate improved live birth rates [18].

Summary box 41.2

- Recurrent miscarriage is associated with parental balanced translocations.
- In the presence of a balanced translocation, couples still have a 70% live birth rate in a subsequent pregnancy.
- Only 1% of offspring from couples with balanced translocations have unbalanced translocations.
- Parental karyotyping is no longer thought to be cost-effective.

Anatomical factors

Congenital uterine anomaly

The prevalence of congenital uterine anomaly, such as septated, bicornuate or arcuate uterus, in the general population is about 6.7% but approximately 16.7% in women with recurrent miscarriage [10], though a direct causative link is uncertain due to the vast difference in criteria and techniques for diagnosing abnormal uterine morphology. Advances in hysteroscopic surgery mean that these malformations can be corrected using a resectoscope. Observational studies suggest that surgery (hysteroscopic metroplasty) may improve pregnancy outcome [19,20] and a recent prospective case-controlled study demonstrated improved live birth outcome in resected septated uteri but not bicornuate uteri [21]. However, there have been no randomized controlled trials of this treatment so efficacy of intrauterine surgery has yet to be demonstrated [19].

Cervical weakness

Cervical weakness is a recognized contributing factor to second-trimester loss. There is no satisfactory objective test of cervical weakness as the diagnosis is a clinical one. Treatment with cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should only be considered in women who are likely to benefit [1]. Cervical cerclage is discussed in more detail in Chapter 28.

Acquired uterine anomaly

Acquired uterine abnormalities such as fibroids or intrauterine adhesions (Asherman's syndrome) have also been associated with recurrent miscarriage (Fig. 41.1). In a study by Saravelos *et al.* [22], the incidence of fibroids in recurrent miscarriage was 8.2% and women with intra-cavitary distortion, whose fibroids were resected, significantly reduced their mid-trimester miscarriage rate (21% to 0%). However, women with fibroids not distorting the cavity behaved similarly to women with unexplained recurrent miscarriage, with 70% birth rates in both groups. There are very few studies of any beneficial intervention for Asherman's syndrome [23].

Summary box 41.3

- Recurrent miscarriage is associated with uterine structural abnormalities.
- Observational studies suggest that hysteroscopic surgery is effective for septate uteri.
- Hysteroscopic surgery is effective in reducing mid-trimester loss if fibroids are distorting the uterine cavity.

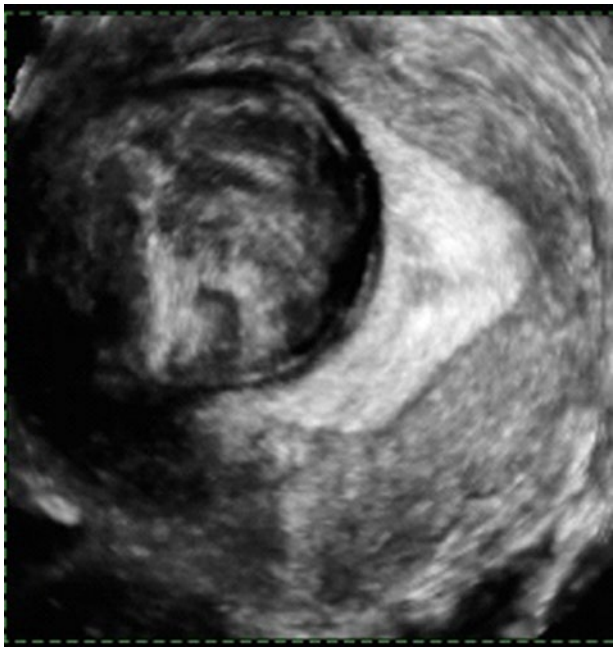

Fig. 41.1 Submucous fibroid projecting significantly into the endometrial cavity.

Prothrombotic factors

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) has a prevalence of 15% in women with first-trimester recurrent miscarriage and this, as well as a single second-trimester miscarriage, is one of the clinical components for diagnosis of the syndrome [24]. Treatment options including low-dose aspirin (LDA), heparin, prednisolone and intravenous immunoglobulin (IVIG) have been investigated. A systematic review showed that prednisolone and IVIG do not improve pregnancy outcomes and are associated with increased risk of diabetes and premature birth [25]. Current RCOG guidance [1] suggests that patients with APS should be treated with LDA and low-molecular-weight heparin but there is a lack of evidence to support this. A Cochrane systematic review in 2014 concluded that there was no evidence of a beneficial effect [26] and a similar conclusion was reached in a Bayesian network meta-analysis [27]. Currently, a randomized controlled trial (ALIFE2) is ongoing in an attempt to finally clarify this issue.

Thrombophilia

Some thrombophilias, such as factor V Leiden mutation, activated protein C resistance, prothrombin gene G20210A mutation and protein S deficiency, have been significantly associated with recurrent miscarriage [12]. However, there is still controversy about the prognostic implications of positive tests. A full thrombophilia screen can produce abnormal results in 20% of women with uncomplicated obstetric histories. Thus it is uncertain if all women with early recurrent miscarriage should be screened for thrombophilia [28]. Treatment with LDA with or without low-molecular-weight heparin has been proposed as thromboprophylaxis to prevent putative placental infarcts or vascular thrombosis. Small initial studies suggest there may be beneficial effects with thromboprophylaxis in terms of improved live birth rates [29,30]. However, more recently, high-quality large randomized controlled trials have failed to substantiate an improvement in live birth rate in women with either idiopathic or thrombophilia-associated recurrent miscarriage [31–34]. Thus, there is no evidence to support the use of LDA and heparin in the treatment of these women with recurrent miscarriage.However, thromboprophylaxis to prevent maternal thrombosis does need to be considered in women with multiple risk factors for this.

Summary box 41.4

- Recurrent miscarriage is associated with thrombophilia.
- In the presence of APS, aspirin and heparin are not thought to be effective treatments.
- In the absence of APS, neither aspirin and heparin nor aspirin alone have been found to prevent miscarriage.

Endocrinological factors

Polycystic ovarian syndrome

There is an association between polycystic ovarian syndrome and recurrent miscarriage. The possible mechanisms for this are hyperandrogenism and insulin resistance [35]. However, the variation in criteria for diagnosing polycystic ovarian syndrome makes it difficult to assess the importance and the prognostic value of detecting it. Nevertheless, a simple, safe and cheap way to reduce pregnancy loss in obese women with polycystic ovarian syndrome is weight loss [36]. Small studies suggest there may be a role for metformin in reducing miscarriage rates, especially in the presence of an abnormal glucose tolerance test, and metformin is now regarded as having low risks in pregnancy [35,37]. There are no randomized controlled trials to support this approach however. A randomized controlled trial in infertile women indicated that clomifene is superior to metformin in achieving live births but made no difference to the rates of miscarriage [38].

Abnormalities of glucose metabolism and thyroid disorders

It is known that well-controlled thyroid disorders and diabetes are not risk factors for recurrent miscarriage. Thus national guidelines do not recommend routine screening in the absence of symptoms [1,28].

Immunological factors

Immunological mechanisms are thought to play a part in the success of pregnancy where the maternal immune system interacts with the allogeneically dissimilar embryo.

Antithyroid antibodies

The presence of antithyroid antibodies has been associated with a higher pregnancy loss rate, the underlying mechanisms of which are either autoimmune or mild

thyroid insufficiency [13,39]. A small study suggested that women with recurrent miscarriage and antithyroid antibodies but normal thyroid function tests may benefit from levothyroxine treatment [40] but further large-scale trials are needed to substantiate this finding.

Natural killer cells

Another immunological factor of interest involves the natural killer (NK) cells that can be found in the peripheral blood or endometrium. Both peripheral and uterine NK cells have been associated with recurrent miscarriage [41,42]. However, there is still considerable controversy regarding the exact role and function of NK cells in recurrent miscarriage and the prognostic value of increased numbers or function of these cells is uncertain [43]. A systematic review of 20 trials of various immunotherapies, such as paternal cell immunization, third-party-donor-cell immunization, trophoblast membrane infusion and intravenous immune globulin, showed no significant beneficial effect over placebo in improving live birth rates [44,45].

Endometrial factors

It is long been suggested that defective implantation my contribute to recurrent early pregnancy loss. However, evidence for this has been lacking until recently. There is now evolving evidence that endometrial stem cells are depleted in cases of recurrent miscarriage, predisposing to pregnancy failure [46,47]. Early work on the role of chronic endometritis and recurrent miscarriage has suggested improved live birth rates in treated cases [48]. Further larger studies are needed to verify these findings.

Idiopathic recurrent miscarriage

Tender loving care

Women with recurrent miscarriage are anxious and appreciate reassurance when they fall pregnant again. Three-quarters of these women with idiopathic recurrent miscarriage will achieve a live birth in the subsequent pregnancy, with tender loving care involving regular reassurance scans and psychological support in a dedicated early pregnancy assessment unit [5,49].

Aspirin

Empirical use of aspirin is common. However, a recent systematic review showed no evidence of an improvement in live birth rates in women with recurrent miscarriage [50] and in a randomized controlled trial there was a trend towards aspirin increasing the chance of miscarriage [32].

Progesterone

Progesterone is needed for successful early pregnancy and thus a lack of progesterone could be surmised to lead to pregnancy loss. A recent randomized, double-blind, placebo-controlled trial (PROMISE) has established that there is no evidence that first-trimester progesterone therapy improves outcomes for women with unexplained recurrent miscarriage [51].

Human chorionic gonadotrophin

Suggestions that the use of human chorionic gonadotrophin in the first trimester might help salvage failing pregnancies by stimulating progesterone production by the corpus luteum would seem to be unlikely based on the PROMISE trial outcome and a recent meta-analysis confirmed the lack of evidence [52].

Conclusions

The management of recurrent miscarriage is challenging because of lack of evidence-based effective treatments. Couples with recurrent miscarriage can be offered investigations but the majority will be negative. Supportive care has been shown to be beneficial. Empirical treatment in women with idiopathic recurrent miscarriage should be avoided and entry into high-quality and methodologically sound trials should be considered whenever possible in order to improve the evidence base for this distressing condition.

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42

Gestational Trophoblast Neoplasia

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Gestational trophoblast neoplasms (GTNs) arise from the cells of conception and form a range of related conditions, from the generally benign partial hydatidiform mole through to the aggressive malignancies of choriocarcinoma and rare placental site trophoblast tumour (PSTT) and epithelioid trophoblastic tumour (ETT) [1]. The combination of this unique biology, relative rarity and effective therapies makes GTNs an extremely interesting and important area of gynaecological and oncological care.

Despite the rarity of these illnesses, patients with molar pregnancies requiring additional treatment after evacuation can expect successful treatment outcomes, with overall cure rates for GTNs approaching 100% [2]. For patients with choriocarcinoma and PSTT/ETT, using the treatments that have been established for over 25 years, the majority of patients can also be treated with a high expectation of cure with minimal long-term toxicity [3,4].

Despite this major progress, developments in management of trophoblast disease are still required to help further reduce toxicity, eliminate remaining deaths and refine diagnostic tools. For over 40 years the UK has had centralized registration of all cases, and human chorionic gonadotrophin (hCG) hormone monitoring, pathology review and management has been essential in achieving the best outcomes for patients. This chapter is based on the experience from the UK's and the world's largest trophoblast tumour centre at Charing Cross Hospital in London.

Classification, demographics and risk factors

The World Health Organization classification of GTNs divides trophoblast tumours into premalignant partial and complete hydatidiform moles and the malignant diagnoses of invasive mole, choriocarcinoma and PSTT/ETT. More recently, we have recognized a new potential premalignant member of the gestational trophoblastic disease (GTD) spectrum known as atypical placental site nodules [5].

The reported incidence of molar pregnancies in Europe and North America is on the order of 0.2–1.5 per 1000 live births [1] and a recent study from the UK has indicated an overall incidence of one molar pregnancy per 591 viable conceptions for the period 2000–2009 [6]. Overall, partial molar pregnancies are slightly more common than complete moles, with an approximate ratio of 60 : 40 in the UK series. Similar data have been reported from other European countries where whole-population analyses are possible [7]. Whilst there are some modest variations in the incidence of molar pregnancies based on race and geography, there are two clearly documented risk factors for an increased risk of molar pregnancy: the extremes of maternal age and a previous molar pregnancy [8,9].

The relative risk for molar pregnancies is highest at the extremes of the reproductive age group. The results from the recent England and Wales analysis, summarized in Table 42.1, indicate that there is a modest increased risk for younger teenagers, a relatively level risk for women aged 16–45 and then increasing risks after the age of 45 and particularly for those over the age of 50. Of interest, the risk of partial molar pregnancy remains relatively unchanged across the age group, with most of the change in overall risk due to an increased incidence of complete molar pregnancies. In the 18–40 age group, complete moles make up about 40% of all molar pregnancies, but in the 45+ age group they account for over 90% of cases [6,8]. Interestingly, most of the risk for a second molar pregnancy resides in complete rather than partial moles and the risk of three consecutive molar pregnancies is almost exclusively for

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 42.1 Risk of molar pregnancy compared with the number of viable conceptions at varying maternal ages in England and Wales.

Age	Per cent partial moles of viable conceptions	Per cent complete moles of viable conceptions	Overall risk of molar pregnancy
13	0.08	0.32	1 in 250
14	0.07	0.20	1 in 370
15	0.04	0.21	1 in 400
20	0.05	0.06	1 in 909
25	0.09	0.06	1 in 666
30	0.11	0.05	1 in 625
35	0.11	0.05	1 in 625
40	0.18	0.09	1 in 370
45	0.29	0.75	1 in 96
50+	0.59	16.2	1 in 6

Source: adapted from Savage *et al.* [6].

complete moles [9]. The latter should raise the possibility of a rare genetic variant known as familial recurrent hydatidiform mole (FRHM) syndrome (discussed in a subsequent section).

Premalignant pathology and presentation

Partial mole

The genetic origins of complete and partial molar pregnancies are demonstrated in Fig. 42.1. Partial moles are triploid with 69 chromosomes comprising two sets of paternal and one set of maternal chromosomes. Macroscopically and on ultrasound scanning during the first trimester, partial mole will often resemble normal products of conception. The embryo can appear viable on an early ultrasound scan but becomes non-viable by week 10–12. The histology of partial mole shows less swelling of the chorionic villi than in a complete mole and there may be only focal changes. As a result the diagnosis of partial mole can often be missed after a miscarriage or evacuation, unless the products are sent for expert pathological review.

The clinical presentation of partial mole is most frequently via a failed pregnancy rather than irregular bleeding or by detection on routine ultrasound. The obstetric management is by suction evacuation and histological review; all patients with partial mole should be followed up by registration and serial hCG measurement.

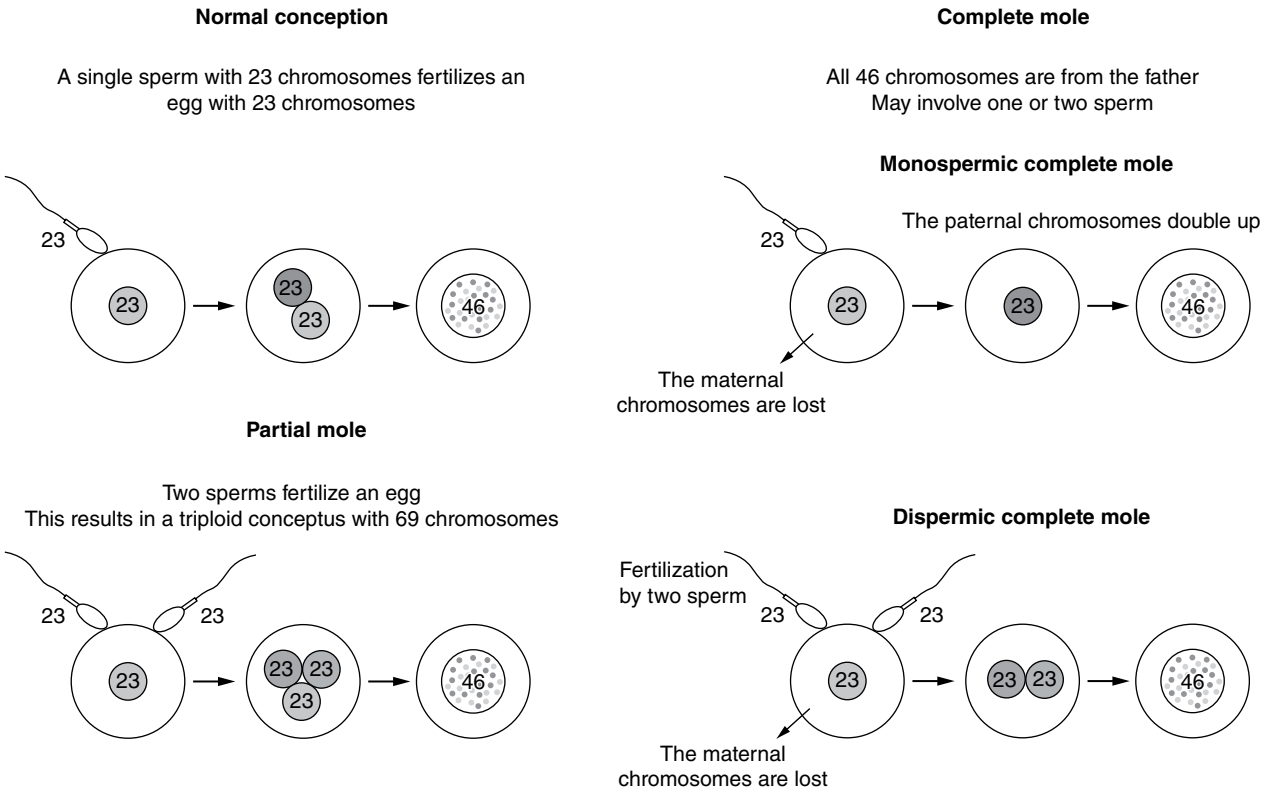

Fig. 42.1 Genetic origin and structure of a normal conception, partial mole and complete molar pregnancy.

Fortunately, partial mole rarely transforms into malignant disease, and there is an overall risk of 0.5–1% of patients requiring chemotherapy after a partial mole [10].

Complete mole

In complete moles the genetic material is totally male in origin (Fig. 42.1), resulting from the fertilization of an 'empty' anucleate oocyte lacking maternal DNA. The chromosome complement is most commonly 46XX, which results from one X chromosome-carrying sperm that duplicates its DNA, or less frequently 46XY or 46XX from the presence of two separate sperm [1].

The clinical diagnosis of complete mole most often occurs as a result of first-trimester bleeding or an abnormal ultrasound. There is no fetal material and the histology shows the characteristic oedematous villous stroma. The textbook 'bunch of grapes' appearance is only seen in the second trimester and as most cases are diagnosed earlier, this is now rarely observed in UK practice. The typical macroscopic appearances of a complete mole are shown in Fig. 42.2. Obstetric management is by suction evacuation followed by registration and serial hCG measurement. Complete molar pregnancies have an appreciable risk of proceeding to invasive disease, with approximately 15% of patients with complete mole requiring chemotherapy.

Familial recurrent hydatidiform mole syndrome

Occasionally we see patients who have repetitive complete molar pregnancies and who have failed to conceive a normal baby. Patients who have had three consecutive complete moles should be genetically tested to determine whether they have FRHM syndrome where the DNA is biparental in origin rather than androgenetic [11]. Thus far, mutations in two genes have been associated with this autosomal recessive condition, *NLRP7* [12] and *KHD3CL* [13], that account for about 75% and 5–10% of cases respectively, so additional gene(s) remain to be discovered [14]. Affected women have rarely been reported to achieve a normal pregnancy, with most just suffering repeated complete moles or pregnancy losses where no pathology is available. Unfortunately, the risk of subsequent malignancy requiring chemotherapy is the same for these patients as for those with androgenetic complete moles. Therefore recommending repeated rounds of attempted natural conception does not seem appropriate. As these genes are normally expressed in both the egg and the genital tract/uterus, the question then arises as to whether the recurrent moles are due to a defective egg or a problem with uterine implantation. To help resolve this, one affected patient agreed to try egg donation from an unaffected relative and this resulted in a normal pregnancy [15]; since then, several other women with FRHM have similarly had normal babies.

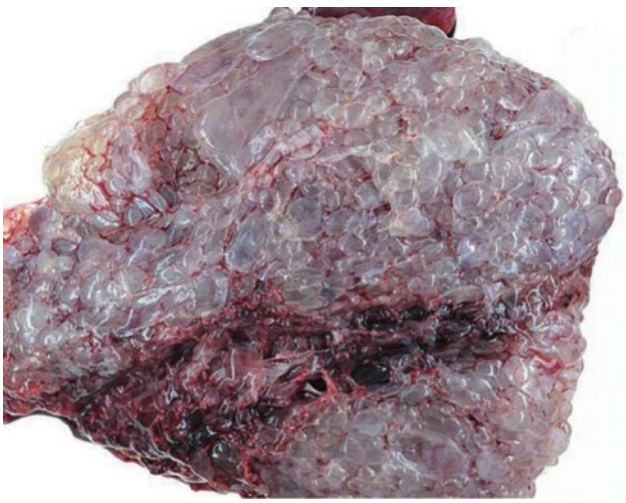

Fig. 42.2 Macroscopic appearance of a complete molar pregnancy from early in the second trimester.

Twin pregnancies

The risk of having a twin pregnancy comprising a complete mole and healthy co-twin is estimated to be 1–5 per 100 000 [16,17]. These pregnancies cause considerable anxiety for both the patient and managing clinicians as there is a perception that they are likely to be associated with an increased risk of serious and potentially life-threatening complications for the mother, including haemorrhage, uterine perforation, pre-eclampsia, toxaemia and malignant change in the mole requiring chemotherapy. In addition, it was thought that the possibility of carrying the healthy co-twin to viability or term was remote. These concerns were underpinned by several small case series based on local hospital reports [17] and so suffered from case ascertainment bias. We examined this issue in a UK population-based series of 77 women that was the largest of its kind and which was not subject to case ascertainment bias. To our surprise, we discovered that the risk of malignancy was not increased by allowing such pregnancies to continue, a fact that we subsequently substantiated in singleton molar pregnancies evacuated in the second and third rather than first trimester [18]. Moreover, nearly 40% of them resulted in a healthy take-home baby with most of the rest undergoing spontaneous loss from presumed continued molar growth. Importantly, there was only a small increased risk in pre-eclampsia that could be safely managed and no cases of uterine perforation or maternal death [17].

Since then a further 90 patients have been offered the choice of early termination versus continuing their pregnancies. This has confirmed our earlier findings, with no maternal losses and no increased risk of malignancy by allowing the pregnancy to continue. Moreover, the healthy take-home baby rate has risen to just under 60% (unpublished observations). The mode of delivery has been a mixture of normal vaginal and caesarean section depending on local assessment of what was considered the safest option. Therefore, after appropriate counselling, it seems reasonable to allow women to continue such pregnancies but under close monitoring to ensure that potential complications are detected early and dealt with promptly.

Atypical placental site nodules

Following a normal pregnancy, placental remnants in the uterine wall usually spontaneously regress and disappear. Occasionally, they may persist and form placental site nodules. These may present with irregular bleeding that often results in dilation and curettage. The subsequent pathology reveals the placental site nodule material. This has always been regarded as a benign condition. However, recent data suggest that some placental site nodules may have atypical histopathological features and, if so, can in 10–15% of cases be associated with or subsequently develop into either a PSTT or ETT [5]. Consequently, patients found to have placental site nodules where there may be atypical features are now having their pathology reviewed centrally in the UK. If atypical placental site nodule is confirmed, then these patients are registered and seen centrally for monitoring. If the nodule is thought to be typical, then at present local MRI pelvis imaging is suggested and if this is normal no further monitoring is currently undertaken. However, as we learn more it is likely that the advice will change.

Registration and surveillance

Overall, 90% of patients with molar pregnancies will not need any additional treatment following their evacuation. In these patients the residual trophoblast tissue cells fail to proliferate and as the cells stop growing, hCG levels return to normal. At present there is no effective prognostic method that allows accurate distinction between the patients who will develop malignant disease after evacuation and the majority who will not [19]. As a result all patients with molar pregnancy should be registered for an hCG follow-up system. The use of this approach allows the early identification of patients whose disease is continuing to proliferate, while also allowing careful observation of patients with more slowly falling hCG levels, so minimizing unnecessary chemotherapy.

Table 42.2 The indications used at Charing Cross Hospital for initiating chemotherapy treatment in patients with gestational trophoblast tumours.

Rising hCG in two or plateaued in three consecutive serum samples
Raised hCG level 6 months after evacuation (even if falling)
Histological evidence of choriocarcinoma
Metastases to the brain, liver, gastrointestinal tract, spleen, kidneys or other solid organs
hCG >20 000 IU/L more than 4 weeks after evacuation
Heavy vaginal bleeding or gastrointestinal/intraperitoneal bleeding
Lung or vaginal metastases >2 cm

hCG, human chorionic gonadotrophin.

Patients taking part in an hCG surveillance programme usually have the need for additional treatment determined by the pattern of their hCG results. Thus, an hCG level that has plateaued or is rising following evacuation of a molar pregnancy is the commonest indication of malignant change requiring chemotherapy. Table 42.2 shows the Charing Cross Hospital recommended indications for treatment. The first four of these are also used by the International Federation of Gynecology and Obstetrics (FIGO) [2]. However, based on our recent work, the second indication has been dropped because nearly all women with a falling but elevated hCG 6 months after evacuation will normalize hCG levels spontaneously without chemotherapy [20]. The last three indications are UK-specific reasons for commencing treatment. Typically, about 1–2% of patients start therapy because of excessive bleeding requiring transfusion even if hCG is falling because the treatment helps to settle the bleeding. An hCG concentration above 20 000 IU/L 4 weeks after uterine evacuation is associated with a high risk of developing malignant change that requires chemotherapy and with a small risk of uterine perforation and accounts for probably another 1–2% of patients who require chemotherapy in the UK. The presence of more than 2 cm lung and/or vaginal metastases as a sole indication for treatment has not been seen for over 25 years, likely because of improved early diagnosis within the first trimester and better surveillance. Those patients recovering from molar pregnancy enrolled in the surveillance service and who go on to require treatment have a cure rate approaching 100% [21], and over 95% will initially fall into the low-risk treatment group.

Malignant pathology and presentation

Invasive mole (chorioadenoma destruens)

Invasive mole nearly always arises from a complete mole and is characterized by invasion of malignant cells into the

myometrium, which can lead to perforation of the uterus. Microscopically, invasive mole has a similar histological appearance to complete mole but is characterized by the ability to invade into the myometrium and local structures if untreated. Fortunately, the incidence of invasive mole in the UK has fallen substantially with the introduction of routine ultrasonography, the early evacuation of complete moles and effective hCG surveillance, and is now rare.

Choriocarcinoma

Choriocarcinoma is histologically and clinically overtly malignant and presents the most frequent emergency medical problems in the management of trophoblast disease. The diagnosis often follows a complete mole, when the patients are usually in a surveillance programme, but can also arise after any other type of pregnancy including a partial mole, a non-molar abortion, miscarriage, ectopic or term pregnancy. The clinical presentation of choriocarcinoma can be due to local disease in the uterus leading to bleeding in two-thirds of cases, or from distant metastases that can cause a wide variety of symptoms, with the lungs, central nervous system (CNS) and liver the most frequent sites of distant disease. About one-third of patients will have no obvious residual abnormality within the uterus [1].

The cases of choriocarcinoma presenting with symptoms from distant metastases can be diagnostically challenging [22]. However, the combination of the gynaecological history and elevated serum hCG usually makes the diagnosis clear and so avoids biopsy, which can be hazardous due to the risk of severe haemorrhage, as demonstrated following a liver biopsy (Fig. 42.3). On the occasions when choriocarcinoma pathology is available, the characteristic findings show the structure of the villous trophoblast but sheets of syncytiotrophoblast or cytotrophoblast cells, haemorrhage, necrosis and intravascular growth are common [1]. The genetic profile of choriocarcinoma can reflect its origin from a complete or partial mole [10] or a normal diploid conception combined with a range of gross abnormalities without any specific characteristic patterns [23]. Some cases will prove to be non-gestational choriocarcinomas that pathologically are identical to gestational choriocarcinomas but are in fact germ cell or epthelial tumours that have trophoblastic differentiation and genetically originate from the patient. These tumours may initially respond well to combination agent chemotherapy used to treat gestational trophoblastic tumours but then revert to their true phenotype, and if epithelial in origin do badly [3].

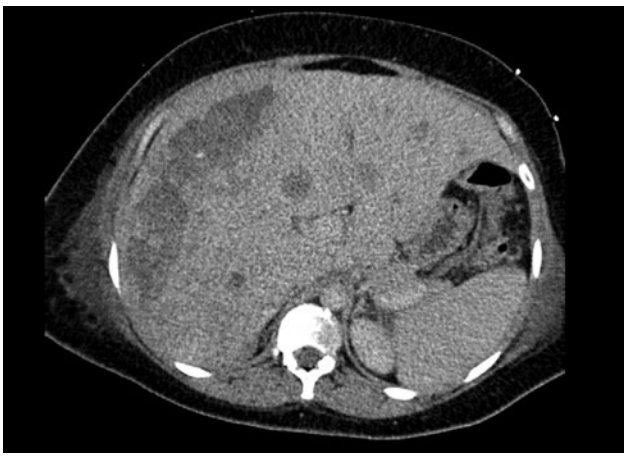

Fig 42.3 CT scan of the abdomen in a patient with choriocarcinoma demonstrating multiple liver metastases and a large subcapsular haematoma secondary to a core biopsy.

Placental site trophoblast tumour and epithelioid trophoblastic tumour

PSTT was originally described in 1976 [6] and is the rarest form of GTD, accounting for 0.2% of all registered cases of GTD in the UK [4]. ETT is an even rarer variant first described in 1998 [24] and although it is thought to behave in a similar fashion to PSTT, in reality we are still learning about the similarities and differences of these two entities [2]. PSTT/ETT most commonly follows a normal pregnancy but can also occur after a non-molar abortion or a molar pregnancy.

In contrast to the more common types of trophoblast disease, which characteristically present fairly soon after the index pregnancy, in PSTT the average interval between the prior pregnancy and presentation is 3.4 years. The most frequent presentations are amenorrhoea or abnormal bleeding. In nearly all cases the serum hCG level is elevated, but is characteristically lower for the volume of disease than in the other GTNs. The tumour can arise after any type of pregnancy including complete and partial moles [25] and is believed to be derived from the non-villous trophoblast. The pathology is characterized by intermediate trophoblastic cells with vacuolated cytoplasm, the expression of placental alkaline phosphatase and hCG, and the absence of cytotrophoblast and villi. ETT develops from the chorionic-type intermediate trophoblast present in other parts of the placenta such as the chorionic plate and fetal membranes. Pathologically, ETT is distinguished from PSTT by its smaller cells, its smaller, more monomorphic cells and by its nested, nodular, well-circumscribed growth pattern unlike the sheet-like infiltrative pattern seen with PSTT [26]. In addition, clinically, ETT tends to secrete even less hCG than PSTT. The clinical presentation of PSTT/ETT can range from slow-growing disease limited to the uterus to metastatic disease, with lung and liver the most common sites of distant spread [7]. Spread to lymphatics is a bit more

common in PSTT/ETT compared with choriocarcinoma where it is exceptionally rare [4].

Role of hCG in trophoblast disease diagnosis and management

Produced predominantly by syncytiotrophoblast cells, hCG is a glycosylated heterodimer protein consisting of α and β units held together by non-covalent bonds. In malignant disease a number of hCG variants can occur, including hyperglycosylated hCG, nicked hCG, hCG missing the β subunit C-terminal peptide and the free β subunit [1]. With the potential exception of a few atypical cases of PSTT/ETT, hCG is constitutively expressed by all forms of premalignant and malignant GTD.

The measurement of hCG allows estimation of tumour bulk, forms an important part of the assessment of the patient's disease risk and provides a simple method to follow the response to treatment. The hCG level can be measured by a variety of immunoassays but at present there is no internationally standardized assay and the various commercially available kits used in different hospitals can vary in their ability to detect different forms of partially degraded hCG molecules and so can give divergent results and occasional false negatives [27]. It is also important to be aware that patients with exceptionally high hCG levels may produce a false-negative result through the high-dose 'hook' effect. Moreover, any assay might produce a false-positive hCG value. Consequently, if the clinical situation does not correspond with an elevated hCG value, then another hCG assay should be employed and/or the hCG should be checked in the urine. This is because heterophilic antibodies, which are the commonest cause of false-positive hCG values by occasionally allowing two independent assays to report positively, are too large (unlike hCG) to pass into the urine [1]. In the UK we are very fortunate to have an hCG assay that detects all forms of hCG produced in cancer and because of the way it is configured is highly unlikely to suffer false-positive results.

In the absence of tumour hCG production, the serum half-life of hCG is 24–36 hours; however, for patients receiving chemotherapy, total hCG levels characteristically show slower rates of fall as the tumour cells continue to produce some hCG as their number decreases with treatment.

Prognostic factors and treatment groups

Data from the early days of successful chemotherapy treatment for trophoblast disease show clearly that there is a relationship between the level of elevation of hCG at presentation, the presence of distant metastases and the reducing chances of cure with single-agent chemotherapy. This relationship and the impact on treatment choice and cure rate were first codified by the Bagshawe scoring system published in 1976 [28]. Subsequently, there have been a number of revisions and parallel systems introduced that are broadly similar to this original. Table 42.3 shows the revised 2000 FIGO prognostic score. From assessment of these parameters, an estimate of the risk category can be obtained and patients offered initial treatment either with single-agent chemotherapy if their score is 6 or less or multiagent combination chemotherapy for scores of 7 and over [29].

Low-risk disease management

In the UK, over 90% women with molar pregnancies who require additional treatment following their initial evacuation fall into the low-risk treatment category as defined by the FIGO prognostic scoring system. The role of

Table 42.3 International Federation of Gynecology and Obstetrics (FIGO) prognostic scoring system employed for assessing the intensity of the initial chemotherapy treatment.

Scores*	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Months from index pregnancy	<4	4–6	7–13	≥13
Pretreatment hCG (IU/L)	<1000	1000–10 000	1000–100 000	>100 000
Largest tumour size	<3 cm	3–5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Brain, liver
Number of metastases	–	1–4	5–8	>8
Previous chemotherapy	–	–	Single agent	Two or more drugs

* Scoring is done using data obtained within 24 hours prior to starting chemotherapy.

repeated uterine evacuation in the management of these patients has been a subject of uncertainty until recently. A number of studies looking at the impact of repeated evacuation in women with rising or static hCG levels following their first evacuation have suggested that a repeated procedure is rarely curative [30,31]. Based on these data, the current recommendation is that a repeated evacuation should only be considered if the hCG level is under 5000 IU/L and tissue is seen in the uterine cavity on ultrasound.

For patients meeting the FIGO standard for low-risk treatment, the most widely used protocol is methotrexate given intramuscularly with oral folinic acid rescue following the schedule shown in Table 42.4. The first course of treatment should be administered in hospital with the subsequent courses administered at home. This is because they have a higher risk of bleeding as therapy starts, particularly if the tumour shrinks rapidly with the initial chemotherapy. Bleeding usually responds well to strict bed rest and less than 1% of low-risk patients require emergency interventions such as embolization, vaginal packing or hysterectomy.

Table 42.4 The low-risk methotrexate and folinic acid chemotherapy treatment schedule.

Day 1	Methotrexate 50 mg i.m. at noon
Day 2	Folinic acid 15 mg p.o. at 6 p.m.
Day 3	Methotrexate 50 mg i.m. at noon
Day 4	Folinic acid 15 mg p.o. at 6 p.m.
Day 5	Methotrexate 50 mg i.m. at noon
Day 6	Folinic acid 15 mg p.o. at 6 p.m.
Day 7	Methotrexate 50 mg i.m. at noon
Day 8	Folinic acid 15 mg p.o. at 6 p.m.

The low-risk chemotherapy treatment is usually well tolerated without much major toxicity. Methotrexate does not cause alopecia or significant nausea and myelosuppression is extremely rare. Of the side effects that do occur, the most frequent problems, occurring in about 2–3% of cases, are mucositis, a gritty feeling in the eyes and, more rarely, pleuritic chest or abdominal pains from serositis. Mild elevation of liver function tests can occur but rarely prevents ongoing therapy. For low-risk patients with lung metastases visible on their chest radiographs, the policy at Charing Cross Hospital is to perform MRI of the head and if normal to add CNS prophylaxis with intrathecal methotrexate administration to minimize the risk of development of CNS disease. A maximum of three doses of intrathecal methotrexate is given unless the cerebrospinal fluid to serum hCG ratio exceeds 1 : 60 [1].

Treatment is continued until normalization of the serum hCG level (0–4 IU/L) and then a further three cycles (6 weeks) to ensure eradication of any residual disease that is below the level of serological detection. In the Netherlands, the policy had been to only give two cycles of consolidation therapy after normalization of the hCG and their relapse rate was double that of the UK so the Dutch have recently modified their policy to emulate the UK [32]. A typical example of the treatment graph for a patient successfully completing methotrexate chemotherapy is shown in Fig. 42.4.

An overview of the data for the 1990s indicates that 67% of patients in the low-risk group will only require treatment with the methotrexate protocol to successfully complete

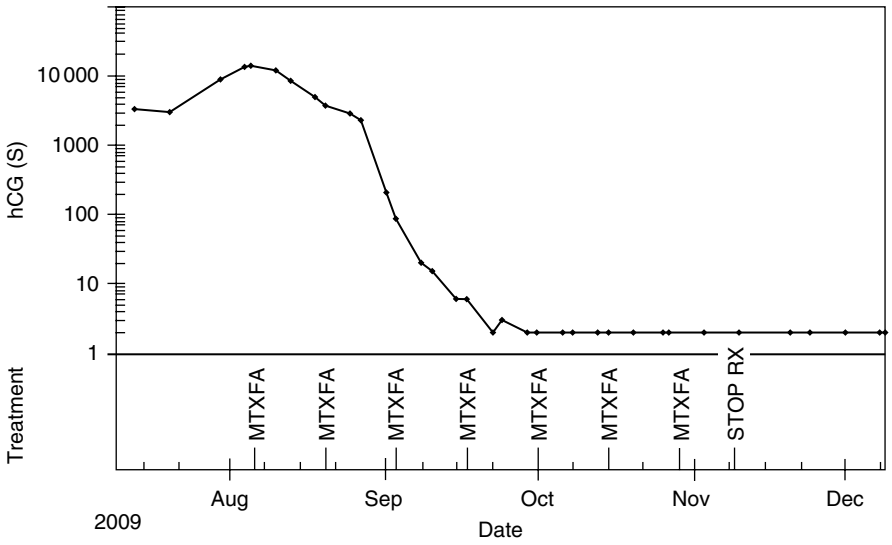

Fig. 42.4 Treatment and human chorionic gonadotrophin (hCG) graph of a low-risk patient with a gestational trophoblast tumour, successfully treated with methotrexate (MTX) and folinic acid (FA) chemotherapy.

their therapy. Patients who have an inadequate response to methotrexate therapy, as shown by an hCG plateau or rise, have their treatment changed to second-line therapy. This comprises single-agent actinomycin D (1.25 mg/m^2 i.v. repeated every 2 weeks) which, like methotrexate, is relatively less toxic than the alternative etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA/CO) combination chemotherapy (Table 42.5). To minimize the number of patients proceeding to EMA/CO we have increased the hCG cut-off at the point of methotrexate resistance from 100 to 300 IU/L, and since this resulted in equally good results [21,33] we are now testing an hCG cut-off of 1000 IU/L.This means that only patients with an hCG above 1000 IU/L at the point of methotrexate resistance proceed to EMA/CO whilst the rest receive a trial of single-agent actinomycin D.

An individual example of the pattern of hCG levels during the course of management is shown in Fig. 42.5.

Table 42.5 EMA/CO chemotherapy.

Week 1	
Day 1	Actinomycin D 0.5 mg i.v. Etoposide 100 mg/m^2 i.v. Methotrexate 300 mg/m^2 i.v.
Day 2	Actinomycin D 0.5 mg i.v. Etoposide 100 mg/m^2 i.v. Folinic acid 15 mg p.o. 12-hourly × 4 doses Starting 24 hours after commencing methotrexate
Week 2	
Day 8	Vincristine 1.4 mg/m^2 (maximum 2 mg) Cyclophosphamide 600 mg/m^2

This demonstrates the rise in hCG that led to the introduction of methotrexate chemotherapy; following this, the hCG initially falls but after two cycles appears to plateau. The introduction of second-line treatment with EMA/CO chemotherapy leads to a rapid fall in hCG to normal and the completion of chemotherapy after 6 weeks of further treatment. Overall the survival in this group is currently running at 100% and the sequential introduction of additional chemotherapy as necessary minimizes the potential long-term carcinogenic risks of excess treatment.

High-risk disease management

Historical data from treatment prior to the introduction of multiagent chemotherapy demonstrated that less than one-third of high-risk patients would be cured with single-agent therapy [34]. The introduction of combination chemotherapy treatments in the 1970s transformed this situation, and modern data indicate a cure rate for high-risk patients of 85–94% using EMA/CO chemotherapy [3,35–37]. This combination delivers a dose-intense treatment with the five chemotherapy agents, delivered in two groups 1 week apart as shown in Table 42.5. Delivering therapy on a weekly as opposed to 3–4 weekly basis appears to be the most effective approach to this rapidly proliferating malignancy. EMA-CO is myelosuppressive and most patients require granulocyte colony-stimulating factor support each week to maintain treatment intensity and to minimize the risk of neutropenic sepsis. Nausea and vomiting are now rarely a problem with modern antiemetics that include the 5HT$_3$

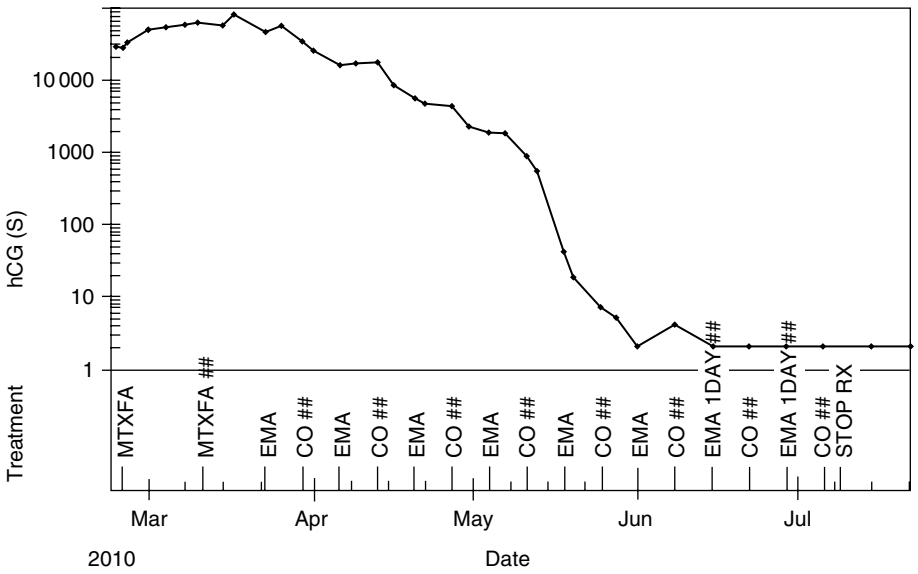

Fig. 42.5 Treatment and human chorionic gonadotrophin (hCG) graph of a low-risk patient with a gestational trophoblast tumour, initially treated with methotrexate (MTX) and folinic acid (FA) chemotherapy, changing to EMA-CO treatment in response to an hCG plateau.

receptor antagonists such as ondansetron combined with domperidone. The addition of dexamethesone is rarely required and we prefer to avoid this given the rare but unpleasant problem of avascular necrosis of the femoral and humeral heads requiring joint replacements in young patients. Increasing lethargy with progressive cycles of EMA/CO is common and some patients develop peripheral neuropathy that can be aided by stopping the vincristine. Overall, the regimen is well tolerated compared with many other multiagent therapies and serious or life-threatening toxicity is very rare.

As in the low-risk situation, treatment is continued for 6 weeks after the normalization of hCG. Moreover, the second day of the EMA comprising etoposide and actinomycin D can be dropped once the hCG is normal. An example of a high-risk patient treated in this case with the high-risk chemotherapy regimen is shown in Fig. 42.6, which demonstrates the resolution of extensive lung metastases and normalization of hCG levels in response to treatment.

Ultra-high-risk disease

Ultra-high-risk disease is a new term to try to define those high-risk patients at greatest risk of death. Analysis of the causes of death in patients with high-risk disease revealed that this occurred either early or late. The early deaths took place within 4 weeks of admission due to organ failure associated with one or more of the following: fatal haemorrhage, metabolic upset from tumour lysis and very adavanced disease. The late deaths were from multiresistant disease. In addition, some deaths were due to cancers that were in fact non-gestational epithelial malignancies histopathologically mimicking gestational choriocarcinomas. Factors associated with early or late deaths included a FIGO score above 12,

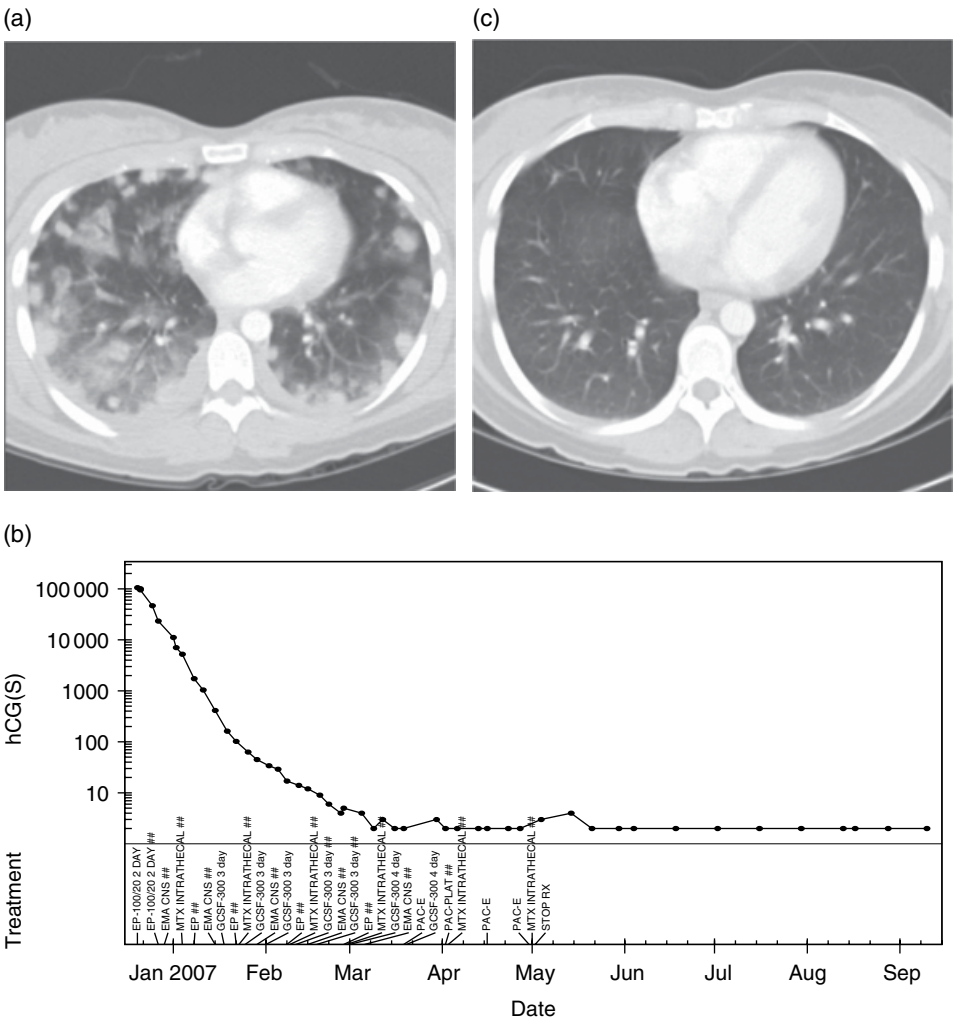

Fig. 42.6 Pre-treatment chest CT scan (a), treatment graph (b) and post-treatment CT scan (c) in a 29-year-old woman presenting with respiratory failure secondary to choriocarcinoma 2 months after the birth of a healthy child.

very advanced lung disease, liver with or without brain metastases, and an interval from the last-known and presumed causative pregnancy greater than 2.8 years [3]. To reduce early deaths, we developed a gentle induction chemotherapy comprising low-dose etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (EP) given intravenously on days 1 and 2 and repeated weekly for up to 3 weeks until the patient is well enough to tolerate standard-dose therapy. This has almost completely eliminated early deaths from patients with advanced GTN [3]. Those patients with liver metastases or liver and brain metastases have a particularly poor long-term survival and so they should be considered for more prolonged platinum-containing therapy. In the UK these patients now all receive etoposide and cisplatin alternating with 1 day of EMA [38]. Moreover, for patients with brain metastases, the methotrexate dose is increased to 1 g/m^2 in the EMA and intrathecal methotrexate is given with the EP to ensure adequate CNS penetration. We also extend the duration of consolidation therapy in ultra-high-risk patients to 8 weeks. Further details of how to manage such complex patients is beyond the scope of this chapter but can be found elsewhere [38–40].

Salvage of EMA/CO failures

Of the high-risk patients treated with EMA/CO, approximately 18–20% develop resistance to this combination and require a change to second-line drug treatment. In this situation, the EP/EMA [41] or TE/TP [42] regimens may be used, which incorporate cisplatin and additional etoposide into the combination along with paclitaxel in the TE/TP regimen. These treatments, combined with surgery, both appear to salvage about 80% of patients failing EMA/CO. Since TE/TP seems much better tolerated and is given every 2 weeks rather than the weekly EP/EMA, TE/TP is now frequently the preferred option for EMA/CO failures [2].

Patients relapsing after EP/EMA and/or TE/TP can still be salvaged by surgery and/or further chemotherapy. Several other agents have activity in these tumours including gemcitabine, pemetrexed and capecitabine either alone or in combinations with other drugs. In addition, high-dose chemotherapy with peripheral stem cell support may help to salvage some patients [2]. Recent work presented at international meetings has suggested that some antibodies that target surface molecules on either the trophoblastic tumour cells or surrounding immune cells may also salvage some patients who have failed all other therapies. Consequently, there is considerable optimism that the remaining 5% of deaths from highrisk disease will be eliminated in the near future.

Management of PSTT/ETT

PSTT/ETT, unlike choriocarcinoma, tend to be much more slow-growing, remain confined to the uterus for longer, have a greater liklihood of lymphatic spread, produce less hCG, and tend to be less chemosensitive. However, like choriocarcinoma, they can metastasize widely.

The FIGO scoring system is not an effective way to determine management. Instead analysis of the UK experience has shown that the key independent prognostic factor is the interval from the last-known or causative pregnancy. Patients presenting beyond 4 years do exceptionally badly whereas those presenting within 4 years have a 98% long-term survival regardless of stage [4]. A more recent and as yet unpublished update suggests that stage is also an independent prognostic factor. Therapy is therefore stage and interval adapted. For patients with stage I disease within 4 years of the causative pregnancy, a simple hysterectomy with lymph node sampling and sparing of the ovaries but without adjuvant chemotherapy is all that is needed. However, those with stage I diease presenting more than 4 years from the causative pregnancy should be considered for adjuvant chemotherapy with or without high-dose chemotherapy given the comparative reduced sensitivity to standard-dose chemotherapy. Women who present with metastatic disease within 4 years are currently treated with EP/EMA chemotherapy until their hCG level is normal for 8 weeks and then offered surgery to remove all residual disease sites. If there is still active disease then high-dose therapy is considered. The latter is now included for all metastatic patients presenting beyond 4 years, along with other novel therapies. Some young patients presenting with PSTT/ETT within 4 years of the presumed causative pregnncy are understandably keen to preserve their fertility and wish to avoid hysterectomy. Several experimental approaches are being examined including focal resection of uterine disease using a modified Strassman procedure, followed by either nothing or adjuvant chemotherapy. Alternatively, neoadjuvant chemotherapy has been tried followed by observation or focal resection if a residual uterine lesion is seen. The problem with these approaches resides in persisting diffuse microscopic disease causing subsequent relapse with the potential to place patients in a poor prognostic group [43]. These approaches therefore remain experimental.

To gain more insight into PSTT/ETT the International Society for the Study of Trophoblastic Diseases has established a database for these cases which is run by Sheffield and Charing Cross in the UK (http://stdc.group.shef.ac.uk/psttuhr/index.html).

Risk of relapse and late treatment complications

For the majority of patients with trophoblast disease who achieve a serological remission the outlook is very bright in terms of the very low risks of relapse, the high possibility of further successful pregnancies and only modest long-term health risks from the chemotherapy exposure. Once the hCG level has fallen to normal, the risk of relapse is less than 4% for patients starting in the low-risk category and 8% for patients in the high-risk EMA/CO category [44]. Generally, recurrences occur within the first 12 months after treatment.

Subsequent fertility

Importantly, fertility is not clearly affected by single-agent therapy with methotrexate and apart from hastening the menapause by 3 years [45], EMA/CO appears to also have no impact on the chances of a successful pregnancy, which for both methotrexate alone or EMA/CO is 83% [46]. Despite this good news, some patients attending for fertility testing have been very worried by reports of low to undetectable anti-Müllerian hormone levels. Fortunately, all these women were menstruating normally, subsequently conceived and have had babies [47].

Further pregnancy should be deferred for 12 months after treatment to avoid any teratogenic effects on developing oocytes and to minimize possible confusion from the rising hCG levels between a new pregnancy and disease relapse. Despite this advice 500 of our treated patients have conceived in the first year of follow-up. Interestingly, the risk of relapse appeared to be lower, there were no abnormal babies and only the expected rate of miscarriages/pregnancy losses and second molar pregnancies. Only one patient suffered severe difficulty with lung metastases but fortunately both the patient and her baby were saved [48,49]. Therefore, for women who are worried about their declining fertility, it seems reasonable to let them make their own informed choice about earlier attempts to conceive.

Many patients after experiencing one molar pregnancy, and particularly those who require chemotherapy, are anxious about the problem occurring again in any subsequent pregnancy. While the data suggest that the risk of a further molar pregnancy is about 10-fold higher than in the normal population, this only equates to an approximate 1 in 100 risk [8,9]. This risk appears to be independent of chemotherapy exposure, being similar for those patients who required chemotherapy and those where the molar pregnancy was cured by evacuation alone.

Long-term toxicities

Although our prior analysis with 15 000 patient-years of follow-up suggested a slightly increased risk of second cancers in patients treated with combination chemotherapies [50], more recent data with over 30 000 patient-years of follow-up has revealed a different story [51]. These data show that EMA/CO if kept under 6 months in total duration carries no overall increased risk of triggering a second cancer in later life [51]. This is very important information to share with our patients. Of course, those that rarely need high-dose chemotherapy may not be in the same position and it is also true that high-dose chemotherapy will almost certainly destroy fertility. Fortunately, though, very few of our patients end up needing this.

Personal and psychological issues

Despite the high cure rate and relatively low long-term toxicity from chemotherapy treatment, it is unsurprising that the diagnosis of a gestational tumour and particularly treatment with chemotherapy can result in a number of psychological sequelae.

The main areas that can lead to stress in the short term include the loss of the pregnancy, the impact of the 'cancer' diagnosis, the treatment process and the delay of future pregnancy. During chemotherapy treatment issues regarding potential side effects, emotional problems and fertility concerns are frequent and patients will benefit from the support of an experienced counsellor. A number of studies have shown that these concerns can remain for many years, with feelings regarding the wish for more children, a lack of control of fertility and an ongoing mourning for the lost pregnancy still frequently reported 5–10 years after successful treatment [52,53]. A number of surveys have demonstrated the wish of many patients to have more support throughout their diagnosis and treatment through counselling and other forms of support. With the rarity of the diagnosis, providing expert counselling close to home is likely to be challenging, but support in the form of the patients internet forum

(https://mymolarpregnancy.com/) has proved extremely useful to many patients in the UK and elsewhere.

Summary

Over 90% of molar pregnancies will be cured with the first evacuation, the cases that require chemotherapy are generally cured with very low toxicity treatment, and the overall cure rate is approximately 100%. Patients presenting with high-risk disease can now expect to be cured in nearly 95% of cases and the development of new therapies provides promise that the remaining 5% of deaths will be eliminated in the not too distant future. PSTT/ETT, the rarest forms of GTN when presenting with advanced disease or beyond 4 years from the presumed causative pregnancy, still cause significant problems and major advances are required to improve cure rates.

In the UK there is a well-established centralized surveillance and treatment service that links all the obstetric and gynaecology teams with an effective registration, follow-up and expert treatment service. There is 24-hour emergency advice and treatment available in both major centres and they are always willing to give advice on any UK and overseas patient. The establishment of similar centralized care elsewhere in the world is to be encouraged to help improve outcomes for women with GTD globally.

Summary box 42.1

- Molar pregnancies occur at an approximate rate of 1 per 500 viable conceptions for women in the UK. The risk of a molar pregnancy increases with maternal age: for women aged 45, the risk is 1 in 96; for women aged 50 and over, the risk is 1 in 6.
- The risk of requiring chemotherapy treatment after the evacuation is approximately 15% for complete molar pregnancies and 1% for partial moles. Modern treatment produces cure rates of nearly 100% using primarily low-toxicity methotrexate chemotherapy.
- Choriocarcinoma is a rare diagnosis, with an incidence of 1 per 50 000–100 000 conceptions. The majority of cases occur after a normal pregnancy but the diagnosis can occur after a molar pregnancy or any other type of pregnancy including miscarriage. The presenting symptoms and findings in choriocarcinoma can be varied and it is recommended that every woman presenting with previously undiagnosed cancer should have a formal laboratory hCG check.
- The UK has a national service for the registration, surveillance and specialist treatment of gestational tumours. All patients with proven or suspected molar pregnancies should be registered and expert advice for emergency cases is available 24 hours a day.

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UK Hydatidiform Mole and Choriocarcinoma Information and Support Service: www.hmole-chorio.org.uk/

43

Ectopic Pregnancy

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The rate of ectopic pregnancy (EP) is 11 per 1000 pregnancies, with a maternal mortality of 0.2 per 1000 estimated EPs [1]. About two-thirds of these deaths are associated with substandard care [2]. In recent decades, there have been significant advances in the diagnosis and management of EP [3]. We have seen EP presentation change from being a life-threatening event requiring emergency surgery to a more benign early pregnancy complication in haemodynamically stable women. Consequently, women with an EP potentially present at earlier gestations, allowing for more conservative management strategies to be considered [3]. Contributing factors to this change are an increased awareness of risk factors for EP, introduction of high-resolution transvaginal ultrasound probes, availability of accurate and rapid serum human chorionic gonadotrophin (hCG) assays and the roll-out of early pregnancy assessment units [3]. Importantly, EP is still the most common cause of pregnancy-related deaths and morbidity worldwide, accounting for 54% of first-trimester maternal deaths in the UK, and 3–4% of all mortalities related to pregnancy [1,2]. This is despite the fact that the mortality from EP has significantly dropped over the last few decades [4,5].

In the emergency department setting, some 6–16% of all women who present with vaginal bleeding and/or lower abdominal pain in the first trimester will have an underlying EP [6]. Because of the often non-specific presentation of women with an underlying EP and the absence of a single diagnostic test, early diagnosis can be challenging in both the emergency department and general practice settings. In the most recent Confidential Enquiry into Maternal Deaths in the UK 2006–2008, gastrointestinal symptoms, particularly diarrhoea, and dizziness in early pregnancy were highlighted as important symptoms of EP. According to the authors, these clinical features need to be emphasized to all clinical staff in the primary care setting [2]. Although transvaginal ultrasound scan (TVS) and the rapid availability of quantitative hCG levels have significantly improved the early diagnosis and optimal management of EP [7–9], one cannot replace clinical acumen and a high index of suspicion for this condition at first presentation remains the key to early diagnosis, achieving the best outcome and avoiding maternal morbidity and mortality [10]. A detailed history, including assessment of possible risk factors for EP, as well as a focused physical examination and a quick office urinary pregnancy test can guide the clinician towards early diagnosis of EP.

Risk factors

Importantly, only about 50% of women diagnosed with an EP have identifiable risk factors. Recognition of these risk factors can assist the clinician not only in the early diagnosis of EP, but also in reducing the risk of massive intra-abdominal haemorrhage and its morbidity and mortality [11]. The incidence of EP increases among women who have a history of EP [12–14]. A woman who has had two prior EPs has a 10-fold increased risk of future EP. This increased risk could be attributable to underlying tubal dysfunction or secondary to the treatment of EP: after surgical or non-surgical management the EP recurrence rate is 8–15% and after conservative management 15% [13,14]. The risk of EP also increases in women who have a history of any type of pelvic surgery. For example, previous appendectomy has a twofold increased risk of EP [15,16]. Among the group of women in whom tubal sterilization has failed, pregnancy can result in an EP rate as high as 33% [13].

The incidence of EP increased by more than twofold during the period 1970–1985, from 7 to 16 per 1000, and then declined by 30% during the years 1985–1997. This was explained by the increase and decline of pelvic

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

inflammatory disease (PID) within those periods [17]. It has also been shown that having multiple sexual partners is a strong risk factor for EP, with an odds ratio of 2.1 [18,19]. There is an association between previous exposure to *Chlamydia trachomatis* and subsequent EP. In a recent study, previous exposure to *Chlamydia trachomatis*, as indicated by serum antibodies, doubled the risk of EP and was highest among women 35 years or older [20,21]. Overall, a history of genital infections including sexually transmitted infection, PID and/or any tubal pathology or surgery is a significant risk factor for tubal EP.

Smoking is a major risk factor for EP [22]. The risk of EP increases by threefold to fourfold in women who smoke more than one packet of cigarettes per day. The level of risk has been related to the number of cigarettes smoked per day. After stratification by the amount of daily smoking during the peri-conception period, the odds ratio rises from 1.6 for women who have smoked one to five cigarettes, to 1.7 for women who have smoked six to ten cigarettes, to 2.3 for women who have smoked 11–20 cigarettes, and to 3.5 for women who have smoked more than 20 cigarettes per day [23].

Historically, EP rates following assisted reproductive technologies are known to have increased over time. The rate of EP is 2–3% higher in women undergoing *in vitro* fertilization (IVF) compared with natural conception [24]. In addition, treatment with gonadotrophin and other drugs such as clomifene in IVF pregnancy increases the incidence of EP [23]. The rate of heterotopic pregnancy in the assisted reproductive population could be up to 1 in 100 to 1 in 45 [25,26]. More recently, however, a population-based retrospective analysis was carried out on all pregnancies following assisted reproductive cycles carried out in the UK between 2000 and 2012, in the anonymized database of the Human Fertilisation and Embryology Authority ($N = 161\,967$ treatment cycles). The authors concluded that EP rates in the UK following IVF/intracytoplasmic sperm injection have progressively decreased, and this appeared to be associated with a reduction in the incidence of tubal factor infertility and the increased use of both a lower number of embryos transferred and extended embryo culture [27].

Intrauterine contraceptive devices containing copper and the Mirena® intrauterine system (IUS) decrease the risk of an EP, but if pregnancy does occur with the device *in situ*, the risk of EP is higher [28–30]. Of the 0.5 per 100 Mirena IUS users who become pregnant in 5 years (cumulatively), half are EPs. Women aged 35–44 years have a three times higher risk of EP compared with younger women [31–33]. Diethylstilbestrol exposure *in utero* increases the relative risk of EP by 3.84 [34].

Summary box 43.1

- Ectopic pregnancy is still the principal cause of maternal death in the first trimester.
- Risk factors include:
  - previous ectopic pregnancy;
  - previous pelvic surgery (tubal ligation, appendicectomy);
  - history of PID, *Chlamydia*;
  - smoking cigarettes;
  - use of assisted reproductive technologies;
  - increasing maternal age;
  - diethylstilbestrol exposure *in utero*.

Types of ectopic pregnancy

Current evidence supports the hypothesis that tubal EP is caused by a combination of retention of the trophoblast/embryo within the fallopian tube due to impaired tubal transport of the embryo and alterations in the tubal environment allowing early implantation to occur [35]. Over 95% of EPs are tubal in origin, with 80% located in the ampullary portion of the fallopian tube [35]. Therefore approximately 5% of cases represent non-tubal EPs.

Non-tubal EPs can be located in the cervix, ovary, interstitial portion of the fallopian tube (i.e. that part of the fallopian tube which traverses the myometrium of a normally shaped uterus), caesarean scar or abdomen [7,8]. Note that cornual pregnancies are extremely rare (1 in 100 000 to 1 in 140 000 pregnancies) [36] and these occur in the non-communicating horn of a unicornuate uterus [37]. The term 'interstitial pregnancy' should not be used interchangeably with 'cornual pregnancy' [38]. Caesarean scar pregnancies occur when there is implantation into a lower anterior uterine segment at the level of a previous caesarean scar [39]. This incidence is quoted to be between 1 in 1800 and 1 in 2226 of all pregnancies, with a rate of 0.15% in women with a previous caesarean scar and a rate of 6.1% of all EPs in women who have had at least one caesarean delivery [40–42].

Summary box 43.2

- Types of ectopic pregnancy:
  - tubal (95%) vs. non-tubal (5%).
- Types of non-tubal ectopic pregnancy:
  - interstitial;
  - cervical;
  - ovarian;
  - caesarean scar;
  - cornual;
  - abdominal.
- The term 'interstitial pregnancy' should not be used interchangeably with 'cornual pregnancy'.

Diagnosis

TVS is the single best diagnostic modality for evaluating women with suspected EP [43–45]. This is the case for both tubal and non-tubal EPs. The presence of abdominal pain and/or vaginal bleeding in a premenopausal woman who is sexually active should prompt urinary pregnancy testing and in the event that this is positive should result in an assessment of the pelvis by an experienced operator using TVS. In a meta-analysis of the use of emergency-physician ultrasonography in the evaluation of patients at risk of EP, bedside ultrasonography provides excellent sensitivity and negative predictive value as a diagnostic test for EP [46]. Visualization of an intrauterine pregnancy by an emergency physician is generally sufficient to rule out EP [46].

In experienced hands, when there are no signs of intrauterine or extrauterine pregnancy on TVS, women should be classified as pregnancy of unknown location (PUL) [1,9,47,48]. Importantly, PUL is a descriptive term and should not be used interchangeably with EP [49,50]. The final outcome for a PUL includes a failed PUL, intrauterine pregnancy, EP or persistent PUL (PPUL), with EP and PPUL considered to be high-risk PUL [45,51]. An EP seen at the first ultrasound scan appears to be more symptomatic and larger in diameter and volume compared with an EP which starts as a PUL [52].

Tubal ectopic pregnancy

In experienced hands, over 70% of EPs are seen on ultrasound on the first scan [52,53] and well over 90% before surgery [54]. The diagnosis of a tubal EP by ultrasonography is based on one of the following grey-scale morphological appearances [54]:

1) an inhomogeneous mass or 'blob' sign adjacent to the ovary and moving separately to this (Fig. 43.1); *or*
2) a mass with a hyperechoic ring around the gestational sac or 'bagel' sign; *or*

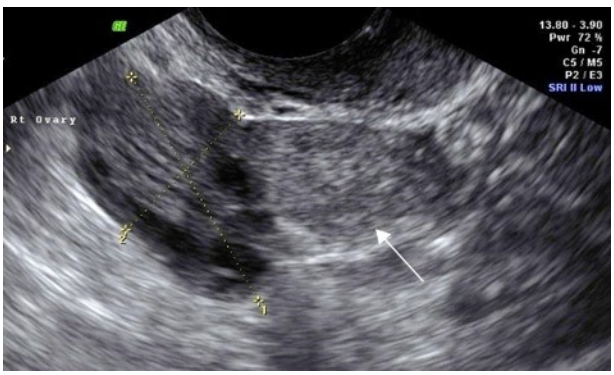

Fig. 43.1 An inhomogeneous mass or 'blob' (arrow) seen on transvaginal ultrasound.

3) a gestational sac with an embryonic pole with cardiac activity, i.e. a viable extrauterine pregnancy; *or*
4) a gestational sac with an embryonic pole without cardiac activity, i.e. a non-viable extrauterine pregnancy.

These various morphological ultrasound forms of tubal EP are reported with the following frequencies: 'blob' sign, 57.9%; 'bagel' sign, 20.4%; or gestational sac with a measurable embryonic pole, with or without positive cardiac beat, 13.2% [54,55]. In a recent meta-analysis assessing the accuracy of first-trimester ultrasound in diagnosis of tubal EP, TVS was more useful for confirming a tubal pregnancy rather than excluding one [56].

Non-tubal ectopic pregnancy

The differences between interstitial, angular and cornual pregnancies on two-dimensional sonography are subtle. Three-dimensional sonography has the advantage of providing coronal views of the uterus that cannot be obtained with conventional two-dimensional sonography, resulting in distinctive differences that assist in differentiating between interstitial, angular and cornual pregnancies [57].

Interstitial pregnancy

The following historical diagnostic criteria have been proposed based on two-dimensional sonography [58]:

1) an empty uterine cavity;
2) a chorionic sac separate and at least 1 cm from the lateral edge of the uterine cavity; and
3) myometrial thinning (a thin, <5 mm, myometrial layer surrounding the gestational sac).

However, these two-dimensional sonographic criteria only detect 40% of interstitial pregnancies. Ackerman *et al.* [59] added the term 'interstitial line', an echogenic line that runs from the endometrial cavity to the cornual region, abutting the interstitial mass or gestational sac. This criterion in particular provides a better sensitivity (80%) and specificity (98%) compared with the previously described eccentric gestational sac location (sensitivity 40%, specificity 88%) [60] and myometrial thinning (sensitivity 40%, specificity 93%) [58].

Although there are limited data on the use of three-dimensional sonography for the diagnosis of interstitial pregnancy, this modality could well be the likely successor to two-dimensional evaluation of potential interstitial pregnancies [57] (Fig. 43.2).

Cornual pregnancy

Mavrelos *et al.* [37] proposed the following ultrasound diagnostic criteria for a cornual pregnancy:

1) there is a single interstitial portion of the fallopian tube in the main uterine cavity;

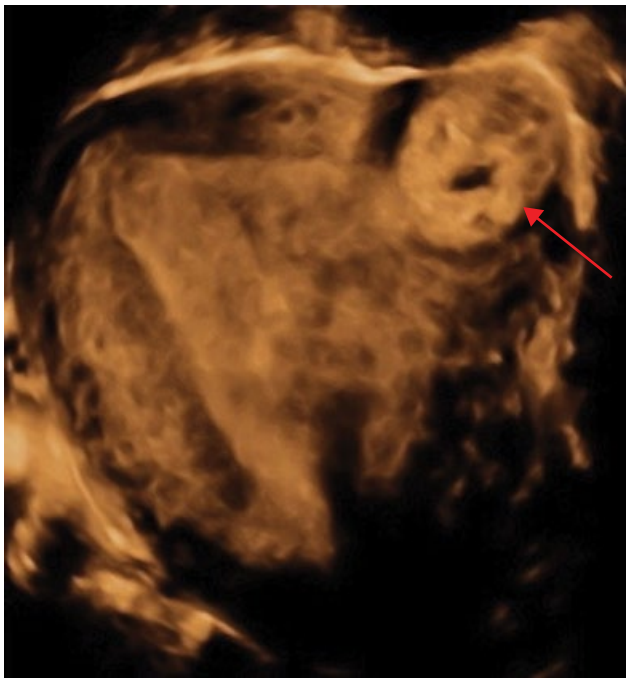

Fig. 43.2 Coronal view of the uterus showing an interstitial ectopic pregnancy (arrow). (*See also colour plate 43.2*)

2) a gestational sac, mobile and separate from the uterus, is surrounded by the myometrium; and
3) a vascular pedicle joins the gestational sac to the unicornuate uterus.

Caesarean scar pregnancy

The following ultrasound criteria have been proposed for the diagnosis of caesarean scar pregnancy [61]:

1) empty uterine cavity and empty cervical canal;
2) presence of the gestation sac with or without a fetal pole with or without fetal cardiac activity (depending on gestational age) located anteriorly at the level of presumed site of the previous scar in the lower uterine segment;
3) Doppler examination showing evidence of functional trophoblastic/placental circulation; and
4) negative 'sliding' sign.

Godin *et al.* [62] further described an empty cervical canal and absence of healthy myometrium between bladder and gestational sac.

Summary box 43.3

- In experienced hands, when there are no signs of intrauterine or extrauterine pregnancy on TVS, women should be classified as PUL.
- PUL is a descriptive term and should not be used interchangeably with EP.
- TVS in experienced hands is the diagnostic tool of choice for the diagnosis of ectopic pregnancy.
- 70% of tubal ectopic pregnancies are seen on ultrasound on the first scan and well over 90% before surgery.
- The various morphological features seen on ultrasound that indicate tubal ectopic pregnancy include:
  - 'blob' sign;
  - 'bagel' sign;
  - a gestational sac with a measurable embryonic pole, with or without positive cardiac beat.

Management

Clinical stability is the most important factor when determining whether the subsequent management of EP is surgical or not [63]. This is relevant to both tubal and non-tubal EPs (management of non-tubal EP is not discussed in this chapter). Ultrasound findings including the morphological appearance of the EP (i.e. the presence of an embryonic pole with or without cardiac activity) and the presence or absence of haemoperitoneum are also important considerations. TVS findings that include the presence of an embryonic pole with cardiac activity and the presence of haemoperitoneum are accepted indicators for surgical intervention [62,63]. The principle of preserving fertility also needs to be taken into account in the decision-making process before management is implemented.

Tubal ectopic pregnancy

Treatment options for tubal EP include surgery (e.g. salpingectomy or salpingotomy, performed laparoscopically or by open surgery), medical treatment using a variety of drugs that can be administered systemically and/or locally by various routes, and expectant management [64].

Conservative management (expectant and medical management)

Expectant management of tubal EP eliminates the need for medical or surgical treatment in more than one-third of women diagnosed with tubal EP, with minimum risk of adverse outcome [65]. Women with a conclusive ultrasound diagnosis of tubal EP who are clinically stable with no or minimal abdominal pain, no evidence of significant haemoperitoneum on ultrasound (Fig. 43.3), EP mass measuring less than 30 mm in mean diameter with no evidence of embryonic cardiac activity on ultrasound scan and serum hCG levels below 1500 IU/L can be selected for expectant management [65]. Importantly, all women selected for expectant management must be followed up until serum hCG levels are less than 5 IU/L.

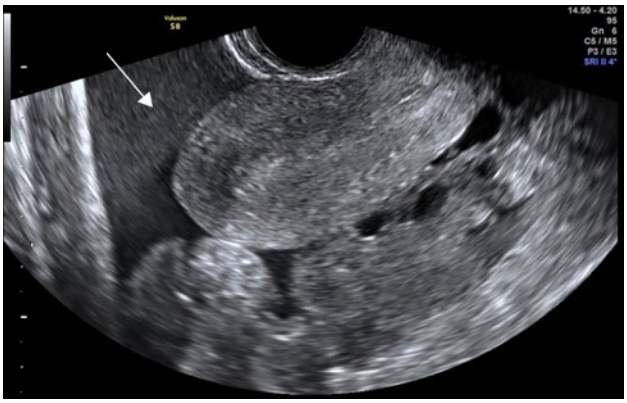

Fig. 43.3 Significant haemoperitoneum on transvaginal ultrasound: note the presence of 'ground glass' fluid (arrow) above the fundus of the uterus.

In another study, also including women with a conclusive ultrasound diagnosis of tubal EP, the most important variable for predicting the likelihood of successful non-surgical management was the pretreatment hCG ratio (defined as hCG 48 hours/hCG 0 hour) [66]. The pretreatment hCG ratio was related to the failure of both expectant (area under curve 0.86) and medical (area under curve 0.79) management.

In a recent randomized controlled trial, women with EP or PUL with low or plateauing hCG levels were assigned to systemic single-dose methotrexate (MTX) treatment or expectant management [67]. There was no difference in primary treatment success rate of single-dose MTX versus expectant management. After expectant management, 60% of women had an uneventful clinical course with steadily declining serum hCG levels without any intervention, indicating that MTX, a potentially harmful drug, can be withheld in these women. One criticism of this study is that women with a PUL were included in the randomization, some of which represented failing PUL, thus potentially overinflating the success in the MTX arm. Another criticism of this study is the inclusion of PUL, which means that these results cannot necessarily be extrapolated to other populations that classify an EP on the basis of conclusive ultrasound evidence.

If MTX is to be given to women with a tubal EP, single-dose MTX (50 mg/m^2) can be administered intramuscularly in selected cases with conclusive ultrasound evidence of an EP. Women need to be clinically stable and have TVS evidence showing an EP mass measuring less than 35 mm in diameter and absence of embryonic cardiac activity and haemoperitoneum [68]. If the serum hCG level falls more than 15% between days 4 and 7, then this is a good prognostic indicator for MTX response. If the serum hCG level falls by less than 15% between days 4 and 7, then a second dose of MTX can be given [68]. Importantly, all women selected for expectant management must be followed up until serum hCG levels are below 5 IU/L. If a woman does not respond to two doses of MTX, it is worthwhile considering other underlying pathologies such as gestational trophoblastic disease [69].

Surgical management

In the event that a woman with a tubal EP has haemodynamic instability and/or the presence of an EP mass containing an embryonic pole with cardiac activity on TVS and/or the presence of significant haemoperitoneum on TVS, then surgery is the appropriate course of action [64] (Fig. 43.4). Compared with laparotomy, the laparoscopic approach is less costly and associated with less blood loss and analgesic requirements and shorter hospital stay [64]. Single-dose MTX is less effective than laparoscopic salpingotomy [64]. Multiple-dose MTX is comparable to laparoscopic salpingotomy but the former has higher costs due to subsequent interventions. Only EPs with low initial hCG levels have cost savings when comparing MTX with laparoscopic salpingotomy [64].

In modern practice, tubal EPs can be surgically treated by laparoscopic salpingectomy, in which the affected fallopian tube is removed, or salpingotomy, in which the tube is preserved. Despite potentially increased risks of persistent trophoblast and repeat EP, salpingotomy is often preferred over salpingectomy because the preservation of both tubes is assumed to offer favourable fertility prospects, although little evidence exists to support this assumption. In the recent ESEP study, 446 women were randomly assigned to either laparoscopic salpingotomy or salpingectomy [70]. The cumulative ongoing pregnancy rate was 60.7% after salpingotomy and 56.2% after salpingectomy. Persistent trophoblast occurred more frequently in the salpingotomy group than in the salpingectomy group [14 (7%) vs. 1 (<1%)]. Repeat EP

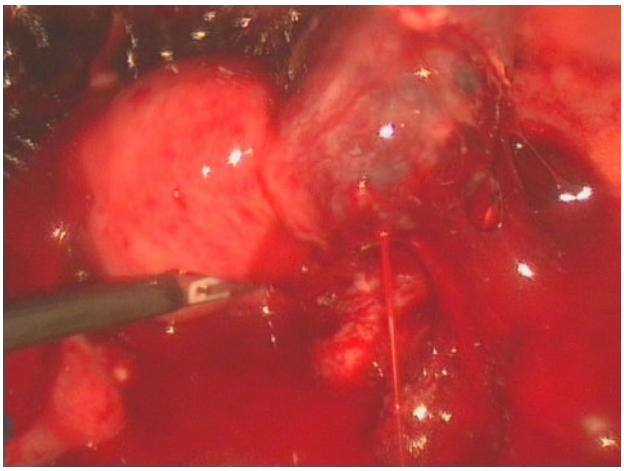

Fig. 43.4 A ruptured ectopic pregnancy at the time of laparoscopic intervention.

Summary box 43.4

- Various management strategies for tubal EP include:
  - expectant;
  - medical;
  - surgical.
- Expectant management is an option if the following are present:
  - there is conclusive ultrasound diagnosis of tubal EP;
  - clinical stability;
  - no or minimal abdominal pain;
  - no evidence of significant haemoperitoneum on ultrasound scan;
  - EP mass measuring < 30 mm in mean diameter with no evidence of embryonic cardiac activity on ultrasound scan;
  - quantitative serum hCG levels <1500 IU/L.

occurred in 18 women (8%) in the salpingotomy group and in 12 (5%) women in the salpingectomy group. The authors concluded that in women with a tubal EP and a healthy contralateral tube, salpingotomy did not significantly improve fertility prospects compared with salpingectomy.

Conclusion

Access to expertise and equipment for high-quality TVS means the majority of women with EP in developed countries can be diagnosed rapidly and accurately. The ultrasound diagnosis of EP not only enables clinicians to set out a clear management plan but also contributes to the improvement in maternal morbidity and mortality outcomes.

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44

Induced Abortion

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Induced abortion is an essential component of comprehensive reproductive healthcare. An estimated 56 million abortions are undertaken worldwide [1] and, in Britain, one in three women will terminate a pregnancy [2]. Over the last decade, the number of abortions undertaken yearly in the UK has remained fairly constant at about 200 000 [3,4]. Over 90% of abortions occur at under 13 weeks' gestation.

Women from all racial/ethnic, religious and socioeconomic backgrounds have abortions. Some demographic characteristics are more strongly associated with the decision to terminate a pregnancy than others. Age is one of the strongest factors, likely reflecting a readiness for parenthood. For example, conception rates in teenagers have declined steeply in Britain but in those under 16 years of age, 63% end in abortion [5]. In contrast, women aged 30–34 have seen continuous increases in conception rates since 1990, yet only 13% of these pregnancies are aborted. The majority of women resident in England and Wales who have abortions are single and white, although those who identify as Asian, Black or Black British are overrepresented relative to the proportion of these ethnicities in the general population. Over 50% of women who have an abortion have already had a child. Scottish statistics demonstrate a clear relationship between greater economic deprivation and a higher rate of abortion.

Just over one-third of women having an abortion in Britain will have had more than one abortion. This percentage has been rising since 2005, possibly due to greater accessibility of abortion services and acceptability of abortion as a means of fertility regulation. Older age and parity are associated with having more than one abortion as well as identifying as Black, leaving school at an earlier age, living in rented accommodation, reporting an earlier age at first sexual experience, being less likely to have used a reliable method of contraception at sexual debut, and reporting a greater number of sexual partners [2]. Intimate partner violence is also associated with having one or more abortions [6].

Although some planned pregnancies end in abortion, most women who have abortions did not intend to become pregnant. In the third National Survey of Sexual Attitudes and Lifestyles, 57% of unplanned pregnancies ended in abortion compared with 33% categorized as ambivalent and 10% as planned [7]. Unplanned pregnancy results from failures of contraception in some cases, but many occur because no contraception was used or because the method was used inconsistently or incorrectly [8]. Pregnancy intention is, however, only a first level signifier of the decision to terminate a pregnancy. Underneath is a complex set of reasons including educational aspiration, financial resources, health concerns or relationship difficulties.

Induced abortion using modern methods is very safe. When performed by trained clinicians with the appropriate resources, the chance of a woman dying from an induced abortion is considerably lower than chance of dying from childbirth. However, where abortion is provided by unskilled practitioners in unhygienic environments, it results in significant morbidity and mortality. Worldwide, an estimated 6.9 million women are treated for complications of unsafe abortion each year and up to 40 000 die [9].

This chapter focuses on elective induced abortion up to 24 weeks gestation; termination of pregnancy for fetal or maternal indications is not considered in detail. At these gestations abortion may be performed surgically or with medications. The choice of method is determined by multiple factors, including a woman's preferences, medical eligibility and service availability.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

The law and abortion

The legal criteria surrounding abortion are country-specific. In the UK, the 1861 Offences Against the Person Act (OAPA) made having or providing an abortion a crime carrying a potential life sentence. The 1967 Abortion Act, which does not extend to Northern Ireland, did not replace the OAPA or decriminalize abortion. Rather, it defined the circumstances in which an abortion could be performed without the risk of prosecution. These include having two registered medical practitioners agree that a woman meets one of five grounds (Table 44.1). This is indicated by signing a certificate (HSA1 form), which must be retained with the woman's clinical notes for a period of at least 3 years. In cases where an abortion is necessary as an emergency to save a woman's life or prevent grave permanent injury, only one doctor need authorize the abortion using an HSA2 form. A notification form (HSA4) must be signed by the doctor taking responsibility for the abortion and forwarded to the Chief Medical Officer of the relevant country. In the case of surgical abortion, the HSA4 form is signed by the doctor who carried out the uterine evacuation. For medical abortion, the doctor who prescribes the medications signs the form, although nurses or midwives commonly administer the drugs. The location where abortion may be performed is also defined in the Act and is limited to NHS hospitals or premises approved by the Secretary of State for Health.

Most abortions in Britain are undertaken under grounds C or D, which state that the pregnancy has not exceeded its 24th week and where continuance of the pregnancy would involve greater risks of injury to the physical or mental health of the woman or her existing children than if the pregnancy were terminated. In determining whether these grounds are met, account may be taken of the pregnant woman's actual or reasonably foreseeable environment. This 'health exception' has been very broadly interpreted by doctors in Britain, tending toward the World Health Organization definition, which states that health is not just the absence of disease but the presence of well-being.

Table 44.1 Statutory grounds for legal abortion in the UK.

A	The continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated
B	The termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman
C	The pregnancy has not exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman
D	The pregnancy has not exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of any existing child(ren) of the family of the pregnant woman
E	There is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped

Since the Abortion Act does not extend to Northern Ireland, abortion there remains highly restricted. Guidance for professionals on the termination of pregnancy in Northern Ireland was published in 2016 [10], reiterating that it is only lawful to perform an abortion in order to preserve the life of the woman or if there is a risk of 'real and serious adverse effect on her mental or physical health, which is either longer term or permanent'. The guidance is explicit in that it is not possible to create a reference list of potential circumstances in which a lawful termination could be carried out but that it is for a doctor to assess, on a case-by-case basis. This guidance appears to have had little effect on improving access to abortion in Northern Ireland. Almost all women needing abortion care travel to Britain or Europe and there is evidence that many obtain medications online to induce their own abortions outside the legal framework [11].

There is a conscientious objection clause within the Abortion Act that permits refusal to undertake abortions. This right is confined to participating in treatment and is excepted when an abortion is necessary to save the woman's life or prevent grave permanent injury to her physical or mental health. The limitation of the right to direct abortion care was reaffirmed by the UK Supreme Court in December 2014. Two midwives claimed that their right was breached when asked to answer telephone calls to book women for abortions and to delegate to or supervise staff providing abortion care. The Supreme Court considered the definition of the word 'participate' in the Act and concluded it to be 'taking part in a hands-on capacity: actually performing the tasks involved in the course of treatment'. Guidance from the General Medical Council also makes clear that while an individual doctor's personal beliefs should be respected, they must not interfere with access to information about and services for treatments to which they object [12]. A doctor with a conscientious objection to abortion is obliged to make sure a woman has enough information to arrange to see another doctor without an objection or, if it is not practical for a woman to arrange to see another doctor herself, provide or facilitate a prompt referral.

An assessment of an individual's capacity to give valid consent is essential before any medical procedure, including abortion. Separate legislation exists in England and Wales, and Scotland regarding medical

decision-making in the absence of capacity (Mental Capacity Act 2005 and Adults with Incapacity (Scotland) Act 2000). The management of women requesting abortion who may lack capacity is discussed in detail in guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) [13]. Particular note is made of the decision-making capacity of girls less than 16 years of age. The Abortion Act does not stipulate that a woman must be of a certain age to request abortion or require parental consent or notification. Legal precedent in England and Wales, as determined in the House of Lords ruling in the Gillick case, and legislation in Scotland (Age of Legal Capacity (Scotland) Act 1991) are similarly constructed in that following demonstration of comprehension of treatment and its consequences, individuals less than 16 years of age are able to consent for medical care. The Fraser criteria, which guides doctors asked to provide contraception to girls who refuse to involve their parents, is applicable to abortion care. The RCOG recommends that practitioners encourage a young woman to involve her parent(s) or another adult but state that this should generally not override the views of the young person.

Summary box 44.1

- Safe abortion is an essential component of comprehensive reproductive healthcare.
- One in three women will have had an abortion, meaning that all healthcare practitioners will encounter a woman who has had or needs an abortion.
- Healthcare providers must be able to manage requests for induced abortion according to principles of good medical practice and within the law.

Assessment for abortion

The assessment of a woman requesting induced abortion is focused on confirming that she is sure of her decision and providing sensitive decision-making support if needed, determining gestational age, identifying any contraindications that will restrict a choice of abortion method or anaesthesia, and determining whether treatment needs to be performed in a hospital setting or with cross-specialty liaison. There is strong evidence supporting a lower risk of complications for abortions undertaken at earlier gestations. Services therefore need to be organized to minimize delay. The assessment also provides an opportunity to discuss and plan for initiation of a contraceptive method, should a woman choose to use one after the abortion, and to screen for genital tract infections that increase the risk of infective complications.

Most women requesting abortion will have decided to have a termination of pregnancy before coming to a healthcare provider for assistance [14]. Compulsory counselling is not recommended as it delays treatment unnecessarily and may be viewed as intrusive by a woman who is certain of her decision. A non-judgemental interaction with a provider, an explanation of treatment options and risks, and prompt referral for treatment summarizes the expectations of most women once the decision to have an abortion has been made. For the small proportion of women for whom the decision is not straightforward, healthcare providers can assist with non-directive decision-making support or arrange for counselling. Either option may be assisted by the use of a tool, such as that created by the Family Planning Association (www.fpa.org.uk), which provides information about abortion, adoption and parenting and a list of considerations when deciding between them. Practitioners and women can be reassured that whether an unintended pregnancy is continued or terminated, the mental health outcomes will be the same [15]. The development of psychological problems after an abortion or a birth is most reliably predicted by a history of mental health problems. Referral pathways to therapeutic counselling should be in place for those situations regardless of the outcome of the pregnancy.

The clinical history should include relevant medical conditions, obstetric and gynaecologic history including prior ectopic pregnancy and sexually transmitted infections, allergies, medications, and recreational drug or alcohol use or abuse. It is important to explore any history of pain or bleeding in the current pregnancy as this may affect the decision to utilize ultrasound for gestational age determination and pregnancy location. There should be routine enquiry about intimate partner violence with appropriate support and information provided.

Most abortions can be safely carried out in day-case units or freestanding clinics. Indications for treatment in hospital include conditions that necessitate prolonged or intensive monitoring, such as severe cardiopulmonary disease, and those which place the woman at high risk of haemorrhage such as placenta praevia in women with prior caesarean deliveries, or coagulopathy. Some conditions, such as obesity or uterine anomalies including large fibroids, can make surgical abortion more challenging so prior knowledge of them is useful for procedure planning.

Establishing gestational age is important because it is the primary determinant of the way in which a medical or surgical abortion will be performed. Limits on gestational age are also integral to most abortion laws, including in Britain. The duration of the pregnancy is often determined by abdominal or vaginal ultrasound, as relevant to the anticipated gestation, where it is readily available. However, this should not be a barrier to service delivery as there is no evidence

that the routine use of ultrasound for this purpose improves either the safety or effectiveness of abortion procedures [16]. Last menstrual period (LMP) and a bimanual pelvic examination are sufficient in most cases with selective use of ultrasound where there is a discrepancy between LMP and uterine size or a concern for an ectopic pregnancy. Ultrasound is also often used to determine placental location in the second trimester in women with prior caesarean deliveries. It is important that a scan is undertaken in a sensitive setting and manner with a chaperone if the woman wishes to have one present. She should be advised that it is not necessary for her to watch the ultrasound examination in progress but she may be allowed to do so if this is her preference. It is useful to ask whether or not she wishes to be informed of any findings, such as multiple gestations.

Physical examination can be tailored to the anticipated treatment and the woman's medical history. Observations and height and weight (to determine body mass index) are routine, with cardiac, pulmonary, abdominal, pelvic or other examinations undertaken as needed. Blood testing is typically limited to determination of rhesus (D) antigen status. The risk of iso-immunization in the early first trimester appears negligible [17], but most services offer anti-D immunoglobulin to rhesus-negative women regardless of gestational age. Testing for haemoglobin is performed when there is a concern for anaemia and, often, if significant blood loss is anticipated, although data to support this practice are limited [18].

Ovulation can resume within 2 weeks of an abortion and many women will resume sexual activity during this time. Therefore, a woman who wishes to use a contraceptive method should initiate it as soon as possible after the procedure. This is facilitated by discussing contraception during the abortion assessment and providing a method at the time of treatment. Initiation of any hormonal method including the contraceptive implant, or insertion of intrauterine contraception (IUC) can occur immediately following completion of an uncomplicated surgical abortion at any gestation [19]. The risk of IUC expulsion may be increased slightly with immediate insertion after second-trimester surgical abortion but is far lower than the risk of not returning at all for insertion at a separate visit. Similarly, women may start any hormonal contraceptive method at the time of a medical abortion. IUC may be inserted once the gestational sac is confirmed as expelled, which is typically by ultrasound 1–2 weeks after taking the medications. Depending on the type used, a cervical cap or diaphragm will require refitting after second-trimester abortion. Condoms (male and female) can be used at any time after abortion and women may be offered emergency contraception (levonorgestrel or ulipristal acetate) to have in advance of need.

Screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is helpful because they increase the risk of post-abortion upper genital tract infection and its long-term sequelae of tubal factor infertility and ectopic pregnancy. The role of bacterial vaginosis (BV) in post-abortion infection is less clear and screening would be atypical. Rates of post-abortion upper genital tract infection vary widely but when objective criteria are used it is diagnosed in less than 1% of cases, regardless of abortion method and gestation.

Prophylactic antibiotics before first-trimester surgical abortion reduces the risk of infection by 41% (95% CI 25–54%) [20]. Evidence is limited in the context of second-trimester surgical abortion but it is reasonable to expect a similar impact on the reduction of infection. Universal prophylaxis before surgical abortion is standard but the evidence is poor for an optimal regimen. Recommendations vary from a single dose or short (3-day) course of doxycycline to presumptive treatment of *Chlamydia* and BV. The benefit of antibiotic prophylaxis with medical abortion is less clear. There have been no randomized controlled trials of antibiotic prophylaxis with medical abortion. Very rare deaths have been reported due primarily to *Clostridium* species. One before-and-after study of 227 823 women in the USA showed a 93% reduction in serious infection when two simultaneous changes were made: implementation of a routine 7-day course of doxycycline and a switch from the vaginal to buccal route of misoprostol [21]. As with surgical abortion, the RCOG recommends presumptive treatment of *Chlamydia* and BV at the time of medical abortion, but gives it a 'C' rating due to the limitations of existing studies.

Opportunistic screening for sexually transmitted infections (STIs), including HIV, also allows for active follow-up and partner notification and treatment. Screening for infections such as syphilis, hepatitis B and hepatitis C may occur on a selective basis, influenced by sexual health risk assessment and population disease prevalence. Cervical screening is not essential to abortion care but is an opportunity to check that screening is up to date and, where it is not, offering a cervical smear. For all tests it is important to ensure that the result can be communicated to the woman and appropriate action taken on any abnormal result.

Summary box 44.2

- Non-judgemental decision-making support and prompt referral for treatment characterizes the needs of most women requesting induced abortion.
- The medical assessment for abortion should be focused on establishing gestational age, eligibility for a choice of treatment options and location of care, and the need for anti-D prophylaxis.
- Discussing contraception and undertaking screening for STIs also form part of pre-abortion care.

Choice of method

Choice is an integral part of abortion care. Provision of information, along with decision-making support if needed, are essential to helping a woman select an abortion method that is right for her and which will optimize her abortion experience. In both the first and second trimesters, presuming no contraindications, abortion may be performed surgically or by the administration of abortifacient medications (Fig. 44.1). Both methods can be used in the case of multiple gestations. Some women prefer surgical abortion because it is predictable and quick, can be performed with a general or local anaesthetic or sedation, and has a low risk of complications. Others prefer medical abortion because it does not involve surgical instrumentation or anaesthesia and is perceived as more natural, like a miscarriage. In addition, medical abortion at a gestation of 70 days or less may be managed safely and effectively by the woman in the privacy of her own home which is preferred by many to care in a clinical setting.

Trials comparing medical and surgical abortion have been challenging to undertake because many women have an a priori preference for a method and refuse randomization. In the few studies available, some of which have included preference arms, acceptability with medical abortion has been found to be lower than with surgical abortion mainly due to greater pain and prolonged or heavier bleeding with medical abortion [22–25]. However, acceptability and satisfaction with either method is greatest when women are able to receive the type of abortion they want. Services with appropriately trained providers should therefore make both methods available at all gestational ages for which abortion is offered. If a service can only offer one method, referral pathways into other providers should be in place.

Information provided to a woman during the decision-making process should include which abortion methods and pain management options are available to her; what will be done before, during and after the procedure including any tests or examinations; what she is likely to experience (e.g. pain and bleeding, side effects, complications); where the procedure will occur; and how long the process is likely to take, including the need for any follow-up. Women undergoing medical abortion in the second trimester should be advised of the variable duration of the induction and possible need for overnight stay. Surgical abortion in the second trimester may require cervical preparation up to 24 hours before the evacuation so women need to be prepared for a procedure over 2 days although admission is not required.

Other aspects of care which may be important to address are whether her partner or another support person may be present during treatment and whether she may see the fetus or need to dispose of the products of conception after the abortion herself (i.e. with medical abortion at home). The World Health Organization's Clinical Practice Handbook for Safe Abortion (www.who.int/reproductivehealth/publications/en/) includes charts comparing the characteristics of various methods.

Summary box 44.3

- Choice between medical and surgical abortion methods is important and a primary determinant of satisfaction with care.
- Services should aim to provide both methods within the gestational age limit at which abortion is offered.
- Most abortions, regardless of method and gestational age, can be safely conducted in non-hospital settings as day-case procedures.

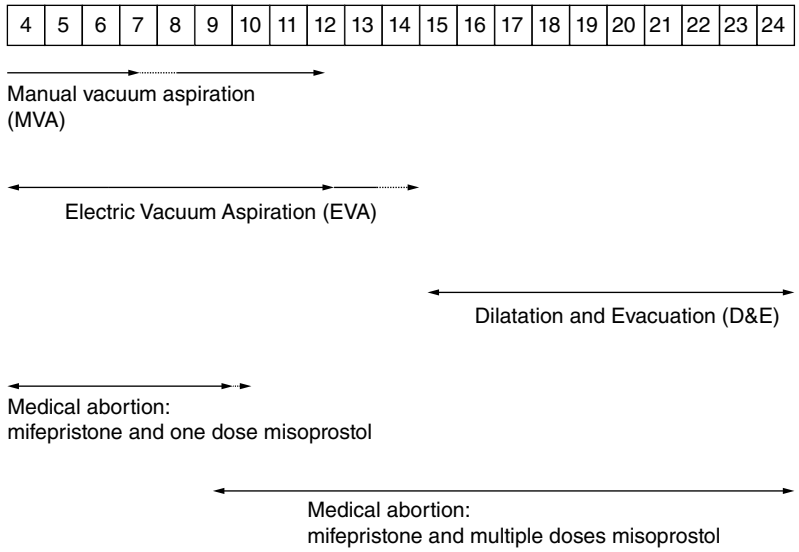

Fig. 44.1 Methods of abortion by gestational age in weeks.

Surgical abortion

Surgical abortion in the first trimester

Vacuum aspiration is the recommended method of surgical abortion in the first trimester. Compared with dilation and sharp curettage (D&C), vacuum aspiration is faster and associated with less pain and blood loss. Vacuum aspiration is also advantageous in that it can be performed in an office setting with local anaesthesia or conscious sedation whereas D&C requires treatment in theatre with general anaesthesia.

Vacuum aspiration may be performed with an electric suction machine or a manual vacuum aspirator which employs one or two valves and a locking plunger in a 60-mL hand-held syringe (Fig. 44.2). Safety, effectiveness and acceptability of electric and manual aspiration are equivalent [26]. Rigid or flexible plastic cannulae are used, the diameter chosen typically being the same in millimetres as the weeks of gestation. It is not uncommon, however, for manual vacuum aspiration to be performed with sequential use of 4-, 5- and 6-mm cannulae, avoiding the need to mechanically expand the cervical os with rigid tapered metal or plastic dilators. The single valve manual vacuum aspirator can accommodate cannulae up to 6 mm in diameter and the double value with cannulae up to 12 mm in diameter. With larger-bore tubing and cannulae available up to 16 mm, electric vacuum aspiration can be used into the second trimester although forceps are often needed to remove larger fetal parts, such as the calvarium or spine [27].

Historically, vacuum aspiration has been avoided under 7 weeks' gestation based on a cohort study that found a higher rate of missed abortion at gestations below 7 weeks' compared with 7–12 weeks' gestation [28]. However, with the increased sensitivity of urine pregnancy tests, many women now present at very early gestations, shortly after a first period has been missed. For these women, it is not acceptable to defer the abortion and their preference might not be for medical abortion; indeed there could be contraindications to medical abortion. Protocols which incorporate routine inspection of the uterine aspirate for the gestational sac, ultrasound and serial serum beta-human chorionic gonadotrophin (β-hCG) levels if ectopic pregnancy or missed abortion is suspected allow for very early surgical abortion to be provided safely with a failure rate ranging from 0.13 to 2.3% [29,30].

Fig. 44.2 Single- and double-valve manual vacuum aspirators. *Source:* Womancare Global. Reproduced with permission of Womancare Global.

Cervical priming agents are often used before vacuum aspiration to reduce or eliminate the need for mechanical dilatation. Options include medications, such as the progesterone antagonist mifepristone and the prostaglandin analogue misoprostol, and osmotic dilators which swell after insertion. Priming agents soften the cervix and open the os, leading to a slightly faster aspiration [31]. One trial demonstrated a decreased need for uterine re-evacuation for incomplete abortion among women who received misoprostol for cervical preparation as compared to a placebo (0.78% vs. 2.26%) [32]. Only osmotic dilators have been shown to reduce the risk of cervical laceration and uterine perforation; studies of pharmacological agents have not been sufficiently powered to determine whether they too lead to a reduction in these rare but serious complications.

Misoprostol is the most commonly used agent for cervical preparation before first-trimester surgical abortion. A dose of 400 μg is effective when administered per vagina 3 hours before the evacuation or sublingually 1 or 2 hours before surgery [33]. Side effects include nausea, vomiting, diarrhoea, chills, cramping and bleeding. Gemeprost is licensed in the UK for cervical priming but is no longer considered a first-line preparatory agent because it requires refrigeration, is expensive and may only be given per vagina. Mifepristone is better tolerated and achieves greater baseline cervical dilation than misoprostol, but requires administration at least 24 hours preoperatively and is significantly more expensive.

Given the side-effect profile of misoprostol and limited evidence of risk reduction, many providers base its use on risk factors for cervical or uterine injury. Common indications are age 17 years or less, prior cervical surgery, and gestational age over 12 weeks.

Pain management options for vacuum aspiration include local cervical anaesthesia with oral analgesia, conscious sedation, and general anaesthesia. Intravenous propofol and fentanyl without intubation characterizes general anaesthesia for abortion care. While there remains a lack of consensus on the ideal cervical anaesthetic, a randomized trial demonstrated improved pain

control with a regimen of 20 mL 1% buffered lidocaine and four deep (3 cm) paracervical injections compared with placebo [34]. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are the mainstay of oral analgesia in abortion care.

Advantages of local anaesthesia include faster recovery, a greater sense of control for the woman, and a reduction in procedural risks such as haemorrhage and cervical laceration [35]. However, local anaesthesia does not eliminate discomfort and some women may find being awake unacceptable. For women who want greater pain and anxiety management than local anaesthesia provides but do not want to be asleep, low-dose intravenous fentanyl and midazolam can be provided to achieve a state of conscious sedation. Women's preference, risk factors for anaesthetic complications, setting and resources should be considered when choosing a method of pain control during surgical abortion.

Performing vacuum aspiration

Vacuum aspiration is a straightforward procedure but careful practice is important so that pregnancies are evacuated completely and safely. Asepsis cannot be maintained during an abortion because contamination of gloved hands occurs once the woman is touched. Operators should employ a no-touch technique, in which the parts of the instruments that enter the uterus (e.g. cannula or dilators tips) are not handled. Careful and gentle instrumentation avoids injury to the cervix or uterus and good communication is needed between the operator, the woman and other members of the surgical team. Precise techniques vary among providers and with anaesthetic regimens. This section describes electric vacuum aspiration with local anaesthesia.

Once pre-procedure checks have been completed, the woman is assisted into the lithotomy position on a gynaecologic couch. After confirming the position, size and shape of the uterus by bimanual examination, a bivalve speculum is placed in the vagina. The cervix and vagina are cleansed with an antiseptic solution such as chlorhexidine. Local anaesthetic is administered by first injecting 1–2 mL 1% buffered lidocaine at the 12 o'clock position on the cervical face. A vulsellum or tenaculum is applied and, with gentle outward traction, an additional 18 mL of buffered lidocaine is injected in equal aliquots paracervically at the 2, 4, 8 and 10 o'clock positions. Cervical dilation to the diameter of the suction cannula is performed with tapered metal or plastic dilators (e.g. Pratts or Hawkin Amblers). The suction cannula is inserted into the mid to upper fundus, taking care not to touch the fundus which causes pain. When the operator is sure of correct placement, suction is engaged until negative pressure of 60 mmHg is reached. During the aspiration, which takes between 3 and 5 min, the cannula is gently rotated and/or moved back and forth, withdrawing only as far as the internal os until the flow of tissue and fluid has ceased and a gritty sensation is felt as the cannula moves against the wall of the contracted empty uterus. At this stage, the woman may feel a strong cramp. Calm and comforting conversation to distract the woman and explaining the meaning of unpleasant sensations will help her tolerate the procedure. Sharp curettage should be avoided. The vulsellum or tenaculum is removed and the cervix inspected for bleeding. Because of low rates of haemorrhage, oxytocics are not routinely administered. The operator should ascertain that the gestational sac and any fetal parts, consistent with the gestational age, have been removed. Continuous ultrasound guidance is increasingly used but is not required if the aspirate will be inspected. Once the operator is certain of completion, the woman should be reassured. Any concomitant procedures (e.g. insertion of IUC) can be performed before the woman is escorted into the recovery area.

Surgical abortion in the second trimester

Electric vacuum aspiration can be performed up to 16 weeks' gestation but the most frequently used method of surgical abortion in the second trimester is dilatation and evacuation (D&E). Characterized by advanced cervical preparation and removal of the fetus and placenta with specialized forceps, D&E is associated with a low risk of complications and is highly acceptable to women. When second-trimester surgical abortion was compared in a randomized trial with medical abortion, significantly fewer women found the surgical option worse than expected (0% vs. 53%, $P = 0.001$), and more would opt for a surgical procedure again if needed (100% vs. 53%, $P \leq 0.001$) [32]. A variant of D&E, intact dilatation and extraction (D&X), is performed after very wide (median 5 cm) cervical dilation is achieved using osmotic dilators over two or more days. This is followed by an assisted partial breech delivery, decompression of the calvarium, and delivery of the fetus otherwise intact. Hysterotomy and hysterectomy are outdated methods and only used when a transcervical approach is not possible. Obstruction by a large, distorting cervical or uterine tumour is an example of when these methods might be employed.

Adequate cervical preparation is essential for safe D&E provision. The amount of cervical expansion needed is related to gestational age, provider skill and the instruments being used. As a general rule, dilation should be sufficient to insert and open the extraction forceps and remove the fetal parts without resistance. Until about 16–17 weeks of gestation, sponge or McClintock forceps may be used so 1–1.5 cm dilation will suffice. After this point, longer forceps with wider

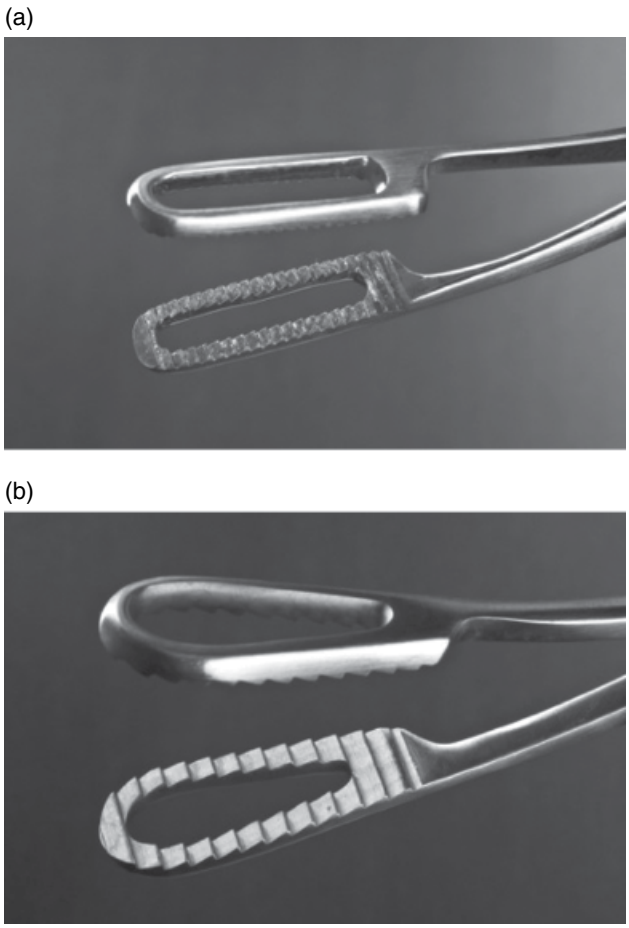

Fig. 44.3 (a) Sopher forceps; (b) Bierer forceps. *Source:* Ipas. Reproduced with permission of Ipas.

serrated jaws are used, requiring 1.5–3 cm or more dilation. Sopher and Bierer forceps, the jaws of which range from 12 to 19 mm in diameter, are typical (Fig. 44.3). Misoprostol or mifepristone can be used for cervical priming before D&E but additional mechanical dilatation is often required. Osmotic dilators provide superior cervical dilation throughout the second trimester [36] and are used by most providers from approximately 18 weeks' gestation. There are two types: laminaria made of compressed seaweed and Dilapan-S made of polyacrylate-based hydrogel. After insertion into the cervical canal, these devices swell over several hours causing expansion of the os. They also induce the release of natural prostaglandins leading to cervical softening. A preference for Dilapan or laminaria is provider-dependent and although more laminaria are required to achieve the same amount of dilation as Dilapan, a comparative trial found no differences in procedure time, blood loss or need for additional dilatation between devices [37].

Feticide is used before D&E by some abortion providers in the belief that the softening of fetal tissue after demise facilitates an easier, faster and safer evacuation. It is also used in response to patient preference or to avoid the risk of transient signs of life should extramural delivery occur. The most frequently used methods are intra-amniotic or intra-fetal injection of digoxin, and fetal intra-cardiac potassium chloride injection. Research is limited, but the few existing comparative studies suggest that feticide before D&E does not confer a clinical benefit and may increase risks. The only randomized controlled trial available found that intra-amniotic digoxin administered 24 hours before D&E did not reduce the duration of the procedure, blood loss or subjective difficulty of the procedure compared with placebo [38]. In addition, a before and after study found low but increased risks of extramural delivery and infection with the digoxin compared to non-use [39]. Cohort studies of fetal intracardiac potassium chloride injection before D&E differ as to whether it decreases operative times but found increased risks of cervical laceration and uterine atony compared with non-use or D&E in the setting of spontaneous demise [40,41].

D&E can be performed with local anaesthesia, conscious sedation or general anaesthesia. General anaesthesia or sedation predominates from about 18 weeks' gestation. In a study of over 11 000 second-trimester surgical abortions with intravenous anaesthesia without intubation, there were no cases of pulmonary aspiration supporting the safety of this technique beyond the first trimester [42].

Performing dilatation and evacuation

As with any surgical procedure, D&E requires competency-based training and ongoing operative experience. Skills are usually acquired in a graduated fashion, with competence demonstrated at earlier gestational ages before advancing to later ones. As with vacuum aspiration, techniques vary. The following describes the typical steps of a D&E with general anaesthesia.

Following pre-procedure checks, anaesthesia is induced and the woman is placed into the lithotomy position. A bivalve or Sims speculum is inserted and any osmotic dilators *in situ* are removed and counted. The cervix and vagina are cleansed. A vulsellum or tenaculum is placed and, applying gentle traction, additional mechanical dilatation is undertaken if required. The amniotic fluid is drained passively or actively with vacuum aspiration. This reduces the risk of amniotic fluid embolism and facilitates extraction from the lower uterine segment, which lessens the risk of perforation. Continuous ultrasound is recommended to guide instrumentation. Maintaining steady traction on the cervix, the forceps are inserted with the tips facing upward. Once the internal os is traversed, and remaining in the lower uterus, the jaws of the forceps are opened widely to grasp the presenting fetal part and then withdrawn while gently rotating. Multiple passes are used although the number can be

limited by achieving ample cervical dilation. Fetal parts and the placenta should be noted as they are removed and inspected afterward for completeness. A final vacuum aspiration is performed to remove any remaining blood or tissue. The amount of bleeding is assessed and the instruments are removed. A bimanual examination can ensure the uterine tone is firm and, if needed, uterotonics administered before the woman is moved into the recovery area.

Complications with surgical abortion

Among 170 000 first-trimester vacuum aspirations in low-risk women, minor complications occurred in 8.5 per 1000 cases and complications requiring hospitalization in 0.7 per 1000 cases [43]. D&E has a similar low rate of complications, although the risk of a major complication increases with gestational age. A history of two or more caesarean deliveries is the strongest predictor of a major complication with D&E (OR 7.4, 95% CI 3.4–15.8) [44].

Uterine perforation during vacuum aspiration ranges from 0.1 to 4 per 1000 procedures. With D&E, perforation occurs in 2–3 per 1000 procedures. A perforation with a small-diameter dilator or cannula in a haemodynamically stable woman may be managed conservatively with careful observation. Larger injuries, including those associated with D&E, or where there is active bleeding or haemodynamic instability, require laparoscopy or laparotomy. Cervical tears occur in 0.1–10 per 1000 procedures. External tears that are bleeding or larger than 1 cm will typically require repair with absorbable sutures. Larger or full-thickness tears at the level of the internal os will usually require operative intervention or embolization. Serious haemorrhage requiring hospitalization or transfusion occurs in fewer than 1 in 1000 cases. Significant bleeding is most commonly due to uterine atony, but may also be caused by trauma, retained tissue or coagulopathy. Retained tissue requiring re-aspiration occurs in up to 2 in 100 cases after first-trimester surgical abortion and up to 3 in 100 following second-trimester surgical abortion. Continuing pregnancy occurs in fewer than 1 in 1000 procedures performed at 12 weeks' gestation or less but is higher with uterine anomalies, multiparity, very early gestational age, and when performed by a less experienced surgeon.

Women and clinicians may be concerned that the amount of artificial dilation needed to perform D&E will affect the integrity of the internal cervical os, resulting in an increased risk of cervical incompetence, miscarriage and preterm birth. Neither retrospective case series nor a case–control study have found an association between D&E preceded by cervical preparation with overnight osmotic dilators and future pregnancy complications [45–47].

Summary box 44.4

- Vacuum aspiration is the preferred method for first-trimester surgical abortion and D&E in the second trimester.
- Surgical abortion may be offered in the earliest weeks of pregnancy following a protocol that includes inspection of the aspirate for the gestational sac and serum β-hCG determination if a missed abortion or ectopic pregnancy is suspected.
- Women should be reassured that the risk of major and minor complications with surgical abortion at all gestations is low.

Medical abortion

Medical abortion up to 9–10 weeks' gestation

The development of simple, highly effective regimens for abortion using mifepristone has transformed abortion care in the UK. Introduced in 1991, it is now the case that 50% of abortions in England and Wales and 81% in Scotland are conducted medically. Along with better funding of and access to abortion services in Britain, widespread availability of medical abortion in the earliest weeks of pregnancy has likely contributed to the growing proportion of abortions performed at less than 10 weeks' gestation. Early medical abortion refers to the use of abortifacient medications up to 63 days' gestation, although some regimens are effective beyond 63 days.

Mifepristone causes cervical softening, decidual necrosis and increased myometrial sensitivity to prostaglandins. Initially studied for use alone in very early pregnancy, it was found to be effective in only 60–80% of cases. However, when administered 24–48 hours before a prostaglandin analogue, efficacy increased to nearly 100%. Multiple randomized trials have since demonstrated that the combination of mifepristone and misoprostol is the most effective, well-tolerated and cost-effective regimen for early medical abortion [15]. Complete abortion without surgical intervention is achieved in upwards of 95% in most studies, with an ongoing pregnancy rate of 1% or less [48]. Misoprostol can be used alone but is less effective.

Contraindications to mifepristone/misoprostol are few but include chronic adrenal failure, inherited porphyria, coagulopathy, hypersensitivity to the medicines, and known or suspected ectopic pregnancy. Mifepristone is an anti-glucocorticoid, and thus caution is also advised for women using long-term corticosteroids or with conditions that may require steroid treatment in case of exacerbation such as severe, poorly controlled asthma. Caution is advised with hepatic or renal failure or malnutrition. If a woman has an intrauterine contraceptive in

place, it will need to be removed before initiating treatment. Most protocols also exclude women with haemoglobin levels less than 90–100 g/L as blood transfusion rates, although very low, are higher with medical than surgical procedures.

The recommended regimen at a gestation of 63 days or less consists of 200 mg oral mifepristone followed 24–48 hours later by 800 μg misoprostol which may be given by the vaginal, sublingual or buccal route. For many years, 600 mg mifepristone was recommended but the lower dose is as effective [49]. Mifepristone and 400 μg oral misoprostol may be used at 49 days or less of gestation, but has an unacceptably high failure rate after this gestation, even if the dose of misoprostol is doubled.

Several studies have explored whether the interval between mifepristone and misoprostol can be reduced below 24 hours or extended beyond 48 hours. A meta-analysis of randomized trials found no difference in overall efficacy with intervals of 0–72 hours, but there was a trend toward lower success with less than 8 hours between medications [50].

The extension of an early medical abortion regimen to 70 days' gestation has been the subject of recent research. A review of published studies using 200 mg oral mifepristone and a range of misoprostol doses and routes showed no statistically significant difference in overall success at 57–63 days' gestation and at 64–70 days' gestation (93.9% vs. 92.3%, $P = 0.08$) [51]. The ongoing pregnancy rate was 3.1% at 64–70 days (95% CI 2.9–4.5) but most women reported satisfaction with treatment.

Most early medical abortions are undertaken outside of a medical facility. In many countries, women are given tablets of misoprostol to take home and use within a specified interval, followed by abortion at home. A large body of evidence demonstrates that this is safe, effective and acceptable to women [52]. Recent research also shows that use of mifepristone at home is safe and preferred by many women. The Secretary of State for Health has the power to allocate 'home' as a class of place for the purposes of early medical abortion in Britain. This has recently occurred in Scotland and is planned for Wales, but it remains the case that women in England may not use medications for abortion outside of a clinical setting. Where home use is not allowed, women must attend for both mifepristone and misoprostol administrations. They need not be admitted after either and the vast majority go home after misoprostol to pass the pregnancy at home.

Symptoms after mifepristone are minimal but some women will bleed in the interval before misoprostol is administered and a small number will miscarry. Misoprostol induces bleeding and uterine cramping within 2 hours of use. Most women will pass the pregnancy within 4 hours and almost all by 24 hours. Oral analgesia with NSAIDs or mild opioids is commonly needed. Paracetamol is less effective than ibuprofen for pain reduction [53]. Other side effects caused by misoprostol include nausea and vomiting, diarrhoea, and transient fever and chills. Vaginal administration is associated with the fewest gastrointestinal side effects and sublingual with the most frequent reports of fever and chills. Information must be provided about expected signs and symptoms as well as the signs of possible complications and whom to contact should they occur. These include vaginal bleeding that soaks more than two sanitary pads for two consecutive hours, a persistent temperature greater than 38 °C, severe abdominal pain unrelieved by analgesics, nausea, vomiting or diarrhoea that continues more than 24 hours after misoprostol administration, and the persistence of pregnancy symptoms 1–2 weeks after medication administration. Women aborting at home should be told what if anything they may see (i.e. gestational sac, clots, fetus) and advised on appropriate disposal of fetal remains [54].

Medical abortion after 9–10 weeks' gestation

Medical abortion may be used throughout the late first and second trimester. Failure rates and bleeding complications are higher with medical than surgical abortion at these gestations; however, if clinicians are not trained to provide D&E, medical abortion is an effective alternative. Mifepristone and misoprostol regimens are the most efficacious with the shortest induction-to-abortion interval (the time between the administration of misoprostol and the passage of the fetus). The median induction-to-abortion interval with a combined regimen is 6–8 hours in most studies. Misoprostol may also be used alone but the median interval is increased significantly to 12–16 hours.

The regimen for which there is the most evidence employs a 200-mg oral dose of mifepristone followed 24–48 hours later by admission to a clinical facility and administration of an initial 800-μg dose of vaginal misoprostol. Every 3 hours, a further 400 μg of misoprostol is administered vaginally, sublingually or orally until expulsion occurs. Routine instrumental removal of the placenta after fetal expulsion is not necessary; misoprostol may be continued.

In a consecutive series of 1076 women at 64–91 days' gestation treated with this regimen, the overall complete abortion rate was 96% and the median induction-to-abortion interval was 4.8 hours (range 0–74.9 hours) [55]. The rate of surgical evacuation increased linearly with gestational age: 2.7% at 64–70 days, 3.3% at 71–77 days, 5.1% at 78–84 days, and 8.0% at 85–91 days ($P = 0.02$). The same group published the outcomes of 1002 cases at 13–21 weeks' gestation and reported that 97% aborted within five doses of misoprostol and the median induction-to-abortion interval was 6.25 hours (range 0–67.5 hours) [56]. The interval between mifepristone and the initiation of misoprostol can be reduced to 12 or 24 hours, which increases the induction-to-abortion interval by 1–2 hours [57].

The severity of pain with medical abortion increases with gestational age and several oral and parenteral NSAIDs and opioids should be made available. Diclofenac given with the first dose of misoprostol between 13 and 22 weeks of gestation does not interfere with the action of the misoprostol and reduces the need for opioid injections [58].

Complications with medical abortion

Serious adverse events with early medical abortion are rare. Among 233 805 early medical abortions provided within a large network of abortion clinics in the USA, the rate of clinically significant adverse events (e.g. hospital admission, blood transfusion, treatment with intravenous antibiotics, death) was 1.6 per 1000 cases. Two significant adverse outcomes were also reported in this study, undiagnosed ectopic pregnancy and ongoing pregnancy, with rates of 7 in 10 000 and 5 in 1000 cases, respectively. Overall, 3–5 per 1000 early medical abortions will require surgical intervention, typically due to persistent bleeding, continuing pregnancy or retained non-viable pregnancy or tissue.

In the late first and second trimester, complications with medical abortion are comparatively higher than with surgical abortion, mainly due to retained placental tissue and associated heavy bleeding. Transfusion is required in 5–7 per 1000 second-trimester medical abortions and surgical intervention in up to 8 per 100 procedures. Cervical and uterine injury is largely obviated by avoiding instrumentation with medical abortion. However, uterine rupture can occur with second-trimester medical abortion and is associated with a prior history of caesarean delivery. A systematic review estimated the risk of uterine rupture in women with prior caesarean delivery to be less than 3 in 1000, and 4 in 10 000 without a history of caesarean delivery [59].

Mifepristone is not feticidal and transient signs of life can present medicolegal and emotional challenges for women and healthcare providers offering medical abortion in the peri-viable period. The RCOG recommends feticide from 22 weeks' gestation to avoid signs of life at delivery [15].

Summary box 44.5

- Mifepristone and misoprostol is the most effective regimen for first- and second-trimester medical abortion and has the shortest induction-to-abortion interval.
- Early medical abortion with mifepristone and misoprostol may be safely undertaken in a non-clinical environment; after 9-10 weeks' gestation, admission to a clinical facility is typically required.
- Complications are mainly due to retained tissue and bleeding and may require surgical managment.

Aftercare

When a surgical or medical abortion is uncomplicated and the success of the procedure is immediately verified, routine follow-up is not necessary. Providing a 24-hour aftercare telephone line is common and ready access to follow-up visits should be available if needed. A woman should be advised to be in contact if she experiences signs of ongoing pregnancy or for other medical reasons such as prolonged heavy bleeding, fever, and persistent or severe pain.

Protocols for early medical abortion undertaken outside of a clinical setting often require the woman to return 7–14 days after treatment to confirm that she is no longer pregnant. Where ultrasound is used, measurement of endometrial thickness as an indicator of incomplete abortion is not recommended as it is an unreliable predictor of the need for surgical evacuation and can lead to unnecessary interventions.

The use of a low- or high-sensitivity urine pregnancy test 2–4 weeks after early medical abortion often alongside a symptom checklist is also accurate at identifying failed procedures and is preferred by women. Protocols may include a telephone assessment of symptoms with a provider or self-assessment. Urine pregnancy tests are affordable, readily available and user-friendly but caution should be used when interpreting a positive result. Even though β-hCG levels drop precipitously after an abortion, highly sensitive tests (25 mIU/mL) are still inconclusive or falsely positive 66% of the time at 2 weeks [60] and 20% of the time at 4 weeks after abortion [61]. In these cases, an ultrasound can be performed to determine whether the pregnancy is continuing. Self-assessment with a semi-quantitative urine pregnancy test that measures urine β-hCG levels of 25, 100, 500, 2000 and 10 000 mIU/mL has been studied with promising results [62]. In a prospective open label trial, the test was performed before and 1 week after medication administration and pregnancy was considered ongoing if the follow-up reading was the same or higher than the baseline results. Sensitivity and specificity were calculated at 100% and 97%, respectively, and 91% of participants found the test to be 'very easy' or 'easy' to use.

Summary box 44.6

- Routine follow-up after surgical abortion or where a medical abortion has been verified as complete is not required.
- All women should be able to access a follow-up visit if they want one.
- Follow-up after early medical abortion conducted outside of a medical facility can be safely and effectively managed without an in-clinic visit by employing a high- or low-sensitivity pregnancy test and checklist of symptoms.

Conclusions

Abortion is an integral part of women's healthcare. Healthcare practitioners should be familiar with the standards of care relevant to this common procedure. Counselling before treatment should be supportive, non-directive and focused on the patient's needs. Surgical and medical abortion methods are both safe and effective throughout the first and second trimesters of pregnancy. A choice should be available to women. For those women wishing to use it, contraception can be easily integrated into abortion care.

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45

Acute Pelvic Infection

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Summary box 45.1

Overview of pelvic infection

- Pelvic inflammatory disease is a common and often asymptomatic problem in young women.
- Confirmation with a microbiological diagnosis is often not possible.
- Antibiotics are very effective in controlling symptoms when present.
- Surgical intervention is seldom required.
- A single episode of pelvic inflammatory disease treated early with appropriate antibiotics is associated with well-preserved fertility.

Pelvic infection is common and usually results from sexually transmitted pathogens ascending from the lower to upper genital tract. Infection can also occur following pelvic surgery, in the puerperium and after instrumenting the uterus.

Epidemiology and risk factors

How common is pelvic inflammatory disease?

Pelvic inflammatory disease (PID) is a major cause of morbidity in young women, although its incidence in primary and secondary care has been falling for several years. About 2% of young women in the UK give a history of PID when asked, and about 1 in 50 consultations made by young women with general practitioners relate to PID [1].

Who gets pelvic inflammatory disease?

The risk factors for PID strongly reflect those of any sexually transmitted infection (STI) – young age, multiple sexual partners, lack of condom use, lower socioeconomic status and Black Caribbean/Black African ethnicity. What is less certain is why some women with lower genital tract infection go on to develop upper genital tract disease. What factors encourage infection to spread from the vagina or cervix to the endometrium and fallopian tubes?

Cervical mucus provides an important barrier to ascending infection. Young women with anovulatory cycles have thinner cervical mucus and this, combined with higher rates of cervical ectopy and riskier sexual behaviour, may account for their high rates of PID. The ability of the immune response to control and contain infection will also determine the risk of upper genital tract involvement. Part of that immune response is genetically determined and an increased risk of PID is observed in women of human leucocyte antigen (HLA) subtype A31, while women with HLA-DQA 0501 and HLA-DQB 0402 have lower rates of infertility following a diagnosis of PID. Polymorphisms in TLR4 and CCR5 antigen receptors, and variable expression of interleukin (IL)-10, may also have a role. It is possible that certain strains of bacteria are more likely to cause PID than others, but the evidence for this is limited (e.g. serogroup A *Neisseria gonorrhoeae,* serovar F *Chlamydia trachomatis*).

Differences in behaviour have been linked to the risk of PID. A clear association can be seen between vaginal douching and PID but more recent longitudinal studies suggest that douching does not cause PID; rather, it would appear that the vaginal discharge and menstrual

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

irregularities associated with PID may themselves lead to more douching [2]. Women who smoke are at higher risk of PID but it is unclear whether this is a marker for high-risk sexual behaviour or a direct effect of smoking itself on immune surveillance.

Many women with PID also have bacterial vaginosis with overgrowth of the normal commensal bacteria in the vagina and loss of vaginal lactobacilli. These same vaginal commensal bacteria are often isolated from the upper genital tract, raising the possibility that bacterial vaginosis may lead to PID. Longitudinal studies do not support a direct causal association, although women who contract gonorrhoea or chlamydia are at higher risk of PID if they also have pre-existing bacterial vaginosis, suggesting some synergy between the different infections [3].

The cost of treating pelvic inflammatory disease

The psychological and fiscal costs of PID are substantial. The uncertainty of the diagnosis and difficulty in predicting the subsequent risk of infertility, chronic pelvic pain or ectopic pregnancy add to the anxiety, and are in addition to the feelings of blame, guilt and isolation that the diagnosis of an STI may instil. Most of the monetary costs of PID arise from surgical interventions to diagnose and treat the consequences of tubal damage, and have been estimated at between £200 and £2000 per case [4]. These costs will rise substantially with improved availability of infertility treatments in the future.

Microbiology

Pelvic inflammatory disease is a polymicrobial infection. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most frequently recognized pathogens but a wide variety of other bacteria and viruses can also be isolated from the fallopian tubes of women with PID (Table 45.1).

Table 45.1 Organisms associated with pelvic inflammatory disease.

Aerobic/facultative anaerobic
Neisseria gonorrhoeae
Chlamydia trachomatis
Ureaplasma urealyticum
Mycoplasma genitalium
Gardnerella vaginalis
Streptococcus pyogenes
Coagulase-negative staphylococci
Escherichia coli
Haemophilus influenzae
Mycoplasma hominis
Streptococcus pneumoniae
Mycobacterium tuberculosis
Anaerobic
Bacteroides sp.
Peptostreptococcus sp.
Clostridium bifermentans
Fusobacterium sp.
Viruses
Herpes simplex virus
Echovirus
Coxsackievirus
Respiratory syncytial virus

Bacteria

Neisseria gonorrhoeae

Neisseria gonorrhoeae is a Gram-negative diplococcus, so that when a sample of cervical discharge is spread and fixed on a slide the bacteria can be seen on microscopy as pairs of red kidney-shaped organisms, mostly sitting within polymorphs. Gonorrhoea causes about 2–3% of PID in the UK (see Table 45.5 and Further reading for data sources).

Neisseria gonorrhoeae initially infects the cervix but ascends to the upper genital tract in 5–10% of untreated cases. Around half of women with gonorrhoea are asymptomatic, but when symptoms are present the vaginal discharge tends to be thick and purulent. Although detecting gonorrhoea from the cervix supports a diagnosis of PID, its absence in the lower genital tract cannot exclude infection in the fallopian tubes or ovaries.

Chlamydia trachomatis

Chlamydia trachomatis is an unusual bacterium as it requires a host cell to grow (obligate intracellular organism), behaving in some ways more like a virus. The availability of sensitive nucleic acid amplification tests (NAATs) allows the use of vulvo-vaginal swabs for testing (which the patient can take herself after appropriate instruction). Urine has a lower detection rate but can be used if it is the only sample available. Light microscopy is not useful since *C. trachomatis* is too small to be seen.

Chlamydia, like gonorrhoea, initially infects the cervix and sometimes also the urethra. It is the commonest identified cause of PID in the UK, accounting for 30% of cases, and causes a more chronic low-grade infection than gonorrhoea. Over two-thirds of women with chlamydial infection are asymptomatic.

Mycoplasma genitalium

The evidence for a role of *Mycoplasma genitalium* in the pathogenesis of PID is substantial [5]. It has been isolated

from the cervix, endometrium and, in a small number of cases, fallopian tubes of women with PID. Tubal factor infertility is strongly associated with past infection with *M. genitalium*, and inoculation of the lower genital tract with mycoplasma causes PID in female monkeys [6]. Testing for *M. genitalium* has recently become available as a commercially available test.

Anaerobes

Anaerobic bacteria are of particular importance in women with severe PID, and can often be isolated from tubo-ovarian abscesses. Their role in mild to moderate PID is less clear. *Bacteroides fragilis*, *Peptostreptococcus* and *Peptococcus* can all be isolated from the genital tract of women with PID and the production of mucinases and sialidases by anaerobic bacteria may break down cervical mucus, thus facilitating the passage of other bacteria into the upper genital tract.

Actinomyces

Actinomyces israeli is occasionally detected in women with an intrauterine contraceptive device (IUCD) *in situ*. If there are no symptoms of vaginal discharge, intermenstrual bleeding or pelvic pain, then the woman should be advised that neither treatment nor removal of the IUCD is required, but she should be reviewed in 6 months or earlier if symptoms develop. If symptoms are present, then at least 2 weeks' therapy with a penicillin, tetracycline or macrolide antibiotic is indicated and the IUCD should be removed.

Mycobacterium tuberculosis

Tuberculous PID is largely limited to patients from developing countries. Pelvic infection usually occurs secondary to haematogenous spread from an extragenital source, but occasionally *Mycobacterium tuberculosis* can be transmitted sexually [7]. Usually it is not possible to detect the organism in the lower genital tract and samples should be obtained by uterine curettage or from the fallopian tubes at laparoscopy to be sent for culture or nucleic acid testing. Standard quadruple antituberculous therapy with isoniazid, rifampicin, ethambutol and pyrazinamide is effective but surgical intervention may be required for extensive disease.

Viruses

A number of viruses have been isolated from the upper genital tract in women with PID (Table 45.1) but their role in pathogenesis is unclear.

Clinical presentation

Clinical features

The clinical diagnosis of PID is based on the presence of lower abdominal pain, usually bilateral, combined with either adnexal tenderness or cervical excitation on vaginal examination (Fig. 45.1). A comprehensive medical history and examination including an accurate menstrual and sexual history may help to reach a diagnosis. A pelvic examination is essential and a speculum examination is useful for identifying lower genital tract inflammation and excluding foreign bodies in the vagina such as retained tampons. The poor specificity and associated low positive predictive value of this approach (65–90%) is justified because a delay in antibiotic therapy of even a few days may increase the risk of impaired fertility [8]. The risks of giving antibiotics to a woman who turns out not to have PID are low, although important differential diagnoses first need to be excluded.

Other clinical features can support a diagnosis of PID but are not essential before starting empirical therapy:

- intermenstrual or post-coital bleeding, resulting from endometritis and cervicitis;
- deep dyspareunia;
- abnormal vaginal discharge, indicating lower genital tract infection;
- fever is non-specific and usually only present in moderate to severe PID;
- nausea/vomiting may occur in severe PID but is more commonly associated with appendicitis.

PID caused by gonorrhoea presents more acutely and is more severe compared with chlamydial PID [9]. It is

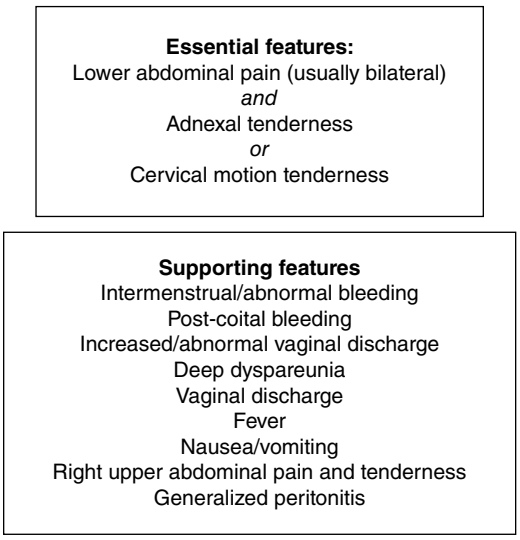

Fig. 45.1 Diagnosing pelvic infection.

worth remembering that for every woman presenting with clinical features of PID there are two others who are asymptomatic.

Fitz-Hugh–Curtis syndrome

Inflammation and infection of the liver capsule (perihepatitis) affects 10–20% of women with gonococcal or chlamydial PID and occasionally dominates the clinical presentation. Patients complain of right upper abdominal pain and have tenderness at the liver edge, occasionally accompanied by a hepatic friction rub.

Differential diagnosis

The main differential diagnoses are given in Table 45.2. The features that classically lead towards a diagnosis of PID are the typical 'G string' distribution of the pain and bilateral tenderness on pelvic examination. In bowel-related disorders the pain tends to be higher in the abdomen and more central or to the left. Other conditions tend to give unilateral pain, at least at their onset. The main diagnoses to exclude are ectopic pregnancy and causes of an acute abdomen, which may require surgical intervention, such as appendicitis and ovarian 'accident' (e.g. torsion or persistent bleeding from a ruptured cyst). If the diagnosis is not clear, then empirical treatment with antibiotics should be commenced, but the patient kept under close observation to ensure that an alternative diagnosis has not been missed.

Table 45.2 Differential diagnosis of pelvic inflammatory disease.

Differential diagnosis	Significant features
Ectopic pregnancy	Menstrual history, initially unilateral pain
Ovarian cyst rupture/torsion	Initially unilateral pain, often mid-cycle
Appendicitis	Gastrointestinal symptoms, right-sided pain
Irritable bowel syndrome	Central or left-sided pain, no cervical excitation, bowel symptoms
Inflammatory bowel disease, e.g. Crohn's disease, ulcerative colitis, diverticular disease	Colicky central or left-sided abdominal pain, bowel symptoms
Urinary tract infection	Urinary frequency with or without loin pain
Bowel torsion	Central abdominal pain
Psychosomatic pain	Usually inconsistent symptoms

Investigation

Summary box 45.2

Before diagnosing pelvic inflammatory disease:

- perform a pregnancy test to help exclude ectopic pregnancy;
- screen for STIs.

Rather like signs and symptoms, the investigations available to diagnose acute PID lack accuracy. Blood tests such as a white cell count, erythrocyte sedimentation rate and C-reactive protein are all relatively non-specific. They may be elevated in PID but in mild cases can be normal. In particular, a leucocytosis is often not seen in non-pyogenic infections.

A urinary pregnancy test is mandatory to exclude an ectopic pregnancy. Ideally this should be performed before commencing empirical antibiotic treatment.

Microbiological tests

All women presenting with possible PID should be offered an NAAT to check for the presence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* on a vulvo-vaginal swab (Fig. 45.2). The alternative enzyme-linked immunosorbent assays lack sensitivity. NAATs for *N. gonorrhoeae* have greater sensitivity than culture but confirmation of a positive NAAT (using a second NAAT which has a different primer target) is required because of the risk of false-positive results. Testing for *Mycoplasma genitalium* is advisable and should be performed when available since it may alter the choice of therapy.

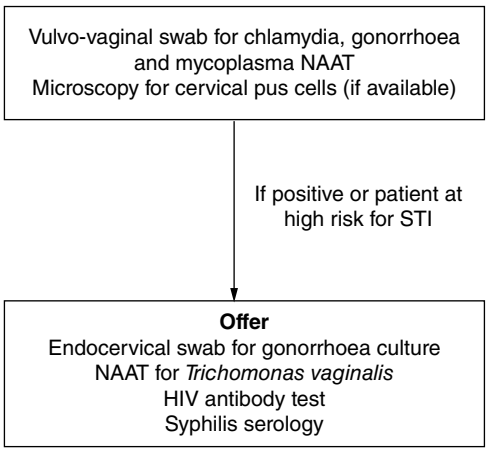

Fig. 45.2 Microbiological investigation of women with pelvic infection.

The detection of gonorrhoea, chlamydia or mycoplasma in the lower genital tract greatly increases the likelihood of PID as the cause of lower abdominal pain, but many women with PID also have a negative infection screen from the lower genital tract.

A lack of polymorphs on a Gram-stained smear of cervical discharge makes PID unlikely but their presence is non-specific, i.e. the absence of polymorphs has good negative predictive value but their presence has poor positive predictive value for PID [10].

Screening for other STIs should be offered to women who test positive for gonorrhoea or chlamydia, and to those who are at higher risk of infection (e.g. two or more partners within the past year, lack of condom use or previous history of an STI). An appropriate screen would include:

- NAAT for *Trichomonas vaginalis* from a vulvo-vaginal sample;
- endocervical swab for *N. gonorrhoeae* culture, which should be placed in transport medium (either Stuart or Amies) and arrive at the laboratory preferably within 6 hours but certainly within 24 hours, otherwise viability is rapidly lost;
- HIV antibody test; and
- syphilis serology.

If laparoscopy or laparotomy is performed, then specimens from the fallopian tube should also be sent requesting bacterial culture, including gonorrhoea. *Chlamydia* NAATs are not licensed for use for fallopian tube samples and therefore require cautious interpretation.

Radiology investigations

Transvaginal ultrasound of the pelvis may be useful where there is diagnostic difficulty. However, there are no features that are pathognomonic of acute PID. Free fluid in the pouch of Douglas is a common normal finding and is therefore not helpful. The value of ultrasonography generally lies in helping to exclude other pathology such as ectopic pregnancy, ovarian cysts or appendicitis, although it can also identify dilated fallopian tubes or a tubal abscess [11]. However, this investigation may not be readily available in an emergency setting.

MRI can assist in making the diagnosis where there is difficulty, but it is also not widely available and has not entered routine management. CT scanning in acute PID may show obscuring of the pelvic fascial planes, thickening of the uterosacral ligaments and accumulation of fluid in the tubes and endometrial canal. In the upper abdomen it can provide evidence of perihepatitis. Enhancement of the hepatic and splenic capsules on abdominal CT scan has been suggested as characteristic of Fitz-Hugh–Curtis syndrome but it is of little value as a routine investigation.

Surgical investigation

For many years the definitive diagnostic procedure for PID was considered to be laparoscopy and it probably remains more sensitive than any other investigation currently available. In many cases there will be clear evidence of dilated hyperaemic tubes with an inflammatory fibrinous exudate covering the tubes and the fundus of the uterus. In mild cases, however, intraluminal inflammation of the tubes may be missed and significant inter- and intra-observer variation in interpreting the appearance of salpingitis at laparoscopy has been reported [12]. It does enable swabs to be taken from the fimbrial ends of the tubes, which may be more accurate than endocervical swabs, but the principal benefit of laparoscopy is to exclude other diagnoses. As an invasive procedure it should be reserved for those cases where there is an element of doubt as to the diagnosis of acute PID or in cases where the patient fails to respond to antibiotics within 48–72 hours.

There is no evidence to support the routine use of hysteroscopy or endometrial biopsy in the diagnosis of acute PID. More invasive endoscopic techniques, such as fallaposcopy, may be potentially dangerous and have no place in management.

Histology and pathology

The spread of infection from the cervix to the endometrium leads to an acute, predominantly polymorph-mediated endometritis [13]. Transcervical suction biopsy of the endometrium allows assessment of the endometrial inflammation, which correlates well with salpingitis. Unfortunately, the usefulness of this approach to diagnose PID is limited by the risk of introducing infection during the procedure, the time delay in fixing and staining the sample, and the uncertain significance of isolated endometritis.

The inflammatory response seen in the fallopian tubes depends on the underlying pathogen. Gonorrhoea infects the non-ciliated epithelial cells but production of tumour necrosis factor and gamma interferon soon lead to collateral damage to the surrounding tissue and invasion of the submucosa. The tissue damage associated with *Chlamydia* is mediated primarily by the immune response to the infection that occurs as a result of a delayed-type hypersensitivity reaction to a chlamydial heat shock protein. This is characterized by a low-grade lymphocytic response compared with the acute neutrophil response of gonococcal salpingitis.

Recurrent infection with *Chlamydia* causes further immune stimulation, possibly mediated by a cross-reaction between chlamydial and human heat shock protein 60 [14]. This exaggerated immune response following

re-exposure to *Chlamydia* may explain the exponential increase in the risk of tubal damage that occurs with repeated infection.

Severe inflammation is associated with tubal occlusion and the production of a tubo-ovarian abscess or hydrosalpinx. Healing following acute inflammation may produce chronic fibrosis with associated damage to the ciliated epithelium, tubal blockage and/or pelvic adhesions. Histologically, this chronic damage produces lymphoid follicles and a mononuclear cell infiltrate.

Treatment

Summary box 45.3

Treating pelvic infection

- Start appropriate antibiotics promptly after making a clinical diagnosis.
- Arrange for the patient's partner to be screened for STI and receive empirical antibiotics.
- Ensure that the patient and her partner(s) are treated concurrently.
- Provide information about future use of condoms.
- Discuss the implications of a diagnosis of PID on future fertility.

Patients who are systemically unwell should be advised to rest and should be prescribed adequate analgesia. Regular review to assess progress is required. If no improvement is observed after 3 days of antibiotic therapy, then alternative diagnoses should be considered. Most patients can be managed as outpatients, but those with severe symptoms, such as an acute abdomen, will require inpatient care. If the diagnosis is in doubt or if intravenous antibiotics are considered to be necessary, the patient should be admitted to hospital.

Antimicrobials

Broad-spectrum antibiotic cover to include gonorrhoea, chlamydia and anaerobes is required. The optimal choice of antibiotics may be affected by knowledge of local bacterial resistance patterns, severity of disease, cost and patient convenience. Parenteral therapy should be continued until 24 hours after clinical improvement and then switched to oral. Randomized controlled trial evidence is available to support the use of the antibiotic regimens listed in Table 45.3 for outpatients and in Table 45.4 for inpatients. Women with *M. genitalium*-associated PID should be treated with moxifloxacin.

Table 45.3 Outpatient antibiotic regimens.

Regimen 1*	Ofloxacin 400 mg b.d. *plus* metronidazole 400 mg b.d.
Regimen 2*	Moxifloxacin 400 mg once daily
Regimen 3*	Ceftriaxone 500 mg i.m. immediately *plus* doxycycline 100 mg b.d. *plus* metronidazole 400 mg b.d.

*To complete 14 days of therapy.
b.d., twice daily.

Table 45.4 Inpatient antibiotic regimens.

Regimen 1	Ceftriaxone 2 g i.v. daily *plus* i.v. or oral doxycycline 100 mg b.d. *followed by** oral doxycycline 100 mg b.d. *plus* metronidazole 400 mg b.d.
Regimen 2	Clindamycin 900 mg i.v. t.i.d. *plus* i.v. gentamicin 2 mg/kg loading dose followed by 1.5 mg/kg t.i.d. (a single daily dose may also be used) *followed by** oral doxycycline 100 mg b.d. *plus* metronidazole 400 mg b.d.
Regimen 3	Ofloxacin 400 mg i.v. b.d. *plus* metronidazole 500 mg i.v. t.i.d. *followed by** oral ofloxacin 400 mg b.d. *plus* oral metronidazole 400 mg b.d.

*Parenteral therapy should be continued until 24 hours after clinical improvement. Oral therapy to continue to complete 14 days of antibiotics in total.
b.d., twice daily; t.i.d., three times daily.

Quinolone resistance in gonorrhoea is common in many areas of the world and is rising in the UK. Ofloxacin or moxifloxacin should therefore be avoided if there is clinical suspicion of gonococcal PID as a result of, for example, clinically severe disease, a history of a partner with gonorrhoea, or sexual contact abroad. Oral metronidazole can be discontinued in those with mild to moderate PID if the patient is unable to tolerate it.

A 'test of cure' to ensure resolution of the infection is required for women infected with *N. gonorrhoeae* (2 weeks after treatment) or *M. genitalium* (4 weeks after treatment).

Management of partners

PID is usually secondary to a sexually acquired infection, so unless the male partner(s) are identified and either screened for infection or treated empirically, the woman with PID is at high risk of recurrence. Current male partners should be offered screening for gonorrhoea and chlamydia (and *M. genitalium* if his partner was found to be infected), and attempts made

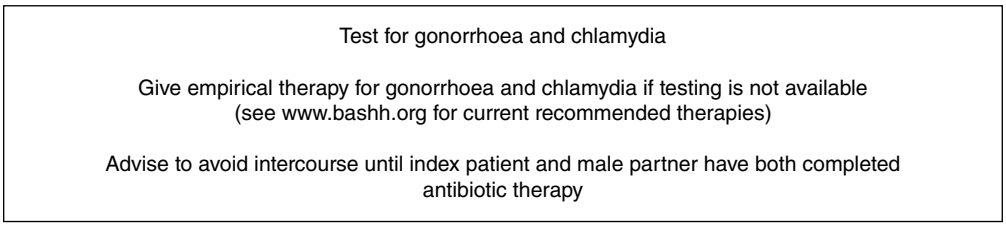

Fig. 45.3 Management of the male partners of women with pelvic infection.

to contact other partners within the past 6 months, although the exact time period will be influenced by the sexual history. If screening for sexually acquired infections is not possible, then antibiotic therapy effective against gonorrhoea and chlamydia should be given empirically to the male partner(s) (see British Association for Sexual Health and HIV guidelines for up-to-date treatment recommendations at www.bashh.org) (Fig. 45.3).

The patient and her partner(s) should be advised to avoid intercourse until both have either completed the treatment course or tested negative for STIs.

Summary box 45.4

Clinical review after PID

- Review response to treatment.
- Ensure that the full course of antibiotics has been taken.
- Check whether the patient's partner(s) has been seen and treated.
- Reinforce advice regarding future condom use.

Surgical intervention

Surgical intervention is rarely required as a treatment for acute PID. Most patients present at an early enough stage of the disease for antibiotic treatment to be fully effective. However, there may be an indication for laparoscopy or laparotomy to drain a pelvic abscess if this is diagnosed on ultrasonography and does not appear to be resolving with conservative antibiotic treatment.

On the rare occasion when pelvic actinomyces is suspected, surgery should be avoided. The history is likely to be more chronic than in acute PID and there is usually clear clinical evidence of a pelvic mass which does not appear to be an abscess on ultrasound scanning. There is also usually a history of recent use of an IUCD. If surgery is performed, then there is a significant risk of bowel damage.

Prognosis

The evidence quantifying the frequency of sequelae of PID is complicated by the variable definitions and diagnostic criteria used to identify the index episode of infection.

Chronic pelvic pain

It is generally accepted that episodes of acute PID can lead to symptoms of chronic pelvic pain. However, the cause of the chronic pelvic pain remains controversial. It may be that damaged tubes act as a nidus for recurrent infections or it may be due to adhesions tethering or encapsulating the pelvic organs. It is even possible that the pain is due to altered behaviour of pelvic nerves damaged by infection. There is also limited evidence as to the incidence of chronic pelvic pain resulting from single or multiple episodes of acute PID. It can be as high as 33% after recurrent episodes [15] and can have a significant effect on a patient's future quality of life [16]. The precautionary use of condoms after an episode of pelvic infection has been found to reduce the risk of chronic pelvic pain developing.

Subfertility and ectopic pregnancy

There is clear, population-based, epidemiological evidence of the relationship between a finding of *Chlamydia trachomatis*-specific IgG antibodies and subsequent tubal subfertility [17]. Some cohort studies have shown a rate of subsequent involuntary infertility of up to 40% after a single episode of PID [18]. There is a relationship between the risk of subfertility and the severity of infection, with a relative risk of 5.6 for severe infection compared with mild infection [19]. More recent prospective studies (in clinically mild/moderate disease) have suggested that infertility rates are not significantly increased following a single episode of PID treated appropriately [15]. There is also clear epidemiological evidence of a relationship between the risk of ectopic pregnancy and a previous episode of PID. In laparoscopically proven cases of PID, the risk of an ectopic in the subsequent index pregnancy

is six times greater than in controls [19]. However, the absolute risk of ectopic pregnancy remains low at 0.5–1%, at least in women with mild to moderate disease [15].

Special circumstances

Pregnancy

PID associated with an intrauterine pregnancy is extremely rare except in cases of septic miscarriage. Cervicitis is more common and associated with increased fetal and maternal morbidity. Treatment regimens will depend on the organisms isolated while avoiding those antibiotics that are contraindicated in pregnancy (e.g. tetracycline). Erythromycin and amoxicillin are not known to be harmful in pregnancy. In cases of septic abortion the organisms are more likely to be pyogenic than sexually transmitted. The use of broad-spectrum antibiotics, such as a third-generation cephalosporin together with azithromycin and metronidazole, would comprise a suitable regimen.

Mild endometritis following surgical termination of pregnancy is relatively common (approximately 1–2%) and needs to be treated aggressively to ensure future fertility. If pretreatment screening for STI has been employed, it is very unusual to find a positive result on repeat swabs. However, it is prudent to treat with a broad spectrum of antibiotics effective against both *Chlamydia* and anaerobes (e.g. ofloxacin plus metronidazole, or moxifloxacin).

Post pelvic surgery

Pelvic surgery such as hysterectomy is invariably associated with a significant risk of postoperative infection because it is virtually impossible to render the vagina totally aseptic. Prophylactic antibiotics are usually used during surgery, but postoperative pelvic infections, usually secondary to haematoma formation, are not uncommon. Most infections are caused by anaerobes and should be treated with a regimen that includes metronidazole or co-amoxiclav.

Pelvic infection and intrauterine contraceptive devices

An IUCD only increases the risk of developing PID in the first few weeks after insertion and, except for subacute infections with *Actinomyces*, there appears to be no evidence of increased risk with the continuing use of an IUCD. Routine screening for chlamydia, gonorrhoea and bacterial vaginosis before insertion is likely to reduce the risk of PID in those women requiring an IUCD. The use of progesterone IUCDs has been associated with very low rates of PID.

The randomized controlled trial evidence for whether an IUCD should be left *in situ* or removed in women presenting with PID is limited [20,21]. Removal of the IUCD should be considered and may be associated with better short-term clinical outcomes [20], but the decision to remove the device needs to be balanced against the risk of pregnancy in those who have had otherwise unprotected intercourse in the preceding 7 days. Hormonal emergency contraception may be appropriate for some women in this situation.

Human immunodeficiency virus

Women with HIV may have a more severe clinical presentation of PID, particularly in late-stage HIV disease associated with severe immunosuppression. No alteration in therapy is required, although caution is needed to check for any interactions between the PID treatment and antiretroviral medication.

Prevention

Chlamydia screening programme

Chlamydia is the commonest identified pathogen causing PID in the UK. Initial infection with *Chlamydia* is usually asymptomatic but, if identified, can be treated simply and cheaply with antibiotics such as doxycycline or azithromycin, thus preventing the development of PID. Screening young women for chlamydia to prevent PID is feasible [22–24], and a national screening programme operates in the UK targeting women under the age of 25 (further information is available at www.chlamydiascreening.nhs.uk).

Instrumentation of the uterus

There is a significant risk of introducing infection into the upper genital tract when instrumenting the uterus, particularly in women at high risk of a subclinical cervical *Chlamydia* infection. The most common indications for instrumenting the uterus are therapeutic surgical termination of pregnancy, insertion of an IUCD and investigations for subfertility. It is appropriate to test for chlamydia and gonorrhoea prior to instrumentation of the cervix for women at risk of STIs (e.g. partner known to have an infection, past history of STI, age <25, new partner within previous 3 months, two or more partners in past year). In cases where prior screening is not possible (e.g. insertion of an IUCD for emergency contraception), testing should

be combined with empirical treatment, such as doxycycline 100mg twice daily for 1 week.

Particular vigilance is needed in patients who are on immunosuppressant treatment (e.g. renal transplant patients) and in those who are immunocompromised because of chemotherapy or HIV.

Contraception

Consistent use of barrier methods has been shown to reduce the risk of recurrent episodes of pelvic infection and also the chronic sequelae of pelvic infection by between 30 and 60%.

All forms of hormonal contraception (e.g. combined oral contraceptive pill, progesterone-only pill, progesterone injections and implants, and Mirena® intrauterine system) have been shown to reduce the incidence of symptomatic PID compared with either the use of a standard IUCD or unprotected intercourse. This is presumed to be due to the protective effect of the progestogens, which decrease the permeability of the cervical mucus to both sperm and pathogens.

Contraception may also have an effect through endometrial suppression or a direct steroid-induced effect on the inflammatory response in the tubes. However, the beneficial effect of the oral contraceptive pill may be limited to PID which is symptomatic and caused by *C. trachomatis* [25] and it has been suggested that hormonal contraception may simply be masking infection rather than preventing it [25]. A study that appeared to suggest that injectable progesterone contraception increased the risk of PID was methodologically flawed and hence may not be valid [26]. The true relationship between hormonal contraception and PID therefore still needs to be elucidated.

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Further reading

Some useful internet sites are listed in Table 45.5. Other relevant further reading includes the following.

Ness RB, Soper DE, Holley RL *et al.* Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. *Am J Obstet Gynecol* 2002;186:929–937. The PEACH trial is one of the largest high-quality PID treatment studies.
Recommendations arising from the 31st Study Group: The Prevention of Pelvic Infection. In: Templeton A (ed.) *The Prevention of Pelvic Infection*. London: RCOG Press, 1996: 267–270.

Table 45.5 Useful internet sites.

PID Treatment Guidelines and Patient Information Leaflet, British Association for Sexual Health and HIV	www.bashh.org
UK Chlamydia Screening Programme, Department of Health	www.chlamydiascreening.nhs.uk
Guideline on Screening and Testing for Sexually Transmitted Infections, British Association for Sexual Health and HIV	www.bashh.org
Pelvic inflammatory disease, *BMJ Clinical Evidence*	http://www.clinicalevidence.com/x/systematic-review/1606/overview.html
UK Health Protection Agency, UK data on the incidence of STI and PID	www.gov.uk www.gov.scot www.wales.nhs.uk www.publichealth.hscni.net

Part 10

Menstruation

46

The Menstrual Cycle

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The human female is monotocous. Multiple pregnancy is a rare event in our species and frequently leads to complications that, in the days before modern medicine, would have led to maternal or fetal demise. Hence we have evolved a complex and highly regulated sequence of events that exists to ensure that only one oocyte is ovulated in any one cycle. Regular monthly menstruation is an obvious marker that the various levels of interaction between hypothalamus, pituitary, ovary and uterus are functional. Interruption of this axis at any point leads to disordered menses. Gynaecologists will frequently have to investigate and treat such disorders and a clear understanding of the regulation of the normal cycle is therefore necessary in order to guide rational management when things go wrong.

The normal menstrual cycle is mostly a reflection of ovarian events. The selection and growth of the dominant follicle leads to increasing concentrations of oestrogens in the blood, stimulating endometrial growth in synchrony with the development of a competent oocyte. Later, following the luteinizing hormone (LH) surge, ovarian oestrogens and progesterone from the corpus luteum induce endometrial secretory changes, and the decline in luteal steroid production in the absence of pregnancy leads to the onset of menstruation. Hence a description of clinical relevance of the menstrual cycle should focus on ovarian physiology, while not overlooking events in the hypothalamus and pituitary and at the level of the uterus.

The menstrual cycle is regulated at both endocrine and paracrine levels. Endocrinologically, there are classical feedback loops that modulate release of gonadotrophin hormones from the pituitary, with the ovarian steroids as the afferent arm. More recent studies have begun to elaborate a complex series of paracrine processes that operate within the tissues of the ovary and uterus to impose local regulation.

Step one: ensuring mono-ovulation

Folliculogenesis and the 'follicular phase'

At birth, the human ovaries contain approximately 1 million primordial follicles, arrested at prophase of the first meiotic division. This number already reflects considerable attrition from the maximum size of about 7 million in the follicle 'pool' at 5 months of fetal life [1]. Further depletion of the follicle pool will continue throughout reproductive life, with regular escape of follicles from the primordial 'resting phase' by re-entry into meiosis. The process of 'escape' from the resting state is not dependent on extra-ovarian influences: follicle depletion occurs before and after menarche, during use of the oral contraceptive pill and during pregnancy, and whether or not regular menstruation occurs. The majority of follicles will never develop beyond the pre-antral stage, travelling instead towards atresia. Of the original pool of 7 million primordial follicles, only about 400 will ever acquire gonadotrophin receptors and the possibility of ovulation [2]. This dramatic attrition defines the female arm of natural selection, mirrored by the huge wastage of spermatogenesis in the male, in which millions of sperm are produced each day during fertile life, with only a tiny proportion ever fertilizing an oocyte.

The early stages of follicle development in the human are independent of gonadotrophins. Studies using transgenic animal species have begun to elucidate the contribution of locally acting intra-ovarian paracrine regulators of primordial follicle development, including bone morphogenetic proteins (BMPs), growth differentiation factor (GDF)-9, anti-Müllerian hormone (AMH) and the Bax family of regulators of apoptosis (Table 46.1).

Such studies are of more than theoretical interest: understanding the mechanisms regulating rate of entry into the pool of growing follicles should help to explain

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 46.1 Specific gene knockouts and their effects on ovarian function in the mouse.

Transgenic/mutant mouse	Ovarian phenotype
C-Kit deficiency, Kit ligand deficiency	Loss of germ cells (migration/proliferation failure)
WT1 knockout	Failure of gonadal development
BMP15/GDF9 knockout	Folliculogenesis arrest (primary stage)
IGF1 knockout	Folliculogenesis arrest (before antral follicle stage)
Kisspeptin/*GPPSU* knockout	Folliculogenesis alternation of LU stage
Oestrogen receptor gene knockout	Failure to ovulate
WNT4 knockout	Reduced germ cell number, masculinization

such common clinical problems as 'idiopathic' premature ovarian failure and early onset of menopause, as well as suggesting means of prolonging the reproductive lifespan. For example, some patients with premature ovarian failure have been found to carry mutations in the *BMP15* gene that lead to defective secretion of bioactive BMP15 dimer. BMPs are involved in the earlier stages of egress of follicles from the primordial pool, and such mutations may provide a diagnosis in cases of previously unexplained premature ovarian failure.

Once a developing follicle reaches the pre-antral stage of development (Fig. 46.1), further progression to the antral and preovulatory stages appears to be absolutely dependent on the presence of gonadotrophins. The temporary elevation in circulating concentration of follicle-stimulating hormone (FSH) seen in the early follicular phase of the ovarian cycle allows a limited number of pre-antral follicles to reach this stage of maturity, creating a cohort of practically synchronously developing follicles. However, only one 'lead' follicle will acquire significant aromatase enzyme activity within its granulosa cells, leading to increased synthesis and secretion of estradiol from androgenic precursors. The 'two-cell, two gonadotrophin' hypothesis specifies the need for both LH, to stimulate production of precursor androgens, particularly androstenedione, by the theca cell layer, and FSH, to drive aromatization to estradiol within the adjacent granulosa cell layer [3]. FSH, LH and human chorionic gonadotrophin (hCG) are structurally similar, sharing an identical α-subunit. Their specificity lies in structural differences in the β-subunit (Fig. 46.2). Hence assays for these molecules use antibodies directed against β-subunit epitopes.

The necessity for both LH and FSH at this stage of the cycle is demonstrated when exogenous gonadotrophin replacement is given to patients with Kallmann's syndrome. These patients are unable to secrete gonadotrophins into the circulation, but have normal ovarian physiology. The results of a study of such a patient are shown in Fig. 46.3. The patient had Kallmann's syndrome with anosmia, primary amenorrhoea and hypogonadotrophic hypogonadism. Ovulation induction was undertaken using two different preparations of gonadotrophin. Treatment with both FSH and LH in the form of human menopausal gonadotrophins (hMG) induces both normal follicle growth, monitored by transvaginal ultrasound (bottom panel), and estradiol secretion (top left panel), leading to high luteal phase progesterone concentrations after an artificial LH surge with hCG injection. This indicates that successful ovulation and luteinization occurred. In contrast, treatment with FSH in the absence of LH, using a recombinant FSH preparation, led to identical follicle development on ultrasound but little elevation in circulating estradiol concentration in the phase of follicular growth and no increase in progesterone after hCG injection. The genetic basis of hypogonadotrophic hypogonadism has recently been partially explained. Study of a patient with Kallman's syndrome and a deletion on the X chromosome led to the identification of the *KAL1* gene as a cause of X-linked Kallman's syndrome. More than 10 other gene defects have been identified in cases of hypogonadotrophic hypogonadism.

The pituitary secretes the gonadotrophins LH and FSH in response to pulses of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, which travel to the anterior pituitary via the hypothalamo-hypophyseal portal tract. LH secretion appears to be closely regulated by GnRH pulsatility, while secretion of FSH is coregulated by hypothalamic GnRH and other factors which act directly on the pituitary, possibly including the inhibins and activins. In the normal follicular phase, GnRH pulse frequency is approximately once per 90 min. GnRH pulses are less frequent in the luteal phase, occurring approximately once in 4 hours. Disorders that slow GnRH pulsatility, such as anorexia nervosa, result in failure of secretion of pituitary gonadotrophins and a state of hypogonadotrophic hypogonadism, with undetectable serum LH and FSH and amenorrhoea.

The peptide kisspeptin acts as a potent stimulant to GnRH secretion in the human and mutations in the

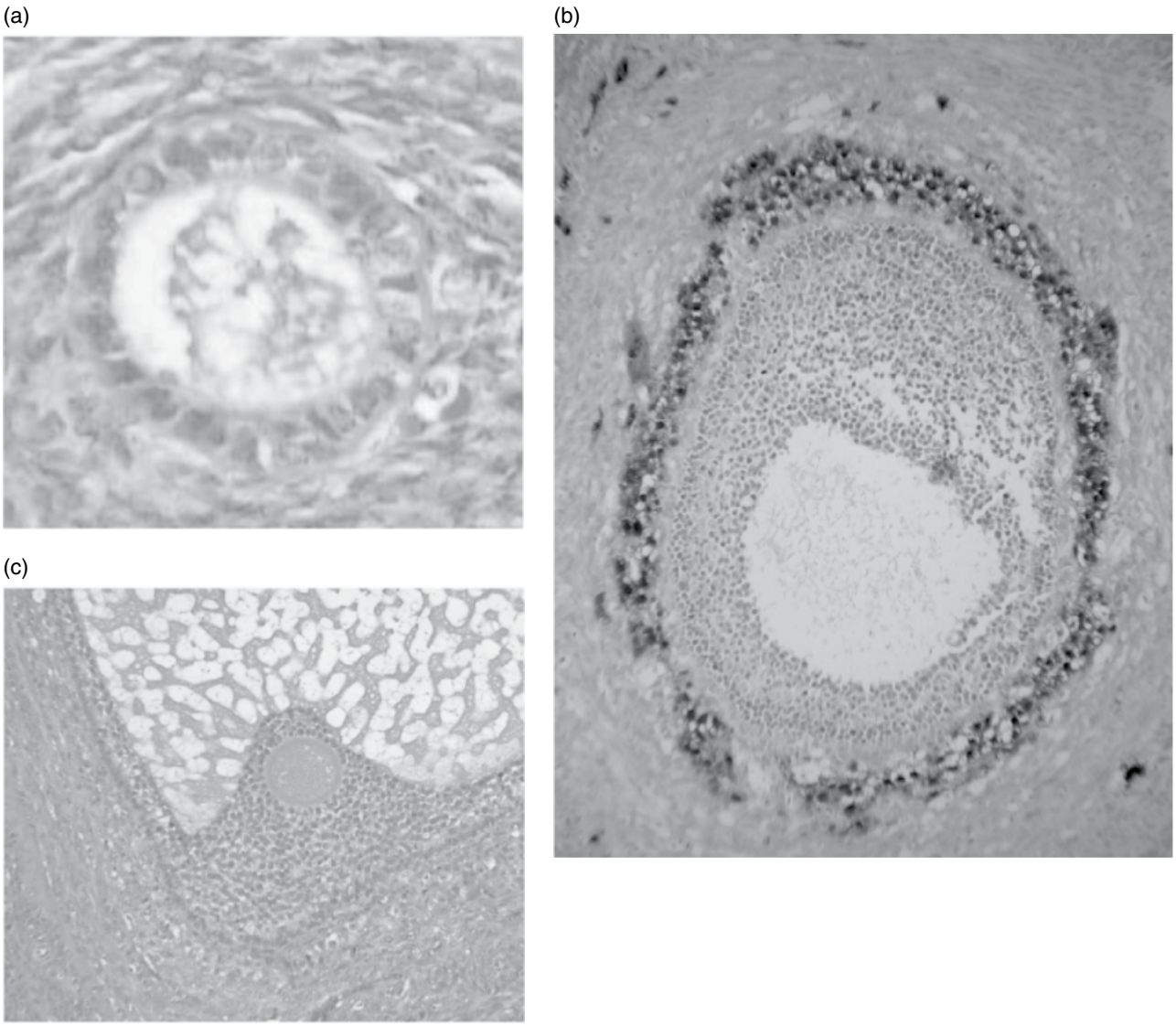

Fig. 46.1 The development of a follicle, from (a) primordial, (b) small antral and (c) preovulatory stages. (a) The primordial follicle is surrounded by a single layer of undifferentiated epithelial cells, and is insensitive to gonadotrophins. (b) The early antral follicle has well-differentiated theca (immunostained brown) and granulosa cell layers surrounding the developing antral cavity with the oocyte. (c) The preovulatory follicle with the oocyte surrounded by the cumulus oophorus with well-differentiated granulosa and theca cell layers.

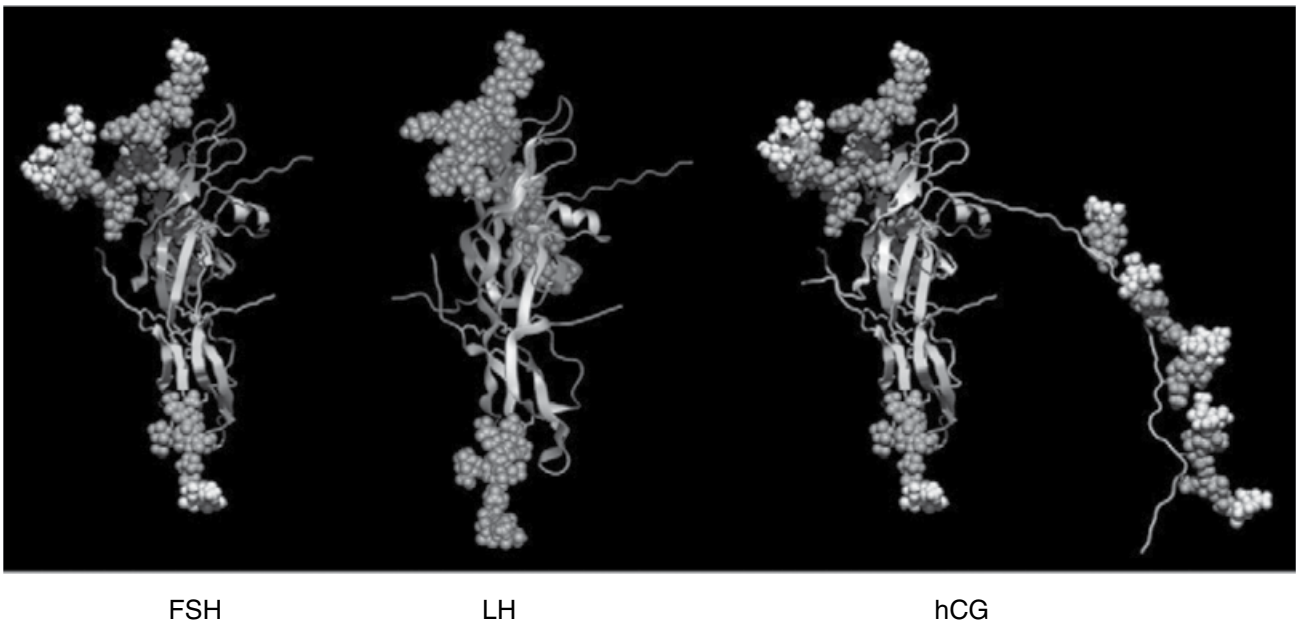

Fig. 46.2 Molecular structure of FSH, LH and hCG.

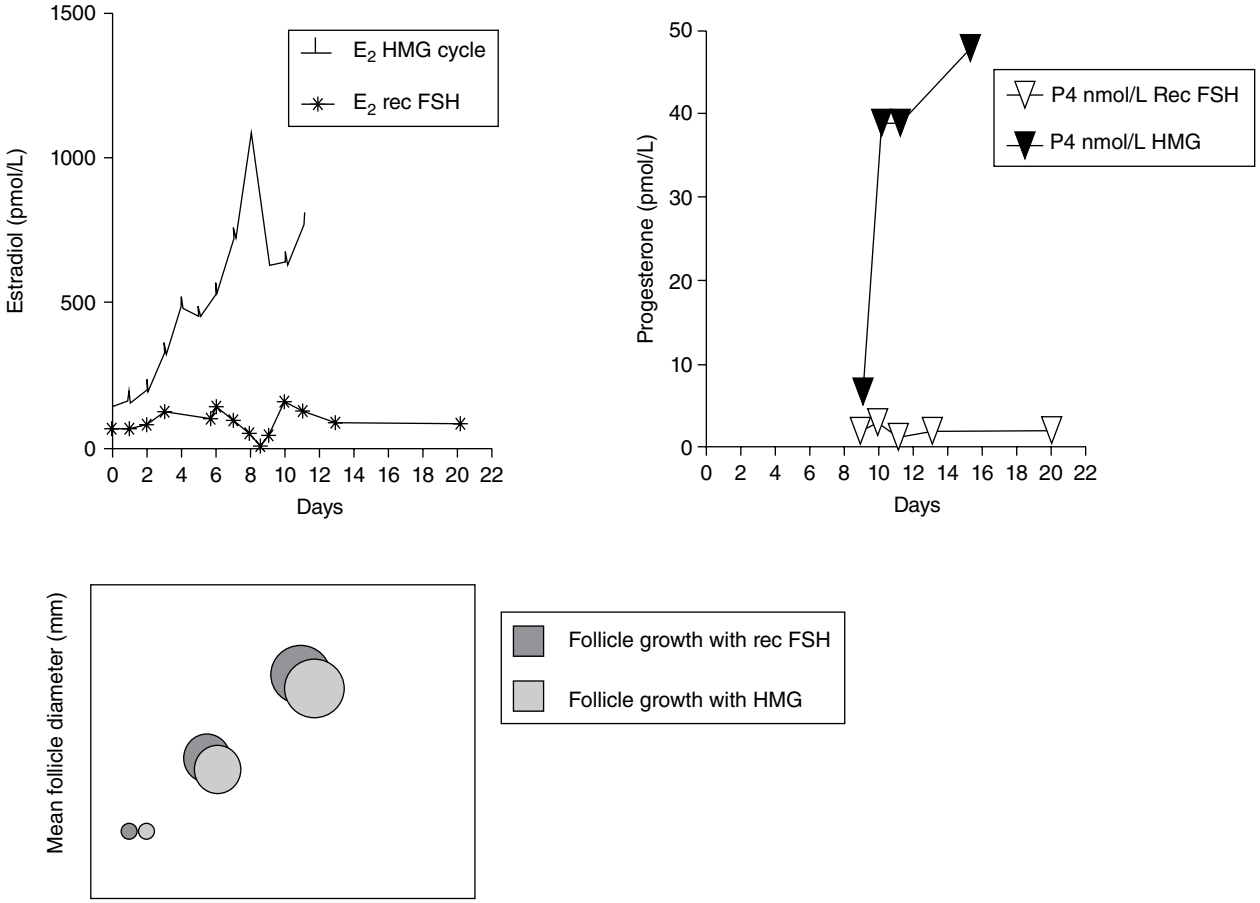

Fig. 46.3 Effects of FSH alone, and FSH and LH in combination on follicle development in a hypogonadotrophic patient with Kallmann's syndrome.

KISS1 gene leading to loss of kisspeptin signalling have been identified as rare causes of hypogonadotrophic hypogonadism [4]. Central kisspeptin release is also modulated by stress and nutritional status, providing a possible mechanism for 'hypothalamic' amenorrhoea in anorexia and in situations of excessive emotional stress. These changes may occur in response to alterations in leptin secretion from adipocytes, leading to kisspeptin-mediated alterations in pulsatile GnRH secretion. Recently, peripheral administration of synthetic kisspeptin has been shown to be effective in inducing ovulation in hypothalamic amenorrhoea and other therapeutic roles in treatment of infertility are being explored. A second neuropeptide, neurokinin B, is also expressed on GnRH neurones and stimulates GnRH secretion and both kisspeptin and neurokinin B expression are down-regulated by oestrogen. Hence it appears likely that kisspeptin and neurokinin B may participate in the relay of feedback from oestrogens, acting at the level of the hypothalamus, to GnRH production, regulating follicle growth and the onset of the LH surge (Fig. 46.4).

Once the concentration of serum estradiol begins to rise in the mid-follicular phase, there is rapid suppression of pituitary FSH production by negative feedback (Fig. 46.5). Recent studies have suggested that suppression of pituitary FSH secretion in the follicular phase might be co-mediated by rising serum concentrations of inhibin B, a glycoprotein secreted by the granulosa cells of the developing dominant follicle. It is perhaps not surprising that a dual mechanism to control follicular-phase FSH secretion has evolved, since mono-ovulation is so essential to healthy reproduction in humans. The resulting decrease in the circulating concentration of FSH withdraws gonadotrophin 'drive' from the remainder of the growing cohort of follicles. The result is progression to atresia for all but the dominant follicle, leading to mono-ovulation [5].

The mechanism by which this selection of a single dominant follicle occurs has been described by the 'threshold' concept, in which the rising concentration of FSH exceeds the threshold and thereby opens a 'window' that allows one follicle to continue growth and

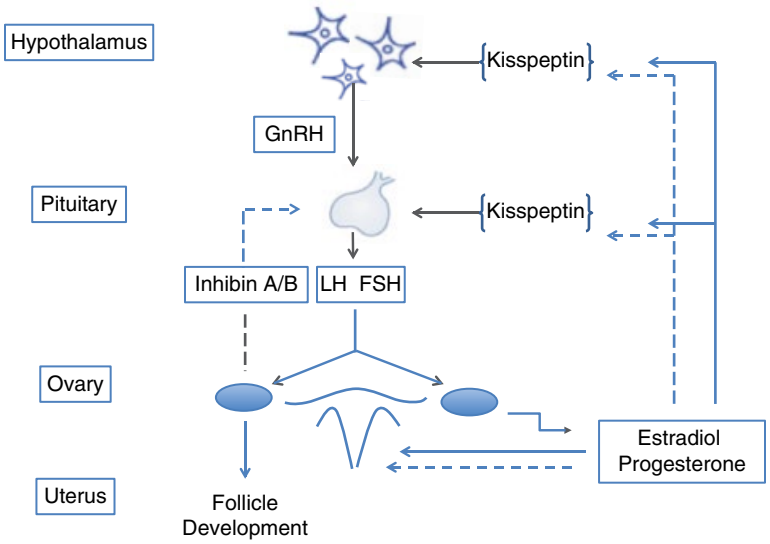

Fig. 46.4 Hypothalamic–pituitary–gonadal axis. *Source:* Dr May Wong. Reproduced with permission of Dr May Wong.

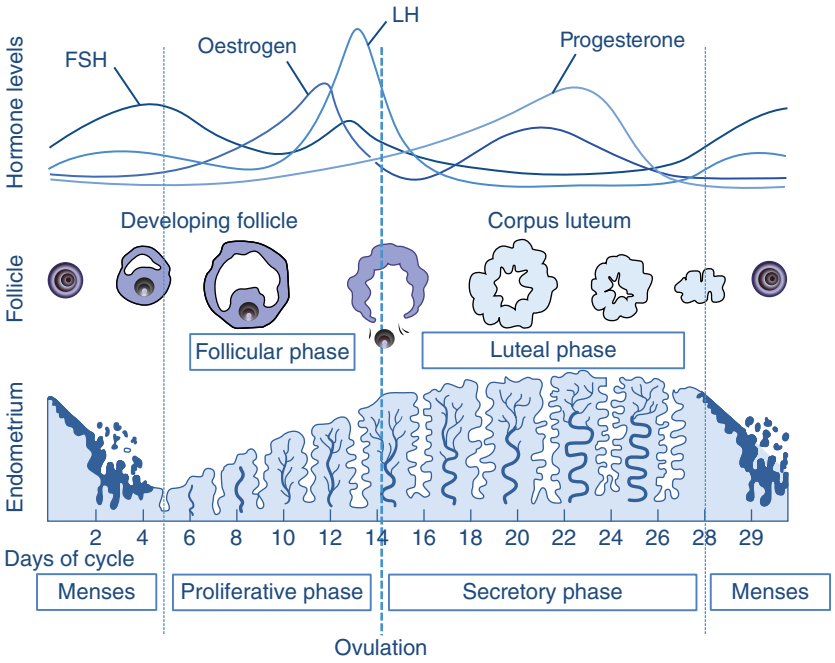

Fig. 46.5 Synchronization of the menstrual and ovarian cycles. *Source:* Dr May Wong. Reproduced with permission of Dr May Wong.

development. Suppression of FSH concentration then closes the window, preventing growth of multiple mature follicles (Fig. 46.6).

The threshold concept is useful in understanding the pitfalls of superovulation, in which daily injections of high doses of FSH are given as part of *in vitro* fertilization (IVF). The aim is to produce a cohort of eight or more mature follicles suitable for ultrasound-guided oocyte retrieval. However, if the follicle pool is small (e.g. if the patient is nearing menopause), then the yield of mature follicles will be disappointing, while if the follicle pool is large (e.g. if the patient has polycystic ovary syndrome), then there is a danger of over-response with ovarian hyperstimulation syndrome. The recent introduction of rapid and reliable automated assays for AMH has allowed measurement of this dimeric glycoprotein before starting exogenous gonadotrophin superovulation. Serum AMH is high in patients with polycystic ovary syndrome who are in danger of over-response and hyperstimulation, and low in patients who are closer to menopause with low ovarian reserve. Hence those women with high AMH are given low doses of gonadotrophins, with careful monitoring, whilst those with low AMH can safely be given higher doses in an attempt to improve oocyte yield.

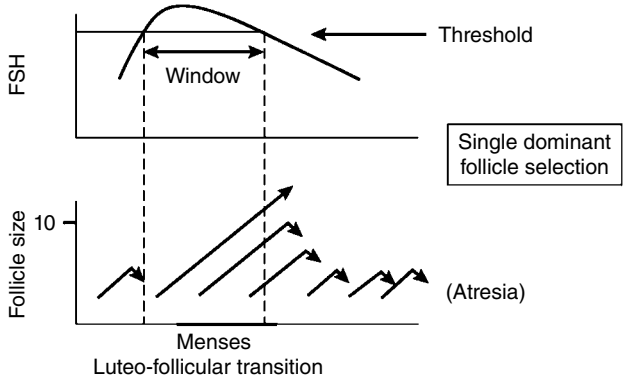

Fig. 46.6 The 'threshold concept' illustrating dependence of advanced follicle growth and maturation on a rise in circulating FSH concentration above an arbitrary threshold, with subsequent suppression of FSH preventing multiple follicle development. *Source:* Macklon NS, Fauser BC. Follicle-stimulating hormone and advanced follicle development in the human. *Arch Med Res* 2001;32:595–600. Reproduced with permission of Elsevier.

Physiologically, AMH is secreted by small antral follicles and is not seen in large preovulatory follicles. Hence measurement gives a direct assessment of the number of small antral follicles in the developing pool, which in turn depends on the size of the primordial follicle pool remaining in the ovaries. Measurement of AMH can therefore provide an estimate of the size of the remaining pool of follicles in the ovaries. Recent studies have suggested that this can provide a reasonably accurate assessment of a woman's time to menopause, with clear clinical implications for management of infertility. The serum concentration of AMH varies little across the menstrual cycle and is not significantly affected by use of combined oral contraceptives, facilitating easy measurement in clinical practice.

Step two: ensuring maintenance of very early pregnancy

The LH surge and ovulation

Final maturation of the oocyte only occurs after initiation of the LH surge. This ensures that the oocyte is mature and ready for fertilization only after release from the follicle into the ampulla of the fallopian tube, where fertilization may occur. The LH surge represents a coordinated discharge of LH from the gonadotroph cells of the anterior pituitary. This occurs in response to the rapid rise in estradiol during the latter days of the follicular phase of the ovarian cycle. Pulses of GnRH from the hypothalamus increase in both magnitude and frequency, triggering the LH surge with a rapid outpouring of LH and, to a lesser extent, FSH from the anterior pituitary (see Fig. 46.5).

The LH surge is also preceded by a rise in serum concentration of progesterone. The contribution of this rise to the periovulatory phase of the cycle is unclear, but prevention of the preovulatory rise in serum progesterone concentration using progesterone receptor antagonists such as mifepristone prevents efficient ovulation. Compounds with effects similar to mifepristone are being tested as possible contraceptive agents, possibly acting by inhibiting both ovulation and implantation.

The LH surge initiates final maturation of the oocyte with completion of meiosis and extrusion of the first polar body, which contains one of the two haploid sets of chromosomes, from the oocyte. The LH surge also induces an inflammatory-type reaction at the apex of the follicle adjacent to the outer surface of the ovarian cortex. A process of new blood vessel formation, with associated release of prostaglandins and cytokines, leads to rupture of the follicle wall and ovulation about 38 hours after the initiation of the LH surge. A chemotactic effect of ovarian cytokines draws the fimbria of the fallopian tube to within close proximity of the rupturing follicle. A thin mucus strand seems to join the mouth of the fallopian tube to the ovular follicle, forming a bridge for transit of the oocyte into the tube.

The 'empty' follicle rapidly fills with blood and the theca and granulosa cell layers of the follicle wall luteinize, with formation of the corpus luteum (see Fig. 46.6). A rapid synthesis of progesterone, along with estradiol, follows. Concentrations of progesterone in serum rise rapidly to above 25 nmol/L, one of the highest concentrations seen for any hormone in the circulation. These concentrations rise still further if pregnancy follows.

Endometrial development during the menstrual cycle and early pregnancy

The follicular phase of the ovarian cycle is characterized by the appearance in the circulation of increasing amounts of estradiol. Estradiol acts on the basalis layer of endometrium, which persists from cycle to cycle in contrast to the monthly shedding of the more superficial layers of endometrium. The follicular phase of the ovarian cycle therefore equates to the proliferative phase of the endometrial cycle as proliferative endometrium develops in synchrony with the growth and maturation of the oocyte and its follicle. An organized endometrial architecture appears, with glandular and stromal compartments. The LH surge is followed by luteinization of the ruptured follicle and formation of the corpus luteum,

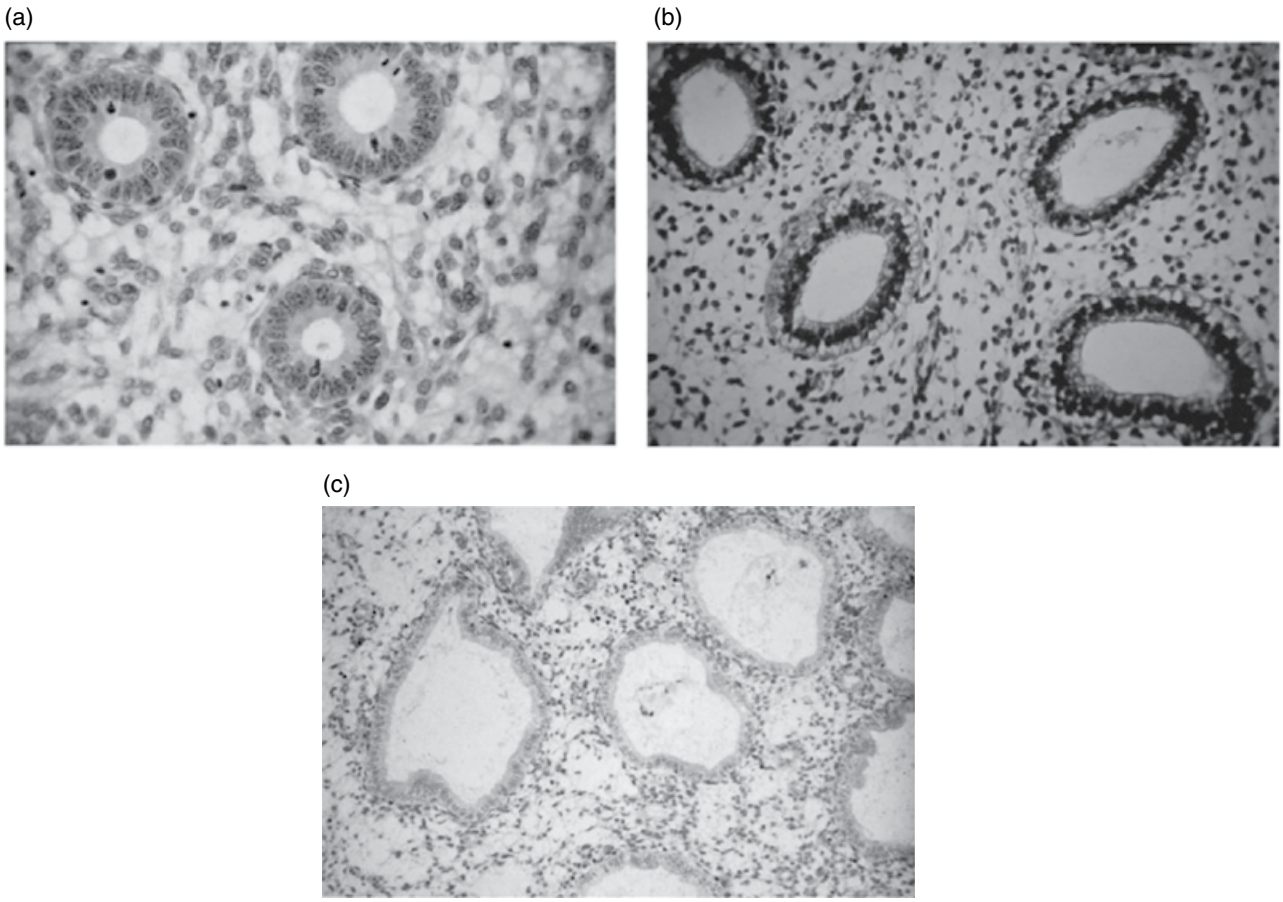

Fig. 46.7 The histological appearances of the endometrial cycle showing the menstrual, proliferative and secretory phases.

with secretion of large amounts of progesterone. This in turn stimulates the onset of secretion from the endometrial glands, initiating the secretory phase of the endometrial cycle in concert with the luteal phase of the ovarian cycle (Fig. 46.7).

A key element in growth of healthy endometrium is formation of new blood vessels (endometrial angiogenesis), which seems to occur by elongation and expansion from pre-existing small vessels in the basalis. Endometrial angiogenesis can be divided into three stages: first, during menstruation, to re-form the vascular bed; second, during the proliferative phase, to develop endometrial vascular supply; and, finally, with spiral arteriole growth and coiling during the secretory phase, with the aim of providing an adequately vascularized site for implantation [6]. Therefore, in contrast to most vascular beds, which keep a persistent structure throughout life, the endometrial vascular network grows and regresses during each menstrual cycle. Numerous angiogenic and angiostatic factors have been identified in the human endometrium. Most of these studies have focused on vascular endothelial growth factor (VEGF) and interleukins, which may be directly responsive to changing concentrations of ovarian steroids.

The development of a healthy secretory endometrium is essential for implantation and successful development of pregnancy. In the human, the oocyte is fertilized in the ampullary portion of the fallopian tube and then travels to enter the uterus on day 3, at the morula stage of development. The blastocyst, with distinct trophectoderm and inner cell mass, forms on day 4. The blastocyst sheds the zona pellucida and then adheres to the endometrial epithelium, beginning the process of implantation. Implantation is the first step in the interaction between the cells of the blastocyst and endometrium, i.e. between the mother and the fetus. Hence this interaction is critical to successful pregnancy, and a number of endometrial proteins have been identified as potential regulators of blastocyst development and implantation. These include endometrial integrins, glycosylated cell adhesion molecule (GlyCAM)-1 and osteopontin [7].

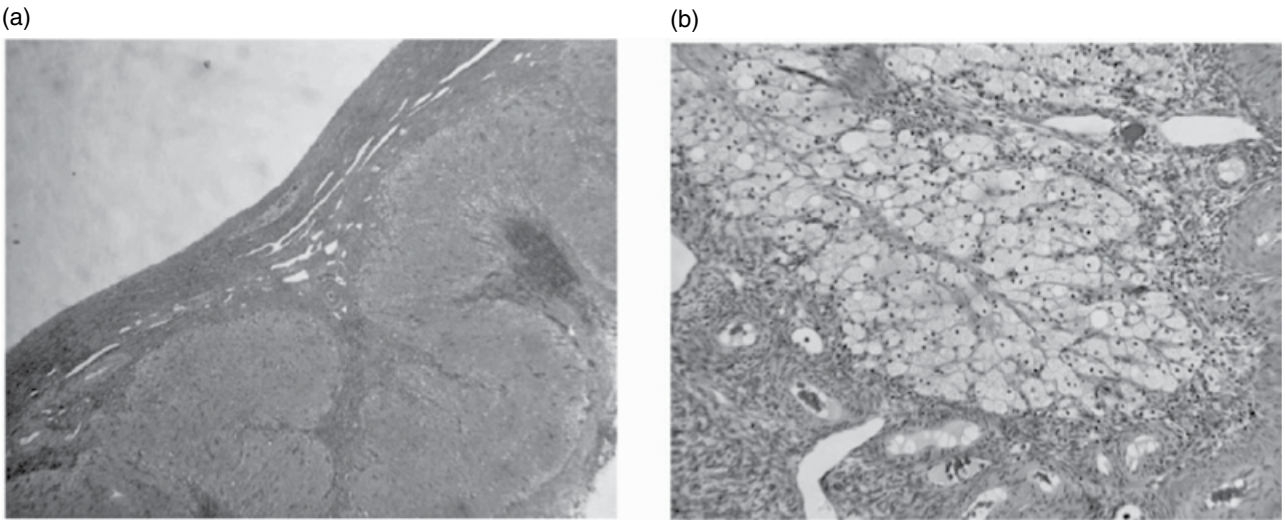

Fig. 46.8 The histological appearances of the corpus luteum, showing (a) an active corpus luteum and (b) regression of the corpus luteum with histiocyte infiltration.

Continuous exposure of the endometrium to progesterone in early pregnancy downregulates progesterone receptors in the epithelia, a process associated with loss of the cell-surface mucin MUC1 and induction of secreted adhesion proteins.

High circulating concentrations of progesterone are essential for the continuation of pregnancy. hCG secretion by the trophoblast of the developing pregnancy 'rescues' the corpus luteum, providing an LH-like stimulus to maintain luteal progesterone secretion. Interruption of luteal progesterone synthesis and secretion, for example using the progesterone receptor antagonist mifepristone, is used in clinical practice to induce termination of early pregnancy. In contrast, luteal-phase support in the form of hCG injection or injected or vaginal progestogens is used to maintain IVF pregnancies, since normal luteinization is interrupted by the GnRH agonist drugs used to prevent premature LH surges and unwanted ovulation.

Menstruation

Menstruation refers to the shedding of the superficial layers of the endometrium with subsequent repair in preparation for regrowth from the basalis layer. Menstruation is initiated by the fall in circulating progesterone that follows luteal regression, i.e. failure of 'rescue' of the corpus luteum by an implanted early pregnancy (Fig 46.8). During luteolysis, progesterone secretion falls despite maintained serum concentrations of LH, since the corpus luteum becomes less sensitive to gonadotrophic support and becomes increasingly unable to maintain production of progesterone. In contrast, in a conception cycle, the increasing block to progesterone synthesis is overcome by the rapidly increasing concentrations of hCG which act on the corpus luteum through its LH receptors.

In the immediate premenstrual phase, progesterone withdrawal initiates a complex series of intrauterine signals, including expression of chemotactic factors that draw leucocytes into the uterus and expression of matrix metalloproteinase enzymes, prostaglandins and other compounds that act on the uterine vessels and smooth muscle. The 'invasion' of leucocytes and subsequent expression of inflammatory mediators has led to menstruation being likened to an inflammatory event [8,9]. Prostaglandins of the E and F series are present in high concentrations in the endometrium, and their synthesis is regulated by the ovarian steroids. Increased production of $PGF_2\alpha$ produces the myometrial contractions and vasoconstriction seen at menstruation, while E series prostaglandins increase pain and oedema, and are vasodilatory. PGE_2 also appears to induce synthesis of the cytokine interleukin (IL)-8, another key inflammatory and chemotactic mediator [10]. Pronounced vasoconstriction in turn leads to localized tissue hypoxia, further reinforcing release of inflammatory mediators. The end result of this cascade of events is constriction of the spiral arterioles with contraction of the uterine muscle, leading to expulsion of the shed tissue (Fig. 46.9).

These studies have clear relevance to clinical management of menorrhagia and other menstrual disorders. Inhibitors of prostaglandin synthesis are widely

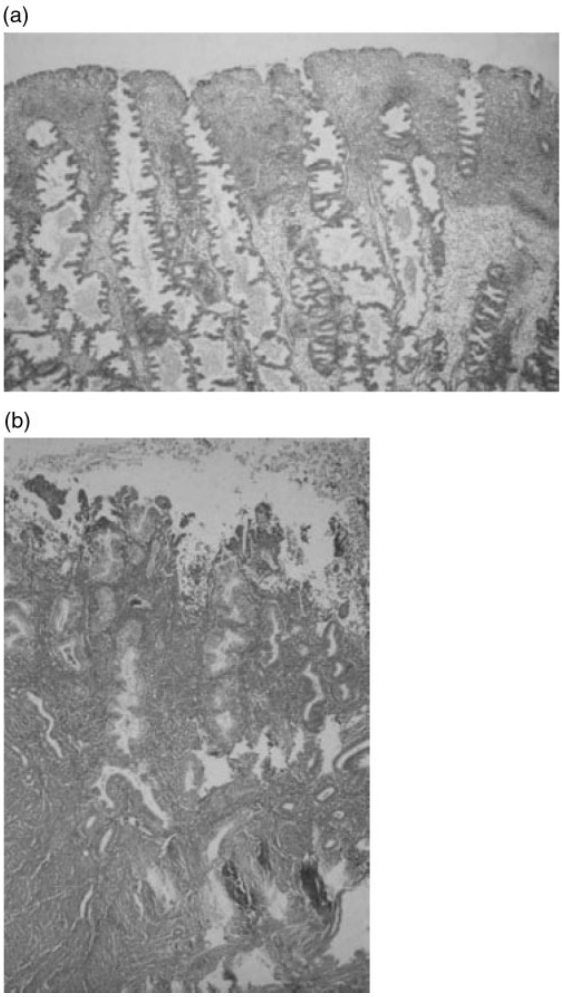

Fig. 46.9 Histological appearance of (a) late secretory and (b) menstrual endometrium. *Source:* Professor M. Wells, University of Sheffield. Reproduced with permission of Professor M. Wells.

used in these conditions, with good scientific basis. However, prostaglandin synthesis is also an important component of ovulation, and the use of powerful inhibitors of prostaglandin synthesis, such as non-steroidal anti-inflammatory agents, can lead to anovular cycles and involuntary infertility.

Conclusion

Although complex, the endocrine and paracrine events that regulate the normal ovarian and uterine cycles are well understood. This chapter illustrates several examples by which understanding of the basic physiology of the cycle has led to scientifically based therapeutics. Further exploration of these regulatory mechanisms will produce new approaches to diagnosis and treatment for gynaecologists and their patients.

Summary box 46.1

- The physiological events of the menstrual cycle represent the outcome of a complex system of inter-regulation by endocrine and paracrine factors.
- Understanding of the physiology of the ovarian and menstrual cycle is critical before attempting to understand the various pathological states associated with anovulation and premature menopause.
- New research into the genetic basis of regulation of re-entry of primordial follicles into the growing pool will provide new insights into the determination of ovarian reserve and timed menopause.

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47

Polycystic Ovary Syndrome and Secondary Amenorrhoea

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Defining polycystic ovary syndrome and secondary amenorrhoea

The current understanding of polycystic ovary syndrome (PCOS) is that it is a condition that presents with ovarian dysfunction and endocrine problems and is also associated with hyperinsulinaemia and metabolic disease. PCOS is a heterogeneous condition which is defined by the presence of two of the following three criteria: (i) oligo-ovulation and/or anovulation, (ii) hyperandrogenism (clinical and/or biochemical), or (iii) polycystic ovaries as seen by ultrasound scan, with the exclusion of other causes of androgen excess and menstrual cycle irregularity or amenorrhoea. PCOS therefore encompasses symptoms of menstrual cycle disturbance and as such is the commonest cause of secondary amenorrhoea and also of anovulatory infertility. The second part of the chapter discusses the pathophysiology and management of other causes of secondary amenorrhoea.

Amenorrhoea is the absence of menstruation, which may be temporary or permanent. Amenorrhoea may occur as a normal physiological condition, such as before puberty and during pregnancy, lactation or the menopause, or as a feature of a systemic or gynaecological disorder. Primary amenorrhoea may be a result of congenital abnormalities in the development of the ovaries, genital tract or external genitalia, or a perturbation of the normal endocrinological events of puberty. Most of the causes of secondary amenorrhoea can also cause primary amenorrhoea.

Examination and investigation of patients with polycystic ovary syndrome and secondary amenorrhoea

A thorough history and a careful examination should always be carried out before investigations are instigated, looking particularly at stature and body form, signs of endocrine disease, secondary sexual development and the external genitalia. A history of secondary amenorrhoea may be misleading, as the 'periods' may have been the result of exogenous hormone administration in a patient who was being treated with hormone replacement therapy (HRT) for primary amenorrhoea. In most cases, however, a history of secondary amenorrhoea excludes congenital abnormalities. A family history of fertility problems, autoimmune disorders or premature menopause may also give clues as to the aetiology.

Exclude pregnancy

It is always important to exclude pregnancy in women of any age, and whereas some may think this statement superfluous, it is not infrequent for women to present with amenorrhoea who are pregnant despite denying the possibility.

Examination

Measurement of height and weight should be performed in order to calculate the patient's body mass index (BMI).

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

The normal range is 20–25 kg/m^2, and a value above or below this may suggest a diagnosis of weight-related amenorrhoea (which is a term usually applied to underweight women).

Signs of hyperandrogenism – acne, hirsutism, balding (alopecia) – are suggestive of PCOS, although biochemical screening helps to differentiate other causes of androgen excess. It is important to distinguish between hyperandrogenism and virilization, which also occurs with high circulating androgen levels and causes deepening of the voice, breast atrophy, increase in muscle bulk and cliteromegaly (see Summary box 47.1). A rapid onset of hirsutism suggests the possibility of an androgen-secreting tumour of the ovary or adrenal gland. Hirsutism can be graded and given a Ferriman–Gallwey score by assessing the amount of hair in different parts of the body (e.g. upper lip, chin, breasts, abdomen, arms, legs). It is useful for monitoring the progress of hirsutism, or its response to treatment, by making serial records, either by using a chart or by taking photographs of affected areas of the body. It should be remembered, however, that not all hair on the body is necessarily responsive to hormone changes (e.g. the upper thighs). There may also be big ethnic variations in the expression of hirsutism, with women from South Asia and Mediterranean countries often having more pronounced problems, whereas those from the Far East may not have much in the way of bodily hair. Furthermore, the degree of hirsutism does not correlate that well with the actual levels of circulating androgens.

A measurement of total testosterone is considered adequate for general screening (Table 47.1). It is unnecessary to measure other androgens unless total testosterone is above 5 nmol/L (this will depend on the normal range of your local assay). Insulin may be elevated in overweight women and suppresses the production of sex hormone-binding globulin (SHBG) by the liver, resulting in a high free androgen index in the presence of a normal total testosterone. The measurement of SHBG is not required in routine practice but is a useful surrogate marker for insulin resistance.

One should be aware of the possibility of Cushing's syndrome in women with stigmata of PCOS and obesity as it is a disease of insidious onset and dire consequences; additional clues are the presence of central obesity, moon face, plethoric complexion, buffalo hump, proximal myopathy, thin skin, bruising and abdominal striae (which alone are a common finding in obese individuals). Acanthosis nigricans is a sign of profound insulin resistance and is usually visible as hyperpigmented thickening of the skin folds of the axilla and neck; acanthosis nigricans is associated with PCOS and obesity (Fig. 47.1).

Summary box 47.1

- A testosterone concentration above 5 nmol/L should be investigated to exclude androgen-secreting tumours of the ovary or adrenal gland, Cushing's syndrome and late-onset congenital adrenal hyperplasia (CAH). Whereas CAH often presents at birth with ambiguous genitalia (see Chapter 35), partial 21-hydroxylase deficiency may present in later life, usually in the teenage years, with signs and symptoms similar to PCOS. In such cases, testosterone may be elevated and the diagnosis confirmed by an elevated serum concentration of 17-hydroxyprogesterone (17-OHP); an abnormal ACTH stimulation test may also be helpful (250 µg ACTH will cause an elevation of 17-OHP, usually between 65 and 470 nmol/L).
- In cases of Cushing's syndrome, a 24-hour urinary-free cortisol will be elevated (>700 nmol per 24 hours). The normal serum concentration of cortisol is 140–700 nmol/L at 8 a.m. and less than 140 nmol/L at midnight. A low-dose dexamethasone suppression test (0.5 mg 6-hourly for 48 hours) will cause a suppression of serum cortisol by 48 hours. A simpler screening test is an overnight suppression test, using a single midnight dose of dexamethasone 1 mg (2 mg if obese) and measuring the serum cortisol concentration at 8 a.m. when it should be less than 140 nmol/L. If Cushing's syndrome is confirmed, a high-dose dexamethasone suppression test (2 mg 6-hourly for 48 hours) should suppress serum cortisol by 48 hours if there is a pituitary ACTH-secreting adenoma (Cushing's disease); failure of suppression suggests an adrenal tumour or ectopic secretion of ACTH. Further tests and detailed imaging will then be required.
- The measurement of other serum androgen levels can be helpful. Dehydroepiandrosterone sulfate (DHEAS) is primarily a product of the adrenal androgen pathway (normal range <10 µmol/L). If the serum androgen concentrations are elevated, the possibility of an ovarian or adrenal tumour should be excluded by ultrasound or CT scan. The measurement of androstenedione can also be useful in some situations.

Amenorrhoeic women might have hyperprolactinaemia and galactorrhoea. It is important, however, not to examine the breasts before taking blood as the serum prolactin concentration may be falsely elevated as a result of physical examination. Stress may also cause minor elevation of prolactin. If there is suspicion of a pituitary tumour, the patient's visual fields should be checked, as bitemporal hemianopia secondary to pressure on the optic chiasm requires urgent attention.

Table 47.1 Endocrine normal ranges.

FSH*	1–10 IU/L (early follicular)
LH*	1–10 IU/L (early follicular)
Prolactin*	<400 mIU/L
TSH*	0.5–4.0 IU/L
Thyroxine (T_4)	50–150 nmol/L
Free T_4	9–22 pmol/L
Triiodothyronine (T_3)	1.5–3.5 nmol/L
Free T_3	4.3–8.6 pmol/L
TBG	7–17 mg/L
Testosterone (T)*	0.5–3.5 nmol/L (ranges depend on the assay being used)
SHBG	16–120 nmol/L
Free androgen index [(T × 100) ÷ SHBG]	<5
Dihydrotestosterone	0.3–1 nmol/L
Androstenedione	2–10 nmol/L
Dehydroepiandrosterone sulfate	3–10 µmol/L
Cortisol	140–700 nmol/L
8 a.m.	0–140 nmol/L
Midnight	<400 nmol/24 hours
24-hour urinary	
Estradiol	250–500 pmol/L
Estrone	400–600 pmol/L
Progesterone (mid-luteal)	>25 nmol/L to indicate ovulation
17-hydroxyprogesterone	1–20 nmol/L
Inhibin B	5–200 pg/mL
AMH	Values should be assessed with respect to age-related nomograms. Low levels indicate poor ovarian reserve, normal levels suggest normal fertility and high values are often seen in women with polycystic ovaries

* Denotes those tests performed in routine screening of women with amenorrhoea.
AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone.

Thyroid disease is common and the thyroid gland should be palpated and signs of hypothyroidism (dry thin hair, proximal myopathy, myotonia, slow-relaxing reflexes, mental slowness, bradycardia) or hyperthyroidism (goitre with bruit, tremor, weight loss, tachycardia, hyperreflexia, exophthalmos, conjunctival oedema, ophthalmoplegia) elicited.

A bimanual examination is inappropriate in a young woman who has never been sexually active, and examination of the external genitalia of an adolescent should be undertaken in the presence of the patient's mother. Furthermore, it may be more appropriate to defer this from the first consultation in order to assure the patient's confidence in future management. A transabdominal ultrasound examination of the pelvis is an excellent non-invasive method for obtaining valuable information in these patients. Although an examination under anaesthetic is sometimes indicated for cases of disorders of sexual development with primary amenorrhoea, it is rarely required in cases of secondary amenorrhoea (Table 47.2).

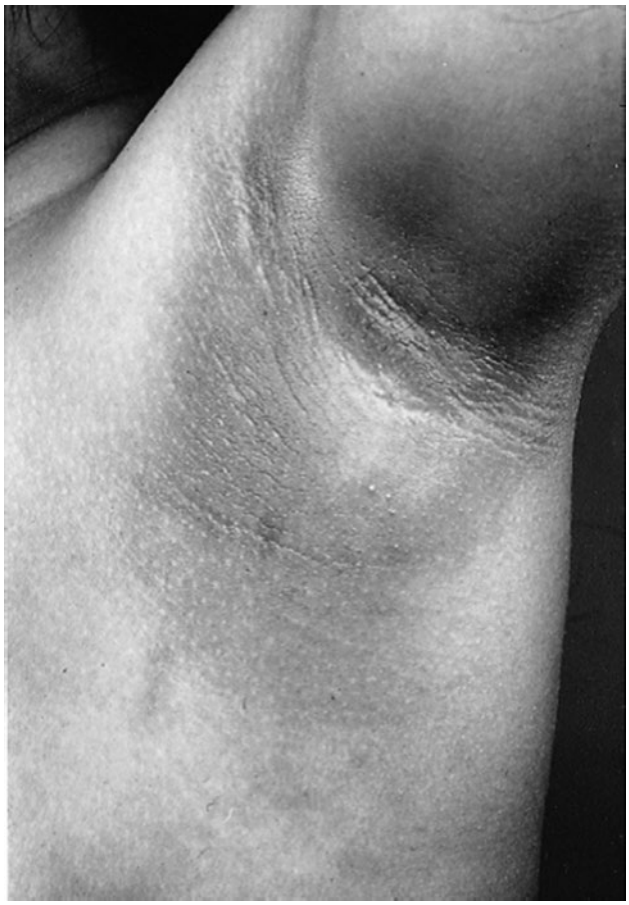


Fig. 47.1 Acanthosis nigricans, as seen typically in the skin folds (axilla, neck, elbow, vulva). *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

A baseline assessment of the endocrine status should include the measurement of serum prolactin and gonadotrophin concentrations and an assessment of thyroid function. Prolactin levels may be elevated in response to a number of conditions, including stress, a recent breast examination or even having a blood test; however, the elevation is moderate and transient. A more permanent, but still moderate, elevation (>700 mIU/L) is associated with hypothyroidism and is also a common finding in women with PCOS, where prolactin levels up to 2500

Table 47.2 Classification of secondary amenorrhoea.

Uterine causes	Asherman's syndrome
	Cervical stenosis
Ovarian causes	Polycystic ovary syndrome
	Premature ovarian insufficiency, formerly known as premature ovarian failure (genetic, autoimmune, infective, radiotherapy/chemotherapy)
Hypothalamic causes (hypogonadotrophic hypogonadism)	Weight loss
	Exercise
	Chronic illness
	Psychological distress
	Idiopathic
Pituitary causes	Hyperprolactinaemia
	Hypopituitarism
	Sheehan's syndrome
Causes of hypothalamic/ pituitary damage (hypogonadism)	Tumours (craniopharyngiomas, gliomas, germinomas, dermoid cysts)
	Cranial irradiation
	Head injuries
	Sarcoidosis
	Tuberculosis
	Chronic debilitating illness
Systemic causes	Weight loss
	Endocrine disorders (thyroid disease, Cushing's syndrome, etc.)

mIU/L have been reported [1]. PCOS may also result in amenorrhoea, which can therefore create diagnostic difficulties, and hence appropriate management, for those women with hyperprolactinaemia and polycystic ovaries. Amenorrhoea in women with PCOS is secondary to acyclical ovarian activity yet oestrogen production by the ovaries continues and so the endometrial thickness will be greater than 6 mm. A positive response to a progestogen challenge test, such as medroxyprogesterone acetate 10–20 mg (depending on body weight) daily for 7 days which induces a withdrawal bleed, will distinguish patients with PCOS-related hyperprolactinaemia from those with polycystic ovaries and unrelated hyperprolactinaemia, because the latter causes oestrogen deficiency and therefore failure to respond to the progestogen challenge because the endometrium is thin.

A serum prolactin concentration of greater than 1000 mIU/L warrants a repeat and then further investigation if still elevated. CT or MRI of the pituitary fossa may be used to exclude a hypothalamic tumour, a non-functioning pituitary tumour compressing the hypothalamus or a prolactinoma. Serum prolactin concentrations greater than 5000 mIU/L are usually associated with a macroprolactinoma, which by definition is greater than 1 cm in diameter.

Serum measurements of estradiol are of limited value as they vary considerably, even in a patient with amenorrhoea. If the patient is well oestrogenized, the endometrium will be clearly seen on an ultrasound scan and should be shed on progestogen withdrawal.

Serum gonadotrophin measurements help to distinguish between cases of hypothalamic or pituitary failure and gonadal failure. Elevated gonadotrophin concentrations indicate a failure of negative feedback as a result of primary or premature ovarian insufficiency (POI, formerly known as premature ovarian failure). A serum follicle-stimulating hormone (FSH) concentration of greater than 15 IU/L that is not associated with a preovulatory luteinizing hormone (LH) surge suggests impending ovarian failure. FSH levels of greater than 40 IU/L are suggestive of irreversible ovarian failure. The exact values vary according to individual assays, and so local reference levels should be checked. It is also important to assess serum gonadotrophin levels at baseline (during the first 3 days of a menstrual period). In patients with oligomenorrhoea/amenorrhoea, it may be necessary to perform two or more random measurements, although combining an endocrine assessment with an ultrasound scan on the same day aids the diagnosis.

An elevated LH concentration, when associated with a raised FSH concentration, is indicative of ovarian failure. However, if LH is elevated alone (and is not attributable to the preovulatory LH surge), this suggests PCOS. This may be confirmed by a pelvic ultrasound scan. Rarely, an elevated LH in a phenotypic female may be due to androgen insensitivity syndrome, although this condition presents with primary amenorrhoea.

Inhibin B is thought to be the ovarian hormone with the greatest influence on pituitary secretion of FSH. Previously, it was thought that serum concentrations of inhibin B might provide better quantification of ovarian reserve than serum FSH concentrations; however, the assay is no longer being used.

Anti-Müllerian hormone (AMH) is best known as a product of the testes during fetal development that suppresses the development of Müllerian structures. AMH is also produced by the pre-antral and antral follicles and appears to be a more stable predictor of the ovarian follicle pool as it does not fluctuate through the menstrual cycle. Indeed, it has been reported that higher AMH concentrations are associated with increased numbers of mature oocytes, embryos and clinical pregnancies during *in vitro* fertilization (IVF) treatment. Assays for AMH are now available for routine use and it is this hormone that currently offers the greatest promise for future assessment of ovarian reserve and function. The number

of antral follicles in the ovary, as assessed by pelvic ultrasound, also correlates well with ovarian reserve and serum AMH levels. Indeed, it is the number of small antral follicles, 2–6 mm in diameter, that declines significantly with age while there is little change in the larger follicles of 7–10 mm, which is still below the size at which growing follicles have been recruited.

Failure at the level of the hypothalamus or pituitary is reflected by abnormally low levels of serum gonadotrophin concentrations, and gives rise to hypogonadotrophic hypogonadism. Kallmann's syndrome is the clinical finding of anosmia and/or colour blindness associated with hypogonadotrophic hypogonadism, usually a cause of primary amenorrhoea. CT or MRI should be performed if indicated.

Karyotype and other tests

Women with POI (under the age of 40 years) may have a chromosomal abnormality, for example Turner's syndrome (45X or 46XX/45X mosaic) or other sex chromosome mosaicisms. A number of genes have also been associated with familial POI, but have not been assessed in routine clinical practice. An autoantibody screen should also be undertaken in women with POI, although it can be difficult to detect anti-ovarian antibodies and many will have evidence of other autoantibodies (e.g. thyroid), which then indicates the need for further surveillance.

A history of a recent endometrial curettage or endometritis in a patient with normal genitalia and normal endocrinology, but with absent or only a small withdrawal bleed following a progestogen challenge, is suggestive of Asherman's syndrome. An ultrasound scan and/or a hysterosalpingogram (HSG) may be helpful and hysteroscopy will confirm the diagnosis (Fig. 47.2).

Measurement of bone mineral density (BMD) is indicated in amenorrhoeic women who are oestrogen deficient. Measurements of density are made in the lumbar spine and femoral neck. The vertebral bone is more sensitive to oestrogen deficiency and vertebral fractures tend to occur in a younger age group (50–60 years) than fractures at the femoral neck (70+ years). However, it should be noted that crush fractures can spuriously increase the measured BMD. An X-ray of the dorsolumbar spine is therefore often complementary, particularly in patients who have lost height.

Amenorrhoea may also have long-term metabolic and physical consequences. In women with PCOS and prolonged amenorrhoea, there is a risk of endometrial hyperplasia and adenocarcinoma. If on resumption of menstruation there is a history of persistent intermenstrual bleeding, or on ultrasound there is a postmenstrual endometrial thickness of greater than 10 mm, an endometrial biopsy is indicated.

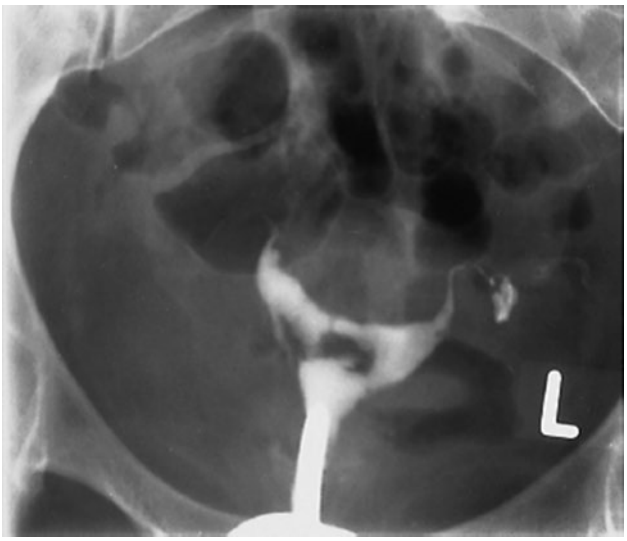


Fig. 47.2 Conventional X-ray hysterosalpingogram demonstrating Asherman's syndrome, with intrauterine synechiae. There is no flow of contrast through the right tube, although thickening of the cornual end of the tube suggests the possibility of tubal spasm. There is flow to the end of the left fallopian tube, although no free spill into the peritoneal cavity. This raises the possibility of sacculated adhesions around the fimbrial end of the tube. *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

Serum cholesterol measurements are important because of the association of an increased risk of heart disease in women with POI. Women with PCOS, although not oestrogen deficient, may have a subnormal ratio of high-density lipoprotein (HDL) to total cholesterol. This is as a consequence of the hypersecretion of insulin that occurs in many women with PCOS.

Glucose tolerance

Women who are obese, and also many slim women with PCOS, may have insulin resistance and elevated serum concentrations of insulin (usually <30 mIU/L fasting, although not measured in clinical practice). A 75-g oral glucose tolerance test should be performed in women with PCOS and a BMI above 30 kg/m^2, with an assessment of the fasting and 2-hour glucose concentration (Table 47.3). It has been suggested that South Asian women should have an assessment of glucose tolerance if their BMI is greater than 25 kg/m^2 because of the greater risk of insulin resistance at a lower BMI than seen in the white population.

Polycystic ovary syndrome

PCOS is a heterogeneous collection of signs and symptoms that form a spectrum of disorders, with mild presentation in some but severe disturbance of repro-

Table 47.3 Definitions of glucose tolerance after a 75-g glucose tolerance test.

	Diabetes mellitus	Impaired glucose tolerance	Impaired fasting glycaemia
Fasting glucose (mmol/L)	≥7.0	<7.0	≥6.1 and <7.0
2-hour glucose (mmol/L)	≥11.1	≥7.8 and ≤11.1	<7.8

ductive, endocrine and metabolic function in others. The pathophysiology of PCOS appears to be multifactorial and polygenic. The definition of the syndrome has been much debated. Key features include menstrual cycle disturbance, hyperandrogenism and obesity. There are many extra-ovarian aspects to the pathophysiology of PCOS, yet ovarian dysfunction is central. The joint ESHRE/ASRM (European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine) consensus defined PCOS as requiring the presence of two of the following three criteria:

1) oligo-ovulation and/or anovulation (i.e. oligomenorrhoea or amenorrhoea);
2) hyperandrogenism (clinical features and/or biochemical elevation of testosterone); and/or
3) polycystic ovaries assessed by ultrasound [2].

The consensus meeting that provided this definition was held in Rotterdam and so the ESHRE/ASRM criteria are often known as the Rotterdam criteria [2].

Other aetiologies of hyperandrogenism and menstrual cycle disturbance should be excluded by appropriate investigations, as described in this chapter. The morphology of the polycystic ovary has been redefined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm^3) [3]. The use of higher resolution ultrasound than was available at the time of the Rotterdam meeting has led some to suggest that more follicles (19 or even 25) should define the polycystic ovary, but no consensus has been reached [4].

There is considerable heterogeneity of symptoms and signs among women with PCOS and for an individual these may change over time [1,2] (Table 47.4). PCOS may be familial, and various aspects of the syndrome may be differentially inherited. Polycystic ovaries can exist without clinical signs of the syndrome, which may then become expressed in certain circumstances. There are a number of factors that affect expression of PCOS, for example a gain in weight is associated with a worsening of symptoms while weight loss may ameliorate the endocrine and metabolic profile and symptomatology.

Genetic studies have identified a link between PCOS and disordered insulin metabolism, and indicate that the syndrome may be the presentation of a complex genetic trait disorder. The features of obesity, hyperinsulinaemia and hyperandrogenaemia, which are commonly seen in PCOS, are also known to be factors that confer an increased risk of cardiovascular disease and non-insulin-dependent diabetes mellitus (NIDDM) [5]. There are studies indicating that women with PCOS have an increased risk for these diseases, which pose long-term risks for health, and this evidence has prompted debate as to the need for screening women for PCOS [5] (Fig. 47.3).

Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being in the order of 20–33% [6]. Although the ultrasound criteria for the diagnosis of polycystic ovaries have not, until now, been universally agreed, the characteristic features are accepted as being an increase in the number of follicles and the amount of stroma compared with normal ovaries, resulting in an increase in ovarian volume. The 'cysts' are not cysts in the sense that they do contain oocytes and indeed are follicles whose development has been arrested. The actual number of cysts may be of less

Table 47.4 Signs and symptoms of polycystic ovary syndrome.

Symptoms
Hyperandrogenism (acne, hirsutism, alopecia – not virilization)
Menstrual disturbance
Infertility
Obesity
Sometimes: asymptomatic, with polycystic ovaries on ultrasound scan

Serum endocrinology
↑ Fasting insulin (not routinely measured; insulin resistance or impaired glucose tolerance assessed by GTT)
↑ Androgens (testosterone and androstenedione)
↑ or normal LH, normal FSH
↓ SHBG, results in elevated free androgen index
↑ Estradiol, estrone (neither measured routinely as very wide range of values)
↑ Prolactin

Possible late sequelae
Diabetes mellitus
Dyslipidaemia
Hypertension, cardiovascular disease
Endometrial carcinoma

FSH, follicle-stimulating hormone; GTT, glucose tolerance test; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

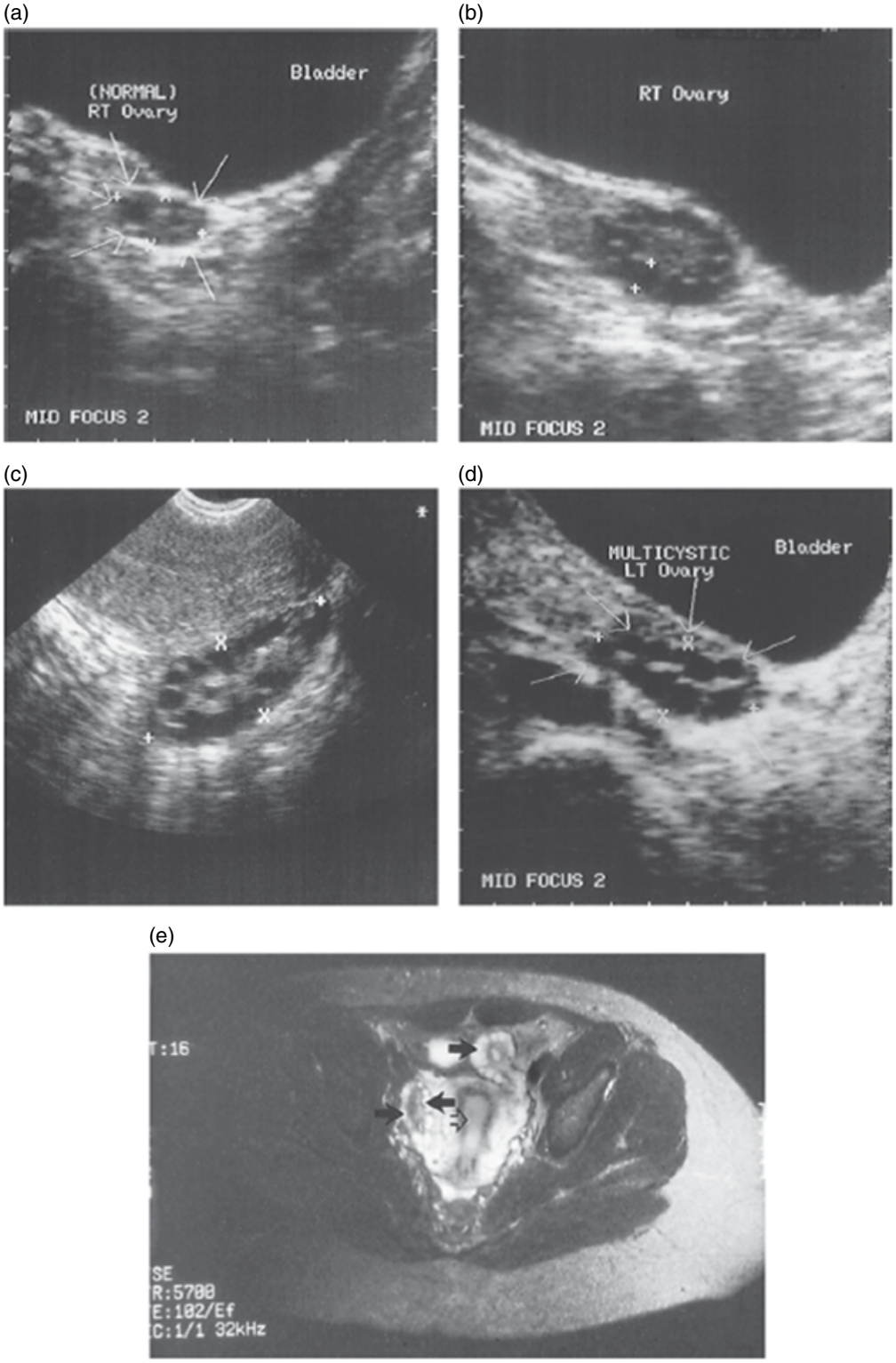


Fig. 47.3 (a) Transabdominal ultrasound scan of a normal ovary. (b) Transabdominal ultrasound scan of a polycystic ovary. (c) Transvaginal ultrasound scan of a polycystic ovary. (d) Transabdominal ultrasound scan of a multicystic ovary. (e) MRI of a pelvis, demonstrating two polycystic ovaries (closed arrows) and a hyperplastic endometrium (open arrow). *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

relevance than the volume of ovarian stroma or of the ovary itself, which has been shown to closely correlate with serum testosterone concentrations.

Genetics of polycystic ovary syndrome

Polycystic ovary syndrome has long been noted to have a familial component. Genetic analysis has been hampered by the lack of a universal definition for PCOS. Most of the criteria used for diagnosing PCOS are continuous traits, such as degree of hirsutism, level of circulating androgens, extent of menstrual irregularity, and ovarian volume and morphology. To perform genetic analyses, these continuous variables have to be transformed into nominal variables. Family studies have revealed that about 50% of first-degree relatives have PCOS, suggesting a dominant mode of inheritance [2,5]. Commonly, first-degree male relatives appear more likely to have the metabolic syndrome [7]. Further discussion of this complex area is beyond the scope of this chapter and much research is being performed to provide a more detailed account of the various genetic abnormalities that may be involved in the pathogenesis of PCOS.

Pathophysiology of polycystic ovary syndrome

Hypersecretion of androgens by the stromal theca cells of the polycystic ovary leads to the cardinal clinical manifestation of the syndrome, hyperandrogenism, and is also one of the mechanisms whereby follicular growth is inhibited with the resultant excess of immature follicles. Hypersecretion of LH by the pituitary – a result of both disordered ovarian–pituitary feedback and exaggerated pulses of gonadotrophin-releasing hormone (GnRH) from the hypothalamus – stimulates testosterone secretion by the ovary. Furthermore, insulin is a potent stimulus for androgen secretion by the ovary, which, by way of a different receptor for insulin, does not exhibit insulin resistance. Insulin therefore amplifies the effect of LH, and additionally magnifies the degree of hyperandrogenism by suppressing liver production of the main carrier protein, SHBG, thus elevating the free androgen index. It is a combination of genetic abnormalities combined with environmental factors, such as nutrition and body weight, which then affect expression of the syndrome.

Racial differences in expression of polycystic ovary syndrome

The highest reported prevalence of PCOS has been 52% among South Asian immigrants in Britain, of whom 49.1% had menstrual irregularity [8]. Rodin *et al.* [8] demonstrated that South Asian women with PCOS had a comparable degree of insulin resistance to controls with established type 2 diabetes mellitus. Insulin resistance and hyperinsulinaemia are common antecedents of type 2 diabetes, with a high prevalence in South Asian people. Type 2 diabetes also has a familial basis, inherited as a complex genetic trait that interacts with environmental factors, chiefly nutrition, commencing during fetal life. We have found that South Asian people with anovulatory PCOS have greater insulin resistance and more severe symptoms of the syndrome than anovulatory white people with PCOS [9]. Furthermore, we have found that women from South Asia living in the UK appear to express symptoms at an earlier age than their white British counterparts [10].

Health consequences of polycystic ovary syndrome

Obesity and metabolic abnormalities are recognized risk factors for the development of ischaemic heart disease in the general population, and these are also recognized features of PCOS. The question is whether women with PCOS are at an increased risk of ischaemic heart disease, and whether this will occur at an earlier age than women with normal ovaries. The basis for the idea that women with PCOS are at a greater risk for cardiovascular disease is that these women are more insulin resistant than weight-matched controls and that the metabolic disturbances associated with insulin resistance are known to increase cardiovascular risk in other populations. Insulin resistance is defined as a diminution in the biological responses to a given level of insulin. In the presence of an adequate pancreatic reserve, normal circulating glucose levels are maintained at higher serum insulin concentrations. In the general population, cardiovascular risk factors include insulin resistance, obesity, glucose intolerance, hypertension and dyslipidaemia.

There have been a large number of studies demonstrating the presence of insulin resistance and corresponding hyperinsulinaemia in both obese and non-obese women with PCOS [5]. Obese women with PCOS have consistently been shown to be more insulin resistant than weight-matched controls. It appears that obesity and PCOS have an additive effect on the degree and severity of the insulin resistance and subsequent hyperinsulinaemia in this group of women. The insulin resistance causes compensatory hypersecretion of insulin, particularly in response to glucose, so euglycaemia is usually maintained at the expense of hyperinsulinaemia. Insulin resistance is restricted to the extrasplanchnic actions of insulin on glucose dispersal. The liver is not affected (hence the fall in SHBG and HDL), neither is the ovary (hence the menstrual problems and hypersecretion of androgens) nor the skin, hence the development

of acanthosis nigricans. Women with PCOS who are oligomenorrhoeic are more likely to be insulin resistant than those with regular cycles, irrespective of their BMI, with the intermenstrual interval correlating with the degree of insulin resistance [5].

Women with PCOS have a greater truncal abdominal fat distribution as demonstrated by a higher waist to hip ratio. The central distribution of fat is independent of BMI and associated with higher plasma insulin and triglyceride concentrations and reduced HDL cholesterol concentrations. From a practical point of view, if the measurement of waist circumference is greater than 80 cm, there will be excess visceral fat and an increased risk of metabolic problems.

Thus, there is evidence that insulin resistance, central obesity and hyperandrogenaemia have an adverse effect on lipid metabolism, yet these are surrogate risk factors for cardiovascular disease. Significantly, Pierpoint *et al.* [11] reported the mortality rate in 1028 women diagnosed as having PCOS between 1930 and 1979. All the women were older than 45 years and 770 women had been treated by wedge resection of the ovaries. A total of 786 women were traced; the mean age at diagnosis was 26.4 years and the average duration of follow-up was 30 years. There were 59 deaths, of which 15 were from circulatory disease. Of these 15 deaths, 13 were from ischaemic heart disease. There were six deaths from diabetes as an underlying or contributory cause compared with the expected 1.7 deaths. The standard mortality rate both overall and for cardiovascular disease was not higher in the women with PCOS than the national mortality rates in women, although the observed proportion of women with diabetes as a contributory or underlying factor leading to death was significantly higher than expected (odds ratio 3.6, 95% CI 1.5–8.4). Thus, despite surrogate markers for cardiovascular disease, no increased rate of death from cardiovascular disease could be demonstrated in this study [5,11].

Polycystic ovary syndrome in younger women

The majority of studies that have identified the risk factors of obesity and insulin resistance in women with PCOS have investigated adult populations, commonly including women who have presented to specialist endocrine or reproductive clinics. However, PCOS has been identified in much younger populations [6], in which women with increasing symptoms of PCOS were found to be more insulin resistant. These data emphasize the need for long-term prospective studies of young women with PCOS in order to clarify the natural history and to determine which women will be at risk of diabetes and cardiovascular disease later in life. A study of women with PCOS and a mean age of 39 years followed over a period of 6 years found that 9% of those with normal glucose tolerance developed impaired glucose tolerance (IGT) and 8% developed NIDDM [12], while 54% of women with IGT at the start of the study had NIDDM at follow-up. The risks of disease progression, not surprisingly, were greatest in those who were overweight.

Whilst PCOS may evolve during adolescence, many of the symptoms (e.g. menstrual irregularity and acne) occur commonly in normal adolescent girls and so it is generally considered unwise to make the diagnosis until more than 2 years after menarche [5].

Endometrial cancer

Endometrial adenocarcinoma is the second most common female genital malignancy, but only 4% of cases occur in women aged under 40 years. The risk of developing endometrial cancer has been shown to be adversely influenced by a number of factors, including obesity, long-term use of unopposed oestrogens, nulliparity and infertility. Women with endometrial carcinoma have had fewer births than controls, and it has also been demonstrated that infertility per se increases the risk [5]. Hypertension and type 2 diabetes mellitus have long been linked to endometrial cancer – conditions that are now known also to be associated with PCOS. However, the true risk of endometrial carcinoma in women with clearly defined PCOS is difficult to ascertain [5].

Endometrial hyperplasia may be a precursor to adenocarcinoma, although the rate of progression is difficult to predict. Although the degree of risk has not been clearly defined, it is generally accepted that for women with PCOS who experience amenorrhoea or oligomenorrhoea, the induction of artificial withdrawal bleeds to prevent endometrial hyperplasia is prudent management [5]. Indeed, we consider it important that women with PCOS shed their endometrium at least every 3 months. For those with oligomenorrhoea/amenorrhoea who do not wish to use cyclical hormone therapy, we recommend an ultrasound scan to measure endometrial thickness and morphology every 6–12 months (depending on menstrual history). An endometrial thickness greater than 10 mm in an amenorrhoeic woman warrants an artificially induced bleed, which should be followed by a repeat ultrasound scan and endometrial biopsy if the endometrium has not been shed. Another option is to consider a progestogen-secreting intrauterine system such as Mirena® (Bayer Pharma, Newbury, UK).

Breast cancer

Obesity, hyperandrogenism and infertility occur frequently in PCOS and are features known to be associated

with the development of breast cancer. However, studies examining the relationship between PCOS and breast carcinoma have not always identified a significantly increased risk [5]. Pierpoint *et al.* [11] assessed mortality from the national registry of deaths and standardized mortality rate (SMR) calculated for patients with PCOS compared with the normal population. The average follow-up period was 30 years. The SMR for all neoplasms was 0.91 (95% CI 0.60–1.32) and for breast cancer was 1.48 (95% CI 0.79–2.54). In fact, breast cancer was the leading cause of death in this cohort.

Ovarian cancer

In recent years there has been much debate about the risk of ovarian cancer in women with infertility, particularly in relation to the use of drugs to induce superovulation for assisted conception procedures. Inherently the risk of ovarian cancer appears to be increased in women who have multiple ovulations – that is those who are nulliparous (possibly because of infertility) with an early menarche and late menopause. Thus, it may be that inducing multiple ovulations in women with infertility will increase their risk, a notion that is by no means proven. Women with PCOS who are oligo-ovulatory/anovulatory might therefore be expected to be at low risk of developing ovarian cancer if it is lifetime number of ovulations rather than pregnancies that is critical. Ovulation induction to correct anovulatory infertility aims to induce unifollicular ovulation, and so in theory should raise the risk of a woman with PCOS to that of a woman with normal ovulation. However, the polycystic ovary is notoriously sensitive to stimulation and it is only in recent years with the development of high-resolution transvaginal ultrasonography that the rate of unifollicular ovulation has attained acceptable levels. There are a few studies which have addressed the possibility of an association between polycystic ovaries and ovarian cancer. The results are conflicting and the ability to generalize is limited owing to problems with the study designs [5]. In the large UK study by Pierpoint *et al.* [11], the SMR for ovarian cancer was 0.39 (95% CI 0.01–2.17).

Management of polycystic ovary syndrome

Obesity

The clinical management of a women with PCOS should be focused on her individual problems. Obesity worsens both symptomatology and the endocrine profile and obese women (BMI >30 kg/m^2) should therefore be encouraged to lose weight. Weight loss improves the endocrine profile, the likelihood of ovulation and a healthy pregnancy. Much has been written about diet and PCOS. The right diet for an individual is one that is practical, sustainable and compatible with her lifestyle. It is sensible to keep carbohydrate content down and to avoid fatty foods. It is often helpful to refer to a dietitian. Bariatric surgery (either gastric banding or gastric bypass procedures) are also very effective for women with a BMI over 35 kg/m^2, although it is inadvisable to conceive immediately after surgery until metabolism has stabilized after the initial rapid loss of weight [13].

Menstrual irregularity

Amenorrhoeic women with PCOS are not oestrogen deficient and are not at risk of osteoporosis. Indeed, they are oestrogen replete and at risk of endometrial hyperplasia (see section on endometrial cancer). The easiest way to control the menstrual cycle is the use of a low-dose combined oral contraceptive preparation. This will result in an artificial cycle and regular shedding of the endometrium. An alternative is a progestogen such as medroxyprogesterone acetate (Provera) for 12 days every 1–3 months to induce a withdrawal bleed, or the continuous provision of progesterone into the uterine cavity by Mirena. It is important once again to encourage weight loss.

Hyperandrogenism and hirsutism

The bioavailability of testosterone is affected by the serum concentration of SHBG. High levels of insulin lower the production of SHBG and so increase the free fraction of androgen. Elevated serum androgen concentrations stimulate peripheral androgen receptors, resulting in an increase in 5α-reductase activity, directly increasing the conversion of testosterone to the more potent metabolite dihydrotestosterone. Women with PCOS do not become virilized (i.e. they do not develop deepening of the voice, increased muscle mass, breast atrophy or clitoromegaly). A total testosterone level greater than 5 nmol/L or rapid onset of signs of hyperandrogenism requires further investigation. Late-onset CAH is not common in the UK but is more prevalent in certain ethnic groups (e.g. Mediterranean, South American and some Jewish populations).

Hirsutism is characterized by terminal hair growth in a male pattern of distribution, including the chin, upper lip, chest, upper and lower back, upper and lower abdomen, upper arm, thigh and buttocks. A standardized scoring system, such as the modified Ferriman–Gallwey score, may be used to evaluate the degree of hirsutism before and during treatments (Fig. 47.4). Many women attend having already tried cosmetic techniques and so it may be difficult to obtain a baseline assessment.

Drug therapies may take 6–9 months or longer before any improvement in hirsutism is perceived. Physical treatments including electrolysis, waxing and bleaching

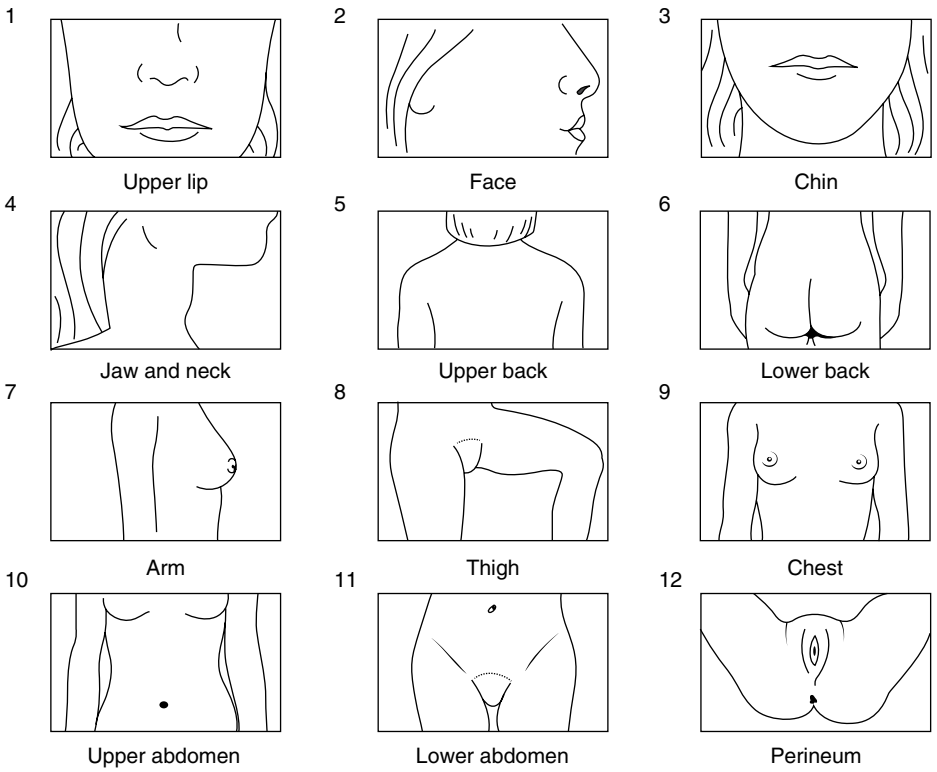


Fig. 47.4 The Ferriman–Gallwey Hirsutism Scoring System. The chart is used both to provide an initial score, with a scale of 0–3 at each of 12 points, depending on severity, and for the monitoring of progress with therapy. *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

may be helpful while waiting for medical treatments to work. Electrolysis is time-consuming, painful and expensive, and should be performed by an expert practitioner. Regrowth is not uncommon and there is no really permanent cosmetic treatment. Laser and photothermolysis techniques are more expensive but may have a longer duration of effect. Comparative studies, however, have not been performed. Repeated treatments are required for a near-permanent effect because only hair follicles in the growing phase are obliterated at each treatment. Hair growth occurs in three cycles, so 6–9 months of regular treatments are typical. The topical use of eflornithine may be effective. It works by inhibiting the enzyme ornithine decarboxylase in hair follicles and may be a useful therapy for those who wish to avoid hormonal treatments, but may also be used in conjunction with hormonal therapy. Eflornithine may cause some thinning of the skin and so high-factor sun block is recommended when exposed to the sun.

Medical regimens should stop further progression of hirsutism and decrease the rate of hair growth. Adequate contraception is important in women of reproductive age as transplacental passage of anti-androgens may disturb the genital development of a male fetus. First-line therapy has traditionally been the preparation Dianette, which contains ethinylestradiol (30 μg) in combination with cyproterone acetate (2 mg). The addition of higher doses of the synthetic progestogen cyproterone acetate (50–100 mg) do not appear to confer additional benefit. The effect on acne and seborrhoea is usually evident within a couple of months. Cyproterone acetate can rarely be associated with liver damage, and liver function should be checked after 6 months and then annually. Once symptom control has been obtained, it is advisable to switch to a combined oral contraceptive pill containing a lower dose of ethinylestradiol because of concerns about the increased risk of thromboembolism with Dianette [5].

In women in whom the combined oral contraceptive pill is contraindicated, spironolactone, a weak diuretic with anti-androgenic properties, may be used at a daily dose of 25–100 mg. Drospirenone is a derivative of spironolactone and is contained in the combined oral contraceptive pill Yasmin, which may also be beneficial for women with PCOS.

Other anti-androgens such as ketoconazole, finasteride and flutamide have been tried, but are not widely

used in the UK for the treatment of hirsutism in women owing to their adverse side effects. Furthermore, they are no more effective than cyproterone acetate [5].

Infertility

Various factors influence ovarian function, and fertility is adversely affected by an individual being overweight or having elevated serum concentrations of LH. Strategies to induce ovulation include weight loss, oral antioestrogens (principally clomifene citrate or tamoxifen), parenteral gonadotrophin therapy and laparoscopic ovarian surgery. Clomifene is the traditional first-line therapy and can be continued for 6–12 cycles of treatment if the patient is ovulating with normal endocrinology. Aromatase inhibitors, such as letrozole, may also stimulate ovulation and appear to be associated with a lower risk of multiple pregnancy; however, they are not currently licensed for the treatment of infertility. For those who do not ovulate, the options include daily injections of either recombinant FSH, human menopausal gonadotrophins (hMGs, which contain both FSH and LH activity) or laparoscopic ovarian diathermy [14]. Women with PCOS are at risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy, and so ovulation induction has to be carefully monitored with serial ultrasound scans.

Improvements in lifestyle, with a combination of exercise and diet to achieve weight reduction, are important for improving the prospects of both spontaneous and drug-induced ovulation. In addition, overweight women with PCOS are at increased risk of obstetric complications, gestational diabetes mellitus and pre-eclampsia, and their fetuses are at increased risk of congenital malformations and miscarriage [15].

Ovulation can be induced with the antioestrogen clomifene citrate (50–100 mg) taken from days 2–6 of a natural or artificially induced bleed. While clomifene is successful in inducing ovulation in over 80% of women, pregnancy only occurs in about 40%. Clomifene citrate should only be prescribed in a setting where ultrasound monitoring is available (and performed) in order to minimize the 10% risk of multiple pregnancy and to ensure that ovulation is taking place [14]. A daily dose of more than 100 mg rarely confers any benefit and can cause thickening of the cervical mucus, which can impede passage of sperm through the cervix. Once an ovulatory dose has been reached, the cumulative conception rate continues to increase for up to 10–12 cycles [14].

The therapeutic options for patients with anovulatory infertility who are resistant to antioestrogens are either parenteral gonadotrophin therapy or laparoscopic ovarian diathermy. Because the polycystic ovary is very sensitive to stimulation by exogenous hormones, it is extremely important to start with very low doses of gonadotrophins and follicular development must be carefully monitored by ultrasound scans. The advent of transvaginal ultrasonography has enabled the multiple pregnancy rate to be reduced to less than 5% because of its higher resolution and clearer view of the developing follicles. Cumulative conception and live-birth rates after 6 months may be 62% and 54%, respectively, and after 12 months 73% and 62%, respectively [16] (Fig. 47.5). Close monitoring should enable treatment to be suspended if more than two mature follicles develop, as the risk of multiple pregnancy increases (Fig. 47.6).

Women with PCOS are also at increased risk of developing OHSS. This occurs if too many follicles (>10 mm) are stimulated and results in abdominal distension, discomfort, nausea, vomiting and sometimes difficulty in breathing. The mechanism for OHSS is thought to be secondary to activation of the ovarian renin–angiotensin pathway and excessive secretion of

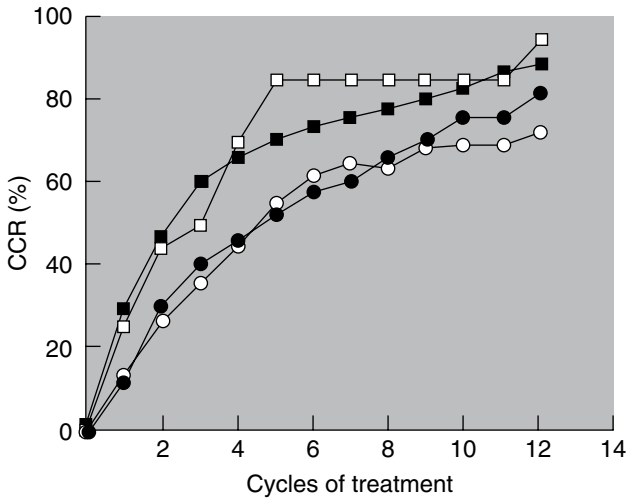
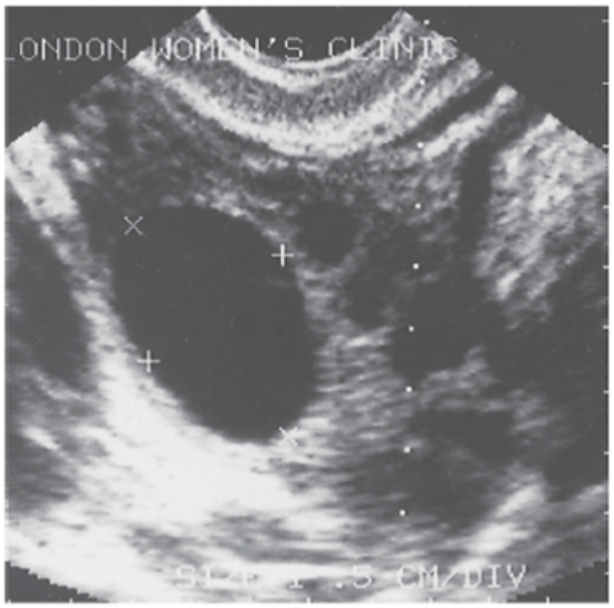


Fig. 47.5 Cumulative conception rates (CCR) over successive cycles in normal women (closed square) and after ovulation induction in 103 women with anovulatory PCOS (open circle), 77 women with hypogonadotrophic hypogonadism (closed circle) and 20 patients with weight-related amenorrhoea (open square). While patients with weight-related amenorrhoea conceive readily after ovulation induction, we now believe that their management should be weight gain before conception (see text). *Source:* Balen AH, Braat DDM, West C, Patel A, Jacobs HS. Cumulative conception and live birth rates after the treatment of anovulatory infertility. *Hum Reprod* 1994;9:1563–1570. Reproduced with permission of Oxford University Press.

(a)



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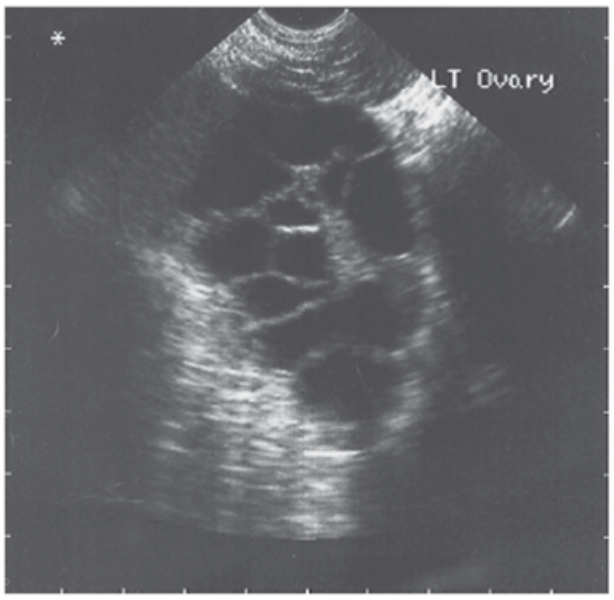

Fig. 47.6 (a) Transvaginal ultrasound scan of unifollicular development in a polycystic ovary and (b) an overstimulated polycystic ovary. *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

vascular epidermal growth factor (VEGF). The ascites and pleural and pericardial effusions exacerbate this serious condition and the resultant haemoconcentration can lead to thromboembolism. The situation worsens if a pregnancy has resulted from the treatment as human chorionic gonadotrophin from the placenta further stimulates the ovaries. Hospitalization is sometimes necessary in order for intravenous fluids and heparin to be given to prevent dehydration and thromboembolism. Although OHSS is rare, it is potentially fatal and should be avoidable with appropriate monitoring of gonadotrophin therapy.

Ovarian diathermy is free of the risks of multiple pregnancy and OHSS and does not require intensive ultrasound monitoring. Laparoscopic ovarian diathermy has taken the place of wedge resection of the ovaries (which resulted in extensive periovarian and tubal adhesions) and carries a reduced risk of multiple pregnancy compared with gonadotrophin therapy in the treatment of clomifene-insensitive PCOS. Pregnancy rates are higher with 6 months of gonadotrophin therapy compared with 6 months after laparoscopic ovarian diathermy [17].

Insulin-sensitizing agents and metformin

A number of pharmacological agents have been used to amplify the physiological effect of weight loss, notably metformin. This biguanide inhibits the production of hepatic glucose and enhances the sensitivity of peripheral tissue to insulin, thereby decreasing insulin secretion. It has been shown that metformin may ameliorate hyperandrogenism and abnormalities of gonadotrophin secretion in some women with PCOS, and therefore it was suggested that it might restore menstrual cyclicity and fertility. The insulin-sensitizing agent troglitazone also appeared to significantly improve the metabolic and reproductive abnormalities in PCOS, although it was withdrawn because of reports of deaths from hepatotoxicity, and other thiazolidinediones such as rosiglitazone and pyoglitazone are not advocated for women trying to conceive.

Most of the initial studies of metformin in the management of PCOS were observational. Metformin appears to be less effective in those who are significantly obese (BMI >35 kg/m^2). The largest appropriately powered, prospective, randomized, double-blind, placebo-controlled study set out to evaluate the combined effects of lifestyle modification and metformin in 143 obese anovulatory women with a mean BMI of 38 kg/m^2 [18]. All subjects had an individualized assessment by a dietitian in order to set a realistic goal that could be sustained with an average reduction of energy intake of 500 kcal/day. As a result, both the metformin-treated and placebo groups managed to lose weight, but the amount of weight reduction did not differ between the two groups. An increase in menstrual cyclicity was observed in those who lost weight but again did not differ between the two arms of the study, reinforcing the key role of weight reduction.

Summary box 47.2

- PCOS is the commonest endocrine disorder in women (prevalence 15–20%).
- PCOS runs in families and affects approximately 50% of first-degree relatives.
- PCOS is a heterogeneous condition. Diagnosis is made by the presence of two of the following three criteria: (i) oligo-ovulation and/or anovulation, (ii) hyperandrogenism (clinical and/or biochemical) or (iii) polycystic ovaries, with the exclusion of other aetiologies of menstrual irregularity and androgen excess.
- Management is symptom-orientated.
- If obese, weight loss improves symptoms and endocrinology and should be encouraged. A glucose tolerance test should be performed if BMI is above 30 kg/m^2 (>25 kg/m^2 if Asian). Dietary advice and exercise are essential components of a weight-reduction programme. Anti-obesity surgery may be indicated.
- Menstrual cycle control may be achieved by using cyclical oral contraceptives or progestogens.
- Ovulation induction may be difficult and require progression through various treatments, which should be monitored carefully to prevent multiple pregnancy.
- Hyperandrogenism is usually managed with Dianette, which contains ethinylestradiol in combination with cyproterone acetate, or Yasmin, which contains drospirenone. Alternatives include spironolactone, and reliable contraception is required.
- There is no place for insulin-sensitizing agents (e.g. metformin) in the absence of impaired glucose tolerance or type 2 diabetes.

Two large randomized controlled trials also concluded that as first-line therapy for the treatment of anovulatory infertile women with PCOS, metformin alone was significantly less effective than clomifene citrate alone, and that the addition of metformin to clomifene citrate produced no significant benefit [19,20]. The recent Cochrane review has also concluded that there is no benefit of metformin in achieving an increased rate of live birth either alone or in combination, and so the use of metformin is only recommended when there is impaired glucose tolerance or type 2 diabetes [21].

Secondary amenorrhoea

Cessation of menstruation for six consecutive months in a woman who has previously had regular periods is the usual criterion for investigation. However, some authorities consider 3 or 4 months of amenorrhoea to be pathological, but this is a debate between the definition of amenorrhoea and oligomenorrhoea. Women with secondary amenorrhoea must have a patent lower genital tract, an endometrium that is responsive to ovarian hormone stimulation and ovaries that have responded to pituitary gonadotrophins.

Secondary amenorrhoea is best classified according to its aetiological site of origin and can be subdivided into disorders of the hypothalamic–pituitary–ovarian–uterine axis and generalized systemic disease. The principal causes of secondary amenorrhoea are outlined in Table 47.2. The frequency with which these conditions present, on the other hand, can be seen in Table 47.5.

Table 47.5 The aetiology of secondary amenorrhoea in 570 patients attending an endocrine clinic [31].

Polycystic ovary syndrome	37%
Premature ovarian insufficiency	24%
Hyperprolactinaemia	17%
Weight-related amenorrhoea	10%
Hypogonadotrophic hypogonadism	6%
Hypopituitarism	4%
Exercise-related amenorrhoea	3%

Management of secondary amenorrhoea

Genital tract abnormalities

Asherman's syndrome

Asherman's syndrome is a condition in which intrauterine adhesions prevent normal growth of the endometrium [22]. This may be the result of an over-vigorous endometrial curettage affecting the basalis layer of the endometrium or adhesions that may follow an episode of endometritis. It is thought that oestrogen deficiency increases the risk of adhesion formation in breast-feeding women who require a puerperal curettage for retained placental tissue. Typically, amenorrhoea is not absolute, and it may be possible to induce a withdrawal bleed using a combined oestrogen/progestogen preparation. Intrauterine adhesions may be seen on an HSG (see Fig. 47.2). Alternatively, hysteroscopic inspection of the uterine cavity will confirm the diagnosis and enable treatment by adhesiolysis. The adhesions bridge the anterior and posterior walls of the uterine cavity

and are usually avascular, although may contain vessels, muscle and even endometrium. Following surgery, high-dose oral oestrogens are initially prescribed followed by a 3-month course of cyclical progesterone/oestrogens. Some clinicians insert a Foley catheter into the uterine cavity for 7–10 days postoperatively or an intrauterine contraceptive device for 2–3 months in order to prevent recurrence of adhesions. A 'second-look' hysteroscopy or HSG may be required.

Cervical stenosis

Cervical stenosis is an occasional cause of secondary amenorrhoea. It was relatively common following a traditional cone biopsy for the treatment of cervical intraepithelial neoplasia. However, modern procedures, such as laser or loop diathermy, have less postoperative cervical complications. It still occasionally occurs following curettage of the uterus which inadvertently damages the endocervix. Treatment for cervical stenosis consists of careful cervical dilatation, usually under ultrasound guidance.

Ovarian causes of secondary amenorrhoea

Polycystic ovary syndrome

See above.

Premature ovarian insufficiency

Ovarian failure by definition is the cessation of periods accompanied by a raised gonadotrophin level prior to the age of 40 years [23]. It may occur at any age. The exact incidence of this condition is unknown as many cases go unrecognized, but estimates vary between 1 and 5% of the female population. Studies of amenorrhoeic women report the incidence of POI (formerly known as premature ovarian failure) to be between 10 and 36%.

Chromosomal abnormalities have been found in up to 70% of patients with primary amenorrhoea and in 2–5% of women with secondary amenorrhoea due to POI. Ovarian failure occurring before puberty is usually due to a chromosomal abnormality or a childhood malignancy that required chemotherapy or radiotherapy. Adolescents who lose ovarian function soon after menarche are often found to have a Turner mosaic (46XX/45X) or an X-chromosome trisomy (47XXX). There are some genetic anomalies that run in families with POI, although these are not assessed in routine clinical practice.

Ovarian autoantibodies can be measured and have been found in up to 70% of women with POI. However, the assay is expensive and not readily available in most units. It is therefore important to consider other autoimmune disorders and screen for autoantibodies to the thyroid gland, gastric mucosa parietal cells and adrenal gland if there is any clinical indication.

Before the absolute cessation of periods of true POI, some women experience an intermittent return to menses, interspersed between variable periods of amenorrhoea. Gonadotrophin levels usually remain moderately elevated during these spontaneous cycles, with plasma FSH levels of 15–20 IU/L. This occult ovarian failure, or resistant ovary syndrome, is associated with the presence of primordial follicles on ovarian biopsy (which incidentally is not a procedure that should be performed to make the diagnosis). Pregnancies are sometimes achieved, although the ovaries are usually resistant to exogenous gonadotrophins as they are to endogenous hormones. It is probable that reports of pregnancy in women with POI represent cases of fluctuating ovarian function rather than successes of treatment [23].

However, it is possible to achieve pregnancy by oocyte donation as part of IVF treatment. For women who are predicted to develop ovarian failure as a result of sterilizing chemotherapy for malignancy, it is now possible to cryopreserve oocytes collected during an IVF-stimulation protocol, which are frozen either as oocytes or as fertilized oocytes (embryos) if the patient has a partner. An alternative approach is the surgical removal of a whole ovary and transplantation of cryopreserved ovarian tissue once the cancer treatment is completed. Live births have been achieved by all these methods, although the technology for oocyte cryopreservation is less efficient than for embryo cryopreservation and ovarian tissue freezing is still in its infancy [23].

The diagnosis and consequences of POI require careful counselling of the patient. It may be particularly difficult for a young woman to accept the need to take oestrogen preparations that are clearly labelled as being intended for older postmenopausal women while at the same time having to come to terms with the inability to conceive naturally. The short- and long-term consequences of ovarian failure and oestrogen deficiency are similar to those occurring in the fifth and sixth decade. However, the duration of the problem is much longer and therefore HRT is advisable in order to reduce the consequences of oestrogen deficiency in the long term [23].

Younger women with premature loss of ovarian function have an increased risk of osteoporosis. A series of 200 amenorrhoeic women between the ages of 16 and 40 years demonstrated a mean reduction in BMD of 15% compared with a control group and after correction for body weight, smoking and exercise [24]. The degree of bone loss was correlated with the duration of the amenorrhoea and the severity of the oestrogen deficiency rather than the underlying diagnosis, and was worse in patients with primary amenorrhoea than in those with secondary amenorrhoea. A return to normal oestrogen status may improve bone mass density, but BMD is unlikely to improve by more than 5–10% and it probably

does not return to its normal value. However, it is not certain if the radiological improvement seen will actually reduce the risk of fracture, as remineralization is not equivalent to the restrengthening of bone. Early diagnosis and early correction of oestrogen status is therefore important.

Women with POI may have an increased risk of cardiovascular disease. Oestrogens have been shown to have beneficial effects on cardiovascular status in women. They increase the levels of cardioprotective HDL but also total triglyceride levels, while decreasing total cholesterol and low-density lipoprotein levels. The overall effect is of cardiovascular protection.

The HRT preparations prescribed for menopausal women are also preferred for young women. The reason for this is that even modern low-dose combined oral contraceptive preparations contain at least twice the amount of oestrogen that is recommended for HRT in order to achieve a contraceptive suppressive effect on the hypothalamic–pituitary axis. HRT also contains 'natural' oestrogens (estradiol) rather than the synthetic ethinylestradiol found in most combined oral contraceptive preparations.

Pituitary causes of secondary amenorrhoea

Hyperprolactinaemia is the commonest pituitary cause of amenorrhoea. There are many causes of a mildly elevated serum prolactin concentration, including stress, and a recent physical or breast examination. If the prolactin concentration is greater than 1000 mIU/L then the test should be repeated, and if still elevated it is necessary to image the pituitary fossa (with CT or MRI). Hyperprolactinaemia may result from a prolactin-secreting pituitary adenoma or from a non-functioning 'disconnection' tumour in the region of the hypothalamus or pituitary, which disrupts the inhibitory influence of dopamine on prolactin secretion. Large non-functioning tumours are usually associated with serum prolactin concentrations of less than 3000 mIU/L, while prolactin-secreting macroadenomas usually result in concentrations of 8000 mIU/L or more. Other causes include hypothyroidism, PCOS (up to 2500 mIU/L) and several drugs (e.g. the dopaminergic antagonists phenothiazines, domperidone and metoclopramide).

In women with amenorrhoea associated with hyperprolactinaemia, the main symptoms are usually those of oestrogen deficiency. In contrast, when hyperprolactinaemia is associated with PCOS, the syndrome is characterized by adequate oestrogenization, polycystic ovaries on ultrasound scan and a withdrawal bleed in response to a progestogen challenge test. Galactorrhoea may be found in up to one-third of patients with hyperprolactinaemia, although its appearance is correlated neither with prolactin levels nor with the presence of a tumour. Approximately 5% of patients present with visual field defects.

A prolactin-secreting pituitary microadenoma is usually associated with a moderately elevated prolactin (1500–4000 mIU/L) and is unlikely to result in abnormalities on a lateral skull X-ray. On the other hand, a macroadenoma, associated with a prolactin greater than 5000–8000 mIU/L and by definition greater than 1 cm diameter may cause typical radiological changes: an asymmetrically enlarged pituitary fossa with a double contour to its floor and erosion of the clinoid processes. Skull X-rays are rarely performed these days as CT and MRI scans now allow detailed examination of the extent of the tumour and, in particular, identification of suprasellar extension and compression of the optic chiasma or invasion of the cavernous sinuses. Prolactin is an excellent tumour marker, and so the higher the serum concentration, the larger the size of the tumour expected on the MRI scan. In contrast, a large tumour on the scan with only a moderately elevated serum prolactin concentration (2000–3000 mIU/L) suggests a non-functioning tumour with 'disconnection' from the hypothalamus (Fig. 47.7).

The management of hyperprolactinaemia centres around the use of a dopamine agonist, of which bromocriptine and cabergoline are the most widely used. Of course, if the hyperprolactinaemia is drug induced, stopping the relevant preparation should be commended. However, this may not be appropriate if the cause is a psychotropic medication, for example a phenothiazine being used to treat schizophrenia. In these cases it is reasonable to continue the drug and prescribe a low-dose combined oral contraceptive preparation in order to counteract the symptoms of oestrogen deficiency. Serum prolactin concentrations must then be carefully monitored to ensure that they do not rise further. Most patients show a fall in prolactin levels within a few days of commencing bromocriptine therapy and a reduction in tumour volume within 6 weeks. Side effects can be troublesome (nausea, vomiting, headache, postural hypotension) and are minimized by commencing the therapy at night for the first 3 days of treatment and taking the tablets in the middle of a mouthful of food. The longer-acting preparation cabergoline appears to have fewer side effects and is more commonly used these days. Longer-term side effects include Raynaud's phenomenon, constipation and psychiatric changes, especially aggression, which can occur at the start of treatment. Bromocriptine and cabergoline have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions and so echocardiography is recommended before starting treatment in order to exclude valvulopathy and this should be repeated after 3–6 months and then annually, although young patients are less at risk than older patients who may be prescribed

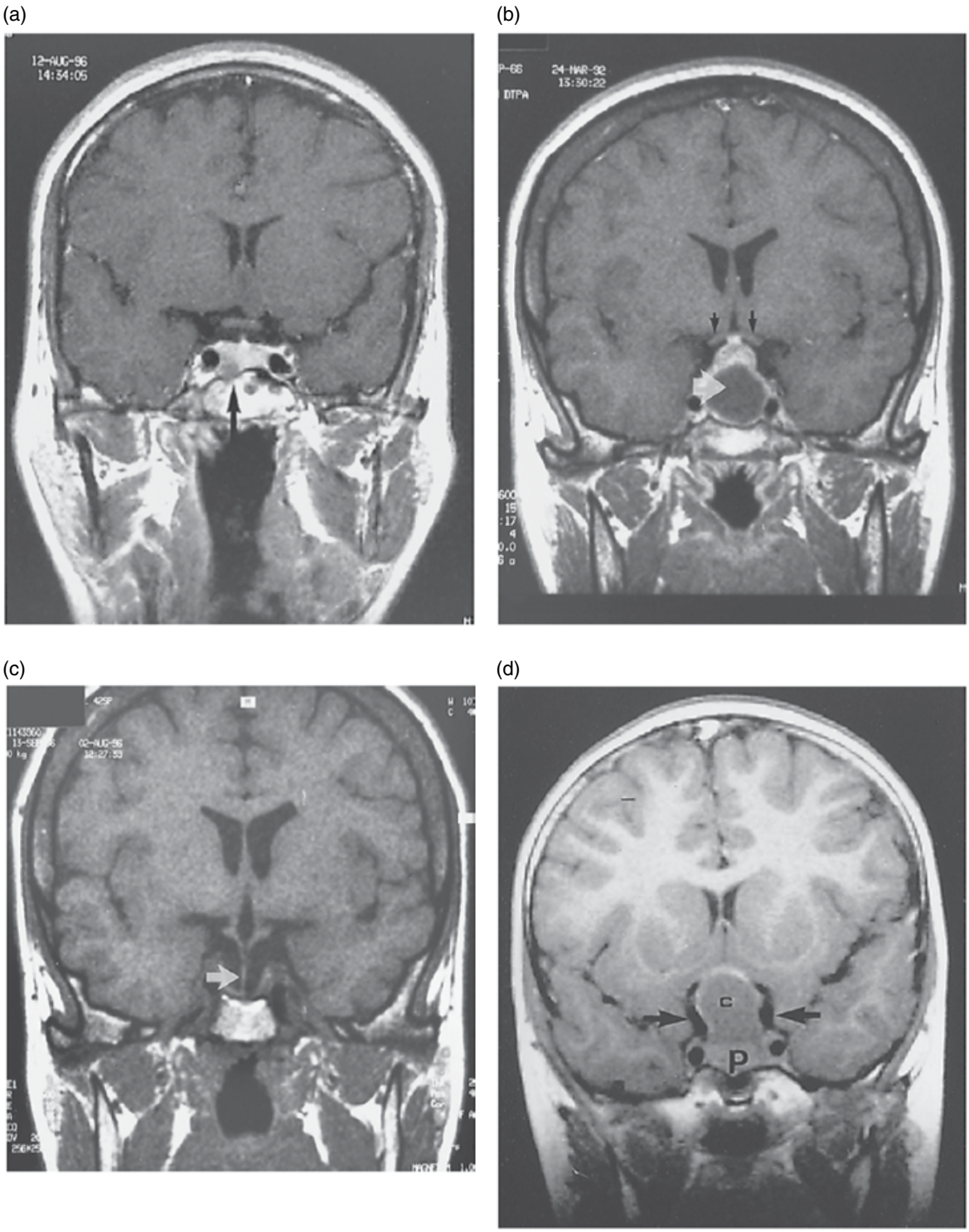

Fig. 47.7 (a) Pituitary microadenoma. Cranial MRI: coronal section T1-weighted spin echo sequence after intravenous gadolinium. The normal pituitary gland is hyperintense (bright) while the tumour is seen as a 4-mm area of non-enhancement (grey) in the right lobe of the pituitary, encroaching up to the right cavernous sinus. It is eroding the right side of the sella floor (arrow). (b, c) Pituitary macroadenoma. MRI scans of a pituitary macroadenoma before and after bromocriptine therapy: (b) T1-weighted image post-gadolinium enhancement demonstrating a macroadenoma with a large central cystic component (large arrow). There is suprasellar extension with compression of the optic chiasm (small arrows). (c) After therapy the tumour has almost completely resolved and there is tethering of the optic chiasm (arrow) to the floor of the sella. (d) Craniopharyngioma. Cranial MRI: coronal T1-weighted section after gadolinium enhancement. The tumour signal intensity on the T1 image and only part of the periphery of the tumour enhances. The carotid arteries have a low signal intensity (black arrows) due to the rapid flow within them and are deviated laterally and superiorly by the mass (C), which arises out of the pituitary fossa (P). *Source:* Balen AH. *Infertility in Practice*, 4th edn. London: Informa Healthcare, 2014. Reproduced with permission of CRC Press.

Table 47.6 Drug therapy for hyperprolactinaemia.

Bromocriptine	2.5–20 mg daily, divided doses	Maintenance usually 5–7.5 mg/day
Cabergoline	0.25–1 mg twice weekly	Maintenance usually 1 mg/week
Quinagolide	75–150 μg daily, at night	

higher doses for the management of Parkinson's disease. The maintenance dose should be the lowest that reduces prolactin to normal levels and is often lower than that needed to initiate a response (Table 47.6).

Surgery, in the form of trans-sphenoidal adenectomy, is reserved for cases of drug resistance and failure to shrink a macroadenoma or if there are intolerable side effects of the drugs (the most common indication). Non-functioning tumours should be removed surgically and are usually detected by a combination of imaging and a serum prolactin concentration below 3000 mIU/L. When the prolactin level is between 3000 and 8000 mIU/L, a trial of bromocriptine is warranted, and if the prolactin level falls it can be assumed that the tumour is a prolactin-secreting macroadenoma. Operative treatment is also required if there is suprasellar extension of the tumour that has not regressed during treatment with bromocriptine and a pregnancy is desired. With the modern skills of neurosurgeons in trans-sphenoidal surgery, it is seldom necessary to resort to pituitary irradiation, which offers no advantages, and long-term surveillance is required to detect consequent hypopituitarism (which is immediately apparent if it occurs after surgery).

Women with a microprolactinoma who wish to conceive can be reassured that they may stop bromocriptine when pregnancy is diagnosed and require no further monitoring, as the likelihood of significant tumour expansion is very small (<2%). On the other hand, if a patient with a macroprolactinoma is not treated with bromocriptine, the tumour has a 25% risk of expanding during pregnancy. This risk is probably also present if the tumour has been treated but has not shrunk, as assessed by CT or MRI scan. The first-line approach to treatment of macroprolactinomas is therefore with bromocriptine combined with barrier methods of contraception. In cases with suprasellar expansion, a follow-up CT (or MRI) scan should be performed after 3 months of treatment to ensure tumour regression before it is safe to embark upon pregnancy. Bromocriptine can be discontinued during pregnancy, although an MRI scan should be performed if symptoms suggestive of tumour re-expansion occur, and it is necessary to recommence bromocriptine therapy if there is continuing suprasellar expansion. These patients also require expert assessment of their visual fields during pregnancy.

If the serum prolactin is found to be elevated and the patient has a regular menstrual cycle, no treatment is necessary unless the cycle is anovulatory and fertility is desired. Amenorrhoea is the 'bioassay' of prolactin excess and should be corrected for its sequelae, rather than for the serum level of prolactin.

Hypothalamic causes of secondary amenorrhoea

Hypothalamic causes of amenorrhoea may be either primary or secondary. Primary hypothalamic lesions include craniopharyngiomas, germinomas, gliomas and dermoid cysts. These hypothalamic lesions either disrupt the normal pathway of prolactin inhibitory factor (dopamine), thus causing hyperprolactinaemia, or compress and/or destroy hypothalamic and pituitary tissue. Treatment is usually surgical, with additional radiotherapy if required. HRT is required to mimic ovarian function, and if the pituitary gland is damaged either by the lesion or by the treatment, replacement thyroid and adrenal hormones are required.

Secondary hypogonadotrophic hypogonadism (HH) may result from systemic conditions including sarcoidosis and tuberculosis as well as following head injury or cranial irradiation. Sheehan's syndrome, the result of profound and prolonged hypotension on the sensitive pituitary gland enlarged by pregnancy, may also be a cause of HH in someone with a history of major obstetric haemorrhage [25]. It is essential to assess the pituitary function fully in all these patients and then instigate the appropriate replacement therapy. Ovulation may be induced with pulsatile subcutaneous GnRH or hMGs. The administration of pulsatile GnRH provides the most 'physiological' correction of infertility caused by HH and will result in unifollicular ovulation, while hMG therapy requires close monitoring to prevent multiple pregnancy (unfortunately the GnRH preparations are no longer manufactured for this use). Purified or recombinant FSH preparations are not suitable for women with HH (or pituitary hypogonadism) as these patients have absent endogenous production of LH, and so while follicular growth may occur, oestrogen biosynthesis is impaired [26]. Thus, hMG, which contains FSH and LH activity, is necessary for these patients.

Systemic disorders causing secondary amenorrhoea

Chronic disease may result in menstrual disorders as a consequence of the general disease state, weight loss or the effect of the disease process on the hypothalamic–pituitary axis. Furthermore, a chronic disease that leads to immobility, such as chronic obstructive airways disease, may increase the risk of amenorrhoea-associated osteoporosis.

Some diseases affect gonadal function directly. Women with chronic renal failure have a discordantly elevated LH, possibly as a consequence of impaired clearance. Prolactin is also elevated in these women owing to failure of the normal inhibition by dopamine. Liver disease affects the level of circulating SHBG and thus hormone levels, thereby disrupting the normal feedback mechanisms. Metabolism of various hormones including testosterone are also liver-dependent; both menstruation and fertility return after liver transplantation.

Endocrine disorders such as thyrotoxicosis and Cushing's syndrome are commonly associated with gonadal dysfunction. Autoimmune endocrinopathies may be associated with POI because of ovarian antibodies. Diabetes mellitus may result in functional hypothalamic–pituitary amenorrhoea.

Management of these patients should concentrate on the underlying systemic problem and on preventing complications of oestrogen deficiency. If fertility is required, it is desirable to achieve maximal health and where possible to discontinue teratogenic drugs.

Weight-related amenorrhoea

Weight can have profound effects on gonadotrophin regulation and release. Weight and eating disorders are also common in women. A regular menstrual cycle will not occur if the BMI is below 19 kg/m^2. Fat appears to be critical to a normally functioning hypothalamic–pituitary–gonadal axis. It is estimated that at least 22% of body weight should be fat in order to maintain ovulatory cycles [27]. This level enables the extra-ovarian aromatization of androgens to oestrogens and maintains appropriate feedback control of the hypothalamic–pituitary–ovarian axis. Therefore, girls who are significantly underweight prior to puberty may have primary amenorrhoea, while those who are significantly underweight after puberty will have secondary amenorrhoea. The clinical presentation depends on the severity of the nutritional insult and its age of onset. To cause amenorrhoea, the loss must be 10–15% of the woman's normal weight for height. Weight loss may be due to a number of causes including self-induced abstinence, starvation, illness and exercise.

Whatever the precipitating cause, the net result is impairment of gonadotrophin secretion. In severe weight loss, oestrogen may be catabolized to the antioestrogen 2-hydroxyestrone rather than to the usual estradiol, which may further suppress gonadotrophin secretion. This pathway is enhanced by cigarette smoking. Weight-related gonadotrophin deficiency is more pronounced with LH than FSH. This, and the reduction in pulsatility of gonadotrophin secretion, may result in a 'multicystic' pattern in the ovary. This appearance is typical of normal puberty and is seen when there are several cysts (about 5–10 mm in diameter) together with a stroma of normal density.

Anorexia nervosa is at the extreme end of a spectrum of eating disorders and is invariably accompanied by menstrual disturbance, and indeed may account for 15–35% of patients with amenorrhoea. Women with anorexia nervosa should be managed in collaboration with a psychiatrist, and it is essential to encourage weight gain as the main therapy. An artificial cycle may be induced with the combined oral contraceptive pill, although this may validate the woman's denial of weight loss as the underlying problem.

Similarly, while it is possible to induce ovulation with exogenous gonadotrophins, treatment of infertility in the significantly underweight patient is associated with a notable increase in intrauterine growth retardation and neonatal problems. Furthermore, since three-quarters of the cell divisions that occur during pregnancy do so during the first trimester, it is essential that nutritional status is optimized before conception. Low birthweight is also now being related to an increased risk of cardiovascular disease, obstructive lung disease and schizophrenia in adult life [28].

Weight-related amenorrhoea may also have profound long-term effects on BMD. The age of onset of anorexia nervosa is also important, as prolonged amenorrhoea before the normal age at which peak bone mass is obtained (approximately 25 years) increases the likelihood of severe osteoporosis.

Worldwide, involuntary starvation is the commonest cause of reduced reproductive ability, resulting in delayed pubertal growth and menarche in adolescents and infertility in adults. Acute malnutrition, as seen in famine conditions, has profound effects on fertility and fecundity. Ovulatory function usually returns quickly on restoration of adequate nutrition. The chronic malnutrition common in developing countries has fewer profound effects on fertility but is associated with small and premature babies.

Psychological stress

Studies have failed to demonstrate a link between stressful life events and amenorrhoea of greater than 2 months. However, stress may lead to physical debility such as weight loss, which may then cause menstrual disturbance.

Exercise-related amenorrhoea

Menstrual disturbance is common in athletes undergoing intensive training, with 10–20% experiencing oligomenorrhoea or amenorrhoea compared with 5% in the general population [29]. Amenorrhoea is more common in athletes under the age of 30 years and is particularly common in women involved in the endurance events

(such as long-distance running). Up to 50% of competitive runners training 80 miles per week may be amenorrhoeic [30].

The main aetiological factors are weight and percentage body fat content, but other factors have also been postulated. Physiological changes are consistent with those associated with starvation and chronic illness.

Ballet dancers provide an interesting subgroup of sportswomen, because their training begins at an early age. They have been found to have a significant delay in menarche (starting at the age of 15.4 years compared with 12.5 years in non-ballet dancers) and a retardation in pubertal development which parallels the intensity of their training. Menstrual irregularities are common, and up to 44% have secondary amenorrhoea. In a survey of 75 dancers, 61% were found to have stress fractures and 24% had scoliosis; the risk of these pathological features was increased if menarche was delayed or if there were prolonged periods of amenorrhoea. These findings may be explained by delayed pubertal maturation resulting in attainment of a greater than expected height and a predisposition to scoliosis, as oestrogen is required for epiphyseal closure.

Exercise-induced amenorrhoea has the potential to cause severe long-term morbidity, particularly with regard to osteoporosis. Studies on young ballet dancers have shown that the amount of exercise undertaken by these dancers does not compensate for these osteoporotic changes. Oestrogen is also important in the formation of collagen, and soft-tissue injuries are also common in dancers. Whereas moderate exercise has been found to reduce the incidence of postmenopausal osteoporosis, young athletes may be placing themselves at risk at an age when the attainment of peak bone mass is important for long-term skeletal strength. Appropriate advice should be given, particularly regarding diet, and the use of a cyclical oestrogen–progestogen preparation should be considered.

Iatrogenic causes of amenorrhoea

There are many iatrogenic causes of amenorrhoea, which may be either temporary or permanent. These include malignant conditions that require either radiation to the abdomen/pelvis or chemotherapy. Both of these treatments may result in permanent gonadal damage, the amount of damage being directly related to the age of the patient, the cumulative dose and the patient's previous menstrual status.

Gynaecological procedures such as oophorectomy, hysterectomy and endometrial resection inevitably result in amenorrhoea. Hormone replacement should be prescribed for these patients where appropriate. Hormone therapy itself can be used to deliberately disrupt the menstrual cycle. However, iatrogenic causes of ovarian quiescence have the same consequences of oestrogen deficiency due to any other aetiology. Thus, the use of GnRH analogues in the treatment of oestrogen-dependent conditions (e.g. precocious puberty, endometriosis, uterine fibroids) results in a significant decrease in BMD in as little as 6 months. However, the demineralization is reversible with the cessation of therapy, especially for the treatment of benign conditions in young women who are in the process of achieving their peak bone mass. The concurrent use of an androgenic progestogen or oestrogen 'add-back' therapy may protect against bone loss.

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48

Heavy Menstrual Bleeding

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Definition

There has been confusion over the various terminologies used for abnormalities of menstrual blood loss. Heavy menstrual bleeding (HMB) is now the preferred symptom description as it is simple and easily translatable into other languages. Use of the word 'menorrhagia' is discouraged [1]. The word itself, meaning to 'burst forth each month', was first used in English medical texts by William Cullen, a professor at the University of Edinburgh in the late 1700s. The term is confusing, being used as a symptom, sign and diagnosis. Similarly, the term 'dysfunctional uterine bleeding' (DUB) should also no longer be used [1]. DUB was traditionally used to describe excessive bleeding (heavy, frequent or prolonged) of uterine origin which was not due to pelvic pathology or systemic disease. Descriptions of menstrual bleeding were standardized in 2009 by the Menstrual Disorders Group (FMDG) of the Fédération International de Gynécologie et d'Obstétrique (FIGO). Definitions of normality were described, nomenclature standardized, and underlying aetiologies classified in a structured manner. HMB is defined as excessive menstrual blood loss (over several consecutive cycles) that has a major effect on a woman's quality of life [2]. The objective definition of HMB (defined as blood loss of greater than 80 mL per menstruation) is no longer used except for research purposes [2]. It is also important in clinical practice to distinguish between regular and abnormal bleeding, such as intermenstrual and post-coital bleeding.

Summary box 48.1

- 'Heavy menstrual bleeding' replaces 'menorrhagia'.
- 'Bleeding of endometrial origin' replaces 'dysfunctional uterine bleeding'.
- Distinguish between 'regular' and 'abnormal' bleeding.

Prevalence and impact

HMB affects one in three women of reproductive age [2]. The complaint of HMB results in significant morbidity and impact on quality of life. In addition to the direct effect on the woman and her family, there are significant socioeconomic costs. Menstrual bleeding complaints are the fourth most common reason for referral to UK gynaecological services [3]. The recent national audit in England and Wales [3] reported that at 1-year post referral, only one-third of women (including those managed with surgery) were 'satisfied' (or better) with the current treatment of their menstrual symptoms [3]. Unfortunately, current medical therapy may be associated with undesirable side effects. As many as one in five women discontinue use of progestin therapies (systemic and locally delivered) for HMB on account of unscheduled bleeding [4]. Despite continually emerging new medical therapies, surgery is still favoured by many women with severe symptoms and HMB remains a leading indication for hysterectomy. In the UK, regional differences in surgical rates for HMB have persisted despite changes in practice and improved evidence, suggesting there is still scope for improving the management of HMB within health services. There remains a pressing need for continuing development of effective and acceptable medical treatment options for women with HMB.

Aetiology

Correct management is facilitated by careful classification of HMB with the now widely used FIGO PALM-COEIN system [1] (Fig. 48.1). The 'PALM' (Polyp, Adenomyosis, Leiomyoma [fibroids], Malignancy) are assessed visually (imaging and histopathology) and the 'COEIN' (Coagulopathy, Ovulatory and Endometrial dysfunction, Iatrogenic and Not otherwise classified) are

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

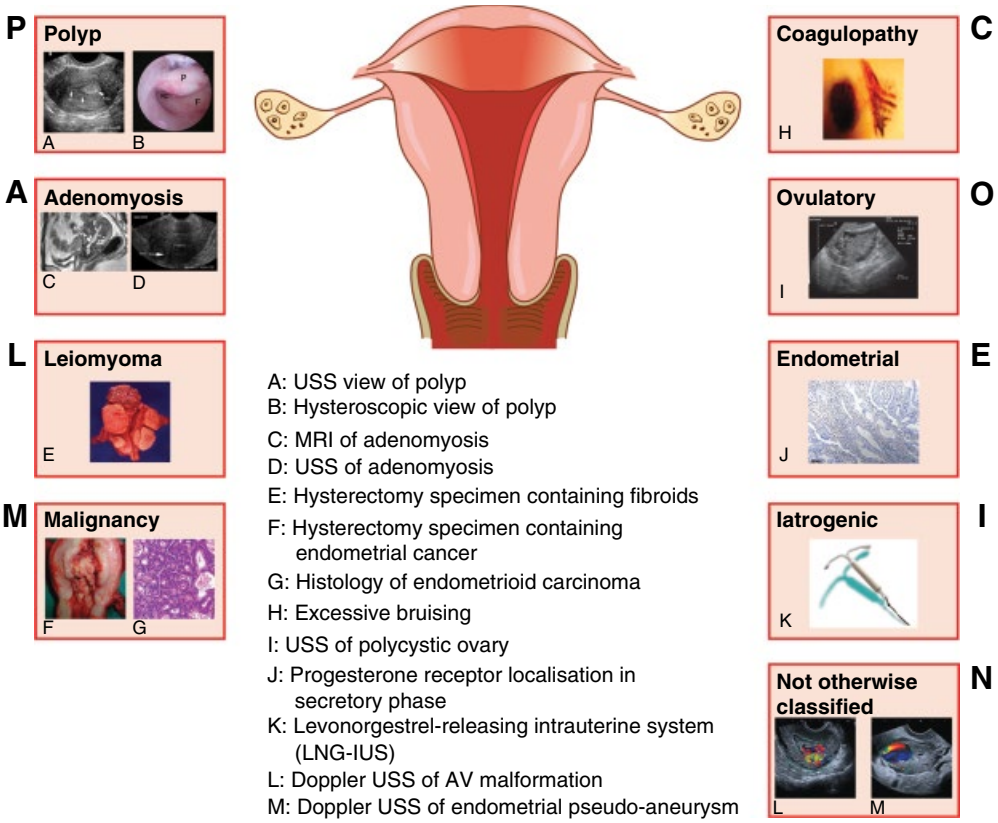

Fig. 48.1 FIGO PALM-COEIN classification of causes of HMB. Reproduced from Whitaker L, Critchley HOD. Abnormal uterine bleeding. *Best Pract Res Clin Obstet Gynaecol* 2016;34:54–65. Creative Commons Attribution License (CC BY 4.0) (https://creativecommons.org/licenses/by/4.0/).

non-structural and are identified through meticulous history-taking and appropriate investigations. The classification system accepts that women may have more than one underlying cause and also that where structural abnormalities are present, many women may in fact be symptom-free.

Polyps

Polyps are common (incidence increasing with age), frequently asymptomatic and their exact cause remains unknown. It is important to be aware that both polyps and fibroids may frequently coexist, and that polyps may be mistaken for submucous fibroids on ultrasound. Polyps may cause unpredictable intermenstrual bleeding as well as being associated with an increased volume of bleeding [5].

Adenomyosis

Any relationship between adenomyosis and HMB is still unclear. Adenomyosis is associated with increasing age and often coexists with endometriosis and fibroids. Adenomyosis is increasingly being diagnosed on MRI and ultrasonography but it is harder to establish the diagnosis of adenomyosis if fibroids are also present.

Leiomyoma (fibroids)

Submucosal and intramural fibroids are the subtype most commonly associated with HMB but the exact number of cases of HMB resulting from fibroids is not known. About 50% of fibroids cause no symptoms. Furthermore, the mechanisms involved in fibroid-associated HMB are yet to be determined. Theories include an increased endometrial surface area and the presence of fragile and dilated vasculature around the fibroid [6]. Knowledge regarding the complex cellular and molecular changes found in association with fibroids is increasing. Data are emerging on the impact of uterine fibroid presence on angiogenesis, on alteration in the production of vasoactive substances and growth factors, as well as modulation of coagulation.

Malignancy (and hyperplasia)

Both endometrial and cervical carcinoma are potential causes of intermenstrual and post-coital bleeding, and rarely HMB. The most relevant premalignant condition that may cause abnormal bleeding is endometrial hyperplasia. Sarcomas of myometrial origin, such as leiomyosarcoma, are rare but not infrequently present with abnormal bleeding in perimenopausal and

postmenopausal women. A recent meta-analysis reported that leiomyosarcoma was diagnosed unexpectedly following surgery for anticipated 'benign' myomas (fibroids) in 2.94 per 1000 women (1 in 340 women) [7]. Age is a risk factor for the development of leiomyosarcoma, with less than one case per 500 among women under 30 years and up to 1 in 98 among women in the age range 75–79 years.

Coagulopathy

As many as 10–20% of women with HMB will have a systemic disorder of haemostasis [6]. These disorders may be inherited or acquired and severity of disorder varies (but the majority are mild to moderate). The overall clinical impact is unknown. The most common inherited disorder is von Willebrand disease, found in 13% of women with HMB. This aetiology should be considered in women who fail to respond to medical management and women who present at a young age. Acquired conditions include severe thrombocytopenia, thrombocytopathies such as Glanzmann's disease, and other rare bleeding/factor deficiencies. Currently, the use of anticoagulants in women with thromboembolic disease also falls within this category.

Ovulatory dysfunction

Anovulatory menstrual cycles may contribute to HMB by the effects of unopposed oestrogen on the endometrium causing marked proliferation. This most commonly occurs at the extremes of reproductive age (adolescence and perimenopause). Anovulatory menstrual cycles are associated with polycystic ovarian syndrome (PCOS), hyperprolactinaemia, hypothyroidism and other factors such as obesity. Women in this group often report menstrual cycles that extend beyond 38 days or vary by more than 21 days. Pharmacological drugs known to impact ovulation by prolactin-related disruption of the hypothalamic–pituitary–ovarian axis (e.g. tricyclic antidepressants and phenothiazines) currently fall within this category.

Endometrial dysfunction

In the majority of cases of HMB, it is likely that the precise cause of heavy bleeding lies at the level of the endometrium itself. This is a diagnosis of exclusion. Hypoxia, inflammation, haemostasis and angiogenesis all play crucial roles in the shedding and subsequent scar-less repair of the functional upper layer of the endometrium. Perturbation of local glucocorticoid metabolism, aberrant prostaglandin synthesis and excessive plasminogen (resulting in premature clot lysis) have all been implicated in HMB. However, the exact endometrial mechanisms leading to HMB remain undefined and an area of active research enquiry [8,9].

Iatrogenic

Iatrogenic causes of HMB include exogenous therapies than may result in unscheduled bleeding. This is typically associated with continuous oestrogen or progestin therapies (intrauterine, systemic or oral delivery). The use of an intrauterine device may cause a low-grade endometritis which may also contribute to HMB.

Not otherwise classified

Inevitably, there are pathologies that do not easily fit within the categories described. Examples include infection and arteriovenous malformations. Data exist to support an association between chronic endometrial infection and abnormal uterine bleeding, both intermenstrual and heavy bleeding [5]. *Chlamydia trachomatis* has been proposed as a cause of HMB, and the prevalence of *C. trachomatis* in women with abnormal uterine bleeding may be underestimated. This is confounded by the fact that 85% of cases of chlamydial infection are asymptomatic. Further research is required to determine whether all women with HMB should be screened for *C. trachomatis*. An arteriovenous malformation (AVM) is a congenital, or acquired, localized collection of abnormally connected arteries and veins. When they occur in the uterus they have been associated with episodes of acute excessive bleeding. Congenital AVMs are rare, as are acquired AVMs, which may occur following uterine curettage after pregnancy. These vascular lesions of the uterus pose difficult management decisions and may present with heavy uterine bleeding following early pregnancy loss. Colour Doppler ultrasound imaging is a useful diagnostic modality if an AVM is suspected. In cases associated with an early pregnancy loss (likely due to sub-involution of the placental bed), the uterine lesion resolves once the human chorionic gonadotrophin (hCG) level has returned to normal. Acute heavy bleeding from an AVM require management with therapeutic uterine artery embolization or intrauterine balloon tamponade.

Summary box 48.2

- In most women no cause for HMB is found.
- Coagulopathies account for 10–20% of cases of HMB.
- Malignancy should always be excluded.
- Remember iatrogenic causes.

Clinical evaluation

History

The primary aim of the history is to determine the full impact that the bleeding is having on the woman's

quality of life and a menstrual diary is often helpful to determine the degree and timing of the bleeding [10], and flooding and clots generally indicate significant loss. An accurate history may also indicate the cause of the bleeding. Intermenstrual bleeding and post-coital bleeding are suggestive of an anatomical cause whereas associated pressure symptoms, including bowel and urinary symptoms, may indicate the presence of a large fibroid(s). A coagulation disorder may be implicated in the complaint of HMB and a structured history to elicit such is valuable and an onward referral for formal haematological assessment may be indicated [5]. A coagulation disorder is likely if there is:

1) a history of excessive bleeding since menarche, postpartum haemorrhage, surgery-related bleeding, or bleeding associated with dental work; or
2) a history of two or more of (i) bruising greater than 5 cm, (ii) epistaxis once a month, (iii) frequent bleeding or (iv) a family history of bleeding symptoms.

A sexual, smear and contraceptive history are essential and should include questioning about the woman's desire for future pregnancy as this will affect therapeutic options for future symptom management.

Table 48.1 Investigations of patients complaining of heavy menstrual bleeding (HMB).

Investigation	Indication
Full blood count	All women with HMB
Coagulation screen	If a structured history is suggestive of a coagulation disorder
Thyroid function tests	Only from women with other symptoms of thyroid disease
Endocervical/high vaginal swabs	If history suggestive of risk of infection
Colposcopic examination	Suspicion of cervical pathology
Histological assessment of the endometrium	Symptomatic women ≥45 years old, younger women when medical treatment has failed, younger women with risk factors (e.g. PCOS, obesity) and all women prior to surgical intervention
Evaluation of the uterine cavity (pelvic ultrasound, MRI, and outpatient hysteroscopy)	Intermenstrual or post-coital bleeding, irregular HMB, suspected structural pathology, or when medical management has failed

Examination

A general evaluation of the patient should be performed to exclude signs of anaemia, evidence of systemic coagulopathy (e.g. bruising, petechiae) and thyroid disease (e.g. goitre). An abdominal examination should be performed to reveal a pelvic mass (eg, fibroid); a speculum examination should be performed to assess the vulva, vagina and cervix (this may reveal sources of bleeding, such as a tumour, or a discharge suggesting infection); and a bimanual examination should be performed to elicit uterine enlargement.

Investigations

A full blood count is indicated in all women with HMB. If the history and examination strongly suggests cyclical HMB without the presence of pathology in a woman under 45 years old, it is appropriate to implement first-line medical treatment without further investigation, so long as no risk factor, such as raised body mass index (BMI), are identified [2]. In older women, and in younger women in whom medical treatment has failed, further investigation is warranted (Table 48.1).

Histological assessment of the endometrium

In the UK, current National Institute for Health and Care Excellence (NICE) guidelines advise endometrial sampling and histological assessment of HMB in women aged 45 years and above who have persistent intermenstrual bleeding or treatment failure. With the increase in rates of endometrial cancer, all gynaecologists should use their clinical judgement for those women aged under 45 years with HMB who have risk factors for premalignant change, in particular PCOS and obesity.

Evaluation of the uterus and uterine cavity

Blind sampling methodologies (outpatient endometrial biopsy) are reasonable screening techniques but they are ineffective at diagnosing focal lesions. Published research has provided the clinician with high-quality data regarding the accuracy of pelvic ultrasound and outpatient hysteroscopy in the diagnosis of structural lesions. In the UK, NICE suggests that pelvic ultrasound should be considered the primary investigation of suspected structural lesions, backed up by hysteroscopy for suspected polyps or submucous fibroids (Fig. 48.1). MRI is also now being used in specific clinical scenarios in the evaluation of HMB. This imaging modality will assist in further identification and localization of fibroids and also features of adenomyosis if present. Pelvic MRI is of value in determining the role of embolization as a treatment option. However, future research needs to be directed towards providing effectiveness and cost-effectiveness data (MRI is expensive) in order to determine the role for this mode of imaging in guiding best clinical practice.

Summary box 48.3

- Objective definition of HMB is no longer used in clinical practice.
- Determine impact of HMB on quality of life.
- Perform structured history to determine coagulation disorder.
- Full blood count should be performed in all patients.
- Controversy remains over clinical utility of imaging modalities.
- Endometrial histology is warranted in women aged over 45 years, in younger women in whom medical treatment has failed and in all women prior to surgical intervention, and should be considered in women with a raised BMI/risk factors for premalignant change in the endometrium.

Management

Management options should be patient-centred and embrace the contraceptive and fertility needs of each woman. For some women the demonstration that their blood loss is in fact 'normal' may be sufficient to reassure them and make further treatment unnecessary. When treatment is advised by the healthcare professional, women with HMB should be given detailed and up-to-date information (ideally supplemented by written or web-based material) about treatment options [2] and given adequate time and support in the decision-making process. These options include non-hormonal, hormonal and surgical approaches [11]. A care pathway for HMB is shown in Fig. 48.2 [2].

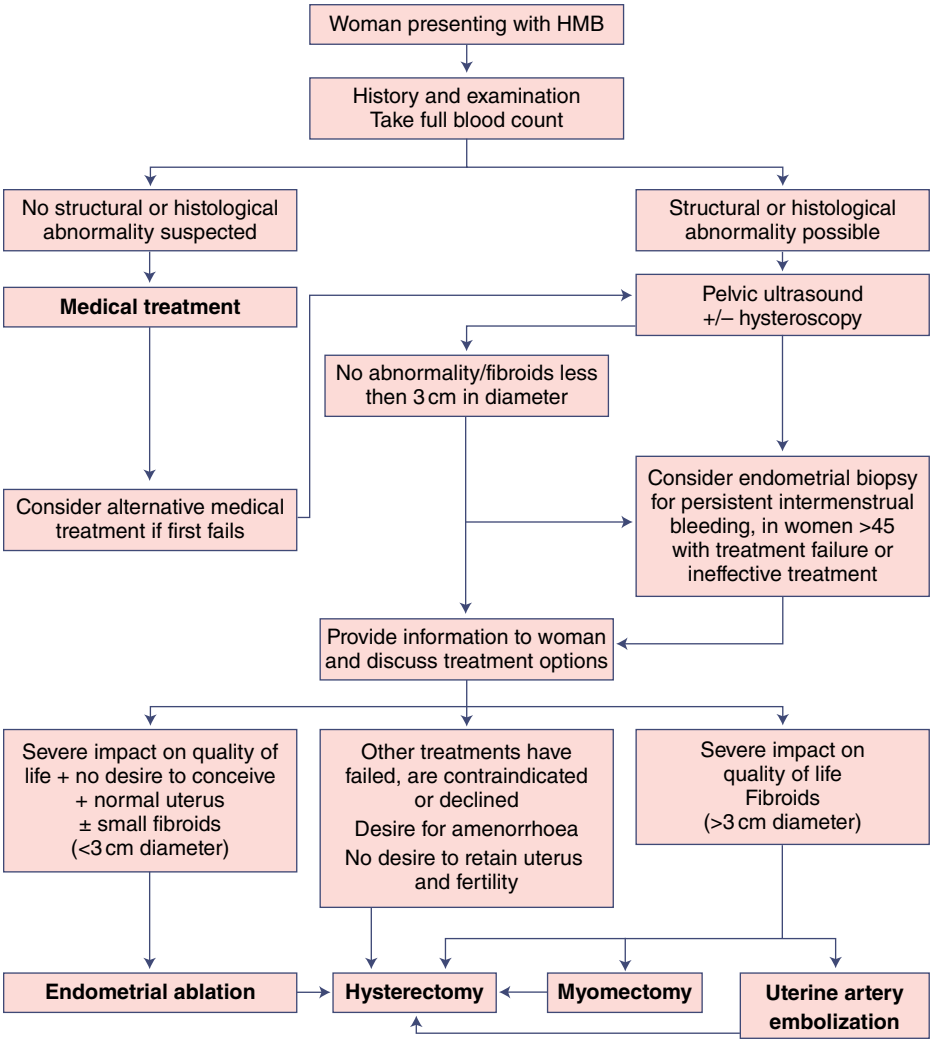

Fig. 48.2 Suggested care pathway for heavy menstrual bleeding (HMB). Adapted from National Institute for Health and Care Excellence [2].

Non-hormonal treatments

If a woman is wishing to conceive, hormonal treatments and most surgical interventions are unacceptable.

Antifibrinolytics

Antifibrinolytics, such as tranexamic acid, reduce blood loss by up to 50% by inhibiting endometrial fibrinolysis [12]. Side effects are rare but include gastrointestinal symptoms. Antifibrinolytics are not prescribed for women with a history of thromboembolism.

Prostaglandin synthetase inhibitors

Prostaglandin synthetase inhibitors, such as non-steroidal anti-inflammatory drugs (NSAIDs), inhibit endometrial prostaglandin production, leading to a reduction in menstrual blood loss. Mefenamic acid is the most frequently used agent and reduces blood loss by approximately 25% [13]. The drug is taken during menstruation and has the advantage of additional analgesic properties. However, NSAIDs are associated with gastrointestinal side effects.

Hormonal treatments

Combined oral contraceptive pill

From clinical experience, the combined oral contraceptive pill (COCP) is generally considered to be effective in the management of HMB. It reduces bleeding by around 50% and has the additional benefit of reducing dysmenorrhea. Furthermore, as amenorrhoea has become more acceptable (and indeed for some women even desirable), many women use the COCP continuously for periods of 3–6 months to avoid menstruation altogether. Risks of COCP treatment include breast cancer, thromboembolic and cardiovascular disease and migraine (increased in the older woman, particularly if she is a smoker [14]). A raised BMI imposes further risk.

Levonorgestrel-releasing intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an excellent alternative to surgery for women with HMB who also seek reliable long-acting reversible contraception [2]. Most women use the LNG-IUS for contraception but the added health benefits of reduced menstrual bleeding and less anaemia makes this, together with the low cost, an attractive option for many women with HMB worldwide. The LNG-IUS may be inserted in the outpatient setting and requires changing every 3–5 years depending on the licence of the preparation inserted. The uptake of LNG-IUS has undoubtedly been further increased because the low dose of LNG released into the uterine cavity leads to endometrial atrophy, so for many women its use is associated with little or no vaginal bleeding. Although the not uncommon side effect of unscheduled bleeding is a problem (one in five users), leading to unacceptability of the method for a minority of women, randomized controlled trials show that the LNG-IUS will reduce menstrual loss by up to 96% after 1 year but that the full benefit may not be seen for 6 months [15]. As its action is local, progestogen-related side effects are much less than with oral agents. However, women should be fully counselled that they are likely to experience unscheduled spotting/bleeding during the initial months of use. At present, effective interventions to prophylactically ameliorate unscheduled bleeding in women using the LNG-IUS still remain elusive.

Oral progestogens

Oral progestogens are helpful in the management of women with irregular (anovulatory) HMB, particularly common at the extremes of reproductive life. Cyclical administration of progestogens for less than 21 days each cycle in ovulatory women is of no benefit. Only norethisterone acetate (5 mg three times daily), if prescribed cyclically for 21 days, is effective treatment for ovulatory HMB. Shorter courses of oral progestogens (14 days) are appropriate for women with definite anovulatory cycles (e.g. PCOS) and at risk of endometrial hyperplasia.

Injected/depot progestogens

It is well recognized that amenorrhoea occurs in many women when injected progestogens are used for contraception and they are commonly used for treatment of HMB. However, like all progestogen-based therapies, a proportion of women will experience unscheduled bleeding.

Gonadotrophin-releasing hormone analogues

Limited use of gonadotrophin-releasing hormone (GnRH) analogues may be considered when all other management options have been explored. GnRH analogues act by downregulating the hypothalamic–pituitary–ovarian axis and induce ovarian suppression, leading to amenorrhoea. Unfortunately, their beneficial effect does not continue after stopping treatment and their adverse effect on bone density limits their use beyond 6 months. If consideration is given to use beyond 6 months, the addition of 'add-back' hormone replacement therapy is recommended.

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are a class of synthetic steroids that can exert agonist, antagonist or mixed effects on progesterone receptor binding in various progesterone target tissues *in vivo* [16]. SPRMs have been reported to reduce menstrual bleeding. The PEARL studies provide clinical evidence for the use of the SPRM ulipristal acetate (UPA) in

women with HMB and fibroids. The PEARL I study was a double-blind randomized controlled trial comparing 5 or 10 mg UPA with placebo for 12 weeks in women with symptomatic fibroids with HMB [17]. Over 91% of those on UPA achieved control of menstrual bleeding within 13 weeks and significant rates of amenorrhoea were reported (73%, 82% and 6% with 5 mg, 10 mg and placebo, respectively). A clinically and statistically significant reduction in fibroid volume was also described. The PEARL II study compared UPA with the GnRH analogue leuprolide acetate and similar rates of menstrual bleeding control and amenorrhoea were reported. There was a more rapid achievement of amenorrhoea in the UPA users. Subsequently, repeat 12-week courses of daily oral UPA have been shown to effectively control menstrual bleeding and to reduce fibroid volume. The potential utility of UPA for management of HMB in women without fibroids is currently being explored (UCON trial Eudra CT 2014-003408-65). Unfortunately, UPA is not suitable for women trying to conceive.

The administration of SPRMs is accompanied by a reversible morphological change in the endometrium, defined by histopathological criteria as progesterone receptor modulator-associated endometrial changes (PAEC) [18]. The implications of PAEC on bleeding pattern are not yet known. Further research is needed into the mechanisms of action of SPRMs [16], which appear to have great potential as a longer-term management option for reducing menstrual blood loss.

Danazol, etamsylate and gestrinone are no longer recommended for routine use in the treatment of HMB in part due to their unacceptable side effects.

Summary box 48.4

- Antifibrinolytics and prostaglandin synthetase inhibitors are appropriate first-line treatments.
- The combined oral contraceptive pill is considered effective.
- The levonorgestrel-releasing intrauterine system is an excellent long-term alternative to surgery.

Surgical treatments

It is unclear whether surgical interventions should be used as the initial treatment for HMB or whether medical intervention should always be tried first. Typically, surgical management is only considered in women who have completed their family, with the exception of polypectomy and myomectomy where fertility may be retained. Dilatation and curettage should not be used as a therapeutic treatment in any clinical situation.

Polypectomy

Endocervical polyps can be avulsed in the outpatient setting. Endometrial polyps can be removed blindly under general anaesthetic, or by hysteroscopic resection either under general anaesthetic or in the outpatient setting.

Endometrial ablation

Endometrial ablation is the targeted destruction of the endometrium and some of the underlying myometrium. The technique is suitable for women who have completed their family and in whom all organic and structural causes of HMB have been excluded (fibroids <4 cm are an exception). First-generation techniques include hysteroscopic transcervical resection of the endometrium using an electrical diathermy loop and roller-ball ablation. These techniques offer treatment for uterine cavities with submucous fibroids. Simpler, quicker second-generation alternatives have subsequently been developed for smoother smaller uterine cavities. These include fluid-filled thermal balloon endometrial ablation and impedance-controlled endometrial ablation. Overall, the existing evidence suggests that success rates and complication profiles of the newer techniques of ablation compare favourably with first-generation hysteroscopic techniques [19]. All can be performed as day-case procedures, either under general anaesthetic (with analgesia) or under local anaesthetic in the outpatient setting. Women who undergo this procedure should be advised that it is essential to use long-term effective contraception. It is also recommended that pre-ablation endometrial histology is obtained and that a hysteroscopy is performed before (following cervical dilatation) and after each treatment to exclude uterine perforation. Postoperatively, patients may complain of transient crampy abdominal pain and a watery brown discharge for 3–4 weeks. Prophylactic antibiotic therapy is often used to reduce the risk of endometritis. Patients must be counselled before the procedure about complications, which may include device failures at the time of the procedure, endometritis, haematometra, fluid overload due to absorption of distension medium (resection only), perforation and intra-abdominal injury (including visceral burns). Endometrial thinning agents (e.g. GnRH analogues) are not usually indicated for the newer ablative techniques but can be employed at the operator's preference for endometrial and fibroid resection. As a general rule, of all women undergoing endometrial ablation with a second-generation technique, 40–50% will become amenorrhoeic, 40–60% will have markedly reduced menstrual loss and 20% will have no difference in their bleeding. Nonetheless, it is clear from longer-term trials that while most women are initially satisfied, many subsequently choose or require repeat endometrial ablation (technique dependent) or hysterectomy.

Myomectomy

Myomectomy (abdominal, laparoscopic or hysteroscopic) is the surgical removal of fibroids from the uterine wall with conservation of the uterus. Advances in surgical instruments and techniques are expanding the role of laparoscopic myomectomy in well-selected individuals. If the fibroid protrudes into the uterine cavity, it may be removed hysteroscopically. GnRH analogues, and more recently SPRMs, are often used for up to 3 months prior to surgical intervention in an attempt to reduce the size and vascularity of the fibroids. Immediate complications of myomectomy usually relate to excessive blood loss and a blood transfusion may be required intraoperatively or postoperatively. Patients should therefore be carefully counselled preoperatively about this risk, including hysterectomy. Intermediate postoperative risks include infection and further bleeding. Pregnancy following myomectomy appears to be safe, with a very low risk of uterine rupture with a vaginal delivery. Indeed there are no reliable data available on the impact of 'full-thickness' myomectomy on the risk of uterine rupture.

As to whether further fibroid growth may occur, then this again is an area where there is a dearth of literature. It has been reported that a small proportion of women who undergo myomectomy may require subsequent intervention for management of their fibroids.

Uterine artery embolization

Uterine artery embolization (UAE) is a well-established technique for treatment of fibroids [20]. The procedure is usually carried out by an interventional radiologist, usually under local anaesthetic with or without sedation. The femoral artery is canalized on one or both sides and fed into the iliac and then uterine artery. Angiography is carried out to confirm the correct position before introduction of the embolic agent. Blockage of both uterine arteries results in fibroids becoming avascular and shrinking. Because the normal myometrium subsequently derives its blood supply from the vaginal and ovarian vasculature, UAE is thought to have no permanent effect on the remainder of the uterus. The procedure requires only a short hospital stay and may be carried out as a day case in selected women. After UAE, a mean reduction in fibroid volume of 30–46% has been reported and symptomatic improvement has been reported in up to 85% of women. However, there is no evidence of benefit of UAE compared with surgery (hysterectomy/myomectomy) for satisfaction [20]. In the immediate postoperative period, patients may experience ischaemic pain (usually responsive to simple analgesics) and infection is not uncommon. Occasionally, following UAE the rapid change in uterine size can result in passage of the fibroid vaginally. Rarely, subserosal fibroids can be adherent to the bowel and UAE can lead to bowel necrosis and peritonitis. Although there is a theoretical risk of premature ovarian failure after UAE, a recent study has shown that there is no evidence of deterioration in ovarian function after 1 year. A small risk of sepsis post procedure is acknowledged, even several months later.

Hysterectomy

A total hysterectomy is the only guaranteed 'no bleed' option for HMB. However, hysterectomy should only be considered in the treatment of HMB when a woman has completed her family and when medical and less invasive surgical options have been offered, failed or are inappropriate. Hysterectomy is an established and effective treatment for HMB that induces amenorrhoea, but this must be balanced against the potential morbidity associated with the procedure and the very low risk of mortality. In young patients with HMB, the ovaries are usually conserved but a bilateral salpingectomy should be carried out simultaneously due to recent evidence suggesting that ovarian cancer may have its origins within the fallopian tube. Those younger women who wish to have their ovaries removed, either by choice or due to family history of ovarian or breast cancer, must be appropriately assessed and counselled about the need for hormone replacement until the age of normal menopause. The routes for hysterectomy include laparoscopic, abdominal and vaginal. Individual patient characteristics and surgical expertise are important determinants of the chosen approach.

Laparoscopic hysterectomy

The proportion of hysterectomies performed laparoscopically continues to increase. Advantages include the opportunity to diagnose and treat other pelvic diseases (such as endometriosis), to carry out adnexal surgery, the ability to secure thorough intraperitoneal haemostasis at the end of the procedure, and a more rapid recovery time. Laparoscopic hysterectomy should be used as a general term, whereas operative laparoscopy before hysterectomy, laparoscopically assisted vaginal hysterectomy (with or without laparoscopic uterine vessel ligation), and laparoscopic total and subtotal hysterectomy should be used to describe the types of laparoscopic hysterectomy. In laparoscopically assisted vaginal hysterectomy, the procedure is performed partly laparoscopically and partly vaginally, but the laparoscopic component does not involve uterine vessel ligation. In uterine vessel ligation laparoscopic hysterectomy, although the uterine vessels are ligated laparoscopically, part of the

operation is carried out vaginally. In total laparoscopic hysterectomy, the entire operation, including suturing of the vaginal vault, is performed laparoscopically. A full description of each of these techniques is outwith the scope of this chapter.

Abdominal hysterectomy

An abdominal approach is indicated in women with an enlarged uterus (e.g. due to very large fibroids) or a long vagina and/or narrow pubic arch that makes the laparoscopic (or vaginal) approach technically difficult. An abdominal hysterectomy involves removal of the uterus and/or cervix (subtotal and total, respectively) through an abdominal incision under general anaesthetic. A subtotal abdominal hysterectomy may be performed due to patient preference or if the surgery is technically difficult due to adhesions or endometriosis. Although a subtotal hysterectomy is associated with decreased morbidity, patients must be warned of a 15% incidence of residual bleeding from the endocervix.

Vaginal hysterectomy

Vaginal hysterectomy is appropriate for women with HMB with a small uterus. Advantages of the vaginal route include the obvious absence of any abdominal wounds and minimal disturbance of the intestines.

Complications of hysterectomy

Mortality is a recognized complication of hysterectomy. The risk of death for the abdominal approach is estimated as 1 in 4000 procedures. Serious risks include damage to the bladder and/or ureters (7 per 1000), damage to the bowel (0.4 per 1000), major haemorrhage (15 per 1000), infection/pelvic abscess (2 per 1000), and thromboembolism (4 per 1000), and long-term increased risk of prolapse and urinary incontinence. Notwithstanding these complications, patient satisfaction following hysterectomy for HMB is as high as 95%.

Summary box 48.5

- Endometrial ablation is safe and effective but may not have longer-term benefits.
- Uterine artery embolization also has a significant re-intervention rate.
- Hysterectomy should only be considered when a woman has completed her family and when medical and less invasive surgical options have been considered.

Severe acute heavy menstrual bleeding

Severe acute HMB may occur due to a coagulopathy (most commonly von Willebrand disease), prolapsed fibroids, AVMs (see earlier section) or the use of anticoagulants. Initial management is based on haemodynamic stability. Prolapsed fibroids would then be managed surgically and AVMs generally by embolization. One reported regimen is ethinylestradiol 30 μg/norgestrel 0.3 mg four times daily for 4 days, followed by three times daily for 3 days, followed by two times daily for 2 days, followed by once daily for 3 weeks. Two further regimens that have been reported to be effective and reasonably well tolerated (randomized controlled trial, albeit limited by sample size) are (i) multidose oral contraceptive pill comprising norethindrone 1 mg/ethinylestradiol 35 μg three times daily for 1 week, then daily for 3 weeks and (ii) multidose medroxyprogesterone acetate 20 mg orally three times daily for 1 week and then daily for 3 weeks. Cessation of bleeding was achieved by 10–14 days in 88% and 76% of patients, respectively, with median time to cessation of bleeding being 3 days. Once the patient is clinically stable, an investigation into the cause of bleeding should be performed.

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49

Premenstrual Syndrome

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Premenstrual symptoms occur in most women and there may have been evolutionary benefit to this. Social behaviour resulting in intercourse would have occurred more frequently at the time of ovulation and less frequently once ovulation had passed. As the female becomes less receptive and possibly aggressive to males during the non-fertile premenstrual phase, the males would seek more receptive ovulating females leading to an increase in the population. This is pure conjecture of course – but that is the nature of evolutionary theory. As with all biological parameters there are extremes so that some women have minimal or no symptoms (5–9%) while a similar number have such severe symptoms that there is major impairment of their lives, that of their families, their interpersonal relationships and normal day-to-day functioning. This extreme is premenstrual syndrome (PMS).

Definitions

The terminology used for premenstrual disorders is complex. Premenstrual tension (PMT) was the term originally used, but it has now become the usual lay term; PMS is the medical term most often used in the UK. Premenstrual dysphoric disorder (PMDD) is the extreme, predominantly psychological end of the PMS spectrum, estimated to occur in 3–8% of women [1]. It is the term used increasingly by psychiatrists in the USA but, strictly speaking, originally only for research purposes. It should be noted that much recent research into aetiology and treatment has been undertaken on women who fulfil the criteria for PMDD, particularly for clinical trials on selective serotonin reuptake inhibitors (SSRIs). Women designated as having PMDD will also fulfil criteria for PMS but not necessarily vice versa.

PMS is defined in the Tenth Revision of the International Classification of Disease (ICD-10): a woman is considered to have PMS if she complains of recurrent psychological or somatic symptoms (or both) occurring specifically during the luteal phase of the menstrual cycle and which resolve in the follicular phase at least by the end of menstruation [2]. PMDD is more specific with regard to psychological symptoms and (reflecting the introduction of the term by psychiatrists) pays little attention to physical symptoms.

Because the ICD-10 definition makes no reference to impairment, it is probably too liberal to be of practical use clinically or for research purposes. The classification in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) is too restrictive for clinical use and may have the detrimental effect of under-recognizing patients who are severely debilitated.

Symptoms and classification of PMS

The International Society for Premenstrual Disorders (ISPMD) has published four consensus statements since the previous edition of this textbook. The first, widely cited, is on classification and diagnosis [3]. Core premenstrual disorders (PMDs) are the most common type of PMS. Because most normal women have some degree of symptomatology in the days leading up to menstruation, it is considered that it is the impact of symptoms, namely that they significantly disrupt normal functioning, that distinguishes those women with PMS from those with no more than normal physiological symptoms. The symptoms of core PMDs are non-specific and recur in ovulatory cycles. They must occur during the luteal phase and resolve as menstruation begins. There is no limit on the type or number of symptoms; however, some

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

women will have predominantly psychological symptoms, some will have predominantly physical symptoms and some will have a mixture of both.

There are also PMDs that are not typical core PMDs. These are called 'variant' PMDs and there are four categories.

1) *Premenstrual exacerbation of an underlying disorder*, such as diabetes, depression, epilepsy, asthma and migraine. These patients will experience symptoms characteristic of their medical condition throughout the menstrual cycle but they significantly worsen premenstrually.
2) *Non-ovulatory PMDs* occur in anovulatory ovarian activity. There is inadequate evidence to fully understand this, but follicular activity is believed to trigger the symptoms.
3) *Progestogen-induced PMDs* are caused by exogenous progestogens present in hormone replacement therapy (HRT) and the combined oral contraceptive pill. This can lead to the recurrence of PMD symptoms in women with extreme sensitivity to progestogens. Even though the same symptoms might occur with progestogen-only preparations, these will not be classified as PMDs due to the non-cyclicity of the symptoms and are thus considered to be adverse effects of the progestogen preparation.
4) *PMDs with absent menstruation* are symptoms experienced by women who have normal ovarian cycles but do not menstruate due to hysterectomy, endometrial ablation or the presence of a levonorgestrel intrauterine system (LNG-IUS).

Psychological symptoms of PMS vary greatly, from depression, anxiety, irritability, loss of confidence and mood swings up to suicidal ideation (and, in extreme cases, suicide) [4]. Physical symptoms are typically in the form of mastalgia and bloatedness.

Summary box 49.1

PMS is a condition that affects an enormous number of women to a significant degree; for a small number it can be devastating for the patient herself and for those family and colleagues around her.

Diagnosis

There are no objective tests (physical, blood, biochemical, endocrine or imaging) to assist the diagnosis of PMS and so the use of prospectively completed symptom charts is essential (Fig. 49.1). Retrospective reporting of symptoms is inaccurate, but significant numbers of women who present to a PMS clinic have separate underlying problems such as perimenopause, thyroid disorder, migraine, chronic fatigue syndrome, irritable bowel syndrome, seizures, anaemia, endometriosis, drug or alcohol abuse and menstrual disorders as well as psychiatric disorders such as depression, bipolar illness, panic disorder, personality disorder and anxiety disorder.

The confirmation of luteal-phase timing with the relief of symptoms by the end of menstruation is diagnostic, providing the symptoms are of such severity to impact on the patient's normal functioning. It is also important to identify patients who have a premenstrual exacerbation of their underlying psychological, physical or medical disorder. For example, there are many documented cases of premenstrual suicide, asthma and epilepsy.

Many validated assessment instruments are available, but they are all paper-based self-assessment scales and are not objective. Most researchers and clinicians opt for the Daily Record of Severity of Problems (DRSP) (Fig. 49.1), which is recommended in the 2016 (downloadable) Green-top Guideline No. 48 from the Royal College of Obstetricians and Gynaecologists (RCOG) [5]. Such charts are invaluable. They enable the clinician to characterize instantly the pattern of premenstrual symptoms, their absence during the follicular phase and the degree of impairment caused. Despite the earlier (2007) guideline's recommendation that the DRSP charts be administered for 2 months prospectively in order to establish the diagnosis before initiating treatment, less than 10% of clinical directors report that this strategy had been adopted in their gynaecology/PMS clinics (O'Brien and Samad, unpublished national survey data) (Fig. 49.2). More recently developed smartphone apps such as Prementrics (for smartphones) may be valuable.

Gonadotrophin-releasing hormone agonists in diagnosis

The use of the so-called gonadotrophin-releasing hormone (GnRH) analogue test may be of benefit in clarifying the diagnosis where there is a mixed or uncertain picture. Although there are several studies to demonstrate that this group of drugs successfully eradicates symptoms in well-defined patients, it has never been proven scientifically as a clinical test nor indeed even assessed as such. It is used extensively by gynaecologists (off-licence and with due discussion with the patient) for the purposes of removing the ovarian cycle to determine which of an individual patient's symptoms are clearly related to the menstrual cycle and which (i.e. those that persist despite suppression of the cycle) are not. It is also a valuable way of demonstrating whether symptoms or medical problems such as premenstrual migraine, asthma and epilepsy are truly related to the cycle or are independent. This can be illustrated by the following

DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings

Name or Initials TF

Month/Year NOVEMBER

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1-not at all, 2-minimal, 3-mild, 4-moderate, 5-severe, 6-extreme.

Enter day(Monday = "M", Thursday = "R",etc)>	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T
Note spotting by entering "S" >																							S	S	S				S	S	S
Note menses by entering "M" >																												M	M	M		
Begin rating on correct calendar day >	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1 Felt depress, sad, "down", or "blue" or felt hopeless; or felt worthless or guilty																															
6																															
5																															
4																															
3																															
2																			X	X	X	X	X	X							
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X	X	X	X	X
2 Felt anxious, tense, "keyed up" or "on edge"																															
6																															
5																															
4																		X	X	X	X	X	X								
3																								X							
2																	X								X	X					
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X											X	X	X	X	X
3 Had mood swings (i.e. suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt																															
6																															
5																															
4																			X	X	X	X	X								
3																		X						X							
2																									X	X					
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X	X	X	X	X
4 Felt angry, or irritable																															
6																															
5																															
4																		X	X	X	X	X	X								X
3																								X						X	
2																	X								X	X					
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X											X	X	X		
5 Had less interest in usual activities (work, school, friends, hobbies)																															
6																															
5																															
4																								X	X						
3																					X	X	X			X					
2																			X	X							X				
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X											X	X	X	X
6 Had difficulty concentrating																															
6																															
5																															
4																															
3																			X	X	X	X	X								
2																		X						X							
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X	X	X	X	X
7 Felt lethargic, tired, or fatigued; or had lack of energy																															
6																															
5				X																											
4																							X	X							
3																				X	X	X			X						
2			X			X	X	X		X		X						X	X							X					
1	X	X			X				X		X		X	X	X	X											X	X	X	X	X
8 Had increased appetite or overate; or had cravings for specific foods																															
6																															
5																															
4																		X	X	X	X	X	X								
3																								X							
2																	X								X						
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									X	X	X	X	X	X
9 Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep																															
6																															
5				X																											
4																			X	X	X	X	X								
3																								X							
2			X			X	X	X	X			X						X							X					X	X
1	X	X			X					X	X		X	X	X	X	X									X	X	X	X		
10 Felt overwhelmed or unable to cope; or felt out of control																															
6																															
5																															
4																															
3																							X								
2																			X	X	X	X		X							
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X	X	X	X	X
11 Had breast tenderness, breast swelling, bloated sensation, weight gain, joint or muscle pain, or other physical symptoms																															
6																															
5																				X	X	X	X								
4							(	J	O	I	N	T		P	A	I	N	)	X					X	X	X					
3						X	X	X	X	X	X	X	X	X	X	X	X	X	X									X				
2																												X		X	X
1	X	X	X	X	X																								X		
At work, school, home or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency																															
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5																															
4																							X								
3																			X	X	X	X		X							
2																		X								X	X				
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X	X	X	X	X
At least one of the problems noted above caused avoidance or or less participation in hobbies or social activities																															
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5																															
4																							X								
3																			X	X	X	X		X							
2																		X								X	X				
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X	X	X	X	X
At least one of the problems noted above interfered with relationships with others																															
6																															
5																															
4																			X	X	X	X	X								
3																								X							
2																										X	X				
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												X	X	X

Fig. 49.1 Daily Record of Severity of Problems (DRSP) chart prospectively completed by a patient suffering from moderately severe premenstrual syndrome (PMS) demonstrating (a) the cyclicity of symptoms, (b) occurrence premenstrually, (c) absence of symptoms in the follicular phase and (d) impairment.

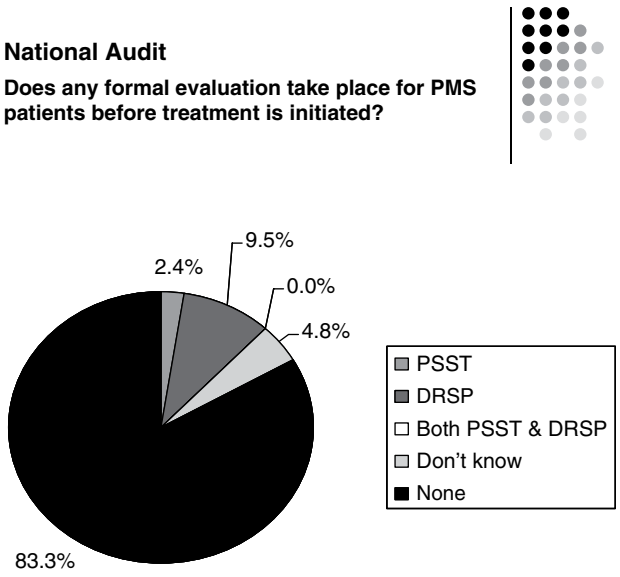

Fig. 49.2 National Survey of Clinical Directors. Implementation of RCOG Guidance on Diagnosis. DRSP, Daily Record of Severity of Problems; PSST, Premenstrual Symptom Screening Tool.

commonly encountered clinical problem. If a woman is to be considered for hysterectomy for a gynaecological indication such as heavy menstrual bleeding due to fibroids, symptom information gathered during GnRH therapy may help the patient make the decision about whether to conserve or remove her ovaries. If her PMS (or other significant premenstrual symptom) is severe and is eradicated by GnRH, it is likely (though not guaranteed) that she would also benefit from removal of ovaries when the hysterectomy is being undertaken. This information would be invaluable in the final preoperative counselling.

Aetiology

PMS is not due to a single factor but its basis is multifactorial, with genetic, environmental and underlying psychological influences being important. This is of course true for all mood disorders but in PMS the ovarian cycle comes into play, with ovulation being almost certainly the key factor.

Ovulation and progesterone

The principal cause of PMS is uncertain. There is evidence to suggest that the cyclical endogenous progesterone produced in the luteal phase of the cycle after ovulation is the key provoking factor. Women with PMS appear to be unusually 'sensitive' to normal levels of progesterone [6]; differences in progesterone levels have not been demonstrated between women with and without PMS [7]. It has been hypothesized that the mechanism of this increased sensitivity is related to a neurochemical factor, and most evidence points to a dysregulation of serotonin metabolism [6].

Throughout reproductive life, progesterone production seems to be linked to women's psychological health. Progesterone and metabolites, such as allopregnanolone, are produced by the ovary and the adrenals, and also *de novo* in the brain. These hormones are effectively neurosteroids that readily cross the blood–brain barrier. Progesterone has known mood-altering and sedative effects when administered. It is well known that women have no PMS symptoms before puberty, during pregnancy or after the menopause; these are times where ovarian hormone cycling has not begun or ceases temporarily or permanently. Not surprisingly, if the assumptions made above are true, PMS-like symptoms can also be reintroduced by the administration of oestrogen/progestogen hormone replacement therapy (HRT) and this is frequently seen in clinical practice.

Suppression of the ovarian endocrine cycle with danazol, by administration of analogues of GnRH or following bilateral oophorectomy results in the elimination of PMS symptoms. Therefore, the hypothesis that ovarian steroids, particularly ovulatory progesterones, have a role in the pathophysiology of the syndrome is intuitively obvious.

Research, none of which is recent, into PMS has generated data which could support theories of progesterone deficiency, oestrogen/progesterone imbalance or progesterone excess. However, the consensus is that ovarian steroid concentrations in blood do not differ in these women. Interactions of fluctuating levels of ovarian steroids or their metabolites with neurotransmitter systems or receptor imbalances in the brain are directly relevant to the pathogenesis of PMS [8]. This is believed to render women more sensitive to physiological levels of progesterone.

Summary box 49.2

Aetiology of PMS is uncertain, although ovulation is almost certainly the trigger in women who are sensitive to endogenous progesterone following ovulation and exogenous progestogen used therapeutically. It is likely that this sensitivity is related to an abnormality of neurotransmitter function. This has yet to be determined, but research evidence points to the serotonergic system.

Neurotransmitters

Oestrogen has clear effects on several neurotransmitters, including serotonin, acetylcholine, noradrenaline, γ-aminobutyric acid (GABA) and dopamine. It cumulatively acts as an agonist on serotonergic function by increasing the number of serotonin receptors, serotonin postsynaptic responsiveness and neurotransmitter transport and uptake. It also increases serotonin synthesis and boosts the levels of the metabolite 5-hydroxyindoleacetic acid (5-HIAA). It is well known that the serotonergic system plays a substantial role in regulating mood, sleep, sexual activity, appetite and cognitive ability. Serotonin dysregulation is a major component in the development of depression. Our knowledge of the role of serotonin in depression has been extended into PMS research [6] and several studies have demonstrated altered serotonin metabolism in these patients. Blood levels and platelet uptake of serotonin have been found to be low in patients with PMDD and acute depletion of tryptophan (the precursor of serotonin) aggravates symptoms of PMS and PMDD. This hypothesis is supported indirectly by the observation that serotonin-receptor concentrations vary with changes in the oestrogen and progesterone level and because the well-known SSRIs fluoxetine, paroxetine, citalopram and sertraline have been shown to be extremely efficacious in treating severe PMS and PMDD [8]. This gives additional, albeit indirect, support to the theory of involvement of serotonin in the aetiology of PMS.

Low activity of GABA has been reported in patients with depression, PMDD and PMS. Oestrogen increases binding of GABA agonists and the upregulation of GABA receptors. In addition to the effect of SSRIs on the serotonergic system, they have been shown to enhance GABA function, hence improving depressive symptoms. The GABA receptor is one of the principal receptors involved in the mechanism of action of alcohol and diazepam. Investigations of the metabolites of progesterone have shown that women with PMS have lower levels of allopregnanolone in the luteal phase [9]. This provides another plausible theory, as allopregnanolone has GABAergic activities and its deficiency can induce symptoms similar to those experienced in PMS (Fig. 49.2).

Vitamin B_6 (pyridoxine) is a cofactor in the final step in the synthesis of serotonin and dopamine from dietary tryptophan. However, no data have yet demonstrated consistent abnormalities of either brain amine synthesis or deficiency of cofactors such as vitamin B_6; supplementation studies have shown that it is possibly effective as a method of treatment but large randomized studies would be required to produce a conclusive answer.

Treatment

Summary box 49.3

Treatment can be achieved effectively either by suppressing or removing ovulation or by modulating central nervous function with psychological interventions or psychotropic drugs. SSRIs are particularly useful.

Non-medical therapies

Claims, mainly unsubstantiated, have been made for the supplementation of calcium, vitamin E, magnesium, dietary change, vitamin B_6, evening primrose oil, exercise, yoga, acupuncture, psychotherapy and many more. There is very little evidence that any of these treatments for PMS are effective, with the exception of exercise, and very limited evidence for the effects of calcium and magnesium. There is, however, strong evidence to support the use of cognitive behavioural therapy (CBT) for treating PMS and RCOG guidance recommends its use as routine early management [5]. It is important to realize that any treatment method may be associated with a very high placebo response, so many therapies appear on the face of it to be effective. Conversely, because of this placebo effect, therapeutic research requires the recruitment of such large numbers of patients to reach the power to demonstrate statistical superiority that many studies are almost impossible to undertake where the additional therapeutic effect over and above that of the placebo is only marginal.

Medical therapies

The management of PMS has, over the past few years, become increasingly easy to undertake, if somewhat more invasive. First, it should be stated that there is overwhelming evidence that progesterone pessaries and oral progestogens are ineffective [10]. Ironically, these are the only drugs in the UK that have a pharmaceutical licence for the management of PMS. All known effective therapies are unlicensed in the UK whilst most SSRIs and an oral contraceptive pill are licensed in the USA.

Our proposed aetiology of PMS suggests that normal postovulatory progesterone gives rise to symptoms in women who have increased sensitivity to endogenous progesterone and this sensitivity is considered to be due to a neurotransmitter dysregulation such as serotonin 'deficiency'. If this is so, then, broadly speaking, treatment should be achievable either by suppressing ovulation or by enhancing serotonin levels in the central nervous system to 'reduce the sensitivity to progesterone'.

The first of these is achieved pharmacologically or by surgical intervention, the former by elevating serotonin levels using drugs such as the SSRIs. Although theoretical, treatment based on this notion is very useful practically.

Psychotropics: selective serotonin reuptake inhibitors

Elevating serotonin levels can readily be achieved by the use of SSRIs [8]. Such treatment is clearly beneficial, although none of these drugs has a pharmaceutical licence for the management of either PMS or PMDD in the UK. Fluoxetine 20 mg daily is usually sufficient to improve symptoms in most women. Side effects such as loss of libido may be partially avoided by administering the drug during the luteal phase only, the effect of the SSRIs being more instantaneous for PMS symptoms than it is for the treatment of symptoms of depression. While SSRIs are not licensed in the UK or Europe for PMS, in the USA fluoxetine and indeed most other SSRIs are licensed for PMDD.

Ovarian cycle suppression

Suppression of the ovarian cycle can be achieved with oestrogen [11], danazol [12], GnRH agonist analogues [13] or bilateral oophorectomy [14].

Summary box 49.4

The few drugs that are licensed to manage PMS are ineffective; those that are effective must be used off-licence and patients should be made aware of this.

Surgery: bilateral oophorectomy

Bilateral oophorectomy with hysterectomy is almost always too invasive for the majority of patients with PMS and, even though it is the only certain cure [14], its use is rarely justifiable other than as a last-resort measure for the most severely affected women: those who have failed to respond to other measures. When removal of the ovaries and uterus is considered appropriate, oestrogen replacement can follow without the need to consider endometrial protection using progestogen, which inevitably would restimulate the PMS symptoms. We should note here that those studies that appear to have described (retrospectively) increased morbidity and mortality in later life if ovaries are removed are methodologically flawed. Women whose ovaries were conserved were compared with those having hysterectomy and bilateral oophorectomy but without any subsequent oestrogen replacement. No gynaecologist would withhold oestrogen replacement in such women and while such studies are not yet available, it would be anticipated that outcomes following bilateral oophorectomy plus oestrogen therapy would actually be far more favourable. It should be added that the studies described surgery for patients with other general gynaecological conditions and not for those undergoing surgery for PMS.

Any treatment technique where the uterus is retained and oestrogen replacement is given will require the administration of progestogen in order to protect the patient from the risk of endometrial cancer in the retained endometrium. Systemic progestogen will then almost certainly cause the reappearance of PMS symptoms in most women. Hence, if the ovaries are to be removed for PMS, then in most cases subsequent management is made simpler and more effective by removing the uterus at the same time. Laparoscopic bilateral oophorectomy has its attractions as it is less invasive, but the subsequent management difficulties posed by the presence of the endometrium are not inconsiderable. Whether it is preferable to use a Mirena® intrauterine system (see section Oestrogen) or to remove the uterus is probably more dependent on patient choice as there is no evidence to influence the decision either way. However, with advances in laparoscopic and robotic surgery, the uterus can also be removed through a minimally invasive route and clear RCOG guidance tends to favour removal of both uterus and ovaries in nearly all cases.

There is no logic in recommending endometrial ablation for PMS because cyclical ovarian function will continue along with the resulting PMS symptoms. Where claims were made for the beneficial effects of ablation, these were based on studies designed to evaluate the treatment of heavy periods and they are not valid for interpretation in terms of PMS treatment.

Danazol

When danazol is given orally, even at doses of 200 mg, it is particularly effective for most symptoms of PMS. Its use has been very much limited by anxieties related to the risk of masculinization. Attempts to reduce side effects by prescribing it for use in the luteal phase only (presumably through its direct effect on target tissue rather than ovulation suppression) have shown it be ineffective for nearly all symptoms of PMS with the exception of cyclical mastalgia [12].

GnRH agonist analogues (and add-back therapy)

GnRH agonist analogues are extremely effective [12]. These are best administered as injected depot preparations (goserelin or leuprorelin) as, unlike nasal preparations, compliance is virtually guaranteed. These drugs are agonist analogues and so omission of nasal doses (or indeed late administration of depot preparations) can result in incomplete suppression and restimulation of cycles.

Treatment without add-back therapy will almost always be successful for PMS, but confusion can arise owing to the development of new symptoms usually associated with the menopause. With continuous add-back therapy (particularly tibolone), the analogues remain equally effective for PMS while eliminating menopause symptoms [13], though not in all patients, hence the resort to surgery in some. It is difficult to know whether long-term use of this combination is justified either medically or economically. It is probably reasonable to use it in those women approaching the menopause and medium term in younger women. In those who do receive longer-term therapy, it is considered advisable to monitor bone density at yearly intervals as is recommended for patients being treated for endometriosis with long-term GnRH analogues and add-back. It is probably also appropriate to advise calcium, vitamin D and regular exercise for bone preservation.

Oestrogen

Suppression of ovulation using oestrogen has significant advantages over oophorectomy and GnRH analogues in that these latter approaches still require the addition of oestrogen to prevent the hypo-oestrogenic effects resulting from the primary treatment approach. Its disadvantage is that in those women who retain their uterus and endometrium, it is necessary to protect from endometrial cancer using potentially 'PMS-inducing' progestogens.

Oestrogen can be given in several ways, including the combined oral contraceptive pill, conventional cyclical or continuous HRT, and estradiol patches or implants. Standard preparations of HRT, be they cyclical, continuous combined or tibolone, are of insufficient dose to suppress ovulation and they would inevitably fail to improve symptoms and increase the incidence of abnormal uterine bleeding. They are only useful as add-back during GnRH therapy.

While the use of conventional combined oral contraception certainly suppresses ovulation, the progestogen component introduces a new progestogen cycle. This may be the reason why oral contraceptive therapy has in the main proven to be ineffective in several well-conducted trials. Progestogen-only pills will most often give rise to PMS-like side effects in these patients. Oral contraceptives containing a relatively newer progestogen, drospirenone, have been introduced. Drospirenone is derived from spironolactone and thus has anti-androgenic and anti-aldosterone properties which may antagonize or at least avoid restimulation of the PMS-like symptoms. Such preparations are licensed for PMDD in women requiring contraception in the USA and some European countries but not the UK. The use of this oral contraceptive therapy continuously would appear to be a logical approach.

Transdermal estradiol (as patches or implants) suppresses the ovarian cycle effectively without inducing the negative consequences of surgically induced premature menopause or 'medical oophorectomy' [10]. Consequently, they reliably treat PMS symptoms and this is demonstrated in a recent Cochrane review [11]. In the presence of an intact uterus, it remains necessary to prevent endometrial hyperplasia and cancer;- this, as has already been discussed, reintroduces 'PMS' [15].

While the possibility of giving oestrogen alone and regularly checking the endometrium with scans or endometrial sampling is feasible, the risk will remain and additionally the likelihood that patients will have troublesome bleeding is very considerable.

Other unresearched and potential alternatives to avoid restimulation of PMS symptoms exist, including:

- administering cyclical progestogen combined with simultaneous SSRI;
- the use of micronized progesterone preparations;
- the use of less androgenic progestogens;
- administration of the progestogen at less frequent intervals.

Probably the most realistic and effective method to achieve endometrial protection without reintroducing PMS would be to administer the progestogen into the uterine cavity using the Mirena LNG-IUS where it will act directly on the endometrium. With this approach, oestrogen suppresses ovulation and avoids menopausal symptoms. The intrauterine progestogen provides endometrial protection without achieving systemic levels (not in all patients) that would act on the central nervous system to reintroduce PMS symptoms. This combination could have the added benefit of improving any menstrual problem and would provide effective contraception. There is only limited evidence to support the use of this combination. There is, however, good evidence to demonstrate that oestrogen in sufficient doses achieves ovarian suppression and elimination of PMS symptoms – there is good evidence that the LNG-IUS can prevent and even reverse established endometrial hyperplasia. There is an enormous amount of clinical anecdotal experience to suggest that the combination is effective. Large-scale studies are required to demonstrate this efficacy as it has the ability to achieve all that hysterectomy and bilateral oophorectomy plus oestrogen achieves but without major surgery.

If general practitioners or gynaecologists should use this approach, it is important that they and their patients are aware that, as well as LNG-IUS-induced bleeding in the months following its insertion, there can be initial absorption of the LNG into the circulation, and thus return of PMS symptoms in the early months. Both are transient in most patients. Finally, O'Brien (unpublished

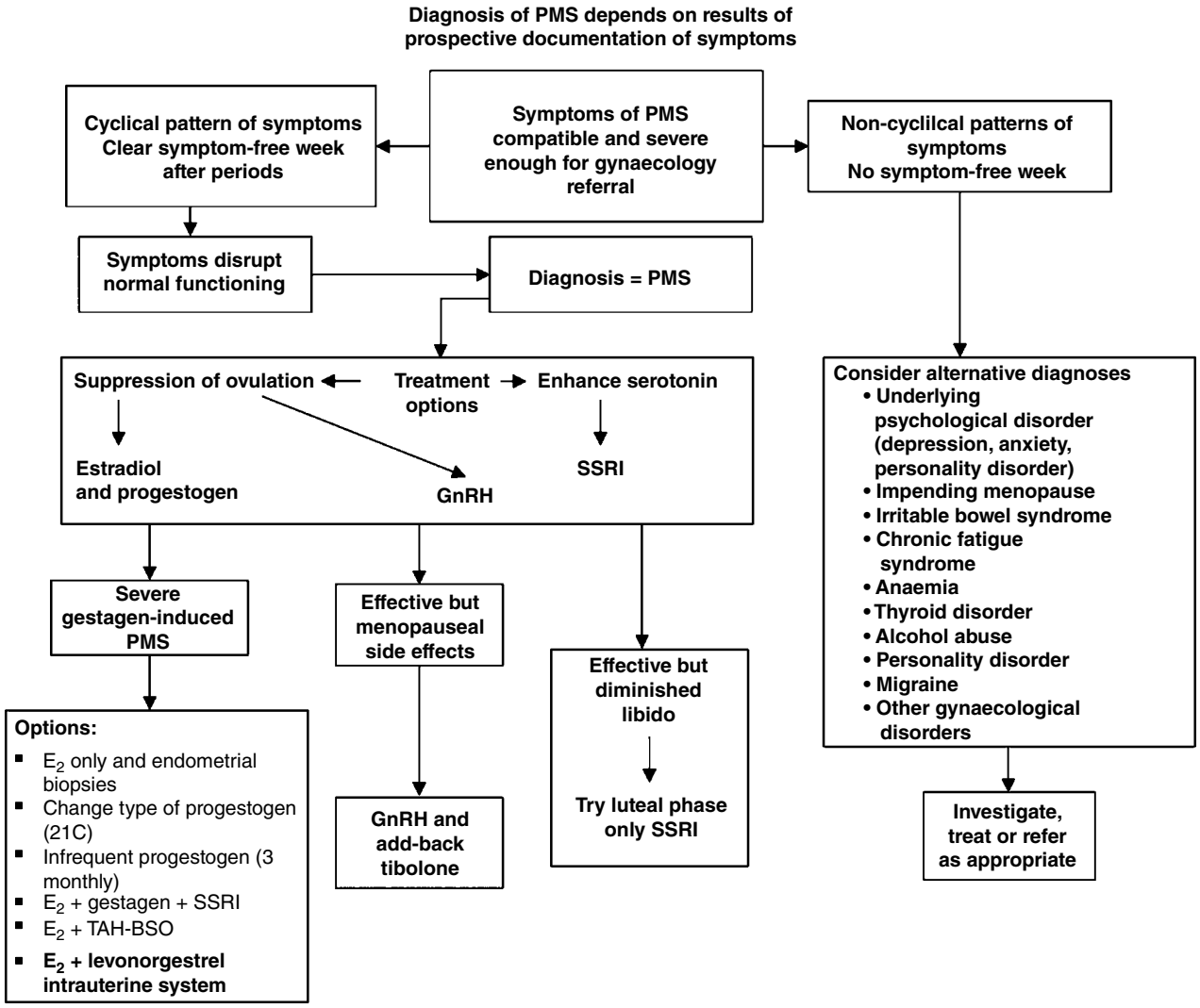

Fig. 49.3 Algorithm for the diagnosis and management of premenstrual syndrome (PMS). TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophrectomy.

data) has shown in a significant number of women who received pretreatment with GnRH suppression before insertion of LNG-IUS during the third month (when presumably the endometrium is thinned and avascular) that both bleeding and PMS are minimized. As yet, this requires formal evaluation in research studies (Fig. 49.3).

Summary box 49.5

In general, the more effective a treatment method is, the more invasive it is. Paradoxically, then, the worse the symptoms are, the easier it is to treat them as the more invasive treatment methods can be justified, assuming of course that the diagnosis is sound.

Conclusion

Suppression of the ovarian cycle eliminates PMS effectively. This can most precisely be achieved by GnRH analogues with add-back tibolone. The scope for long-term therapy using this approach is limited, and if it is required (rarely) it is prudent to monitor bone mineral density. Bilateral oophorectomy with hysterectomy is a last resort for all but a few well-selected women. Transdermal oestrogen suppresses ovulation reliably and eliminates PMS without generating menopausal side effects. Intrauterine progestogen (LNG-IUS) can be used to protect the endometrium and avoid restimulation of premenstrual symptoms; it also reduces periods and provides contraception. There can be initial bleeding and

restimulation of symptoms in the first months. The oral contraceptive pill appears to have extremely limited efficacy using conventional pills. Drospirenone-containing oral contraceptives have the potential to suppress ovulation without reintroducing PMS and should probably be used continuously. SSRIs are the simplest and most effective non-hormonal approach to treatment. Some consider that they should be used as first-line medical therapy, although many patients consider this form of therapy to be stigmatizing.

St John's Wort and agnus castus have been shown to be effective when used for depression. They could be tried as a self-help measure in PMS as there is limited evidence for their efficacy; there are known interactions if taken at the same time as SSRIs. There is evidence to demonstrate that exercise and particularly CBT are effective, but access to clinical psychology services and lifestyle intervention programmes within the National Health Service are extremely limited in the UK.

Other non-medical treatments are of doubtful efficacy but are usually harmless. They can be tried before resorting to medical therapy when there are no risks other than the inevitable delay in initiating a known effective therapy. The majority of patients can be treated simply in community-based practices by general practitioners or by self-help. Patient groups such as the National Association for PMS (NAPS) are very useful for this approach http://www.pms.org.uk.

Making a correct diagnosis is all important, and those patients without a symptom-free week probably have a continuous underlying psychological disorder. They should be referred back to the general practitioner or, in severe cases, referred on to a psychiatrist. Suicidal ideation and suicide attempts call for urgent referral to doctors with the specific skills to manage these problems.

Only the most severely affected patients with clear-cut PMS requiring medical or surgical intervention should be referred for secondary gynaecological management. Gynaecologists, preferably those with an interest, understanding and expertise in the area, should be asked to manage PMS patients only when symptoms are severe enough to justify such endocrine or surgical intervention.

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50

Menopause and Postmenopausal Health

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Menopause, from the Greek *menos* (month) and *pausis* (cessation), is defined as the last menstrual period after a minimum of one year's amenorrhoea. The average age of the female menopause (51 years) has remained unchanged since ancient Greek and Roman times even though the average lifespan has increased. Thus, an increasing number of women are now spending almost half their lifespan in a hypo-oestrogenic state. The physiological changes which result in the final menstrual period start many years before the cessation of periods during the perimenopause. This episode of dynamic neuroendocrine change occurs due to a progressive reduction in ovarian reserve and is commonly associated with distressing physical and psychological symptoms in the last decade of a woman's reproductive lifespan. These endocrine, biomarker and menstrual changes have recently been studied and documented by the Stages of Reproductive Aging Workshop + 10 (STRAW + 10) [1] (Fig. 50.1).

Recent publication of the UK National Institute for Health and Care Excellence (NICE) menopause guidelines [2] has provided a much-needed rigorous analysis of the data on the diagnosis and management of the menopause. It is now vitally important that this information is efficiently disseminated to healthcare professionals, especially in primary care and gynaecology. This chapter uses the analyses of the NICE guidelines and the recently published guidelines from the various menopause societies as core information, which will be conveyed to the reader in a practical manner with signposts to key sources of information.

Consequences of the menopause

Aetiology of hot flushes and sweats

It is generally accepted that oestrogen plays an integral role in the genesis of vasomotor symptoms but the precise aetiology remains unknown. The hypothesis proposed by Robert Freeman still seems the most plausible [3,4]. In the asymptomatic woman there is a thermoneutral zone (about 0.4 °C) within which fluctuations of core body temperature do not trigger compensatory autonomic mechanisms such as flushing or sweating. In the symptomatic woman the thermoneutral zone is considerably reduced, so that even minor fluctuations in core body temperature reach the limits of the zone and initiate a thermoregulatory response. The narrowing of the zone may be due to elevated central noradrenergic activation and probably precipitated by changes in oestrogen. Recent data suggest that vasomotor symptoms such as flushes and sweats may be associated with an increased risk of cardiovascular disease [5,6].

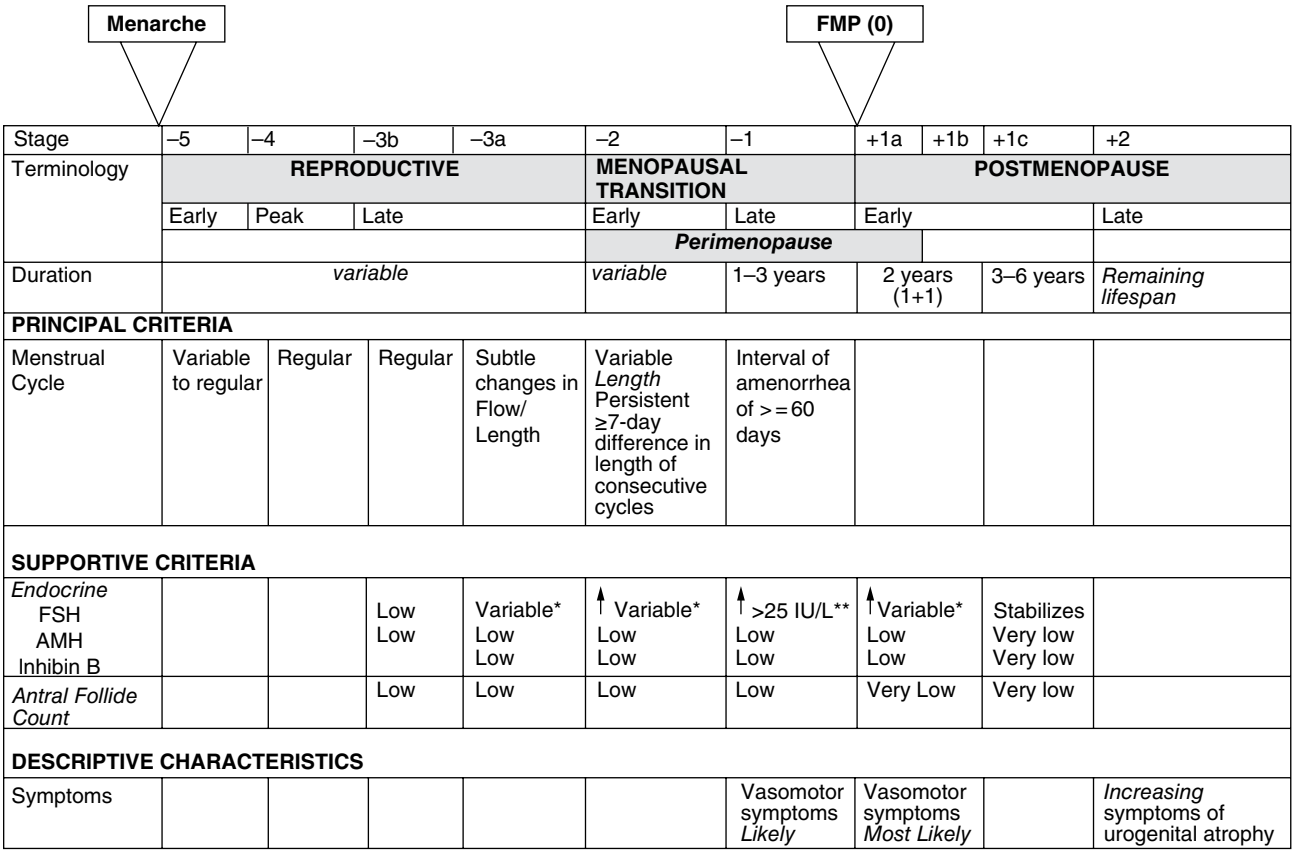
Other early symptoms

Other typical immediate menopausal symptoms include insomnia, anxiety, irritability, memory loss, tiredness, poor concentration and musculoskeletal aches and pains. Falling oestrogen levels are thought to lead to similar falls in neurotransmitter levels, such as serotonin, which trigger mood symptoms. Women who have suffered from postnatal depression and premenstrual syndrome appear to be particularly predisposed to depression in the perimenopause [7]. The menopause transition is often associated with a significant reduction in sexuality and libido that is multifactorial but at least partly related to falling androgen levels [8].

Intermediate symptoms

Oestrogen deficiency leads to the rapid loss of collagen, which contributes to the generalized atrophy that occurs after the menopause. In the genital tract this is manifested by dyspareunia and vaginal bleeding due to

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.



Stage	–5	–4	–3b	–3a	–2	–1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	Variable *Length* Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very low Very low	
Antral Follide Count			Low	Low	Low	Low	Very Low		Very low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated

** Approximate expected level based on assays using current International pituitary standard [67–69]

Fig. 50.1 The Stages of Reproductive Aging Workshop (STRAW) + 10 staging system for reproductive ageing in women. AMH, anti-Müllerian hormone; FMP, final menstrual period; FSH, follicle stimulating hormone. *Source:* adapted from Harlow *et al.* [1].

vulvovaginal atrophy (VVA). In the lower urinary tract, atrophy of the urethral epithelium occurs with decreased sensitivity of urethral smooth muscle and decreased amount of periurethral collagen. All this results in dysuria, urgency and frequency, commonly termed the urethral syndrome. The position statement from the International Menopause Society emphasizes the importance of enquiring about urogenital symptoms, the history of which might not be readily volunteered by the menopausal patient [9]. Recent studies have shown that the incidence of VVA is higher than originally thought due to under-reporting and that these symptoms often have a devastating effect on relationships [10]. A new classification system which encompasses VVA and urinary tract problems has recently been proposed in North America called the genitourinary syndrome of menopause (GSM) and could be adopted universally in due course [11].

Long term

Osteoporosis and sarcopenia

Osteoporosis is a systemic skeletal disorder of the bone matrix resulting in a reduction of bone strength, to the extent that there is a significantly increased risk of fracture when a woman suffers a fall from her own body height. Bone strength is determined by bone density and microarchitectural integrity. Osteoporosis is predominantly a disease of women, who achieve a lower peak bone mass than men and are then subjected to an accelerated loss of bone density following the menopause due to loss of oestrogen. Women lose 50% of their skeleton by the age of 70 years, but men only lose 25% by the age of 90 years. The loss of height occurs not only due to vertebral fractures but also loss of the intervertebral disc space as a result of deterioration and loss of collagen [12]. Osteoporosis-related fractures cause considerable morbidity in the

elderly, requiring prolonged hospital care and difficulties in remobilization. There is increasing awareness that avoiding sarcopenia (muscle loss and weakness) through regular exercise will maintain strength and posture and reduce the risk of injuries including osteoporosis-related fractures. Hormone therapy may help muscle as well as bone strength but this requires confirmation [13].

Cardiovascular

Cardiovascular disease is the principal cause of morbidity and mortality in women. Women are protected against cardiovascular disease before the menopause, after which the incidence rapidly increases, reaching a similar frequency to men by the age of 70 years. The protective effect of oestrogen in premenopausal women is also thought to be mediated by a favourable effect on the ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL), by nitric oxide-mediated vasodilatation leading to increased myocardial blood flow, by an antioxidant effect on endothelial cells and by a direct effect on the aorta decreasing atheroma. Cross-sectional and prospective observational studies have shown that women going through the menopause transition have elevation of cholesterol, triglyceride and LDL levels, a reduction in HDL2 levels and a rise in insulin resistance. As oestrogen levels begin to fall, the somatotrophic axis becomes less active leading to insulin resistance and a rise in central adiposity. This in turn leads to the change in body shape from the female gynaecoid shape to the male android shape, itself an independent risk factor for coronary heart disease (CHD) [14]. A number of factors are involved in perimenopausal weight gain including genetic predisposition, socioeconomic influences, reduction in caloric need and expenditure, reduced lean body mass and a reduction in resting basal metabolic rate. Major primary prevention measures include smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise and diabetes and lipid control.

Central nervous system

During the menopause transition, poor concentration and other cognitive problems are common [15]. Although these symptoms do not usually persist long term, the incidence of Alzheimer's dementia is significantly higher in women compared with men. Studies have demonstrated that oestrogen may improve cerebral perfusion and cognition in women below 60 years. Oestrogen appears to have a direct effect on the vasculature of the central nervous system and promotes neuronal growth and neurotransmission. In the long term, exogenous oestrogen may prevent diseases with a vascular aetiology such as vascular dementia and Alzheimer's, but long-term randomized data are required to confirm this. The failure of oestrogen to show benefit for dementia in women commencing treatment above 60 years, and possibly an increased risk in some studies, may reflect the predominance of the prothrombotic effect of oestrogen in women of this age group.

Advances in prediction of menopause

The prediction of menopause has progressed significantly over the last 5 years. These are not tests that are widely performed but can be useful where premature ovarian insufficiency (POI) is suspected or where there is a family history of POI. Follicle stimulating hormone (FSH) levels can be misleading even when the test is timed to the early follicular phase of the cycle and levels often vary from cycle to cycle depending on ovarian activity. The most accurate predictors of ovarian reserve currently available appear to be measurement of anti-Müllerian hormone (AMH) production by the primordial and pre-antral follicles and estimation of antral follicle count by ultrasonographic estimation. AMH is independent of the day of cycle and its predictive value of ovarian reserve is claimed to last for up to 2 years from when the sample is taken. A systematic review [16] was recently carried out to appraise data on prediction of age at natural menopause (ANM) based on AMH, antral follicle count and mother's ANM to evaluate clinical usefulness and to identify directions for further research. It found that AMH was currently the most promising marker for prediction of ANM. However, prediction models do not predict the extremes of menopause age very well and have wide prediction intervals. Markers need improvement before they can be used for individual prediction of menopause in the clinical setting.

Summary box 50.1

Routine FSH testing is not required in women aged 45 years or over with classic menopause symptoms such as hot flushes and sweats.

Patient assessment and ongoing monitoring

Initial diagnosis

The diagnosis of natural menopause can usually be made from the characteristic history of the vasomotor symptoms of hot flushes and night sweats and/or amenorrhoea.

Measurement of the concentrations of plasma hormones such as estradiol, FSH and luteinizing hormone (LH) in women over the age of 45 years with classical symptoms is not indicated as it is unlikely to change clinical management [2]. However, in the young woman aged below 45 years (and certainly under 40 years) or after hysterectomy with ovarian conservation, where the diagnosis is more difficult and the metabolic implications may be more serious, measurement of FSH levels may be helpful, in which case repeated concentrations of 40 IU/L or above may be regarded as being in the menopause range. Women diagnosed with spontaneous POI should, in addition to hormonal investigations, also have an autoantibody screen (thyroid and adrenal) and should be offered karyotype and fragile X genetic analysis, particularly if they are below 30 years of age. Online programs such as Manage my Menopause can be helpful for both the woman and the healthcare professional in individualizing overall care and specific management [17].

Monitoring

The NICE menopause guidelines recommend that women should be followed up within 3 months of initiation of treatment and annually thereafter. An oestrogen level is only helpful if there has been inadequate response to treatment due to low levels or if side effects suggest that the dose of estradiol is too high. Annual screening should include assessment of body mass index (BMI), blood pressure and a review of medication. A white paper written by cardiologists and menopause experts has highlighted the important role that gynaecologists can play in cardiovascular screening [18]. Fasting lipid profile and estimation of insulin resistance are recommended in women with risk factors (e.g. increased waist circumference or personal/family history of diabetes/cardiovascular disease).

Although advice should be given to women about being aware of changes in their breasts and perineum, routine breast palpation and pelvic examination is unnecessary; these need only be performed if clinically indicated. Mammography should be performed as part of the national screening programme every 3 years unless more frequent examinations are clinically indicated. However, if a woman chooses to use hormone replacement therapy (HRT) beyond the current age of breast screening cessation (70 years), mammographic screening should also continue. In women over 45 years of age it is best to arrange screening before starting oestrogen therapy to identify patients with subclinical disease. Ultrasound examination of the pelvis and/or endometrial biopsy are not a necessary prerequisite to treatment with HRT unless there is undiagnosed bleeding.

The gold standard measurement of the risk of osteoporosis is still dual-energy X-ray absorptiometry (DEXA) measurement of the lumbar spine and hip; some units are now using CT to perform this assessment. Markers of bone formation and breakdown can be useful in that changes occur more rapidly than with bone density, but their use is largely confined to research. The Royal College of Physicians advises that DEXA scans are performed no more frequently than every 2 years because changes in bone mineral density are so small that they often do not exceed the margin of error of the equipment and assessor. The World Health Organization (WHO) has advised that the decision to treat osteoporosis is made by taking into account bone mineral density, age and BMI. The formula for calculating the probability of fracture (FRAX) is available online [19].

Premature ovarian insufficiency

Premature ovarian insufficiency remains poorly understood and under-researched. It describes a syndrome consisting of early cessation of periods, sex steroid deficiency, and elevated levels of the pituitary hormones FSH and LH in women below the age of 40 years. POI can be primary (spontaneous POI) or secondary (induced by radiation, chemotherapy or surgery). Controversy persists over nomenclature, with terms such as 'premature menopause', 'premature ovarian failure/dysfunction' and 'primary ovarian insufficiency' still in use. POI has been estimated to affect about 1% of women younger than 40 years, 0.1% of those under 30 and 0.01% of those under 20. However, as cure rates for cancers in childhood and young women continue to improve it is likely that the incidence of prematurely menopausal women will rise. Data from Imperial College London suggest that the incidence of POI may be significantly higher than originally estimated. Islam and Cartwright [20] studied 4968 participants from a 1958 birth cohort. They found that 370 (7.4%) had either spontaneous or medically induced POI. Smoking and low socioeconomic status were predictive of POI, and poor quality of life (as determined by the SF36 Quality of Life Questionnaire) was twice as common in POI. The incidence of POI also varies according to the population studied. It appears to be significantly higher, greater than 20%, in some Asian populations (personal communications with Indian Menopause Society and Chinese Gynaecological Endocrinology Society).

In the past, the focus of medical care has been on improvement of survival rates. Very little attention has been given to the maintenance of quality of life in the short term and to the avoidance of the long-term sequelae of POI. One of the main reasons for this has been the

bias of economic expenditure and medical endeavour to the prolongation of life (e.g. cancer treatments) rather than towards optimizing quality of life in cancer survivors. Should this trend continue we are in danger of creating a population of young women who have been given back the gift of life but left without the zest to live it to its full potential.

Causes of spontaneous POI include idiopathic (no known cause), genetic, autoimmune and infective. The typical presentation of spontaneous POI is erratic or complete cessation of periods in a woman younger than 40 years, which may or may not necessarily be accompanied by symptoms. These symptoms may not be typical vasomotor in nature and include mood disturbances, loss of energy and generalized aches and pains. Our data indicate that the next most disturbing aspect of POI after the loss of fertility is the adverse impact on sexual responsiveness and other psychological problems [21]. Thus women with POI require integrated care to address physical, psychosocial and reproductive health as well as preventative strategies to maintain long-term health. Until recently, there has been an absence of specific evidence-based guidelines for diagnosis and management of POI, but this has recently been addressed by the European Society for Human Reproduction and Embryology (ESHRE) [22].

POI is a difficult diagnosis for women to accept, and a carefully planned and sensitive approach is required when informing the patient of the diagnosis. A dedicated multidisciplinary clinic separate from the routine menopause clinic will provide ample time and the appropriate professionals to meet the needs of these emotionally traumatized patients. At the West London Menopause Service we have restructured our services and created dedicated clinics for the POI patients. Counselling should include explanation that remission and spontaneous pregnancy can still occur in women with spontaneous or medical POI. Specific areas of management include the provision of counselling and emotional support, diet and nutrition supplement advice, HRT and reproductive healthcare, including contraception and fertility issues. In the UK, the Daisy Network, a voluntary support network for women with POI, provides excellent support and information for POI sufferers.

As a minimum, the initial investigation of patients presenting with erratic periods, for which pregnancy should be excluded, includes measurement of serum FSH, estradiol and thyroid hormones. If FSH is in the menopausal range (>40 IU/L), the test should be repeated 4–6 weeks later for confirmation, as levels can fluctuate. Young women with spontaneous POI have pathologically low oestrogen levels compared with their peers who have normal ovarian function. The NICE [2], British Menopause Society [23], International Menopause Society [24] and ESHRE [21] guidelines state that in women with POI, systemic hormone therapy is recommended at least until the average age of the natural menopause (51 years). Hormone treatment with HRT, or the contraceptive pill if pregnancy is not desired, is required not only to control vasomotor and other menopause symptoms, but also minimize risks of cardiovascular disease, osteoporosis and dementia, as well as to maintain sexual function. Three small prospective randomized trials thus far have compared HRT with the combined contraceptive pill in POI. Limited data suggest that both options are effective but HRT appears to be superior in increasing bone mineral density and in its beneficial effects on cardiovascular risk markers. There is an urgent need for large-scale long-term randomized prospective studies to determine the optimum routes and regimens of hormone replacement in POI. Outcome measures should include vasomotor, urogenital, quality of life and psychosexual health and the long-term effect on cardiovascular, cognitive and skeletal health.

In the absence of such long-term trials, a POI registry, funded by Imperial College London, has been developed to collate good-quality prospective data from healthcare professionals globally [25–27]. There is an unmet need to determine long-term response to interventions such as the contraceptive pill and HRT and in those not receiving treatment. This is particularly important in women with rare causes and hormone-sensitive cancers where randomized trials are unlikely to be ever performed. The registry will be used to create a global genetic biobank for genetic studies, with an ultimate goal of defining the specific pathogenic mechanisms involved in the development of POI. The database has the potential to define and characterize the various presentations of POI along the lines of the STRAW + 10 guidelines for natural menopause [1]. It could also be used to further refine the role of biomarkers such as AMH to precisely predict the course and timing of natural and early ovarian insufficiency.

Interventions

Lifestyle measures

The modern approach to optimizing health in the menopause should start from public education in school and the workplace. Common-sense lifestyle and dietary approaches instituted well in advance of the menopause will maximize that chances of good health through midlife and beyond. As recommended by the British Menopause Society position statement [28], every woman should be encouraged to take plenty of regular

exercise in addition to having a well-balanced diet, avoiding smoking and minimizing alcohol consumption. Data suggest that women who are more active tend to suffer less from the symptoms of the menopause and have higher bone mineral densities compared with sedentary controls. There is also evidence for reduction in bone loss by ensuring adequate calcium (1000 mg) and vitamin D_3 (800–1000 IU) in the diet. However, excessive calcium intake can increase the risk of adverse events such as myocardial infarction [29]. Routine supplementation with calcium is not now recommended unless deficiency has been detected. Ensuring adequate vitamin D_3 levels will not only improve calcium absorption but may also have a beneficial effect on general well-being and musculoskeletal symptoms. A reduction in alcohol and caffeine intake can also reduce the severity and frequency of vasomotor symptoms.

Hormone replacement therapy

Oestrogen

Dose

There is a general consensus that the minimum effective dose of estradiol should be prescribed and the dose increased if required to alleviate symptoms. However, it is important that the dose is high enough to fully alleviate symptoms. Although there is little evidence that higher doses of exogenous oestrogen are associated with increased risk of breast cancer, there are dose–response effects with venous thromboembolism and stroke. Lower doses of oestrogen are less likely to cause breast tenderness and bleeding problems (due to less endometrial stimulation), which will encourage continuation of therapy.

The recommended starting doses of currently available systemic oestrogen are as follows:

- 0.3 mg oral conjugated equine oestrogens;
- 1 mg oral micronized estradiol or estradiol valerate;
- 25–50 μg transdermal estradiol;
- two metered doses of estradiol gel or 0.5–1.0 mg estradiol sachets;
- 25–50 mg implanted estradiol (note that estradiol implants are currently unlicensed for commercial reasons).

Data suggest that in many women the benefits of estradiol for symptom relief and bone protection can be achieved with a 0.5-mg dose when combined with progestogen [30]. Side effects such as bleeding problems are minimized by this dosage and a neutral effect on breast symptoms and mammographic density is possible [31]. Women who suffer POI or early menopause need higher doses of oestrogen to reproduce the physiological hormone levels which would have been present if the ovaries had not failed early.

Summary box 50.2

The dose and route of administration of estradiol should be tailored to the requirements of the woman in order to optimize benefits and minimize side effects and risks.

Route of administration

Prior to the menopause the physiological state consists of an estradiol/estrone ratio of 2 : 1. This can only be achieved if estradiol is delivered transdermally, thus avoiding first-pass hepatic metabolism. Oral estradiol preparations are partially metabolized to estrone by hepatic first-pass metabolism and therefore do not fully restore this ratio. There are now observational and case–control data showing that the thromboembolic risk is neutralized by avoidance of first-pass stimulation of coagulation factors, even in women who are obese and thrombophilic [32]. This is particularly important in women who are obese or smokers and are therefore at increased risk of venous thromboembolic disease.

There are twice-weekly or once-weekly transdermal systems containing both oestrogen and progestogen that can be used either sequentially or as continuous combined HRT. The hormone is adsorbed onto the adhesive matrix and this avoids the skin reactions caused by the old alcohol reservoir patches. Dot matrix patches are the smallest and best-tolerated patches, with a very low incidence of skin irritation. Estradiol gel is also available either dispensed from a pump or as a low-volume daily sachet. It is hoped that non-oral estradiol development will resume to produce commercially available nasal and sublingual tab/wafer products that also avoid first-pass hepatic metabolism. An expanded product armamentarium facilitates individualized hormone replacement.

Vaginal oestrogen

The most effective treatment for VVA is local application of oestrogen. This can be achieved through the use of creams, tablets and rings delivering estriol and estradiol. There is no significant systemic absorption of oestrogen from these products and therefore do not lead to endometrial hyperplasia or bleeding problems. Long-term endometrial biopsy data are limited but 1-year data are consistently reassuring. Endometrial protection with progestogens is not required. The British and International Menopause Societies recommendations [23,24] and recent NICE guidelines [2] highlight the importance of identifying VVA symptoms, which can be very distressing and are easily and safely alleviated with vaginal oestrogen. The regulatory authorities in the UK have granted an 'indefinite use' licence to 10-μg estradiol vaginal tablets. These were developed with the aim of providing the minimum effective dose for

relief of urogenital symptoms; a year of use will expose the user to only 1.4 mg of estradiol in total. However, some women require higher doses to fully alleviate their symptoms. The NICE menopause guidelines [2] recognize this and indicate the possibility of higher doses being used judiciously.

Options for local vaginal oestrogen are as follows:

- 0.01% estriol cream and pessaries;
- 0.1% estriol cream;
- 10 μg per 24 hours estradiol vaginal tablets;
- 7.5 μg per 24 hours estradiol-releasing silicone ring.

Summary box 50.3

Local application of oestrogen is highly effective for VVA but the benefits only last whilst the preparations are used.

New options for treating VVA

Ospemifene is an orally active selective oestrogen receptor modulator that has oestrogen-type activity in the urogenital tract [33]. It is licensed in a few countries, such as the USA and Italy, for treatment of moderate to severe dyspareunia and has recently been made available in the UK. The avoidance of oestrogen may be of advantage in women with a past history of hormone receptor-positive malignancy whose menopause symptoms are often compounded by the use of tamoxifen or aromatase inhibitors.

CO_2 laser and erbium laser technology is being used to rejuvenate atrophic vulval and vaginal tissue by facilitating the regeneration of collagen and elastin through improved blood flow [34]. Although the preliminary data are promising, longer-term randomized placebo-controlled studies are required to confirm the benefits and duration of effect.

Progestogens/progesterone

Regimens

Progestogens or progesterone are required in women using systemic oestrogen to minimize the risk of endometrial hyperplasia and carcinoma. If the last menstrual period occurred less than 1 year prior to starting HRT, a sequential combined regimen is recommended (i.e. continuous oestrogen with progestogen for 12 days per cycle). A progestogen challenge should be considered after 3 months of oestrogen alone in women who have had a subtotal hysterectomy to test for residual endometrium. An ultrasound scan could also be performed to check for residual endometrium. Low-dose continuous progestogen should also be used after endometrial ablation and pelvic radiotherapy and should also be considered in women following hysterectomy for severe endometriosis.

The typical dosages of the more commonly used progestogens are shown in Table 50.1.

Bleeding problems

If bleeding is heavy or erratic, the dose of progestogen can be doubled or duration increased to 21 days. Persistent bleeding problems beyond 6 months warrant investigation with an ultrasound scan and/or endometrial biopsy. After 1 year of therapy (2 years in POI) women can switch to a continuous combined regimen that aims to give a bleed-free HRT regimen, which will also minimize the risk of endometrial hyperplasia. Alternatively, women can be switched to the tissue-selective agent tibolone. Both these regimens may be associated with some erratic bleeding to begin with but 90% of those that persist with these treatments will eventually be completely bleed-free. If starting HRT *de novo*, a bleed-free regimen can be used from the outset if the last menstrual period was over a year ago.

Progestogenic side effects

One of the main factors for reduced compliance is that of progestogen intolerance. Progestogens have a variety of effects apart from the one for which their use was intended, that of secretory transformation of the endometrium. Symptoms of fluid retention are produced by the sodium-retaining effect of the renin–aldosterone system which is triggered by stimulation of the aldosterone receptor. Androgenic side effects such as acne and

Table 50.1 Minimum doses of progestogen given orally in HRT as endometrial protection.

Progestogen type	Sequential combined daily dosage	Continuous combined daily dosage
Testosterone-derived progestogens		
Norethisterone	5 mg	0.1 mg
Levonorgestrel	75 μg	N/A
Levonorgestrel intrauterine system	N/A	20 μg
Norgestrel	150 μg	50 μg
Progesterone-derived progestogens		
Cyproterone*	2 mg	1 mg
Medroxyprogesterone acetate	5 mg	2.5 mg
Micronized progesterone	200 mg	100 mg
Cyclogest pessaries	400 mg	200 mg
Crinone gel (8%)	Alternate days/12 days per cycle	Twice weekly
Spironolactone-derived progestogens		
Drospirenone	N/A	2 mg

*Not available in the UK at these dosages.

hirsutism are a problem of the testosterone-derived progestogen due to stimulation of androgen receptors. Mood swings and premenstrual syndrome-like side effects result from stimulation of the central nervous system progesterone receptors.

Minimizing progestogen side effects

The dose can be halved and duration of progestogen can be reduced to 7–10 days. However, this may result in bleeding problems and hyperplasia in a few cases (5–10%) so there should be a low threshold for performing ultrasound scans and endometrial sampling in these women. Natural progesterone has fewer side effects due to progesterone receptor specificity and is now available in an oral micronized form, vaginal pessaries and gel (see Table 50.1). HRT regimens containing natural progesterone can minimize the metabolic impact and reduce the risk of thromboembolism [35]. The levonorgestrel intrauterine system, recommended for endometrial protection for up to 5 years, minimizes systemic progestogenic side effects by releasing the progestogen directly into the endometrium with low systemic absorption. Drospirenone, a spironolactone analogue, has been incorporated with low-dose oestrogen in a continuous combined formulation. It is not only progesterone receptor specific but also has anti-androgenic and anti-aldosterone effects, the former making it useful for hirsutism and the latter for fluid retention. It is also mildly antihypertensive [36]. A new product which may be the ideal solution to the progestogen intolerance problem is a combination of conjugated oestrogens with bazedoxifene (BZA), a member of the tissue selective oestrogen complex [37]. In this product, the progestogen has been replaced by BZA, a selective oestrogen receptor modulator, which protects the endometrium against endometrial hyperplasia and carcinoma. Not only is the endometrium protected but there may also be some protection against breast cancer; this requires confirmation from long-term randomized controlled trials.

Bio(body)-identical HRT

Bio-identical hormones are precise duplicates of estradiol, progesterone and testosterone as synthesized by the human ovary. They are manufactured from plant sources in the laboratory and are available as micronized oral tablets, transdermal patches, implants and gels. Regulated bio-identical products must not be confused with unregulated products from compounding pharmacists. In order to avoid confusion, regulated products should be referred to as body-identical rather than bio-identical [38]. The regulatory authorities are attempting to bring the compounding pharmacies under the same regulation as standard hormone therapy products. Compounded bio-identical hormones are not recommended by the British Menopause Society or by NICE in the recent menopause guideline [2].

The published data thus far suggest that differential effects can be achieved by the use of body-identical hormones in comparison with synthetic non-body-identical HRT. The E3N cohort study, part of the European Prospective Investigation into Cancer and Nutrition (EPIC), showed that oestrogen/progesterone combination HRT was associated with a significantly lower relative risk (neutral for 'ever use' of HRT) than for other types of combined HRT (RR 1.7–2.0) [39]. There are also data now indicating that micronized progesterone has a modulating effect on venous thromboembolism (VTE). The risk of VTE appears to be lower with micronized progesterone than it is with more androgenic progestogens when combined with oral oestrogen. The metabolic neutrality of progesterone has been seen as an advantage in avoiding attenuation of the benefits of oestrogen in cardiovascular disease prevention. This is discussed later in the chapter in connection with the new pilot studies which have been performed recently and the need for further major prospective randomized controlled trials will be highlighted.

Androgens

Women with distressing low sexual desire and tiredness should be counselled about the possibility of using androgen supplementation [40]. In the past, 100 mg implanted testosterone pellets were licensed for female testosterone replacement. These are currently only available as unlicensed preparations as the licensed implants were withdrawn for commercial reasons. The 300-μg testosterone transdermal system was developed to treat hypoactive sexual desire disorder, the American Psychiatric Association's definition of distressing low sexual desire. A series of randomized controlled trials showed a significant improvement in the number of satisfying sexual episodes in women with surgical menopause and also in women with natural menopause. Benefits were seen in women using concomitant oestrogen and in those using testosterone alone. Similar to the testosterone implants, the licence for the patches was also withdrawn for commercial (profitability) reasons.

These developments have restricted the available options for female androgen replacement. Testosterone male gel (Tostran 2% gel) can be used at lower doses off label on an alternate day basis to achieve female physiological levels. Alternatively, 1% testosterone cream (AndroFeme) marketed for female use in Australia, can be accessed internationally, but is only available for private use at time of writing. In my clinical experience, if the free androgen index [(testosterone × 100)/sex hormone-binding globulin] is kept within the physiological range (<5.0%), there are rarely any side effects such

as hirsutism and acne. Scalp hair loss and virilizing effects are rare, and this has been shown in recent meta-analyses of the data [41,42]. Cardiovascular and breast safety data have been reassuring thus far, although the regulators would like to see further long-term studies before licensing further female androgen products. A 5-year study on cardiovascular and breast safety has been completed in the USA but analysis of the data (more than 7000 women-years of use) has not yet been carried out due to lack of funding.

Dehydroepiandrosterone (DHEA) is a weak androgenic steroid produced by the adrenal gland that has androgenic properties. It is mostly produced in a sulfated form (DHEA-S), which may be converted to DHEA in many tissues. Blood levels of DHEA drop dramatically with age. This had led to suggestions that the effects of ageing can be counteracted by DHEA 'replacement therapy'. DHEA is being increasingly used in the USA, where it is classed as a food supplement, for its supposed anti-ageing effects. Some studies have shown benefits on the skeleton, cognition, well-being, libido and the vagina but these data require confirmation [43].

Benefit–risk balance of HRT

Coronary heart disease and overall mortality

Concerns about the risks of HRT were raised by the Women's Health Initiative (WHI) study [44] and the Million Women Study (MWS) [45]. The WHI study claimed that there was an excess risk of cardiovascular disease, stroke and breast cancer in women regardless of age group. However, these studies were heavily criticized due to their design, particularly the WHI study where the average age of recruitment was 63 years and with an excess of obesity, hypertension and pre-existing cardiovascular disease. There is now strong and consistent evidence that oestrogen therapy may be cardioprotective if started around the time of menopause (referred to as the 'window of opportunity' or 'timing' hypothesis) and may be harmful if started more than 10 years after menopause.

In the 13-year follow-up of women in the WHI study, the cumulative data in the 50–59-year-old age group showed a reduction in CHD (hazard ratio, HR 0.65, 95% CI 0.44–0.96) [46]. The risk of myocardial infarction was also significantly decreased (HR 0.60, 95% CI 0.39–0.91). Women less than 10 years since menopause who received conjugated oestrogens plus medroxyprogesterone acetate showed a non-significant reduction in CHD (HR 0.90, 95% CI 0.56–1.45), suggesting a potential attenuation of the coronary benefit with this particular regimen using a continuous progestogen. Meta-analyses of randomized controlled trials, including data from the WHI study, have shown a significant reduction in CHD as well as mortality in women treated with oestrogen under the age of 60. In the WHI study, the cumulative results showed a reduction in all-cause mortality in the 50–59-year-old age group with oestrogen alone and oestrogen–progestogen. When mortality data for conjugated oestrogens and conjugated oestrogens plus medroxyprogesterone acetate from the two WHI trials were combined, the reduction in all-cause mortality was significantly reduced by 30%.

In the most recent Cochrane analysis [47], women within 10 years of menopause had a reduction in all-cause mortality of 0.70 (95% CI 0.52–0.95) and in cardiovascular mortality of 0.52 (95% CI 0.29–0.96). An observational study from Finland [48] recently reported that estradiol products (oral and transdermal) with and without progestogen decreased coronary and all-cause mortality significantly (12–54%); of note in this study, while longer duration of use decreased mortality, age of initiation did not make a difference.

A number of recent randomized controlled studies (DOPS, KEEPS and ELITE) have shown that cardiovascular risks can be minimized and benefit maximized using HRT in younger populations. The Danish Osteoporosis Prevention Study (DOPS) [49] studied younger women at the onset of menopause who prospectively received standard doses of estradiol and norethisterone in an open-label fashion or no treatment for 10 years and had 16 years of follow-up. There were significant reductions in mortality and in hospitalizations for myocardial infarction and congestive heart failure.

The Kronos Early Estrogen Prevention Study (KEEPS) [50] showed no difference between conjugated oestrogens 0.45 mg, transdermal estradiol 0.05 mg and placebo for intermediate end-points: carotid artery intima–media thickness and coronary calcium. These young healthy women had virtually no coronary artery disease and it is possible that there was insufficient progression over 4 years to detect differences between the groups.

The Early versus Late Intervention Trial with Estradiol (ELITE) (oral estradiol 1 mg and placebo in two groups of women, <6 years from menopause and the other >10 years) showed a reduction in carotid intima–media thickness over time in the younger women, and no change in the older population, confirming that the timing of oestrogen treatment is important in influencing the progression of coronary disease [51].

Summary box 50.4

There appears to be a 'window of opportunity' in the early menopause transition when treatment with HRT confers cardiovascular benefits.

Stroke

Stroke is a rare event before age 60. Stroke incidence may be increased when HRT is initiated in women over 60 years of age, but this is not common practice. Initiation of HRT in women less than 60 years of age or less than 10 years since menopause has no effect on the risk of stroke according to data from the 13-year follow-up data from the WHI study [46] and the Cochrane analysis [47]. The risk of ischaemic stroke with HRT may be related only to standard-dose oral therapy, with lower doses having a smaller risk and no significant risk occurring with standard and low-dose transdermal therapy, according to the large GP research database in the UK.

Venous thromboembolism

The incidence of VTE is higher during the first year of oral oestrogen use, with or without progestogen. The initiation of menopausal hormone therapy in older women and, to a lesser extent, the continued use of such therapy is associated with an increased risk compared with non-users. In the WHI study [46] in the 50–59-year-old age group, the excess risk of pulmonary embolism was six additional cases per 10 000 woman-years for oestrogen–progestogen therapy, and four additional cases with oestrogen. Both are far less than the risk of VTE in normal pregnancy. Meta-analyses of these epidemiological studies have shown that transdermal oestrogen does not increase the risk of VTE.

Cognitive function and dementia

HRT initiated after the onset of dementia symptoms does not benefit cognitive function or slow disease progression. HRT initiated and used after midlife increases risk of dementia whereas when initiated during midlife is associated with a reduced risk of Alzheimer's disease and dementia. As with CHD, the prevention of Alzheimer's disease seems to be dependent on commencing HRT in the 'window of opportunity' [15]. Most data are from observational studies as extremely long-term randomized trials would have to be conducted to prove primary prevention benefits conclusively.

Breast cancer

The degree of association between breast cancer and HRT remains debatable. Most longer-term studies largely reflect the use of one combination of HRT, oral conjugated oestrogens and medroxyprogesterone acetate. These suggest a possible increased risk with increasing duration of usage. The WHI oestrogen and progestogen trial and several large observational studies have reported an increased risk after at least 5 years of use, suggesting a possible promoter effect on existing tumours. When adjusted for risk factors, significance was no longer reached [46]. The recent meta-analysis of data by the NICE guideline group stated that the degree of risk for oestrogen and progestogen combined HRT was an extra five cases per 1000 women over a 7.5-year period (i.e. approximately one extra case per 1000 women per annum) [2]. HRT using oestrogen alone is associated with a neutral impact on breast cancer risk in most studies and even possibly a reduction in risk [24].

Ovarian cancer

Controversy exists as to whether HRT increases the risk of ovarian cancer. A recent meta-analysis of data from 52 studies suggested that for women aged 50–54 years the absolute risk was about 1 per 10 000 women per year of use, with a base rate of 1.2 per 1000 per 5 years and an absolute excess of 0.55 per 1000 per 5 years [24,52]. Further good-quality data are needed to allow definitive statements about ovarian cancer risk and HRT.

Osteoporosis

The goal of osteoporosis treatment is the prevention of fractures and the choice of therapy should be based on a balance of effectiveness and safety. HRT decreases the incidence of all fractures, including vertebral and hip fractures, even in women not at high risk of fracture. HRT is the only therapy available with proven efficacy of fracture reduction in patients with osteopenia. Although HRT prevents fractures at any age after the menopause, age at initiation of menopausal hormone therapy is important. In the age group 50–60 years or within 10 years after menopause, the benefits of HRT generally outweigh risks and can be considered as first-line therapy [23,24]. In women over 60 years of age, alternatives to HRT such as bisphosphonates should be considered as first-line therapy. If HRT is to be considered in this age group, the minimum effective dose should be used, with oestrogen ideally delivered transdermally.

Contraindications to HRT

Generally speaking, HRT is contraindicated in women with a history of active cardiovascular disease or recent stroke. Data from one pilot study suggest that there can be beneficial effects in women post myocardial infarction or acute coronary syndrome but this requires confirmation. Although contraindicated in venous thromboembolic disease, there is some evidence that transdermal preparations are safer through avoidance of first-pass hepatic metabolism [32].

When transdermal oestrogen is given to normotensive or hypertensive women it does not elevate blood pressure, and when given in combination with oral natural progesterone or drospirenone may actually lower blood pressure [36]. There is therefore little justification for withholding appropriate HRT from controlled hypertensive women and this is reflected in the recent NICE menopause guidelines [2].

Use of HRT in patients with early-stage endometrial cancer does not seem to increase the risk of recurrence according to observational data and one randomized study [53]. A recent meta-analysis of two randomized and four cohort trials in women with a past history of epithelial ovarian cancer has not indicated an increased risk of recurrence but more data are required, particularly on the role of hormone receptor status and influence on outcome [54]. Squamous cell carcinoma of the cervix is not thought to be oestrogen sensitive but good data are lacking. Women with a past history of these malignancies are usually offered HRT if they wish to use it. Data are lacking on the influence of HRT on vaginal and vulval carcinoma but it is not thought to have an adverse effect due to lack of hormone sensitivity.

Women with a past history of severe endometriosis should be treated with continuous combined therapy even after hysterectomy to prevent recurrence of the endometriosis.

Hormone receptor-positive breast cancer is regarded as the principal contraindication to oestrogen treatment, but high-risk women with a strong family history of breast malignancy or those with benign breast disease should not necessarily be denied treatment. Some women may continue to have intractable menopausal symptoms despite all the recognized alternatives having been tried in which case they should be helped to make an informed choice regarding the use of HRT to restore their quality of life.

It is unclear what the precise risk of breast cancer recurrence is with HRT use. The HABITS study [55] showed an increased risk whereas the Stockholm trial [56] did not; both studies were stopped early due to the WHI study findings. In the Stockholm study a greater proportion of women were using tamoxifen. A large randomized placebo-controlled study (LIBERATE) in breast cancer survivors using tibolone demonstrated a marginal increase in recurrence rates (RR 1.4) [57]. Patients with the *BRCA1*/*BRCA2* genes who undergo prophylactic bilateral salpingo-oophorectomy are usually offered HRT if they are young and have not had breast cancer. The many benefits of HRT on quality of life and primary prevention in early menopause and POI are thought to outweigh risk of possibly attenuating the benefits of the bilateral salpingo-oophorectomy.

There is a pressing need for more research in breast cancer survivors, as indicated in the NICE guideline research recommendations [2]. These women often have the most severe symptoms, not just because of menopause but because their endocrine therapy often makes symptoms worse.

Duration of therapy

Advice from the menopause societies almost universally states that the advantages outweigh the disadvantages for treatment to continue whilst symptoms persist. It is now accepted that symptoms last on average for 5–7 years, while in approximately 10% of women symptoms persist for life. If the underpinning principle of HRT is that it should be used to improve and maintain a good quality of life, arbitrary time limits should not be applied but should be individualized. Although the risks of breast cancer appear to be duration dependent, evidence suggests that overall mortality is actually reduced in women commencing HRT before the age of 60 [47,48]. Thus, duration of therapy requires careful judgement of the benefits and risks to each woman, who should be facilitated to make a fully informed choice. The decision to continue should be reviewed on an annual basis. If therapy is to be discontinued, the dose should be reduced in a stepwise fashion over a minimum of 6 months to reduce the risk of immediate severe symptom resurgence, although this does not change the incidence of symptom persistence in the long term.

Summary box 50.5

Arbitrary limits should not be placed on duration of treatment with HRT: women should be given individualized information about the benefits and risks.

Official prescribing advice

It is still recommended by the regulatory authorities in the UK (Medicines and Healthcare products Regulatory Agency or MHRA) that HRT should be used primarily for symptom relief in the short term at the lowest effective dose and that alternatives should be considered in the long term for prevention of osteoporosis. Annual reappraisal of HRT use should be carried out, with weighing up of the pros and cons on an individual basis. Recent consensus statements advise that HRT can be prescribed as a first-line agent in women at risk of osteoporosis-related fractures. Primary prevention of cardiovascular disease and dementia with HRT is not advised at this stage except for women who have undergone POI.

Alternatives to HRT

Women seeking advice about managing their menopause should always be informed how to optimize their lifestyle and diet and given information about complementary and other alternative therapies as well as hormonal options. An integrated approach to the management of vasomotor symptoms should be considered in women wanting to consider alternatives to (or contraindicated to) HRT [58]. A possible algorithm drawn up by a consensus group of international

experts integrating lifestyle, complementary and pharmacological interventions is shown in Fig. 50.2. The algorithm is not intended for women with premature menopause or for those with other risk factors such as osteoporosis. The network meta-analysis in the NICE menopause guideline recommended St John's wort and isoflavones as possible evidence-based therapeutic options which are better than placebo [2].

Non-pharmacological alternatives

Gels for vaginal symptoms

Vaginal bioadhesive moisturizers and lubricants are a more physiological way of replacing vaginal secretions than with preparations such as KY jelly. Moisturizers are hydrophilic and actually rehydrate the vaginal tissues. Lubricants should be pH and concentration balanced to prevent drying and irritation of the vaginal tissues [59].

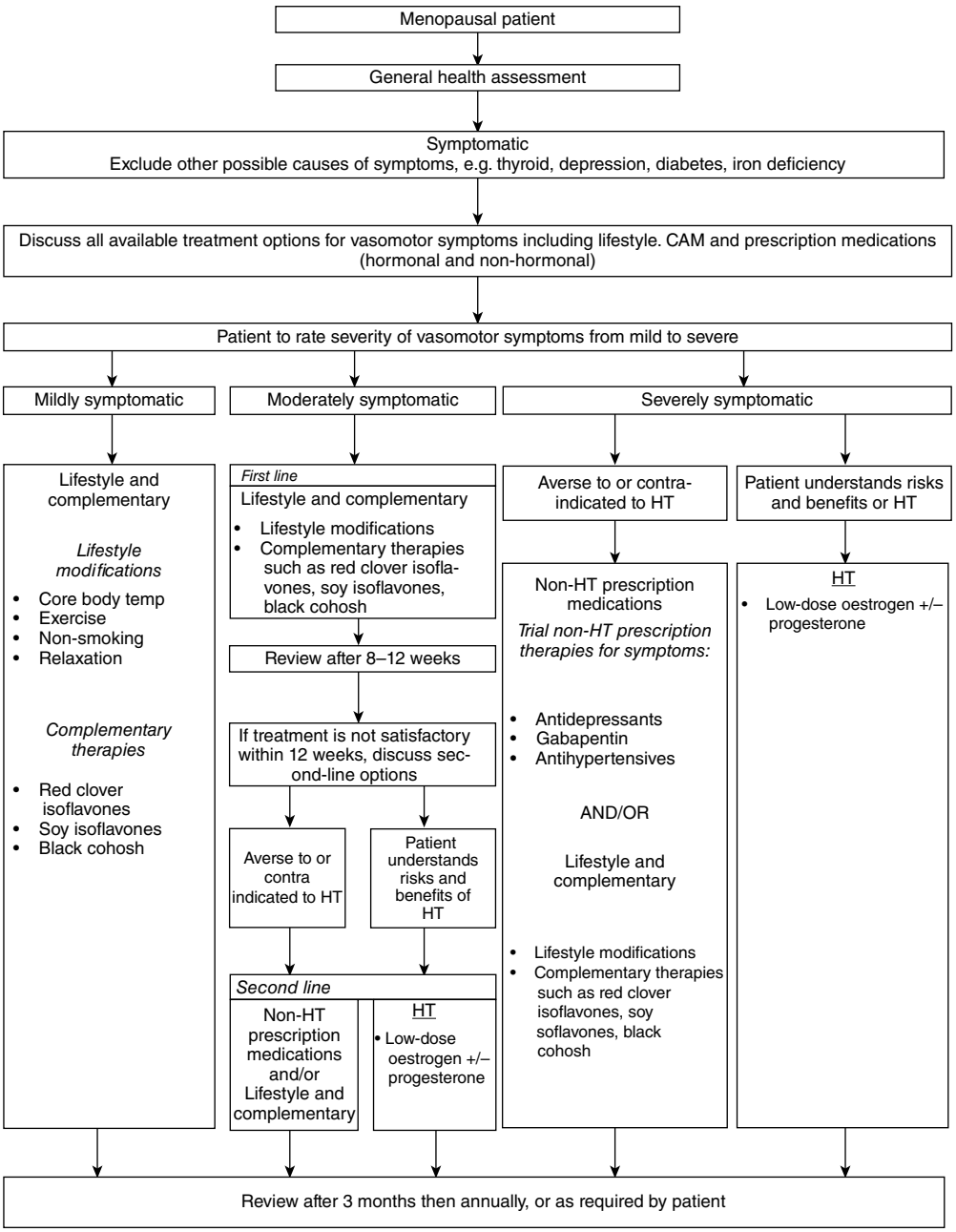


Fig. 50.2 Vasomotor symptom treatment algorithm: a conservative clinical approach. CAM, complementary and alternative medicine; HT, hormone therapy. *Source:* adapted from Panay [58].

Women in whom vaginal oestrogen is contraindicated (e.g. those on aromatase inhibitors) or those wishing to avoid oestrogen can derive some relief from these preparations.

Pharmacological alternatives

Alpha-2 agonists

Clonidine, a centrally active α_2-agonist, has been one of the most popular alternative preparations for the treatment of vasomotor symptoms. A recent meta-analysis of the few randomized controlled trials has shown a marginal benefit of clonidine over placebo. However, this preparation has been largely superseded by the selective noradrenaline reuptake inhibitors (SNRIs) and gabapentin [60].

Selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors

Although the NICE network meta-analysis did not show conclusive evidence of benefit with these preparations, a significant amount of evidence exists for the efficacy of selective serotonin reuptake inhibitors (SSRIs) and SNRIs in the treatment of vasomotor symptoms. Most of these data are derived from small studies in breast cancer patients. The best data are for the SNRI venlafaxine at a dose of 37.5 mg twice daily [60]. SSRIs such as fluoxetine and paroxetine should be avoided in patients using tamoxifen as they can interfere with its metabolism [2]. The key effect with these preparations appears to be stimulation of the noradrenergic as opposed to the serotonergic pathways, hence the preferential effect of SNRIs. Desvenlafaxine succinate, a derivative of venlafaxine, is licensed in a few countries as a way of maintaining the benefits of the parent molecule but minimizing side effects.

Summary box 50.6

SSRIs and SNRIs should not be used routinely to treat vasomotor symptoms in women who do not have contraindications to HRT.

Gabapentin

Gabapentin, a neuropathic analgesic, has been shown in some studies to be superior to placebo for vasomotor symptoms. In a study using gabapentin at a dose of 900 mg/day, a 45% reduction of hot flush frequency and a 54% reduction in symptom severity was demonstrated [60]. Further work is being conducted to confirm the efficacy and safety of this preparation but for the moment its use is restricted to specialist centres. Its use is limited by side effects such as drowsiness and somnolence, particularly at high doses.

Complementary therapies: phytoestrogens

The evidence for efficacy and safety of some of these complementary therapies can be extremely limited or non-existent [61]. In order to enable women to make a fully informed choice, it is important that when a recommendation is made regarding a specific complementary therapy, it should focus on preparations for which a significant dataset exists for efficacy and safety and in which there is ongoing research and development.

The Traditional Herbal Registration (THR) scheme [62] was introduced in 2009. Where a herbal medicine carries the certification mark, this means that the MHRA has assessed the product to ensure that is acceptably safe when used as intended, is manufactured to good quality standards, and is accompanied by reliable and accurate product information for the public and patients. The authorized usage and dosage of the medicine is based on evidence of its traditional use. The effectiveness and safety of the product has not otherwise been assessed by the MHRA.

Data from some phytoestrogen-containing preparations appear to demonstrate benefits, not only for symptom relief but also on the skeleton and cardiovascular system. Efficacy for vasomotor symptom relief is lower than with traditional HRT (maximally 60–70% symptom reduction compared with 90–100% with traditional HRT). Beneficial effects have been shown on cardiovascular risk markers such as lipids and arterial compliance and on bone markers/density, with possible selective oestrogen receptor modulator (SERM)-type effects. There are still no hard data on major outcome measures such as CHD and fractures. Laboratory data suggest avoidance of stimulation of oestrogen receptors in the endometrium and breast and safety in observed populations but, once again, sufficiently powered randomized controlled trial data on endometrial and breast cancer incidence are absent.

Summary box 50.7

Alternatives to HRT relieve symptoms by up to 60% maximally; recommendations for usage should be confined to those preparations that have an evidence base for efficacy and safety and the THR kite mark.

Future research

In order to optimize benefits and minimize side effects and risks, targeted agents are being developed that are able to switch on receptors in tissues where this is

desirable and avoid receptors in tissues such as the breast and endometrium. For example, the ideal SERM would be agonistic in the bone, cardiovascular system and urogenital tract and antagonistic in the endometrium and breast, while at the same time alleviating vasomotor and other menopause symptoms. This does not yet exist. Understanding the processes that regulate the activity of different oestrogen receptor co-regulator complexes is a key next step in the development of SERM/oestrogen receptor ligands with improved functional selectivity.

Pharmacogenomic approaches may help identify women with different oestrogen dose requirements based on identification of genetic variants in enzymes involved in hormone/drug metabolism and impacting hormone/drug targets. The goal of pharmacogenomics is to use genetic information to predict how an individual will respond to a drug, with the ultimate objective of enabling healthcare professionals in selecting the right drug, in the right dose, at the right time, for each individual patient in order to maximize effectiveness and minimize side effects. Environmental and biological factors also impact menopause symptoms, including BMI, tobacco, alcohol or caffeine, stress and anxiety. Further work is required to understand the mechanisms by which these environmental and biological factors affect symptoms. They may be independent variables or may be intertwined with variation in gene–environment interactions.

One might argue that the ideal solution to menopause-related problems is to reverse the process. This was not thought to be possible due to irreversible loss of follicles/oocytes. However, recent research has demonstrated the presence of oogonial stem cells in adult ovaries, and work is ongoing to try to initiate replication in these stem cells with a view to producing new oocytes [63]. This would be a particularly welcome breakthrough in young women with POI.

Conclusions

Effective management of the menopause is taking on ever-increasing importance in view of our ageing population, which is increasing both the health and economic burden on society. Economic expenditure to optimize health in the menopause and beyond has not kept pace with the ageing population. Many of our doctors and nurses have become de-skilled in managing the menopause over the last decade and menopause services have been withdrawn due to the media scares of the early 2000s. There are six key action points that require urgent implementation if we are to reverse this process.

1) Health departments/regulators/politicians: encourage a change of negative policy towards menopause and HRT.
2) The prescribers: expand education and training for healthcare professionals to optimize menopause management and achieve consensus among all menopause societies as detailed in the recent Revised Global Consensus Statement on Menopausal Hormone Therapy [64].
3) Media: engage positively, highlighting favourable data and putting risks into perspective.
4) Pharma industry: reverse negative commercial research and development decisions and encourage the exploration and development of novel regimens.
5) The menopausal woman: improve access to information to allow informed choice and increase proactive confidence to maintain menopausal health.
6) HRT: clarification of differences in action/risk profiles to maximize benefits and minimize adverse effects.

Summary box 50.8

Key points for effectively managing menopause

1) Discussion of lifestyle measures, HRT and alternatives should take place from the outset.
2) Management should be individualized, taking into account risks and benefits.
3) The main indication for use of HRT should be for symptom relief but there may also be primary prevention opportunities.
4) HRT should generally be commenced at a low dose and increased if necessary to achieve effective symptom relief, except in POI where higher doses are physiological.
5) Androgen therapy should be offered to women with persistent low libido and energy levels.
6) Rigid cut-offs in duration of therapy should be avoided, with regular reappraisal (at least annually) of the benefits and risks for each individual.
7) Delivery of menopause services should ideally be from a multidisciplinary team in primary care with close liaison with allied specialties and menopause experts.

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Additional websites

Top recommendations

British Menopause Society, www.the-bms.org (see consensus statements)
International Menopause Society, www.imsociety.org (see consensus statements)
European Menopause Society, http://emas.obgyn.net/

Other

Medical and Healthcare products Regulatory Agency, www.mhra.gov.uk
National Osteoporosis Society, www.nos.org.uk (professionals and patients)
North American Menopause Society, www.menopause.org
European Medicines Agency, http://www.emea.eu.int/
National Center for Complementary and Alternative Medicine, https://nccih.nih.gov/
NIH Office of Dietary Supplements, http://dietary-supplements.info.nih.gov

Patient information and contacts

https://hormonehealth.co.uk (Useful information about women's hormone health)
www.menopausematters.co.uk (informative menopause website)
www.daisynetwork.org.uk (Premature Ovarian Insufficiency society)
www.pms.org.uk (National Association for Premenstrual Syndromes)
http://www.womens-health-concern.org/ (Women's Health Group, including 'Ask the experts')

Part 11

Reproductive Problems

51

Subfertility

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Importance

Infertility is the second most common reason for women of childbearing age to visit their general practitioner. As approximately one in seven heterosexual couples have problems conceiving, infertility affects around 3.5 million people in the UK. There has been a small but steady increase in the prevalence of fertility problems and a greater proportion of people now seek help for such problems.

Infertility is associated with significant psychological morbidity for both partners and, where there is underlying pathology, physical morbidity too both through the conditions associated with infertility and their associated treatment. If left untreated, infertility can result in stress, depression and emotional distress. However, investigation and treatment is also associated with psychological and physical trauma that is often exacerbated by the length of treatment and the multidisciplinary approach that is involved.

Infertility is regarded as an upsetting and difficult life experience for some women, resulting in anxiety and depression comparable to those associated with other serious medical conditions such as heart disease, cancer, hypertension and HIV infection.

Definition: what is infertility?

Infertility is rarely absolute. Unless the male partner has suffered testicular failure and/or does not produce sperm or the woman is menopausal and/or does not have a uterus, conception is usually still possible. It is the chance of conception that really defines fertility and this is very much dependent on how long the couple have been trying, female age and the underlying cause. Subfertility is therefore a more appropriate term for most couples. It is defined by the duration a couple have been trying to conceive without success after which formal investigation is justified and treatment, where indicated, implemented.

A woman of reproductive age, who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. Single women and same-sex couples should be offered formal investigation after six cycles of unsuccessful artificial insemination. Couples should be referred earlier where the woman is 36 years or over or if there is a known clinical cause of infertility or a history of predisposing factors for infertility, including amenorrhoea, oligomenorrhoea, pelvic inflammatory disease or undescended testes.

Aetiology

The main causes of infertility in the UK are shown in Table 51.1. Male factor is now the most common cause of primary subfertility closely followed by ovulatory disorders. In about 40% of cases, fertility disorders are found in both the man and the woman. Tubal disease is the most common cause of secondary infertility.

There are no identifiable factors in one in four couples. This does not mean there is no underlying problem and a significant proportion of women will be shown to have low ovarian reserve or other problems if they go on to have assisted conception treatment, which is not only an effective treatment but also provides an informative assessment.

Ovulatory disorders

The World Health Organization (WHO) categorizes ovulation disorders into three groups based on serum

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 51.1 Causes of infertility in the UK.

	Prevalence (%)	
Cause	**Primary**	**Secondary**
Unexplained	25	20
Ovulatory disorders	25	15
Tubal disease	20	40
Male factors	30	20
Uterine or peritoneal disease	10	5

measurements of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol.

Group I ovulation disorders

Group I ovulation disorders (10%) are caused by hypothalamic–pituitary dysfunction or failure, which results in hypo-oestrogenic amenorrhoea. They are characterized by low gonadotrophins, a normal prolactin and low oestrogen levels. Three conditions are included: hypothalamic amenorrhoea, hypogonadotrophic hypogonadism and hypopituitarism.

Hypothalamic amenorrhoea is characterized by secondary amenorrhea with low or normal gonadotrophins and hypo-oestrogenism. It is often caused by excessive exercise, lean body mass, weight loss, severe dietary restriction, anorexia or bulimia nervosa or chronic illness. The treatment must be aimed at the underlying cause.

Hypogonadotrophic hypogonadism is caused by gonadotrophin-releasing hormone (GnRH) deficiency. Kallmann's syndrome is congenital and thought to result from the disruption of embryonic migration of GnRH neurones. Acquired causes include central nervous system (CNS) or pituitary tumours, infiltrative diseases, infection, brain/pituitary radiation, pituitary apoplexy, head trauma, and drugs such as glucocorticoids, narcotics and chemotherapy.

Hypopituitarism is typically caused by a pituitary tumour or its treatment by surgery and/or radiotherapy but may be due to extra-pituitary tumours, sarcoidosis, haemochromatosis and Sheehan's syndrome. The clinical manifestations depend on the cause and both the type and degree of hormonal insufficiency. Patients may be asymptomatic or present with symptoms related to hormone deficiency or a space-occupying lesion.

Group II ovulation disorders

Group II ovulation disorders (85%) are defined as dysfunction of the hypothalamic–pituitary–ovarian axis. They are characterized by normal oestrogen levels, normal or low FSH levels, and normal or high LH levels. This group of disorders results in anovulatory oligomenorrhoea, predominantly involving women with polycystic ovaries, which are present in about 80–90% of women with oligomenorrhoea and 30% of women with amenorrhoea. Women with polycystic ovaries often have associated clinical symptoms such hyperandrogenism presenting as hirsutism, acne or androgen-dependent alopecia.

Group III ovulation disorders

Group III ovulation disorders (5%) are caused by ovarian failure, or ovarian insufficiency as it is now called. They are characterized by raised levels of FSH and LH and a low oestrogen. Ovarian insufficiency is often unexplained but may be associated with gonadal dysgenesis, including Turner's syndrome, or be subsequent to bilateral oophorectomy or treatment with chemotherapy or radiotherapy.

Tubal disease

The incidence of tubal disease is very dependent on whether the woman has primary or secondary infertility. Primary infertility refers to a woman who has never conceived whilst secondary infertility relates to any previous pregnancy irrespective of whether that resulted in a live birth or not. Women with secondary infertility, especially those who have had an ectopic pregnancy, have a much higher incidence of tubal disease.

Uterine and/or peritoneal disorders

Uterine and/or peritoneal disorders are the least common cause of infertility but this may, in part, relate to the difficulty in identifying and defining pathology.

Endometriosis does not necessarily cause infertility but there is an association with fertility problems, although the cause is not fully established. Even with severe endometriosis, natural conception is still possible and up to 70% of women with mild to moderate endometriosis will conceive without treatment. However, up to 30–50% of women with endometriosis may experience infertility irrespective of the severity of the disease and infertile women are six to eight times more likely to have endometriosis than fertile women. Endometriosis is thought to influence fertility in several ways, including distorted pelvic anatomy, adhesions, pelvic inflammation, altered immune system functioning and impaired implantation. Women with endometriosis may also have endocrine and ovulatory disorders, including luteinized unruptured follicle syndrome, impaired folliculogenesis, luteal phase defect, and premature or multiple LH surges.

Adhesions are reported to be the leading cause of secondary infertility in women and are thought to be

responsible for approximately 22% (15–40%) of all infertility cases [1]. Adhesions cause infertility by distorting adnexal anatomy and the tubo-ovarian relationship and/or by preventing or impairing the ability of the fallopian tube to pick up the oocyte at ovulation and then transport it. This may be due to the ovary being encapsulated by adhesions or by adhesions that limit tubal/fimbrial movement. The American Fertility Society classification for adnexal adhesions [2] can be used to quantify the severity of the adhesions, which is predictive of term pregnancy rates. Of patients who have undergone major gynaecological surgery, 60–90% will develop adhesions.

Fibroids have been associated with infertility. Intracavity and intramural fibroids are thought to exert a mechanical effect leading to cavity distortion. However, recent data suggest that fibroids may still have a negative effect on fertility even if the cavity appears hysteroscopically normal due to effects on uterine blood flow, impaired embryo implantation or abnormal sperm migration. Despite this, many women with relatively large fibroids conceive without difficulty.

Intrauterine adhesions reduce conception. When associated with amenorrhoea, they are referred to as Asherman's syndrome. The adhesions lead to partial or complete obliteration of the uterine cavity and/or the cervical canal, resulting in menstrual abnormalities and/or recurrent pregnancy loss. Secondary infertility is seen in 43% of women with intrauterine adhesions and may be due to obstruction of sperm into the cervix or prevention of embryo migration and/or implantation.

Male factor

In the UK, seminal fluid analysis is found to be the only cause of infertility in about 20% of couples, and is a contributory factor in a further 25% of couples. However, impaired semen quality, azoospermia and inadequate coitus are contributing factors in nearly 50% of infertile couples.

Abnormal semen characteristics are usually idiopathic and occur in 26% of infertile men. The spermatozoa are mostly dysfunctional and unable to fertilize an oocyte but a proportion are often functionally normal. Sperm function may also be impaired by anti-sperm antibodies.

Azoospermia may be due to hypothalamic–pituitary failure, primary testicular failure (non-obstructive azoospermia) or obstruction of the genital tract (obstructive azoospermia). Primary testicular failure is the most common cause of male infertility due to azoospermia or severe oligozoospermia and may be the result of cryptorchidism, testicular torsion or trauma, orchitis, chromosome disorders (Klinefelter's syndrome, Y-chromosome microdeletions), systemic disease, or follow radiotherapy or chemotherapy, although in the majority of cases (66%) the cause is unknown. Obstructive azoospermia is uncommon, with a prevalence of less than 2%. It is often associated with congenital bilateral absence of vas deferens, which itself is commonly associated with cystic fibrosis mutations or renal tract abnormality.

Anejaculation and retrograde ejaculation are relatively uncommon but may result from spinal cord injury, prostatectomy, retroperitoneal lymph node dissection, diabetes mellitus, transverse myelitis, multiple sclerosis, or be of psychogenic origin.

Varicoceles are more common in men with abnormal semen than men with normal semen (25.4% vs. 11.7%) and are associated with decreased ipsilateral testicular volume. It is unclear if, or why, varicoceles impair fertility and spermatogenesis but any effect is likely to be due to elevated scrotal temperature and impaired semen quality.

Principles of management

Given the various causes and presentations of infertility, it is essential that patients are managed as individuals from their initial referral through to their ultimate treatment. Investigations must be directed on the basis of a critical consideration of clinical features and used to inform patient management and counselling. All healthcare practitioners working in fertility must therefore have a comprehensive understanding of tests and treatments and be able to give patients and couples advice on their personal chances of natural and/or assisted conception so that they can make an informed decision as to how to proceed.

For the remainder of this chapter I shall refer to the typical management of a heterosexual couple for the simple reason that this reflects most referrals to secondary care. However, same-sex couples and single women are increasingly seeking advice and treatment and their assessment and management, save the obvious need for donor sperm, is comparable in most instances. Please substitute 'no partner' or 'second female partner' where relevant when referring to your own clinical practice.

Take a critical history

Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. Furthermore, women have been shown to be more satisfied when seen with their partners.

The consultation should start with an understanding of the duration of infertility and the age of the woman or couple. It is important to specifically enquire about

sexual history, including the frequency and timing of intercourse. Without this information it is not possible to define 'subfertility' and therefore the need for investigation or treatment.

Other key factors that influence assessment and treatment include previous pregnancies in the female partner and whether the couple have children together or through a previous relationship. The former influences the tests offered to the woman and her prognosis, while the presence of children invariably has implications for funding. It is also important to assess the couple's lifestyle as this impacts on their chance of natural conception and influences the success of treatment. Finally, consider any religious or ethical objections the couple may have in respect of their potential treatment. This information is often volunteered and does not require direct questioning.

Primary care physicians generally have a good understanding of fertility and in most cases will have performed some tests prior to, or in conjunction with, their referral. Make sure these are available and confirm the couple are aware of the results. Missing a diagnosis of severe oligospermia or azoospermia or failing to realize this until the end of the consultation will mean that much of the conversation was meaningless and will not reassure the couple. Make sure you gather all clinically relevant information and any test results before you see the couple and share these with them at the appropriate time depending on what they show and what the couple know.

It is, of course, important to finish by taking a general history from both partners to establish their current and past health, any medications they are using and any known allergies.

Female

Having already ascertained the woman's age and parity, the history should now focus on identifying or excluding an underlying cause of subfertility.

Cycle regularity gives an indication of ovulation. Most women (95%) who menstruate every 23–35 days are ovulating. Those with irregular menstrual cycles or who are amenorrhoeic are not ovulating or, if they are, ovulate infrequently.

Women with severe premenstrual pain are more likely to have endometriosis or chronic pelvic infection. These conditions may also be associated with chronic pelvic pain and/or deep dyspareunia. All of these symptoms are consistent with pelvic pathology and, in most cases, warrant pelvic and ultrasound examination followed by laparoscopy.

Heavy periods may reflect dysfunctional uterine bleeding but could be due to fibroids, adenomyosis, endometriosis or endometrial polyps, all of which may impair implantation. Similarly, intermenstrual or post-coital bleeding could be hormonal or reflect local or endometrial pathology. Again, these symptoms would be an indication for pelvic and ultrasound examination possibly followed by hysteroscopy and/or laparoscopy depending on the findings.

The history should then focus on risk factors for tubal disease and abdomino-pelvic adhesions. This influences the test of tubal patency that you will offer. Tubal disease and adhesions that may impair the tubo-ovarian relationship are more common after pelvic infection, sexually transmitted infection, abdomino-pelvic surgery, particularly that involving the pelvic organs, and ectopic pregnancy irrespective of how it was managed. They may also occur in women with endometriosis.

Male

The male history is often redundant, as most couples will be referred with the results of a seminal fluid analysis. Providing this is normal and shows a good number of motile, morphologically normal sperm, there is little value in taking a detailed history from the male partner. However, a specific enquiry regarding any psychosexual problems including erectile or ejaculatory dysfunction is essential.

For men who have not had a seminal fluid analysis or those who have been shown to have abnormal results, a more detailed history is indicated. A history of problems with testicular descent, puberty, trauma or surgery, mumps, and past local infection or inflammation may provide a reason for a low sperm count or impaired motility but do not influence current management.

Questions about current health, medications and lifestyle are more relevant as they can be modified where necessary in most cases. No cause will be identified in approximately 30–50% of men with poor semen quality.

Perform a relevant examination

Just like the clinical history, examination of the male and female partner is often unremarkable. It may not even be indicated in some cases and should only be performed if it will influence management. General inspection, both during the consultation and at examination, also provides an opportunity to consider lifestyle issues such as smoking and obesity, which may be readily evident. As a minimum, weight and body mass index (BMI) should be calculated and recorded. This influences management and has implications for funding. Where relevant, a general inspection should be conducted to look for signs of systemic disease, such as thyroid dysfunction, acromegaly and other endocrine disorders, and phenotypic abnormalities.

Female

Polycystic ovary syndrome (PCOS) and other causes of hyperandrogenism may manifest with acne and hirsutism. More rarely, insulin resistance may lead to acanthosis nigricans. Virilism can lead to male pattern baldness and clitoromegaly. Breast examination is often not indicated but when performed should include Tanner's staging.

Abdominal examination may reveal scars from previous abdominal surgery. Large pelvic masses including ovarian cysts and fibroids, palpable abdominally, clearly influence management and may militate against a laparoscopic approach if surgery is indicated. However, it is rare to find an unexpected mass or demonstrate abdominal tenderness.

Pelvic examination should be considered for women with menstrual dysfunction. Inspection of the vagina and cervix may reveal local pathology that is responsible for irregular or post-coital bleeding and therefore provides reassurance as this is unlikely to affect fertility or influence management. It also provides an opportunity to take swabs for microbiological assessment if there is a history of sexually transmitted infection or signs and symptoms of current infection. A cervical smear should not be performed opportunistically or if cervical pathology is evident; the latter requires referral for colposcopic examination.

Bimanual examination can provide critical information that impacts on investigation and management. A fixed, tender, retroverted uterus is highly suggestive of adhesions and the presence of chronic pelvic inflammation or endometriosis. Such findings warrant an ultrasound scan and, in most cases, an operative laparoscopy with intention to treat any disease and divide any adhesions. In more severe cases, where nodules of endometriosis are visible or palpable or there is evidence of thickening and induration of the uterosacral ligaments, consideration should be given to pelvic MRI to assess the rectovaginal septum and exclude superficial or full-thickness bowel involvement.

Male

Most men do not need to be examined, but where it is considered essential the key examination is that of the genital organs. The scrotum and its contents should be gently palpated to identify the vas deferens and exclude any masses or local pathology. The volume of each testicle should be assessed using an orchidometer and recorded. A prostate examination is rarely needed but if indicated is probably best performed by a urologist.

Perform directed investigations

People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and improves satisfaction.

The female partner

Serum FSH and LH should be checked in the early follicular phase between days 2 and 5 of the menstrual cycle. The levels of these hormones cannot be interpreted in the absence of serum estradiol and all three tests are needed to assess hypothalamic–pituitary–ovarian function. Most women have normal FSH, LH and estradiol levels.

Low FSH and LH levels in conjunction with a low estradiol suggest hypogonadotrophic hypogonadism and type I anovulation. Thyroid function and prolactin should be checked along with other hormones depending on the clinical picture. Elevated serum LH or a raised LH/FSH ratio are no longer used to diagnose PCOS but may provide prognostic information so should be noted and recorded.

An early follicular phase FSH level above 15 IU/L is very suggestive of impaired reserve whilst levels persistently above 30 IU/L are consistent with ovarian failure. The National Institute for Health and Care Excellence (NICE) [3] states that the FSH should be less than 9 IU/L and that levels above this cut-off indicate impaired ovarian reserve. However, there are more accurate tests for ovarian reserve, namely antral follicle counts and serum anti-Müllerian hormone (AMH) levels. These have been used to triage treatment as they provide some information about egg quality. However, this requires more research and, at present, there is insufficient evidence to preclude treatment or fast-track patients on the basis of an ovarian reserve test. NICE suggests that a total antral follicle count of four or less, AMH level of 5.4 pmol/L or less, and FSH level above 8.9 IU/L are predictive of a low response. Age, although not an independent factor, must always be considered under such circumstances as many younger women conceive naturally or after treatment despite having seemingly poor ovarian reserve.At present, NICE suggests any of the three tests may be used but most fertility experts rely on antral follicle counts and serum AMH and not FSH unless the latter is significantly raised.

Women with a regular cycle should have a mid-luteal progesterone to confirm ovulation, but a day 21 progesterone is only relevant for women with a 28-day cycle. There is little value in measuring serum progesterone in a women with amenorrhoea or oligomenorrhoea and it is better to assume anovulation. Thyroid function and prolactin should be checked under such circumstances along with tests to exclude PCOS. Thyroid function and prolactin are not indicated in women with a regular cycle unless there are associated clinical features. The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended.

Current rubella immunity should be checked and the woman immunized where necessary. Treatment should

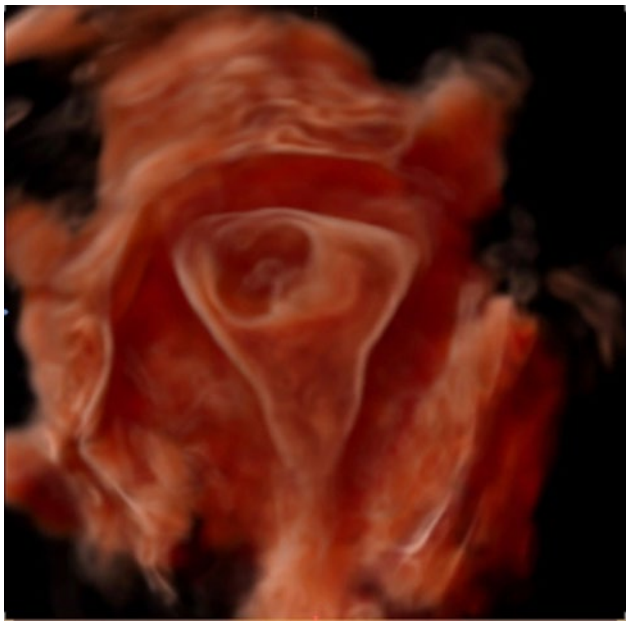

Fig. 51.1 Rendered three-dimensional ultrasound scan showing a type 0 fibroid in the endometrial cavity. (*See also colour plate 51.1*)

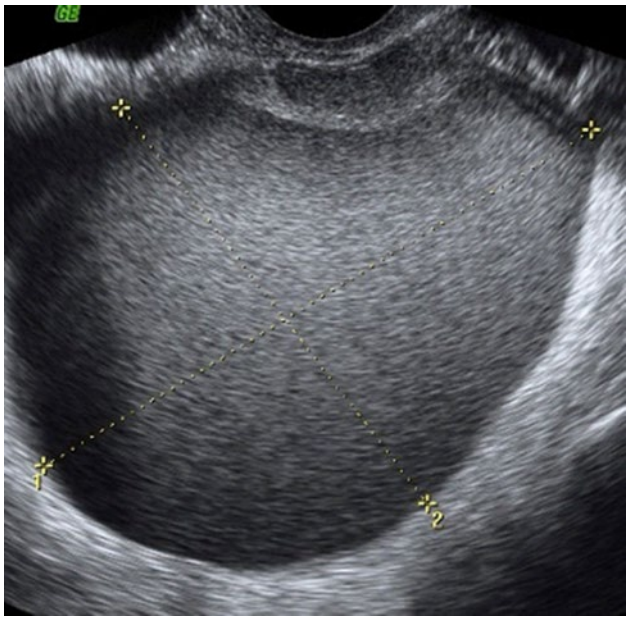

Fig. 51.2 Typical unilocular cyst with 'ground glass' contents consistent with an endometrioma.

be delayed for at least 1 month during which time the couple should avoid intercourse or use appropriate contraception. Immunity should be rechecked and treatment then offered. Some women do not mount an immune response despite repeated immunization.

Ultrasound is not indicated for all patients at initial assessment. It should be reserved for women with menstrual dysfunction, abdominal or pelvic pain, dysmenorrhoea or dyspareunia or where pathology is suspected on examination. In such cases, it may reveal fibroids (Fig. 51.1), adenomyosis, endometrial polyps, hydrosalpinges, or ovarian cysts including an endometrioma (Fig. 51.2), which provides a non-invasive diagnosis of endometriosis.

Ultrasound can also be used to diagnose the polycystic ovary and should be performed in any woman with an irregular cycle and/or hyperandrogenism, along with serum testosterone and sex hormone-binding globulin to allow the free androgen index to be calculated. Women with high levels and those with signs of virilism should also have other androgens checked, including androstenedione and dehydroepiandrosterone sulfate as well as 17-hydroxyprogesterone if relevant.

Ultrasound can also be used to count the number of antral follicles, as outlined above, and provide an objective assessment of ovarian reserve but this is typically reserved for women considering assisted conception as it provides information about the likely response to controlled ovarian stimulation.

The last investigation, but arguably one of the most important, is a test of tubal patency. The results of semen analysis and assessment of ovulation should be known before a test for tubal patency is performed. Hysterosalpingography (HSG) and laparoscopy with dye are the two most widely used methods to test for tubal pathology. Both are invasive procedures but HSG is less so. However, laparoscopy is more accurate and therefore the gold standard. When HSG suggests the presence of tubal obstruction this is confirmed by laparoscopy in only 38% of women. HSG is therefore not a reliable indicator of tubal occlusion. However, when HSG suggests that the tubes are patent, this will be confirmed at laparoscopy in 94% of women, and so is a reliable indicator of tubal patency.

Women who are not known to have comorbidities should therefore be offered HSG to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion and it is less invasive than laparoscopy. Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time [3]. Comorbidities include pelvic inflammatory disease, previous ectopic pregnancy, pelvic adhesions, and endometriosis. Hysterosalpingo-contrast ultrasonography is an alternative to HSG for women who are not known to have comorbidities since it is as effective but requires appropriate expertise.

Chlamydial antibody testing is comparable to HSG in the diagnosis of tubal pathology [4]. Elevated titres of chlamydial antibodies are significantly associated with tubal disease, with higher titres predicting more severe tubal pathology. Negative titres do not justify avoidance

of a test of tubal patency but support HSG as opposed to laparoscopy unless there are clinical features or a history suggestive of past sexually transmitted infection or pelvic inflammatory disease. Women undergoing HSG or any procedure requiring instrumentation of the uterus must be screened for *Chlamydia* or offered prophylactic antibiotics. Women who are screened and found to have chlamydial infection, and their sexual partners, should be referred for appropriate management with treatment and contact tracing before proceeding with further investigation.

Women with no risk factors for tubal disease can be offered ovulation induction or intrauterine insemination without a test of tubal patency. Tubal assessment should be performed after three cycles if treatment has been unsuccessful. Women with a history suggestive of tubal damage should be offered tubal assessment before treatment. However, all women may choose to have a test of tubal patency prior to treatment if they prefer this approach.

Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established. The routine use of post-coital testing of cervical mucus in the investigation of fertility problems is no longer recommended because it has no predictive value on pregnancy rate.

The male partner

Semen analysis is the primary assessment tool for male fertility and outweighs all other tests, and should be compared with the WHO reference values [5] (Table 51.2). Variations in laboratory techniques significantly influence the reliability of the results of semen analysis and so the accuracy of the result is dependent on following accredited methods of analysis that should be regularly audited and subject to quality control. Screening for anti-sperm antibodies should not be offered, as there is no evidence of effective treatment to improve fertility.

Table 51.2 World Health Organization reference values for seminal fluid analysis.

Semen volume: ≥1.5 mL
pH: ≥7.2
Sperm concentration: ≥15 million per mL
Total sperm number: ≥39 million per ejaculate
Total motility (progressive and non-progressive motility): ≥40% motile or ≥32% with progressive motility
Vitality: ≥58% live spermatozoa
Sperm morphology: ≥4% normal forms

Oligospermia is used to describe seminal fluid analyses where the concentration of spermatozoa is below the lower reference limit. Asthenozoospermia and teratozoospermia refer to the percentage of progressively motile and morphologically normal spermatozoa, respectively. Oligoasthenoteratozoospermia therefore refers to seminal fluid analyses showing a low number of spermatozoa with reduced progressive motility and normal morphology. Azoospermia refers to the total absence of spermatozoa in the ejaculate.

However, the reliability of the WHO reference values and their ability to predict conception has been questioned and, unless there is azoospermia, the predictive value of subnormal semen variables is limited. No functional test has yet been established that can unequivocally predict the fertilizing capacity of spermatozoa, including sperm function tests such as computer-assisted semen analysis.

If the result of the first semen analysis is abnormal it should be repeated. The repeat test should be undertaken 3 months after the initial analysis to allow for a cycle of spermatogenesis unless there is azoospermia or severe oligozoospermia, when it should be repeated as soon as reasonably possible. This is important because a single-sample analysis will falsely identify about 10% of men as abnormal. Repeating the test reduces this to 2%.

Male infertility due to severe oligozoospermia and azoospermia has been associated with a number of genetic factors, including numerical and structural chromosomal abnormalities, microdeletions of the Y chromosomes and mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, commonly associated with congenital vas deferens abnormalities. Men with severe oligozoospermia and azoospermia should be offered genetic testing and counselling before undergoing fertility treatment.

Men with azoospermia or severe oligozoospermia should should also have a full endocrine profile to exclude testicular failure or hypothalamic–pituitary–testicular dysfunction. As a minimum, it is essential to check serum levels of FSH, LH and testosterone along with thyroid function and prolactin. More detailed assessments may be needed depending on the result of these tests but should be performed in conjunction with an endocrinologist.

Men with severe oligozoospermia should consider freezing sperm for subsequent use provided they have been shown to have an apparently normal karyotype.

Treat patients as individuals

Choice is an integral part of any decision-making process. Patients should have access to evidence-based information that they can use to inform decisions regarding their

care and treatment. Verbal information should be supplemented with written information or audio-visual media and provided in a form that is accessible to people who have additional needs and those who do not speak or read English.

The NICE quality standard [6] describes a concise set of statements that summarizes what the best possible care should comprise, states that previous children, sexual orientation and relationship status should not be a factor in determining eligibility for treatment, and that counselling should be available throughout treatment.

Lifestyle measures

People who are concerned that it is taking longer than expected to conceive should be given advice on the impact that lifestyle can have on their chances of getting pregnant. Both partners should be informed that the effects of caffeinated beverages (tea, coffee and carbonated drinks) on fertility is unclear. Some prescription, over-the-counter and recreational drugs may interfere with male and female fertility and so should be disclosed to the healthcare practitioner. The same is true of occupations, especially those that involve exposure to chemicals or excess heat.

Patients should be offered lifestyle advice and access to specialist services and consultation, where appropriate, to address factors that influence fertility and the success of treatment such as body weight, smoking, drinking and drug use.

- Women who have a BMI of 30 or over should be informed that they are likely to take longer to conceive and that weight loss is likely to increase their chance of conception if they are not ovulating. Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. Group programmes involving exercise and dietary advice increase the chance of pregnancy more than weight loss advice alone.
- Smoking, both active and passive, may reduce male and female fertility. Smokers should be offered referral to a smoking cessation programme.
- Women should drink no more than 1 or 2 units of alcohol once or twice per week and avoid episodes of intoxication as this reduces the risk of harming a developing fetus. Consumption of 3–4 units per day for men is unlikely to affect their semen quality.
- Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality. It is uncertain whether wearing loose-fitting underwear improves fertility.
- Women should take 0.4 mg of folic acid per day before conception and up to 12 weeks' gestation as this reduces the risk of having a baby with neural tube defects. Women who have a previously affected infant, who take antiepileptic medication or who have diabetes should take 5 mg/day.

The relationship between psychological stress and fertility problems is complex and the individual response to stress situations is variable. Work-related stress may reduce conception rates and psychological stress can negatively affect a couple's relationship and libido, which may impact on their chance of conception. Couples undergoing fertility tests and treatment have been shown to experience a higher frequency of male sexual disturbances, including loss of libido and a decrease in the frequency of sexual intercourse. Both partners should therefore be informed that stress in the male and/or female partner can affect the couple's chance of conception and their relationship. All efforts should be made to limit stress wherever possible.

The effectiveness of complementary therapies, for both men and women, has not been properly evaluated and further research is needed before such interventions can be recommended.

Reassurance

Women with unexplained subfertility should not be offerred oral ovarian stimulation agents such as clomifene citrate, anastrozole or letrozole. Clomifene citrate, as a stand-alone treatment, does not increase the chances of a pregnancy or a live birth. Rather, they should be reassured and given advice on natural conception and the timing and frequency of sexual intercourse. They should be offered *in vitro* fertilization (IVF) treatment if they have not conceived after 2 years, including up to 1 year before their fertility investigations, of regular unprotected sexual intercourse. Couples with mild male factor infertility and minimal and mild endometriosis should be treated in exactly the same way.

Treat the cause

While it is possible to adopt a generic approach to fertility treatment, it is paramount to individualize care and consider the underlying cause. Women who are not ovulating should be managed according to the likely problem. The management of women with hypothalamic hypogonadism is totally dependent on whether there are issues with weight, stress, thyroid disease or hyperprolactinaemia. They should not be offered ovulation induction until these issues are addressed as it is unlikely to work. Furthermore, correction or moderation of the underlying cause often leads to resumption of ovulation, mitigating the need for treatment. This is a safer and more practical approach.

Male factor

A specific male factor should be identified and corrected where possible.

- The term 'mild' male factor infertility is used to describe two or more semen analyses that have one or more variables which fall below the 5th centile and where the effect on the chance of pregnancy occurring naturally through vaginal intercourse within a period of 24 months would then be similar to people with unexplained infertility or mild endometriosis. Mild male factor infertility should therefore be treated in the same way and couples encouraged to have regular sexual intercourse for a maximum of 2 years.
- Men with mild to moderate oligozoospermia may conceive naturally but the chances are lower than for men with normal seminal fluid analyses. They can continue to try naturally but intrauterine insemination does not appear to increase the chance of conception. They should not be offered anti-oestrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs because they have not been shown to be effective. Men with leucocytes in their semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates.
- Men with severe oligozoospermia and azoospermia are unlikely to conceive naturally. The most effective treatment is assisted reproduction. While IVF is feasible in mild to moderate oligozoospermia, intracytoplasmic sperm injection (ICSI) is usually required to achieve fertilization, especially in moderate to severe oligozoospermia, asthenozoospermia or teratozoospermia.
- Men with obstructive azoospermia should be offered surgical correction of epididymal blockage, as an alternative to surgical sperm recovery and IVF, because it is likely to restore patency of the duct and improve fertility. In non-obstructive azoospermia there are foci of spermatogenesis in about 50% of cases. Lifestyle measures may return sperm to the ejaculate but most cases are managed by surgical sperm recovery from the epididymis or testis followed by ICSI because of the number and immaturity of the recovered sperm.
- Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs in a similar manner to women.
- Men should not be offered surgery for varicoceles because it does not improve pregnancy rates.
- Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures and is recommended. A variety of options is available and the choice will depend on individual circumstances.

Ovulation induction

Where indicated, ovulation induction should be offered. The aim is to induce a monofollicular response to insure this occurs, and a multifollicular response is avoided, all patients undergoing ovulation induction should have ultrasound monitoring through their first cycle of treatment. This ensures they are taking a dose that minimize the risk of multiple pregnancy. Differentiating between the three causes of Group I ovulation disorders is essential as it governs the approach to ovulation induction and is prognostic of treatment outcome. Treatment may involve lifestyle modifications (normalizing weight and exercise regimes), pulsatile GnRH, or gonadotrophin therapy with human menopausal gonadotrophin (hMG). Lifestyle modifications are more appropriate for hypothalamic amenorrhoea while pulsatile GnRH is recommended for patients with hypothalamic hypogonadism as it is more physiological and induces monofollicular ovulation. However, neither of these strategies is appropriate for patients with hypopituitarism. In this circumstance, gonadotrophins need to be directly replaced and this requires the administration of both FSH and LH. This is usually achieved through the use of hMG, which contains both hormones in a ratio of 1 : 1. This approach is very successful in women with hypogonadotrophic hypogonadism and hypothalamic amenorrhoea, resulting in cumulative conception rates of 82.1% and 65.4% and cumulative live-birth rates of 95.0% and 85.3%, respectively, over the course of a year.

Women with Group II ovulation disorders should be offered clomifene citrate, metformin or a combination of these. Clomifene citrate should not normally be continued for longer than 6 months as there are more effective treatment options. Women prescribed metformin should be informed of the side effects associated with its use, such as nausea, vomiting and other gastrointestinal disturbances. These can be lessened by reducing the dose, taking the medication with food, or through the use of a slow-release formulation. Women with a Group II ovulation disorder and BMI over 30 should be encouraged to lose weight as this alone may restore ovulation; if it does not, it will improve their response to ovulation induction agents and have a positive impact on pregnancy outcomes. Women who prove resistant to increasing doses of clomifene citrate should be offered laparoscopic ovarian drilling, combined treatment with clomifene citrate and metformin if not already offered as first-line treatment, or gonadotrophins. Concomitant treatment with GnRH agonist, pulsatile GnRH, growth hormone and/or hMG during ovulation induction in women with PCOS who do not respond to clomifene citrate is not recommended because there is no evidence they improve pregnancy rates. Tamoxifen and aromatase inhibitors may be used as alternatives to clomifene.

Women with Group III ovulation disorders require treatment with donor eggs. The use of donor oocytes is also effective for certain cases of IVF treatment failure, where there is evidence of poor oocyte quality or poor

response to ovarian stimulation, and where there is a high risk of transmitting a genetic disorder to the offspring.

Tubal disease and adhesions

Tubal surgery has largely been replaced by IVF. It still has a role in select cases and in women who do not want IVF or who are unable to self-fund treatment. It should only be offered in centres where appropriate expertise is available.

For women with mild tubal disease, tubal surgery may be more effective than no treatment. For women with proximal tubal obstruction, selective salpingography plus tubal catheterization, or hysteroscopic tubal cannulation, may improve the chance of pregnancy.

In women undergoing IVF, the presence of hydrosalpinx is associated with early pregnancy loss and poor implantation and pregnancy rates. Hydrosalpinges large enough to be visible on ultrasound are associated with the poorest outcome, including increased miscarriage rates. Women with hydrosalpinges should therefore be offered treatment before IVF because this improves the chance of a live birth. Various surgical treatments including salpingectomy, salpingostomy, proximal tubal ligation or clipping, and transvaginal aspiration have all been used to improve IVF outcome. Laparoscopic salpingectomy has been shown to increase ongoing pregnancy rates following IVF by about 50% and is therefore the current standard treatment, although laparoscopic proximal tubal ligation/clipping has a similar effect. Transvaginal aspiration does not improve outcome. The hysteroscopic placement of Essure® intratubal devices to occlude the fallopian tube and prevent leakage of fluid back into the uterine cavity is not effective and is associated with lower ongoing pregnancy rates (26.2%) than after laparoscopic salpingectomy (55.8%). A hysteroscopic approach may still be valid in women who cannot undergo laparoscopic salpingectomy as there is no alternative, but there is no evidence to show benefit.

Fertility can be improved by the division of adhesions. Pregnancy rates increase by 38–52% in previously infertile patients following laparotomy with adhesiolysis. In women with infertility as a result of adnexal adhesions, pregnancy rates of 32 and 45% at 12 and 24 months, respectively, have been reported following adhesiolysis, compared with 11 and 16% at corresponding time intervals in untreated women. Higher pregnancy rates (12% vs. 29%) have also been reported 3 years after tubal surgery. Division of adhesions around the ovary has also been shown to increase pregnancy rates by over 50%.

Adhesions re-form in most patients (mean 85%) regardless of the method of adhesiolysis used or the type of adhesion being lysed. Women must be made aware of this and, even when successful, that fallopian tubes may become blocked again. If natural conception does occur in women with tubal disease and/or adhesions, there is a higher risk of that pregnancy being ectopically located. This is also true after tubal surgery and adhesiolysis. The risk is thought to be around 10% but will vary depending on individual circumstances. Any woman with tubal disease or adhesions who does conceive should seek early referral and an ultrasound scan around 7 weeks' gestation or sooner in the event of any symptoms of ectopic pregnancy, of which they should be fully informed.

Uterine factors

Infertile women with large fibroids or submucosal/intramural fibroids that affect the uterine cavity are often offered myomectomy. However, there is no robust evidence to show this is effective. Women may decide to avoid myomectomy and this is reasonable. Uterine artery embolization has been used but its effects on fertility are unclear and it can lead to premature menopause or impaired ovarian reserve and persistent amenorrhoea. These complications are unpredictable but more common in older women and may result from non-target embolization.

Whilst endometrial polyps are likely to negatively impact on fertility and impair implantation, the evidence for this is far from clear and there are no randomized controlled trials to show polypectomy is beneficial. However, polypectomy is a relatively straightforward procedure with minimal risks that can often be performed as an outpatient procedure and should be offered to all women with a polyp prior to treatment. Broad-based polyps often recur and may need to be formally resected rather than simply avulsed or blindly curetted to reduce this happening.

Women with amenorrhoea and intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy. However, the key to intrauterine adhesions is their prevention rather than their subsequent treatment. They most commonly occur following uterine instrumentation of a pregnant uterus. Women of childbearing age who wish to preserve their fertility should be made aware of the risk at the time of evacuation of retained products and offered alternative management, especially if they require repeated procedures.

Hysteroscopy provides a minimally invasive way to remove polyps and submucosal fibroids and divide intrauterine adhesions. There is no robust evidence to show this improves fertility but their presence does impair implantation and there is a biological rationale as to why their removal may improve fertility.

There are no treatments for adenomyosis that improve fertility. Treatment should be based on symptom control. GnRH agonists can be used but there are no data to show

they lead to an increase in spontaneous pregnancy or improve the outcome of IVF.

Endometriosis and peritoneal disease [7–9]

Suppression of ovarian function to improve fertility in minimal–mild endometriosis is not effective and should not be offered for this indication alone. There is no evidence of its effectiveness in more severe disease. Indeed, more harm than good may result from treatment, because of adverse effects and the lost opportunity to conceive.

Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal–mild endometriosis is effective and improves ongoing pregnancy and live-birth rates but the role of surgery for moderate–severe disease is uncertain and there are no randomized controlled trials or meta-analyses to inform management. When surgery is performed, laparoscopy is preferred to laparotomy as it is associated with pregnancy rates of 54–66% compared with 36–45% after laparotomy in women with moderate and severe endometriosis.

Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. Laparoscopic cystectomy for ovarian endometriomas is better than drainage and coagulation as it reduces symptoms and the risk of recurrence. Excision of the endometrioma capsule increases the postoperative spontaneous pregnancy rate, compared with drainage and electrocoagulation of the endometrioma wall. Nevertheless, both techniques carry potential risks for ovarian reserve, either by removal of normal ovarian tissue during excision or by thermal damage to the ovarian cortex during ablation. It should also be noted that there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates in infertile women with endometrioma larger than 3 cm. In this case, cystectomy should only be considered to improve endometriosis-associated pain or the accessibility of follicles.

IVF is appropriate treatment, especially if tubal function is compromised, there is also male factor infertility and/or other treatments have failed. Whilst IVF pregnancy rates are lower in women with endometriosis than in those with tubal infertility, endometriosis does not appear to adversely affect pregnancy rates. Treatment with a GnRH agonist for 3–6 months before IVF in women with endometriosis may increase the rate of clinical pregnancy.

The complete surgical removal of endometriosis may also improve live-birth rate in infertile women with AFS/ASRM stage I/II endometriosis undergoing laparoscopy prior to treatment with assisted reproductive technologies although the benefit is not well established.

Intrauterine insemination

Intrauterine insemination, with or without ovarian stimulation, is no longer recommended for people with unexplained infertility, mild endometriosis or mild male factor infertility who are having regular unprotected sexual intercourse. Intrauterine insemination may be considered in exceptional circumstances such as when people have social, cultural or religious objections to IVF. Unstimulated intrauterine insemination may benefit couples who are unable, or would find it very difficult, to have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem.

Unstimulated intrauterine insemination with donor sperm, often referred to as donor insemination, is the recommended treatment for men with azoospermia due to testicular failure or severe deficits in semen quality who do not wish to undergo ICSI. Donor insemination may also be considered where there is a high risk of transmitting a genetic disorder or infectious disease to the offspring or the latter to the woman from the man. It may also be used for couples with severe rhesus isoimmunization. Donor insemination is the treatment of choice for people in same-sex relationships and single women. However, as these individuals invariably have to self-fund their treatment, some elect to have IVF with donor sperm.

People who have not conceived after six cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semen analysis, can be offered IVF or a further six cycles of unstimulated intrauterine insemination.

Assisted conception

NICE recommends that women under 40 who have been trying to get pregnant for 2 years should be offered three full cycles of IVF. Women aged between 40 and 42 who have been trying for two or more years and have not previously received IVF or have low ovarian reserve should be offered one full cycle of treatment. The overall chance of having a live birth after IVF treatment falls with rising female age and also decreases as the number of unsuccessful cycles increases. ICSI is indicated and should only be offered if there are severe deficits in semen quality, obstructive azoospermia, non-obstructive azoospermia or if previous IVF treatment resulted in failed or very poor fertilization.

Counselling and support

People experiencing fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment for fertility problems, can cause emotional stress. Counselling should be offered before, during and after investigation and treatment.

People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group. There are several patient organizations and support groups available throughout the UK that offer general or specific advice. Fertility Fairness, formerly the National Infertility Awareness Campaign, has campaigned for people to have comprehensive and equal access to a full range of appropriate NHS investigations and treatments for infertility, including the right to access up to three full cycles of IVF treatment free on the NHS [10].

Welfare of the child

The welfare of the child who may be born as a result of fertility treatment, including the need of that child for supportive parenting, and of any other child who may be affected by the birth must be considered prior to offering treatment in accordance with Human Fertilisation and Embryology Authority (HFEA) regulations [11]. Each patient should be assessed to decide whether there is a risk of significant harm or neglect to any child.

Prognosis

Natural conception

Over 80% of couples will conceive within 1 year if the woman is aged under 40 years and they have regular sexual intercourse every 2–3 days. Half of the couples who do not conceive in the first year will conceive in the second year such that the cumulative pregnancy rate over 2 years is over 90%.

A prospective cohort of women aged 35–39 years, from the European Fecundability Study, suggested even higher rates of conception after 2 years (Table 51.3). Pregnancy rates did decrease with increases in female age. Men aged 40 years having intercourse twice per week have approximately 10% lower cumulative success rates compared with men aged 35 years over the same time period. All subfertile patients should therefore be made aware that female fertility and, albeit to a lesser extent, male fertility decline with age [12].

Coital frequency also influences conception rates. At least 94% and 77% of fertile women aged 35 years and 38 years, respectively, conceive after 3 years of trying if they have intercourse two or three times per week. Conception rates within 12 months fall from 92% for women aged 19–26 years to 86% for women aged 27–34 years and 82% for women aged 35–39 years for couples having intercourse twice per week. Conception rates fall further to 85%, 76% and 71%, respectively, for couples having intercourse once per week. Furthermore, sperm motility is highest in semen emission every 3–4 days on average. Coitus every 2–3 days is therefore likely to maximize the overall chance of natural conception, as spermatozoa survive in the female reproductive tract for up to 7 days after insemination.

In terms of timing, most pregnancies can be attributed to sexual intercourse during a 6-day period starting 5 days before ovulation and including the day of ovulation, with the highest estimated conception rates associated with intercourse 2 days before ovulation.

Table 51.3 Cumulative probability of conceiving a clinical pregnancy by number of menstrual cycles based on female age.

Age (years)	Pregnant after 1 year (12 cycles) (%)	Pregnant after 2 years (24 cycles) (%)
19–26	92	98
27–29	87	95
30–34	86	94
35–39	82	90

Source: National Institute for Health and Care Excellence [3].

Assisted conception

NICE suggests that most women typically achieve success rates of 20–35% per cycle with a cumulative success of 45–53% after three full cycles of IVF, which is why it recommends three IVF cycles as it is both the most cost-effective and clinically effective number for women under the age of 40. Patient and public engagement has shown that many patients think that an 80% chance of getting pregnant through IVF is excellent and anything less than 50% is poor. However, these figures need to be considered and directly compared with natural fecundity as young healthy couples only have around a 20% chance of conceiving naturally in a month.

Funding

Although NICE has made its recommendations clear, funding for fertility treatment and assisted conception is ultimately determined by clinical commissioning groups (CCGs). Different CCGs use different eligibility criteria, with female age, BMI, previous children, relationship status and sexuality all deciding factors. Most CCGs do not offer funding for women who are overweight (BMI >30 kg/m^2) and all have an upper age cut-off that varies from 35 to 43 years. Most CCGs will not support couples who have children irrespective of whether these were conceived together or with a different partner.

Summary box 51.1

- Infertility is the second most common reason for women of childbearing age to visit their GP and affects one in seven heterosexual couples.
- Infertility is defined by the duration a couple have been trying to conceive without success, after which formal investigation is justified and treatment, where indicated, implemented. For most couples this will be after 1 year of unprotected vaginal sexual intercourse but couples should be referred earlier where the woman is 36 years or over or if there is a known clinical cause of infertility or predisposing factors for infertility.
- Male factor is now the most common cause of primary infertility closely followed by ovulatory disorders. There are no identifiable factors in one in four couples. Tubal disease is the most common cause of secondary infertility.
- Patients must be managed as individuals, from their initial referral through to their ultimate treatment. Investigations should be directed on the basis of a critical consideration of clinical features and used to inform patient management and counselling.
- Choice is as an integral part of any decision-making process. Patients should therefore have access to evidence-based information that they can use to inform decisions regarding their care and treatment.
- All patients should be given advice on the impact that lifestyle can have on their chances of getting pregnant, both naturally and following treatment.
- Couples with unexplained subfertility, mild male factor infertility and minimal to mild endometriosis should be reassured and given advice on natural conception and the timing and frequency of sexual intercourse. They should be offered IVF treatment if they have not conceived after 2 years, including up to 1 year before their fertility investigations, of regular unprotected sexual intercourse.
- While it is possible to adopt a generic approach to fertility treatment, it is paramount to individualize care and treat the underlying cause.
- People experiencing fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause emotional stress. Counselling should be offered before, during and after investigation and treatment.
- The welfare of the child who may be born as a result of fertility treatment must be considered prior to offering treatment in accordance with HFEA regulations.
- Over 80% of couples will conceive within 1 year if the woman is aged under 40 years and they have regular sexual intercourse every 2 –3 days. Half of the couples who do not conceive in the first year will conceive in the second year, such that the cumulative pregnancy rate over 2 years is over 90%. However, all subfertile patients should be made aware that female fertility and, albeit to a lesser extent, male fertility decline with age.

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52

Assisted Reproduction

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Assisted conception is the facilitation of natural conception by some form of scientific intervention. It has been available for many years, but one of the first recorded and possibly best-known instances of assisted conception was that performed by the eminent surgeon John Hunter in London in 1785. The husband, in this infertile couple, had hypospadias and artificial insemination of ejaculated sperm was performed on the wife. This resulted in a successful pregnancy and subsequent birth. This basic assisted conception continued until scientific techniques improved in the middle of the twentieth century. The advent of improved techniques, particularly in the form of ovulation induction and controlled ovarian stimulation, has allowed the successful treatment of the anovulatory female. The purification and use of human menopausal gonadotrophins (hMGs) in the 1960s led to multiple follicular development allowing *in vitro* fertilization (IVF). Over the last 40 years there have been dramatic improvements in the treatment of both the infertile female as well as the male. There is now a full panoply of techniques with acronyms ranging from the more well known such as IUI, IVF, ICSI and PGD, through to ones that have now become more esoteric due to lack of success rates such as DOT, PROST and even DIPI (Table 52.1). With these advances it is possible to treat the vast majority of subfertile men and women successfully and give them the child they so desire.

Investigations prior to assisted conception

Even though the diagnosis may have been made and the most appropriate form of treatment decided upon, there are a few essential investigations that should be performed prior to any form of assisted conception. These will not only ensure the best results when the assisted conception is performed, but also reduce the chance of any diagnosis being missed before multiple cycles are embarked on with the subsequent emotional and financial cost to the patient if they are unsuccessful.

Female

Tests of ovarian reserve have been utilized for many years; previously an early follicular phase follicle- stimulating hormone (FSH) level was used and is still the mainstay in most countries. The use of anti-Müllerian hormone (AMH) is now more widespread and gives a more accurate assessment of ovarian reserve. It has better intra- and inter-cycle variability and has a better correlation with ovarian response to superovulation and better success rates than any other blood test. Indeed it is often used to assess the patient's suitability for techniques such as IVF prior to treatment. A very low level (<3 pmol/L) would suggest a live-birth rate of less than 2% and hence IVF using the patient's own eggs would rarely be successful. Conversely, a high level (>50 pmol/L) would suggest very sensitive ovaries and a higher chance of developing ovarian hyperstimulation syndrome (OHSS) if the dose of FSH is not reduced and an antagonist protocol used.

Most forms of assisted conception, excluding egg donation, require normal ovarian reserve to have any significant chance of success. If the patient has irregular periods, then prolactin, thyroid function and, if appropriate, testosterone and sex hormone-binding globulin (SHBG) levels should also be measured.

If the patient is undergoing a licensed form of assisted conception under the 1990 Human Fertilisation and Embryology Act, then both the male and female partner have to be screened for hepatitis B, hepatitis C and HIV. If either partner

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 52.1 Assisted contraception abbreviations.

Acronym	Definition
IVF	*In vitro* fertilization
IUI	Intrauterine insemination
ICSI	Intracytoplasmic sperm injection
PGD	Pre-implantation genetic diagnosis
PGS	Pre-implantation genetic screening
DOT	Direct oocyte transfer
PROST	Pronuclear stage transfer
DIPI	Direct intraperitoneal insemination
MESA	Microepididymal sperm aspiration
PESA	Percutaneous epididymal sperm aspiration
TESE	Testicular sperm extraction
GIFT	Gamete intrafallopian transfer

is positive for the above conditions this does not preclude them from being treated but unless specific embryo cryopreservation facilities are available, embryo freezing of surplus embryos cannot be performed because of the theoretical risk of cross-infectivity between the patient's embryos and unaffected embryos from other patients.

Ultrasound

Virtually all ultrasound scanning in assisted conception is performed transvaginally. The initial scan assesses several areas.

- Ovarian morphology: if there are underlying polycystic ovaries, they may be hyperresponsive to stimulation with gonadotrophins.
- Presence of ovarian cysts: if present, suitable treatment should be arranged.
- Many centres now also measure the antral follicle count (AFC) as this is also used in the dose calculation of FSH for the stimulation phase of IVF.
- The ovaries are assessed for accessibility, not just for the monitoring itself but also if transvaginal oocyte retrieval (TVOR) is planned in order to ensure that this can be performed without undue difficulty. Sometimes in patients who have abdominal adhesions due to iatrogenic causes, previous pelvic inflammatory disease or endometriosis, then gentle abdominal pressure can be applied during the screening ultrasound to ensure that the ovary can be moved down to a more accessible position for egg collection.
- The uterus is also assessed for the presence of abnormalities such as uterine fibroids to ensure the endometrium appears normal and there are no other abnormalities.
- The rest of the pelvis is also screened in a systematic fashion to exclude other pathology.

Uterine cavity and tubal patency

Both the uterine cavity and the fallopian tubes should be examined prior to all forms of assisted conception. For techniques such as IUI, where either one or both fallopian tubes are required to be patent, it is obvious why both the cavity and the tubes should be checked. Less obviously, the fallopian tubes require inspection for techniques such as IVF, even though they are not required for the actual procedure. We know from grade A evidence [1] that the presence of hydrosalpinges can significantly reduce the implantation rate due to reflux of the hydrosalpingeal fluid into the uterine cavity. The integrity of the uterine cavity should be evaluated as various forms of pathology, including intrauterine adhesions, congenital abnormalities such as large septate uterus, submucous fibroids and intrauterine polyps, can all significantly reduce the implantation rate and hence the subsequent live-birth rate from all forms of assisted conception. If a significant problem is noted in the uterine cavity, this would normally be corrected prior to the assisted conception cycles being performed. The uterine cavity and the fallopian tubes can be investigated using the following methods.

Hysterosalpingography

Hysterosalpingography (HSG) has been used for many decades but had a reputation for being painful. With newer techniques, and in particular the advent of suction caps and small balloon catheters, the need for unnecessary trauma is obviated. It allows assessment of both the uterine cavity and the fallopian tubes and it is an extremely useful screening test that can be performed with a high degree of accuracy without the need for a general anaesthetic. It is recommended that chlamydial screening be performed beforehand, preferably as part of the initial work-up of the female partner, and antibiotic cover for the procedure should be used.

Hystero-contrast sonography

Several ultrasound techniques have been developed to try to assess tubal patency. In most an echogenic fluid is instilled inside the uterine cavity and into the fallopian tubes, which can be tracked by transvaginal ultrasound. This can be a good method for assessing tubal patency, but due to the high echogenicity of the fluid it can sometimes miss uterine cavity lesions such as mild intrauterine adhesions and the subtle distortions caused by submucous fibroids [2]. This can be avoided by initially using sterile saline to outline the endometrial cavity before using ultrasound contrast medium, which by design is relatively echogenic.

Laparoscopy and hysteroscopy

These are commonly performed infertility investigations, particularly if the patient has other presenting complaints, especially pelvic pain.

If a screening test such as HSG has been performed and an intrauterine lesion found, then hysteroscopy would also be performed. If the diagnosis is confirmed the lesion is removed, for example intrauterine adhesions can be divided hysteroscopically, or submucus fibroids can be extracted by transcervical resection.

Male partner

A comprehensive semen analysis should be performed on all males referred for assisted conception to ascertain the most appropriate technique suitable for the patient. Most assisted conception units look at the normal World Health Organization (WHO) sperm criteria including sperm morphology; generally, IVF is used if the parameters are good and intracytoplasmic sperm injection (ICSI) if there is a problem with any of the parameters. The presence of other problems, such as anti-sperm antibodies within the ejaculate, are also ascertained and, if present, further samples can be obtained with the patient ejaculating directly into culture medium to try to lessen the impact of these antibodies on sperm function. This can sometimes mean that a sample severely affected by anti-sperm antibodies only deemed suitable for IVF can sometimes be 'upgraded' to techniques such as IUI if ejaculation into medium is performed. Overall, the proportion of IVF and ICSI procedures performed worldwide is roughly equal, although the popularity of ICSI is increasing.

Important coexistent pathologies

There are several other coexistent pathologies that can significantly reduce the successful outcome of assisted conception or increase the complication rates associated with it.

Uterine fibroids

Uterine fibroids are very commonly detected by transvaginal scanning of the infertile woman. It has always been difficult to ascertain the causality between these fibroids and the patient's infertile status, but the presence of fibroids does not necessarily mean there is a direct causal link between fibroids and infertility. On the other hand, there are a number of reported case series where removal of fibroids resulted in subsequent improved conception rates of between 30 and 80% [3]. It was previously thought that fibroids only significantly reduced implantation rates if the uterine cavity was distorted. Two series examined the effect of fibroids in other locations on implantation in IVF cycles. In the first of these, Eldar-Geva [4] showed that intramural fibroids significantly reduced implantation rates; this was then confirmed by Hart *et al.* [5]. Both of these studies confirmed the impact of fibroids that do not distort the uterine cavity but this appears to be only true for fibroids above 3 cm in size. Therefore, any patient who has fibroids larger than 3 cm, and in particular who has recurrent implantation failures, should be considered for myomectomy prior to further assisted conception. Although treatment of these fibroids does appear to have an impact on implantation rates, in a randomized trial Surrey *et al.* [3] failed to demonstrate improved live-birth rates.

Hydrosalpinges

There have been several studies that have shown the adverse effect of hydrosalpinges on IVF outcome. Indeed, three randomized controlled trials were included in the Cochrane review [6] to see if salpingectomy would be useful for patients with hydrosalpinges prior to undergoing IVF. Surgical treatment of these hydrosalpinges versus non-surgical treatment increased the odds of live birth plus ongoing pregnancy (odds ratio, OR 2.13, 95% CI 1.24–3.65) and of pregnancy (OR 1.75, 95% CI 1.07–2.86). It has now been shown that removal of these diseased tubes by salpingectomy prior to IVF leads to the implantation rates that would be expected in patients unaffected by hydrosalpinges. Whether these hydrosalpinges should be removed or blocked in the proximal portion (by clipping or coagulation) will depend on several factors such as degree of damage and whether the patient has pain associated with the hydrosalpinges. Salpingectomy used to be the routine recommendation but more units are now coagulating the proximal portion because of the worry that salpingectomy may compromise ovarian vasculature and reduce subsequent response to stimulation [7 6]. Most practitioners would individualize the treatment of hydrosalpinges and take all other variable parameters into consideration, ranging from any male factor present through to degree of tubal disease, as well as the known ovarian function of the patient prior to removing them.

Polycystic ovaries

Polycystic ovaries as seen by ultrasound are an extremely common finding in women of childbearing age and can occur in about 30% of patients. Patients with polycystic ovaries can be more difficult to stimulate with gonadotrophins for either IUI or IVF. Initially there can be a degree of resistance at lower doses but then a very narrow therapeutic window before the patient hyperstimulates, and this can quite often lead to cycle cancellation. In view of the severe complications resulting from OHSS, one should always start with a low dose and then increase in small increments until the appropriate therapeutic window is achieved. Some have advocated the use of laparoscopic ovarian drilling to try to improve this

therapeutic window, as well as the pre-cycle administration of insulin-sensitizing agents such as metformin. There is now evidence that metformin does not improve the success rate but can improve the safety of the cycle.

Endometriotic cysts

Endometriosis is a common coexistent pathology in patients undergoing assisted conception. Although there is little evidence that the routine treatment of peritoneal endometriosis results in a significant improvement in assisted conception cycles, there can be benefit in treating large endometriomas (>44 cm) prior to IVF. It is thought this may benefit the cycle in several ways, including the ovarian response itself and overall number of eggs obtained (particularly in the ovary containing the endometrioma). The second concern with ovarian endometriomas is that these can be inadvertently punctured during TVOR and there is a significant increase in ovarian abscess formation if this occurs. Pre-cycle drainage by needle aspiration can also be a cause of ovarian abscesses and this is generally not advised. If the size of the ovarian endometrioma is felt to be significant so that it may adversely affect cycle outcome or increase the chance of inadvertent needling, then it is better for the endometrioma to be surgically treated prior to initiation of the cycle. Prolonged downregulation with GnRH analogues can shrink the cysts and also improve the overall success rates.

Smoking

Patients should be advised that smoking significantly reduces the effectiveness of all forms of assisted conception and that they should therefore quit smoking.

Obesity

It is recommended that a patient should have a body mass index (BMI) of between 19 and 30. Outside this range success rates of assisted conception are reduced. If the BMI is above 30, not only are success rates lower but miscarriage rates higher and complications such as OHSS increased. It is therefore recommended that the female partner should be encouraged to lose weight.

Types of assisted conception

There are many types of assisted conception available in the modern unit. These range from less invasive procedures such as IUI through to the widely known IVF, with or without ICSI. The use of other procedures such as gamete intrafallopian transfer (GIFT) has reduced due to the improving success rates of IVF. Other techniques associated with assisted conception cycles such as pre-implantation genetic diagnosis (PGD) and pre-implantation genetic screening (PGS) are also performed in a few specialized centres.

Intrauterine insemination

Intrauterine insemination (IUI) is where a prepared sample of sperm (normally produced by masturbation) is inseminated into the uterine cavity at the appropriate time of the patient's menstrual cycle. Approximately 2 weeks later a pregnancy test is performed to see if the cycle has been successful.

Protocols

IUI can be performed in a natural cycle, with Clomid alone, with Clomid and then FSH injection, or purely with FSH. If any form of ovulation induction has been used, it is also quite common to use a single human chorionic gonadotrophin (hCG) injection approximately 36 hours prior to the insemination to ensure optimal timing with ovulation.

Monitoring

Although for unstimulated cycles it is possible just to perform urinary luteinizing hormone (LH) monitoring using home dipstick methods, this does not give the best success rates. If any form of ovulation induction has been used, then it is recommended that more accurate monitoring is performed. This is normally achieved by transvaginal ultrasound and has benefits of not only deciding the best time to give the dose of hCG and hence the timing of the insemination, but also ensuring that ovulation induction is having the desired effect, i.e. one (or at most two) developing follicle(s) over 18 mm. If there are more than two follicles, this can be detected by ultrasound, the cycle cancelled and the patient advised against having unprotected intercourse due to the increased risk of higher-order multiple pregnancies.

The overall success rate, as with any subfertile couple, depends on multiple factors, most importantly female age and, with IUI, the quality of the sperm. Though IUI can be used for mild male factor problems, it is not recommended for anything more severe. Success rates of around 5% per cycle have been quoted for unstimulated IUI, increasing to 8–10% per cycle for stimulation with Clomid and 12–18% per cycle when FSH is used in the protocol. Although success rates of 35% have been quoted in literature, these tend to be highly selective series and not necessarily representative of a general case mix of patients across a wider age range [8].

Complications

The main complication of IUI is higher-order multiple births and occurs when FSH has been used. Most centres would expect a twinning rate of 10–15% and a triplet rate

of less than 1%. If the triplet rate is higher than 1%, and in particular if there are even higher numbers than this, then this is normally due to inadequate monitoring and inadequate numbers of cycles being cancelled when an over-response of the ovaries has been seen.

Although ovarian hyperstimulation can occur, particularly in the protocols where FSH is used, this would normally be mild to moderate at most, and it is very unusual to get a case of severe hyperstimulation in IUI cycles. If this happens it tends to be when an inappropriate starting dose of FSH has been used and again when inadequate monitoring has been performed.

The patient should also be warned about the possibility of ectopic pregnancies, and most clinics would offer an early ultrasound scan in the patients who have had a positive pregnancy test at between 6 and 7 weeks' gestation.

Advantages

IUI is a relatively simple technique that is cost-effective and can be offered by both secondary and tertiary fertility centres. It is not as invasive as IVF and allows fertilization to occur within the fallopian tubes and therefore it is generally acceptable to most religious groups.

Disadvantages

The success rates are lower than those with IVF, and if the cycle fails less information is obtained than with an IVF cycle, particularly pertaining to possible egg or subsequent embryo quality. It also requires at least one healthy fallopian tube and reasonable sperm parameters. If monitoring is suboptimal, then there can be a significant increase in higher-order multiple births, with the expected sequelae.

Indications

- Unexplained infertility.
- Mild male factor.
- Ejaculatory problems.
- Cervical problems.
- Ovulatory disorders.
- Mild endometriosis.
- To optimize the use of donor sperm.

In vitro fertilization

In vitro fertilization is where the mature oocyte is surgically removed from the ovary and then fertilized with sperm in the laboratory. The world's first successful IVF baby was delivered by Patrick Steptoe in 1978 after a number of years collaborating with Robert Edwards. Over the last 25 years the success rates and types of IVF have greatly improved and at present there are well over 2 million babies born throughout the world by this technique.

Indications

- Severe tubal disease: tubal blockages.
- Severe endometriosis.
- Moderate male factor.
- Unexplained infertility.
- Unsuccessful IUI.

Protocols

Initially, simple forms of ovulation induction using Clomid and hMGs were used. Over the last 20 years protocols have been refined and these are now classified into three main categories:

1) natural cycle;
2) long protocol (agonist cycles);
3) short protocol (antagonist cycles).

Although there are other short protocols using agonists, these are now less used due to poorer success rates.

Agonist cycles

Long protocols are still at present the most widely used protocols throughout the world. They involve the use of a GnRH agonist that can be taken nasally on a daily basis (e.g. buserelin, nafarelin) or as a daily subcutaneous injection (e.g. buserelin, leuprorelin) or as a depot preparation (goserelin, leuprorelin). The agonist is given continuously and initially increases the production of gonadotrophins (FSH and LH) from the pituitary gland. If this continuous administration is maintained, then downregulation of the GnRH receptors is achieved. This causes a reduction in LH and FSH levels and thus a reduction in stimulation of the ovary. As a result folliculogenesis is suppressed and blood estradiol levels fall to menopausal levels within 3 weeks. As long as the agonists are continued then the ovary is suppressed unless exogenous gonadotrophins are given. The start of agonist administration can be on either day 2 of the menstrual cycle or, more commonly, day 21. The rationale behind using these long protocols is to create a temporary menopause from which the ovaries can then be stimulated by the daily use of FSH/hMG injections.

In a mid-luteal start (normally around day 21), the patient is reviewed when her period starts approximately 7–10 days after the agonist is initiated. A scan and often a blood estradiol level are performed to ensure the patient is adequately suppressed. If this is the case, then gonadotrophins are started the following day and continued until an adequate ovarian response is gained.

An early follicular, or day 2, start can also be used and the patient bought back for her scan and blood test on average 2 weeks later to see if she is suppressed. As in the luteal start, if adequate suppression is obtained, then exogenous gonadotrophins are started and then continued until satisfactory ovarian response is obtained.

Antagonist protocols

Antagonists (ganirelix and cetrorelix) have been in common use for the last 10 years. The antagonist has an almost immediate effect on the pituitary and, unlike agonists, does not need several days to achieve menopausal levels of the pituitary-derived gonadotrophins. Therefore the patient is prevented from having a premature LH surge and ovulating spontaneously within an hour of the start of the antagonist. A daily dose of 0.25 mg is normally given and there is also a 3-mg dose of cetrorelix that can last for several days. The drugs are given subcutaneously and are started either on a fixed day of FSH stimulation (normally on the 5th day of stimulation) or when the lead follicle is a certain size by ultrasound monitoring (normally 14 mm). The antagonists are continued alongside the gonadotrophin stimulation until an adequate response is achieved and then stopped prior to the hCG injection.

The benefits of antagonists over agonists are:

- no menopausal side effects;
- no cyst formation from the initial gonadotrophin surge;
- shorter cycle duration;
- less gonadotrophin required per cycle, therefore lower drug costs;
- antagonist cycles should be used in patients with polycystic ovaries as they have a lower incidence of OHSS which allows the use of an agonist trigger.

Monitoring

It is essential that adequate monitoring is performed during stimulation of the ovaries with exogenous gonadotrophins. Serial transvaginal ultrasound to assess follicular growth should be used. A decreasing number of units continue to use serial estradiol levels to add to the information obtained from the ultrasound. The use of serial estradiol can be useful in some patient groups, particularly if an under- or over-response is anticipated. An under-response can sometimes be anticipated in the older patient or the patient with previously raised FSH levels. An over-response can sometimes be anticipated if there has been a previous over-response or if the patient has polycystic ovarian morphology on her initial diagnostic ultrasound. There seems to be no value in routine estradiol monitoring.

Monitoring during the stimulatory phase allows the dose to be increased or decreased, if appropriate, as well as the timing of the hCG injection.

hCG injection

This is used to induce final maturation of the oocytes prior to oocyte retrieval. Generally, recombinant hCG 250 μg subcutaneously in a prefilled pen is used. If urinary hCG is used, then a dose of 10 000 IU is given, although in patients with an over-response this can be decreased to 5000 IU. hCG should be given when either one or two lead follicles have reached 18 mm. The injection is normally given around midnight to allow for oocyte retrieval approximately 35 hours later prior to physiological ovulation occurring. If the hCG injection is incorrectly administered, then either very few or no eggs are obtained at the egg collection.

Agonist trigger

If the patient is at significant risk of OHSS then, rather than using an hCG trigger with a prolonged half-life and subsequent prolonged stimulation of the corpora lutea, an agonist trigger can be used. This gives a more normal LH surge with a shorter half-life. This has been shown to significantly reduce the rates of severe OHSS. If an agonist trigger is used, then the luteal phase support is often modified (see section on luteal phase support). Agonist triggers are also used in egg donor cycles where the risk of OHSS has to be lower and the embryos are nor replaced in the donor herself.

Oocyte retrieval

Originally, this was done laparoscopically but the advent of real-time ultrasound has allowed a less invasive oocyte retrieval by ultrasound-directed needling of the ovaries. Smaller and better-quality ultrasound probes, particularly with the advent of transvaginal scanning, has allowed both the monitoring of the ovary during stimulation and the actual retrieval itself to be performed transvaginally. Virtually all oocyte retrievals are performed by this transvaginal ultrasound-directed route. The laparoscopic route is still occasionally used if the ovaries are inaccessible transvaginally. This can occasionally occur in frozen pelvises or when the ovaries have been moved out of the pelvis prior to pelvic irradiation.

TVOR can be performed under general anaesthesia or, more commonly, local anaesthesia or some form of intravenous sedation. The procedure generally takes 20–30 min, depending on how many follicles are present. Either a single-use disposable needle is used or a double-channel needle that allows 'flushing' of the follicle if the egg is not obtained on simple aspiration. The needle is inserted under ultrasound control directly into the follicles of one ovary and the fluid aspirated and given directly to the embryologist. If the egg is not found after all the fluid has been aspirated, then the follicle is flushed and re-aspirated to try to find the egg, as well as using gentle needle agitation (Fig. 52.1). After all the follicles have been exhausted from one ovary, the needle is then withdrawn and reinserted under ultrasound control into the other ovary and the process repeated. After the ultrasound probe is removed, the vaginal vault is checked for

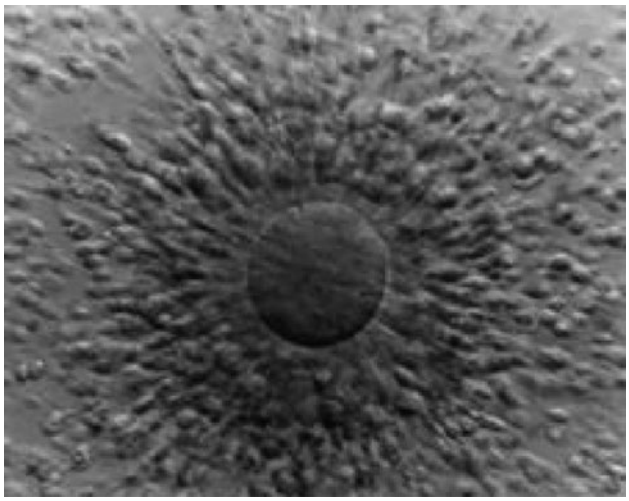

Fig. 52.1 Human oocyte with cumulus cells.

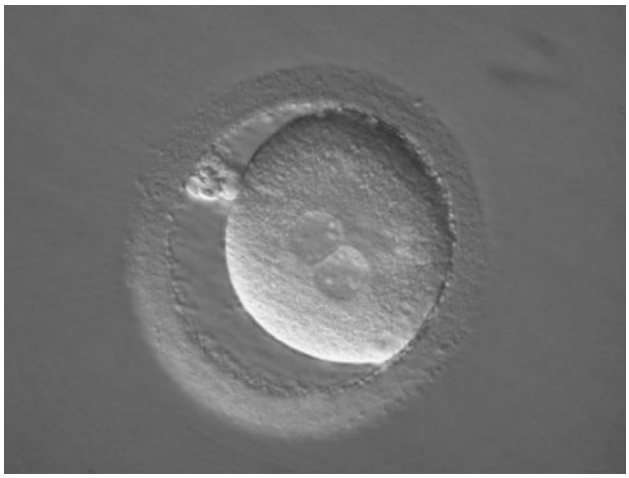

Fig. 52.2 Human embryo 2 pronuclear (PN) stage day 1, normal fertilization.

bleeding; although bleeding is usually not a problem, occasionally an absorbable suture has to be inserted under direct vision for a specific bleeding point. Most patients go home a few hours after the procedure has been completed.

Embryo transfer

Eggs are fertilized either by routine insemination with a concentration of approximately 100 000 normally motile sperm per millilitre or by ICSI (see later section). They are incubated in a commercially prepared culture medium under strict laboratory conditions. The temperature within the incubators is carefully controlled, as are the gas content, humidity and pH.

Traditionally, most embryos were transferred at day 2 or 3 following egg collection. There is now good evidence that if embryos are left in extended culture conditions and transferred on day 5 (at the blastocyst stage), higher pregnancy rates can be achieved [9]. Indeed, day 5 or blastocyst transfer is the default position in most units. Approximately 55–60% of all mature eggs fertilize normally and these are graded by the embryologist on day 2 (Fig. 52.2). At present, the guidelines in the UK from the Humam Fertilisation and Embryology Authority (HFEA) state that only two embryos should be transferred in people under the age of 40, unless exceptional circumstances are present, but over the age of 40 three embryos can be transferred. With increasing success rates and concerns over multiple births, many units now electively transfer one embryo if the patient is under 38 years old, unless she has had multiple previous failed cycles. Although this may have a slight effect on success rates, the other normal embryos are frozen and hence if a cycle is unsuccessful, the patient can undergo repeated single embryo transfers from frozen embryo replacement cycles. Evidence from elective single embryo transfer programmes in Scandinavia and Belgium has shown that twin rates can be virtually eliminated whilst maintaining acceptable overall pregnancy rates [10].

The potential benefits of a day 2 transfer are that a single-stage culture medium can be used and also that the majority of normal embryos survive to this stage. After two or three embryos have been replaced, there may be surplus embryos of a satisfactory quality that are suitable for cryopreservation. The potential downside of a day 2 transfer is that in a normal menstrual cycle, the day 2 embryo is still in the fallopian tube and not in the uterine cavity. Also it is much more difficult to accurately grade a day 2 or 3 embryo. The benefit of a day 5, or blastocyst, transfer is that the embryo has been replaced when it would physiologically be in the uterine cavity –this may have some benefits regarding certain growth factors that can improve embryo development. Blastocyst transfer also allows better selection of embryos as some abnormal embryos perish between day 2 and day 5 (Figs 52.3–52.6).

Embryo transfer is performed without anaesthetic. A Cuscoe's speculum is generally used to visualize the cervix, which is cleaned carefully, and a sterile single-use embryo transfer catheter is carefully inserted through the cervical canal. Where in the uterine cavity the embryos are replaced is a topic of great debate, but it is not uncommon for them to be placed in the mid-cavity portion and generally to stop insertion of the catheter before the fundus where it could potentially cause some slight trauma and bleeding. Evidence suggests that embryo transfer should be performed under ultrasound guidance as this allows more accurate placement of the embryos in the uterine cavity and has been shown to significantly improve success rates [11].

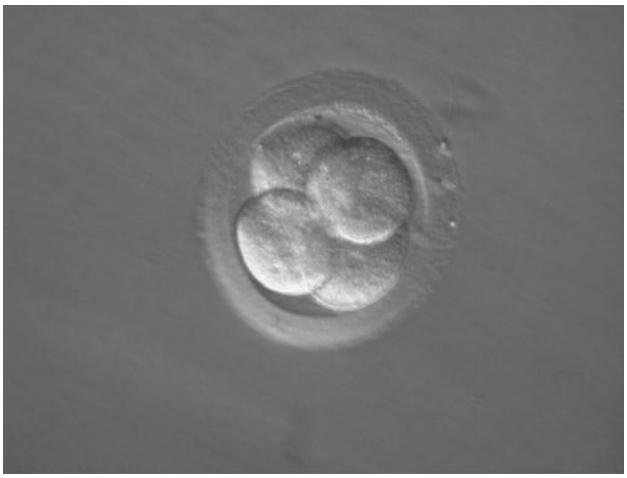

Fig. 52.3 Four-cell stage, day 2.

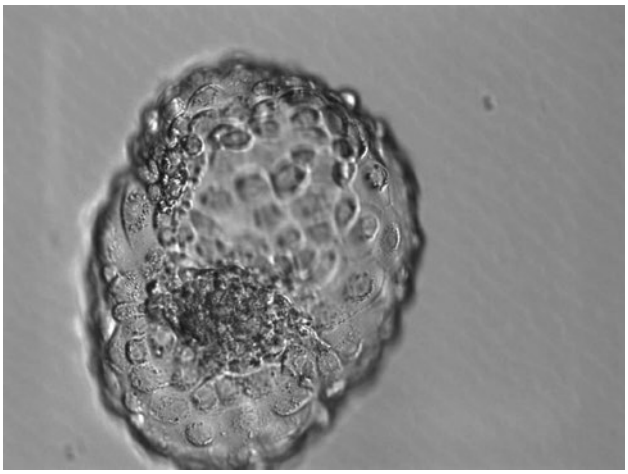

Fig. 52.6 Blastocyst, day 5.

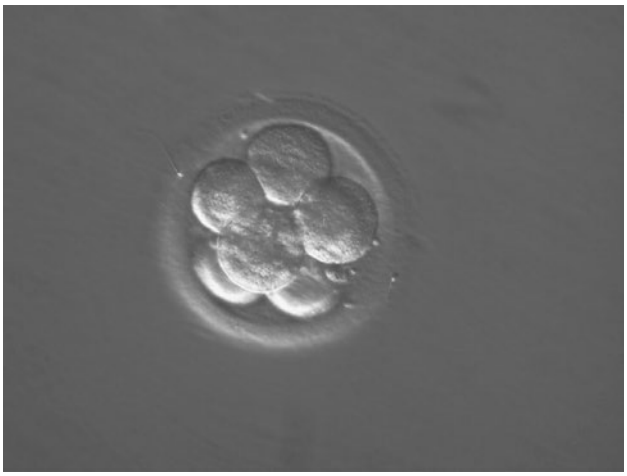

Fig. 52.4 Eight-cell stage, day 3.

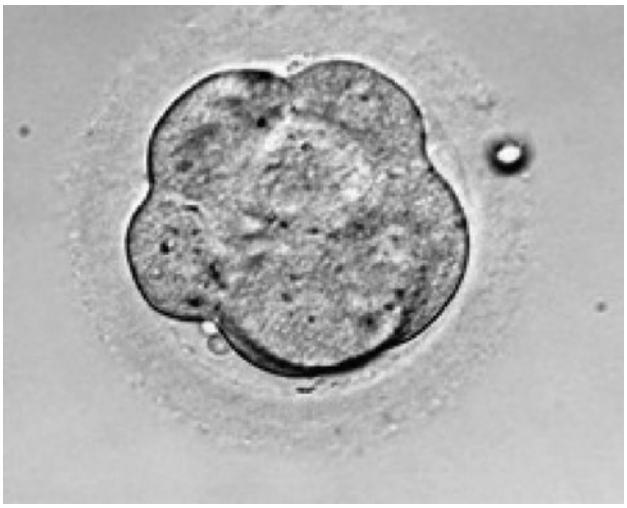

Fig. 52.5 Morula, day 4.

After the outer sheath has been inserted in the correct location, an inner catheter containing the embryos is inserted into the outer sheath. When it is in the correct position a very small aliquot of fluid is used to emit the embryos from the end of the catheter. The inner catheter is then removed and handed back to the embryologist to confirm that no embryos have been retained in the inner catheter. If the catheter is clear, the outer sheath is gently withdrawn and the speculum removed.

Although there is no chance that the embryos can 'fall out', many patients are not surprisingly very cautious at this stage and quite often are allowed to rest in a supine position for up to 2 hours before being allowed to leave the hospital. There has been no evidence that leaving the patients in a supine position increases pregnancy rates, but it may help the patients psychologically.

Luteal phase support

With modern assisted conception utilizing either agonist or antagonist protocols, some form of luteal phase support (LPS) is necessary. Although natural cycle IVF does not need this, superovulation may impair normal corpus luteal function and the use of LPS has been shown to improve success rates [12]. The use of LPS with antagonist cycles is more debatable, but pregnancy rates without it are generally thought to be significantly lower [13]. LPS is broadly divided into three types: (i) use of luteotropic preparations such as hCG, (ii) use of progestogens or progesterone and (iii) use of more intense regimens when there has been an agonist trigger. hCG is given by subcutaneous injection in small aliquots that stimulates the patient's own ovaries to produce more progesterone. It has been shown to be as efficacious as progesterone

but does require an injection and also increases the risk of OHSS in some patients.

The use of progesterone is more common and it can be given as tablets, injections, vaginal gel or vaginal pessaries/rectal suppositories. Intravaginal or rectal use of progesterone achieves extremely good tissue levels very rapidly. It is known that LPS should be given for a minimum of 2 weeks, but some clinics routinely offer it up to 12 weeks or even later. However, there is little good evidence that continuing it beyond 2 weeks significantly improves pregnancy rates. The minimum dose is 200 mg/day but the most commonly prescribed dose is 400–800 mg/day.

The more intense regimens utilize injectable intramuscular progesterone with estradiol supplementation, normally in the form of tablets. The progesterone and estradiol are both routinely continued if the pregnancy test is positive. It is not uncommon for the injectable progesterone to be changed to a vaginal preparation at around 8 weeks of gestation because of the pain caused by the repeated deep intramuscular injections required for the oil-based progesterone preparation.

Pregnancy test

The wait between the embryos being replaced and the pregnancy test is the most psychologically stressful time for the majority of patients. Some patients can start bleeding early, prior to the pregnancy test. Progesterone supplementation can also delay bleeding, even if the pregnancy test is negative. Generally, pregnancy tests are performed around 14 days from embryo transfer and can either be done at home with a urinary pregnancy test or at the clinic with a serum pregnancy test. A home pregnancy test is more convenient for the patient, and the currently available kits have excellent levels of sensitivity down to detection rates of 25 IU. If the pregnancy test is positive and in the normal range, then it is usual to offer the patient a transvaginal scan 2–3 weeks later to ensure that the pregnancy is intrauterine and also to assess its viability. If the initial hCG level is low, then this is often repeated 48 hours later to assess the rise; it if it is suboptimal, then the possibility of an ectopic pregnancy or miscarriage has to be considered and appropriate follow-up organized.

Results

All assisted conception treatment cycles in the UK have to be reported to the national regulator, the HFEA. Details of all these treatments can be accessed by both patients and professionals on the HFEA website (www.hfea.gov.uk). The latest consolidated figures are from 2013 and show that 49 636 women had 64 600 cycles of IVF or ICSI, and 4452 cycles of donor insemination were performed; 14 062 pregnancies were reported as a result of this treatment. There has been a significant increase in the number of patients having an elective single embryo transfer, and as a result multiple pregnancy rates have fallen significantly while overall pregnancy rates have shown a small increase (Table 52.2). This table also reflects the very significant impact that female age has on the chance of a successful pregnancy outcome. In comparison, male age has very little impact.

Treatment cycle numbers are increasing at approximately 3.9% per annum, with 13 839 babies born as a result of IVF treatment using fresh eggs. Over recent years there has been a proportionately greater increase in the number of treatments using frozen and thawed embryos compared with treatment cycles using fresh embryos. In 2013, 12 320 cycles using frozen embryos were performed (10% annual increase). The age-stratified pregnancy rates are presented in Table 52.3, where it can be seen that age has less of an impact because the embryos transferred were collected when the woman herself was younger.

Table 52.2 Pregnancy rates (%) per embryo transfer for IVF using the patient's fresh eggs.

Age (years)	2012	2013
18–34	41.5	41.8
35–37	35.9	38.3
38–39	29.7	30.2
40–42	21.6	23.1
43–44	10.6	12.4
≥45	3.4	7.0
All ages	34.6	35.5

Table 52.3 Pregnancy rates (%) per frozen embryo transfer.

Age (years)	2012	2013
18–34	30.0	33.4
35–37	28.3	30.9
38–39	25.0	29.1
40–42	22.7	25.2
43–44	14.2	13.0
≥45	9.3	13.0
All ages	27.5	30.6

Summary box 52.1

Latest trends in IVF and ICSI in the UK

- Numbers of treatment cycles using 'fresh' eggs have stabilized.
- Numbers of treatment cycles using thawed frozen embryos has significantly increased.
- Treatment cycles using donor gametes are increasing.
- Pregnancy and live-birth rates show a modest increase.
- Multiple pregnancy and live-birth rates continue to decline.
- The percentage of blastocyst transfers continues to grow.
- Rapid increase in the number of egg freeze cycles.

Intracytoplasmic sperm injection

Intracytoplasmic sperm injection is where individual morphologically normal sperm are immobilized and injected into a mature oocyte that has had its surrounding cumulus and corona cells removed. An inverted microscope with a heated stage and micromanipulating equipment is used (Fig. 52.7). The oocyte is carefully positioned using a holding pipette under gentle suction. A very sharp glass injecting pipette is slowly inserted to rupture the oolemma, and the immobilized sperm injected into the oocyte with a very small volume of the medium. The injecting pipette is then carefully removed and the oocyte incubated under the usual stringent laboratory conditions.

Indications

- Severe male factor including azoospermia and subsequent surgical sperm retrieval by MESA, TESE or PESA (see Table 52.1).
- Severe oligoasthenoteratozoospermia.
- Poor or total non-fertilization from previous IVF cycles.
- Pre-implantation genetic diagnosis cycles.

Most IVF units would have approximately 40–60% of their total IVF cycles using ICSI. Studies have been performed to determine if ICSI with normal sperm improves pregnancy rates, but there is no evidence for this strategy [14]. Despite this, the incidence of ICSI appears to be increasing, with one of the driving factors the desire to avoid failure of fertilization at IVF.

Results

Pregnancy rates of 36.5% per transfer are reported [15] with live-birth rates of 30.4% per transfer based on over 28 800 cycles.

Safety

ICSI has been in clinical use since the early 1990s and all the results of the follow-up studies are generally reassuring. Many centres will also recommend male karyotype screening if sperm concentrations are below 5 million/cm^3. Some centres also advocate the use of Y chromosome microdeletion screening, although this is not routinely offered. Cystic fibrosis screening is essential in cases of azoospermia, particularly if it is related to the

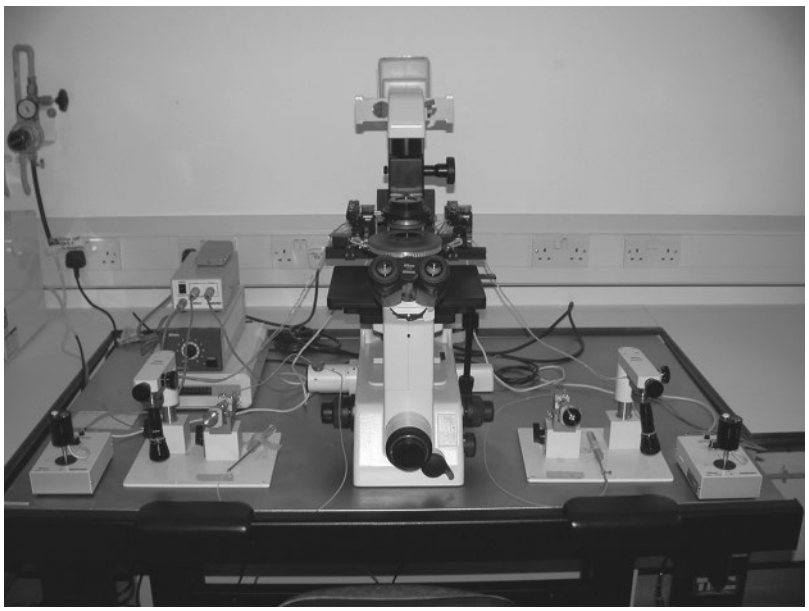

Fig. 52.7 Intracytoplasmic sperm injection micromanipulator.

condition of congenital bilateral absence of the vas deferens, as a significant proportion of these patients will be carriers of the cystic fibrosis mutations. Being a carrier does not preclude them being treated as a couple, but the female partner is then offered screening, and if she also is found to be a carrier, then they should be referred for consideration of IVF–ICSI with PGD.

If all the above results are normal, patients should be counselled carefully that there is a slight increase in genetic abnormalities in the offspring. Most of these abnormalities are thought to be minor and the major congenital malformation rate is generally thought to be similar to that of the general population.

Gamete intrafallopian transfer

Gamete intrafallopian transfer was first used around 1984 and here the eggs are collected laparoscopically, identified by the embryologist and then placed back in the fallopian tube, again laparoscopically, with a small aliquot of specially prepared highly motile sperm. The use of GIFT reached a peak in the early 1990s and has been diminishing since then.

Advantages

GIFT was initially developed to increase the availability of assisted conception due to the scarcity of suitable laboratory facilities and embryological skills. As the eggs did not have to be cultured outside the body, few of the usual laboratory facilities were needed. It appears to be very physiologically sound as both the egg and sperm are in the appropriate place at the appropriate time. The embryo travels physiologically down into the uterine cavity and hence there is no disruption of the endometrial environment, as there would be with normal embryo transfer from IVF.

Disadvantages

It is more invasive than IVF as a laparoscope is used to replace the embryos and sperm through the fimbrial end of the fallopian tube. The eggs are generally collected by transvaginal egg collection as it has been shown that more eggs are obtained by this route. As part of good clinical practice, only a limited number of eggs are replaced, even though it is not known whether these will fertilize normally by the sperm that is added. Therefore less information is obtained than with an IVF cycle. At least one fallopian tube should be healthy. Normal sperm parameters are also optimal, although GIFT can be used in cases of mild male factor disease.

The place of GIFT in the third millennium is often debated and its routine use is now very limited. Most European centres would only use it in cases where IVF is not allowed for religious reasons. Since conception occurs within the body, GIFT is often acceptable even though IVF is not. In some cases of totally unexplained infertility, where there has been repeated IUI and IVF failures, GIFT may also have a small place.

Success rates

These vary enormously depending on patient selection, but success rates in appropriate circumstances can be 30% live birth per transfer [13]. Apart from a few advocates, the use of GIFT in most large clinics accounts for less than 0.5% of all their assisted reproductive technology cycles.

Frozen embryo replacement cycle

The first pregnancy resulting from a frozen human embryo was in 1985 and since then the use of frozen cycles has increased dramatically. Freezing surplus morphologically normal embryos allows the use of those embryos that otherwise may have been wasted. Freezing surplus good-quality embryos is now routine, and this allows a significantly increased cumulative chance of pregnancy per egg collection. Normally, embryos are frozen on day 5 after the selected ones have been replaced fresh, but can be frozen any time from day 1 through to day 5. The use of day 1 freezing is normally confined to elective freezing of all embryos when there is a high risk of OHSS occurring. Slow freezing protocols of embryos have now generally been replaced by ultra-rapid vitrification protocols. The increased use of blastocyst culture and the highly successful warming rates post vitrification are both leading to increased success rates with cryopreserved embryos. Some centres believe that elective freezing of all embryos might improve both efficacy and safety for mother and fetus, and prospective randomized controlled trials are currently underway to assess this.

Transfer of frozen embryos

There are two main ways to transfer frozen embryos: first, replace them in a spontaneous menstrual cycle or, second, suppress the patient's own menstrual cycle with GnRH agonists and then supplement with oestrogen to thicken the endometrium prior to embryo replacement.

Natural cycle

The patient has to have regular menstrual cycles for this to be a feasible option and the patient's cycle is then monitored by serial ultrasound scan as well as hormone profiling, including estradiol and LH measurements. As long as there are no adverse factors noted on these measurements, the embryos are thawed and replaced approximately 6 days after the LH surge has been detected (if the embryo is vitrified at the blastocyst stage). Approximately 80% of frozen blastocysts survive the

thaw process and, depending on the age of the patient, one, two or three embryos are replaced. No LPS is required as the ovaries are not downregulated, and sufficient natural progesterone is produced from the patient's own corpus luteum.

Medicated cycles

The majority of frozen embryo replacement cycles (FERC) employ suppression of the patient's own menstrual cycle as this gives better control, although there is some controversy as to whether this gives better results. A GnRH agonist is used for suppression of the menstrual cycle and is normally started on day 21. If the patient is menopausal, then this is not required and only oestrogen supplementation is used. After adequate suppression has been achieved, hormone supplementation in the form of oestrogen is used. This is generally an increasing regimen with either tablets or patches until sufficient endometrial thickness has been achieved. The embryos are replaced in a similar fashion to IVF and, because of ovarian suppression, LPS is required. If the patient is pregnant this is continued up to approximately 12 weeks of pregnancy.

All IVF units should have a frozen embryo replacement programme and it is not only generally accepted as a safe and effective means of treatment but also one that is cost beneficial, maximizing the use of the patient's fresh cycle.

Summary box 52.2

Frozen embryo replacement cycles

- There is a significant increase in the use of thawed frozen embryos.
- Vitrification has become the main technology for cryopreservation.
- Both natural cycle and medicated frozen cycle treatments remain popular.
- Shorter GnRH antagonist medicated cycles are available.
- The concept of 'freeze-all' embryos is currently being evaluated in prospective randomized controlled trials.
- Elective freezing or 'segmentation' of treatment cycles may reduce the incidence of OHSS.

Egg donation

Oocyte donation is where a donor oocyte obtained from a fresh IVF cycle from a suitable screened donor is fertilized with the sperm from the recipient's partner and the fertilized embryo replaced in the recipient. The first successful pregnancy from an egg donation cycle was in 1983.

Procedure

Unfertilized mature oocytes are obtained from a donor who, in the UK, should be less than 37 years old, healthy and preferably of known fertility. The donor is screened for hepatitis B, hepatitis C and HIV as well as for appropriate genetic diseases. It is generally recommended that both the donor and recipient undergo counselling with regard to the implications of egg donation and the possible outcome. A routine IVF cycle is then performed and, depending on the sperm parameters of the male partner of the recipient, the eggs fertilized either routinely or with ICSI. The resultant embryos can be replaced fresh or in a frozen cycle.

The recipient is prepared in a similar way to FERC. If the menstrual cycle is regular, the embryos can be replaced in a natural cycle (although this is unusual as recipients rarely have normal menstrual cycles). More often than not, they are replaced as in a suppressed FERC with the use of oestrogen to produce an optimum endometrium for implantation.

Indications

- Ovarian failure, either premature or physiological.
- Patients with very poor ovarian function where previous IVF has repeatedly failed.
- Patients over the age of 45 and with severe male factor disease necessitating ICSI.
- Patients with hereditary genetic disease where using the patient's own gametes is not advisable.

Benefits

The recipient adopts the success rate corresponding to the age of the donor. Therefore success rates with egg donation are generally high. Any resultant offspring have the aneuploidy rates of the age of the donor as well. Therefore for a patient who is over the age of 40, the success rates are far greater and the risks of genetic disease, such as Down's syndrome, significantly lower.

Problems

The main problem with oocyte donation is obtaining eggs. In the UK it is illegal at present to pay donors for their eggs and they are only allowed to be compensated minimally for their time and inconvenience. Since 1 April 2005, anonymity for the donors has also been repealed and any resultant offspring can trace their genetic mother from the age of 18. At present, demand for donor eggs in the UK outstrips supply, and this has led to many patients seeking cross-border reproductive care in countries where legislation differs and donors are more plentiful.

Egg share programmes can be used where a person requiring IVF for personal reasons agrees to donate half

her eggs to an unknown recipient in lieu of having a reduced cost for her own IVF cycle.

Surrogacy

Surrogacy is used when a patient's uterus is either absent or unable to maintain a pregnancy, and a surrogate or host uterus is used to carry the pregnancy. Generally this procedure is used where a young patient has lost her uterus to cancer or to uncontrollable bleeding, for example postpartum haemorrhage or following a difficult myomectomy. The patient's own eggs are obtained as in an IVF cycle, fertilized by her partner's sperm and the resultant embryos replaced within the surrogate. Counselling is obligatory for both the patients and the surrogate. Generally, surrogates are women who have already had children themselves and are recruited either by the patients or through charitable organizations. Surrogacy is legal in the UK and the surrogate can be compensated for time lost away from employment during the pregnancy. However, the child's legal mother is the woman who delivers the child and therefore the patient and the husband have to undergo formal court order procedures to become the legal parents of their genetic offspring which the surrogate has delivered. The laws governing surrogacy vary widely from country to country.

Egg freezing

Egg freezing is where eggs are obtained from an IVF cycle, but rather than being fertilized with sperm are left unfertilized and then frozen for future use. Unfortunately, using slow-freezing techniques unfertilized eggs did not survive the freeze–thaw process anywhere near as well as an embryo due to the large size of the unfertilized eggs and the high water content. This caused problems during the freezing process as ice crystals can form within the egg, disrupting the delicate structures and resulting in its demise when thawed. Egg freezing programmes using conventional slow-freezing techniques are associated with low pregnancy rates of under 10% per transfer. As a result of these poor results such treatment was usually only recommended for young patients with cancer facing treatments such as chemotherapy, radiotherapy or sterilizing surgery. Recently, an alternative approach to cryopreservation called vitrification has been attempted. Improvements in thaw rates are seen (>80%) and pregnancy rates of up to 35% per transfer have been reported [16]. This new technology may justify an expansion of the indications of egg storage from fertility preservation in oncology patients who have no partner to the so-called 'social' egg freezing that may be popular with professional women trying to delay the impact of age-related decreases in ovarian function and egg quality.

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis is a form of very early prenatal diagnosis. It combines the techniques of assisted conception with molecular genetics and cytogenetics to detect genetic disease in embryos at the pre-implantation stage. It allows couples who carry serious genetic disorders to have embryos free of these diseases transferred into the uterus, allowing the woman the secure knowledge that she is starting off the pregnancy with an unaffected embryo. This prevents the need for invasive prenatal diagnosis and the difficult decision on whether to terminate an affected pregnancy. The technique was pioneered at the Hammersmith Hospital in the early 1990s [17], and can now be applied to almost all hereditary conditions where the mutation is known.

Indications

- Single gene defects such as cystic fibrosis, thalassaemia or sickle cell disease.
- Chromosomal rearrangements such as translocations.
- HLA matching for donor sibling stem cell transplantation.
- Predisposition genes, e.g. *BRCA*.

Procedure

The embryos are obtained as with any routine IVF procedure, although generally ICSI is now used to minimize the potential for genetic contamination. Biopsy may be of the polar body (at the MII oocyte phase), at the cleavage stage of development on day 3, or more commonly at the blastocyst stage on day 5. The zona pellucida of the embryo is opened by using either acid-tyrodes or special lasers, and several trophoblast cells are removed for the specific test itself. The genetic material is amplified and a variety of different approaches are used to make the genetic diagnosis, including comparative genomic hybridization (CGH) and, most recently, next generation sequencing (NGS). Unaffected embryos are then transferred to the uterus.

Pre-implantation genetic screening

Chromosomal aneuploidy in human embryos is one of the commonest reasons for failure of implantation following IVF. These aneuploidies may be age-related aneuploidies in the egg (meiotic) or related to early cell division in the embryo (post-zygotic). Pre-implantation genetic screening is the use of PGD techniques to detect these aneuploidies in an attempt to ameliorate the impact of female age on IVF. Initial indications for the technique were advanced maternal age, recurrent IVF failure at the

stage of implantation, previous aneuploid pregnancies and recurrent miscarriage. The technique originally used multicolour fluorescence *in situ* hybridization and was controversial not because of its attractive self-evident hypothesis but its lack of a robust evidence base. Eventually, following prospective randomized controlled trials it was shown to be ineffective. Advances such as whole genome amplification, CGH and NGS have led to a renewed interest in PGS and these novel exciting approaches are currently under evaluation.

Surgical sperm retrieval

In cases where there is either azoospermia or necrozoospermia, surgical sperm retrieval can be performed to obtain sperm directly from the epididymus (MESA) or the testis (TESE or PESA). A biopsy should always be taken from each testis and sent to histopathology, as carcinoma *in situ* can be found in approximately 1% of subfertile men.

These techniques can be performed under either local anaesthetic or a light general anaesthetic. The patient should be screened for cystic fibrosis and karyotyping prior to the procedure. There are major chromosomal abnormalities in just over 2% of infertile men, which is three times the normal incidence. In the case of azoospermia this increases to over 15%. If semen results are in the normal range, then chromosomal abnormalities are significantly lower. An FSH level is also beneficial: if in the normal range, then the chance of obtaining usable spermatozoa is much higher (around 90% if testicular volumes are normal); if FSH is markedly raised, then the chance is significantly lower (less than 10% if testicular volumes are reduced).

Any sperm obtained through these techniques is then cryopreserved for future use. The sperm can be used fresh if the operation is timed to coincide with the oocyte retrieval on the female side. ICSI has to be used in all cases of surgical sperm retrieval as there are inadequate motile sperm for normal fertilization.

Donor sperm

If no usable sperm are obtained from surgical sperm retrieval or from ejaculation, then the use of donor sperm is generally offered. Donor sperm is obtained by masturbation from healthy screened donors. All donor sperm in the UK has to be quarantined, and then the donor screened again. Sperm can then only be released for use after both sets of screening have been found to be negative.

Indications

- Azoospermia.
- Carriers of severe genetic disease.
- Lesbian/single women.

Use

Donor sperm used to be inseminated around the cervix using an unprepared specimen close to what was thought to be the fertile time. Now a prepared sample of sperm is used and inseminated directly into the uterine cavity as part of an IUI programme. The patient has the usual screening tests, including a test of tubal patency, and as long as the menstrual cycle is regular, the cycle is monitored and at the appropriate time, around ovulation, the prepared sample is inseminated directly into the cavity. If the patient has irregular cycles or unstimulated IUI has been unsuccessful, then stimulated IUI can be performed and success rates are generally higher. If the fallopian tubes are severely damaged or blocked, then the donor sperm has to be utilized with techniques such as IVF. Success rates are almost entirely dependent on the age of the patient.

Complications of assisted conception

Multiple births

The most common complication of assisted conception is that of multiple births. Of all the patients that have become pregnant through IVF programmes, approximately 24% have twins when two or three embryos are transferred. Triplet rates vary depending on the percentage of embryo transfers that are three embryos or more. In the UK a maximum of three embryos can be transferred, but only under exceptional circumstances or if the patient is 40 years old or greater. The majority of embryo transfers in the UK at present are two-embryo transfers. Even with a twin pregnancy, the risk of cerebral palsy is up to eight times greater than that of a singleton pregnancy. In triplet pregnancies, the rate can be as high as 47 times greater. The offspring also are at risk of all the other multiple sequelae of prematurity [18].

To try to reduce the rate of multiple births, the HFEA has made strong recommendations to move towards elective single embryo transfers. As clinical and laboratory techniques improve, this should maintain acceptable pregnancy rates and reduce the twin rate to monozygotic twins only. Indeed in some Scandinavian countries, if the patient is 35 years old or under, then elective single embryo transfer is the only route allowed. One embryo is transferred fresh and all the other embryos are frozen, and the patient undergoes repeated single embryo transfer until the desired outcome or all the embryos are used up. Although there is increasing evidence to support the advocacy of elective single

embryo transfer, it can be difficult to persuade patients as many see a twin pregnancy as a desirable outcome. There has been tremendous progress in reducing the incidence of multiple pregnancy through elective single embryo transfer strategies.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome is an iatrogenic condition that can occur in any IVF cycle, but usually is only mild to moderate. It is characterized by an excessive ovarian response resulting in multiple follicular growth and large numbers of eggs collected. Severe OHSS can be life-threatening and is associated with intravascular fluid depletion and thrombosis, ascites and pleural effusion. It generally occurs in specific at-risk groups, in particular young patients who have polycystic ovaries. In these situations the starting dose of gonadotrophins should be lowered to take account of the increased sensitivity of the polycystic ovaries. Even in the best centres with adequate monitoring there can be a surprisingly brisk ovarian response and the ovaries can hyperstimulate. In these situations several options are available. The cycle can be abandoned and then restarted at a lower dose or the eggs collected, fertilized and all the embryos electively frozen as severe hyperstimulation tends to be most serious in patients who become pregnant from a fresh transfer. Lastly, if the risks have been fully considered and still thought acceptable, the embryos can be transferred and the patient very carefully monitored. If OHSS develops, admission to hospital is essential for monitoring fluid balance and plasma protein levels. Human albumin solution should be given if hypoproteinaemia develops. If the patient develops tense ascites, it can be drained on a daily basis, limited to 1 L in multiple aliquots, as this often gives great relief and increases urinary output but avoids abrupt hypoproteinaemia. If the patient develops pleural effusions, these also can be tapped, although draining the ascites helps these as well. Because of the increased risk of thromboembolism, patients should also receive thromboprophylaxis in the form of antithrombotic stockings and low-molecular-weight heparin daily. Generally the condition is self-limiting but the patient should be kept in hospital and closely monitored until the OHSS has resolved. The condition does not appear to adversely affect the fetus and the subsequent pregnancy is generally successful. On the rare occasions where the situation is deteriorating and the patient's life is at risk, the pregnancy may need to be terminated. New strategies involving the use of GnRH antagonist protocols, GnRH agonist triggers and elective cryopreservation of embryos have now made severe OHSS a very rare occurrence.

Ectopic pregnancy

Ectopic pregnancy can occur with any of the assisted reproductive techniques, and not only in patients with tubal disease – any patient undergoing any form of assisted conception is at a greater risk. In IVF programmes the generally accepted rate is between 2 and 5%, even though the embryos are transferred directly into the uterine cavity. This may be due to uterine contractions and it is probable that embryos move into the fallopian tubes at some stage but return to the uterine cavity. Patients successfully pregnant following assisted conception should always be offered an early scan to ensure that the pregnancy is intrauterine. If the pregnancy is found to be extrauterine, then the full range of treatment options should be discussed with the patient. With the increasing number of salpingectomies performed for hydrosalpinges, it is hoped that the incidence of ectopic pregnancy with IVF will reduce.

Transvaginal oocyte retrieval

There are always accepted risks of complications from ultrasound-guided oocyte retrieval, and these can range from infection of the ovaries causing ovarian abscess, through to damage to the bowel. These are generally quoted at 1% or less, and all patients should be counselled about them prior to starting their treatment [19].

Summary

More than 5 million babies have now been born following IVF. Assisted conception treatments continue to grow internationally and in some developed countries they now account for more than 2% of live births. There has been a steady improvement in success rates due to scientific advances, despite the increased age of patients accessing treatment. IVF treatments are becoming safer and there have been significant reductions in the rate of OHSS, principally through the introduction of GNRH agonist triggers. Multiple pregnancy rates following IVF are also reducing through the use of elective single embryo transfer. Cryopreservation is proving to be an increasingly important part of assisted conception treatment, with fertility preservation becoming ever more popular for medical and non-medical reasons as oocyte vitrification techniques improve.

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Part 12

Pelvic Pain

53

Endometriosis

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The contemporary definition of endometriosisis is an inflammatory disease associated with pelvic pain or infertility that is characterized by lesions of endometrial-like tissue outside the uterus [1]. It is thus more than the presence of endometrial glands and stroma outside the uterus, the experience of pelvic pain or infertility by women with the disease being the important defining features. It is preferable to take a patient-centred approach to endometriosis, with a focus on patient-centred outcomes, rather than the lesion-based approach that has been the hallmark of much clinical research in recent decades.

Endometriosis affects approximately 176 million women of reproductive age worldwide [2]. While its underlying cause is uncertain, it is likely to be multifactorial including genetic factors with epigenetic influences, and perhaps promoted through environmental exposures [3]. Endometriosis has elements of a pain syndrome with central neurological sensitization [4], and is a proliferative, oestrogen-dependent disorder with growing evidence of progesterone resistance [4]. There is overlap with other conditions characterized by pelvic/abdominal pain and infertility. Some symptomatic women with pelvic pain who do not have diagnosed endometriosis may benefit from similar treatments.

Epidemiology

Aetiology

The oldest proposal for the formation of endometriosis is Sampson's theory of *retrograde menstruation* [5] or, more aptly, retrograde passage and implantation of endometrial tissue. Menstrual material containing viable cells is transported into the peritoneal cavity in a retrograde direction along the fallopian tubes and the refluxed endometrium then implants onto the surface of exposed tissues, principally the peritoneum. The amount of menstrual backflow seems important as higher prevalence rates occur in women with increased menstrual exposure due to (i) obstructed outflow associated with Müllerian anomalies, (ii) short menstrual cycles, (iii) increased duration of bleeding, and (iv) decreased parity [6]. In addition, endometriosis is found more commonly on the left side of the pelvis, thought to be due to the cleft created by the sigmoid colon's peritoneal reflections. However, Sampson's theory does not explain all endometriosis since it can occur before menarche, in women with amenorrhoea, despite menstrual suppression, at the umbilicus, and (incredibly rarely) in men. Hence the theory of *coelomic metaplasia*, the pluripotential of coelomic epithelium to develop not only into the more appropriate normal tissue but also, through a programming defect, into endometriotic tissue. Furthermore, despite the ubiquitous occurrence of retrograde menstruation, which gynaecologists often view at the time of laparoscopy during menses, endometriosis occurs only in a minority of women, and this is explained by the third theory, the contribution of *immunologic surveillance defects* (which also explains the association of endometriosis with other autoimmune diseases). The expression of factors such as cell adhesion molecules, proteolytic enzymes and cytokines affecting the adherence, implantation and proliferation of tissue within the peritoneal cavity may differ between women, as may clearance of endometrial cells from the pelvis, and altered systemic humoral immunity (altered B-cell function and antibody production) has also been implicated. It is unclear whether such abnormalities are truly a cause or a result of the disease. Finally, *embolic transport* of endometrial cells through the blood and lymphatic stream may contribute to the very rare

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

occurrences of endometriosis at sites distant from the pelvis, including lungs, brain and nasal tissues (responsible for the rare case reports, so loved by journal editors, of catamenial pneumothorax and haemoptysis, catamenial epilepsy and catamenial epistaxis).

Risk factors include age, increased peripheral body fat and greater exposure to menstruation (short cycles, long duration of menses and reduced parity), whereas smoking, exercise and oral contraceptive use (current and recent) may be protective [6]. However, there is no evidence that the natural history of the disease can be influenced by controlling these factors. There is clear genetic predisposition: endometriosis is six to nine times more common in the first-degree relatives of affected women than in controls; and in an analysis of more than 3000 Australian twin pairs, over 50% of the variance of the latent liability to the disease was attributable to additive genetic influences [7]. Stage 3–4 disease has a stronger genetic linkage than stage 1–2 disease [8]. Endometriosis is inherited as a complex genetic trait, similar to diabetes or asthma, meaning that a number of genes interact to confer disease susceptibility, but the phenotype probably only emerges in the presence of environmental risk factors. (Other than the known risk factors outlined above, specific promoting environmental agents have proven elusive. One of the most appealing environmental exposure theories, that the environmental pollutant dioxin might be an underlying cause of the disease [9], was ultimately difficult to confirm.) Genome-wide association studies (GWAS) [8,10–12] have confirmed genetic associations and nine genome-wide significant genetic susceptibility loci have been reported in at least one dataset. However, there is no indication of high-risk mutations, such as the *BRCA* mutation in breast cancer. The logarithm of the odds (LOD) score for the genetic loci on chromosome 7 [13] and chromosome 10 [14] is between 3 and 4, compared with the LOD score of over 20 for the *BRCA1* gene. The currently recognized nine endometriosis gemetic loci explain only 3.5% of the heritability of endometriosis, compared with the *BRCA1* gene which is considered to account for 60–70% of cases of familial breast cancer.

Prevalence

The prevalence is estimated to be 8–10% in women in the reproductive years [6]. Reported rates of endometriosis have long been recognized to be highly variable in different populations of women (Summary box 53.1).

Summary box 53.1

Prevalence rates at laparoscopy for different indications

	Number of studies	Number of patients	Number with disease	Percent with disease (range)	Percent with stage I–II disease (range)
Pelvic pain	15	2 400	688	24.5 (4.5–62.1)	69.9 (61.0–100)
Infertility	32	14 971	2812	19.6 (2.1–78.0)	65.6 (16.3–95.0)
Sterilization	13	10 634	499	4.1 (0.7–43.0)	91.7 (20.0–100)

Source: Eskenazi & Warner [6]. Reproduced with permission of Elsevier.

Natural history of endometriosis and associated comorbidities

Whilst endometriosis occurs most commonly in the reproductive years, it should also be considered in adolescents with suggestive symptoms; in fact most women with endometriosis date the onset of symptoms to their teens [15]. Women with endometriosis appear to have a higher risk of obstetric complications, including preterm delivery, antepartum haemorrhage, pre-eclampsia and need for caesarean section, with rare occurrences of intra-abdominal bleeding from endometriotic lesions requiring urgent surgery [1]. Even though 97% of women with endometriosis become pain-free after menopause [16], symptoms of endometriosis may also persist after natural or surgical menopause. If hormone replacement treatment (HRT) is required for women with a history of endometriosis, it is wise to use a combined oestrogen/progestin preparation. Evidence is emerging regarding comorbidity for women with endometriosis. There may be subtle associations with ovarian and breast cancers, cutaneous melanoma, asthma and some autoimmune, cardiovascular and atopic diseases, and women with endometriosis appear to be at decreased risk of cervical cancer [17]. Endometriosis has been recently shown to have a significant association with coronary heart disease (relative risk, RR 1.62, 95% CI 1.39–1.89) [18]. There is an association between endometriosis and clear-cell,

low-grade serous and endometrioid ovarian cancer [19], but the overall risk of ovarian cancer among women with endometriosis remains low, with a relative risk ranging from 1.3 to 1.9 [20]. This equates with an increased lifetime risk of ovarian cancer of no more than 1 in 100, which is not considered sufficient to mandate routine ovarian cancer screening for women with a history of endometriosis. Much more rarely, endometriosis may present as an invasive disease while remaining histologically benign, with ascites, sometimes even pleural effusions, and invasive lesions affecting not only the pelvis but also the diaphragm, bowel and abdominal side-walls, and thus may be impossible to distinguish clinically and on imaging from intra-abdominal malignancy.

Endometriosis phenotypes at laparoscopy

Although a stronger focus on the symptoms experienced by women and their outcomes is currently needed, it is also important to retain an understanding of endometriosis lesions, as this features prominently in the literature. It is also of practical importance, as endometriotic lesions that are not absolutely typical often remain unrecognized by less experienced laparoscopists (Fig. 53.1).

Peritoneal (or typical) endometriosis

Peritoneal endometriosis comprises superficial lesions scattered over the peritoneal, serosal and ovarian surfaces. The appearance has been described as 'powder-burn' or 'gunshot' deposits.

Cystic ovarian endometriosis (endometriomas)

Endometriomas develop as cystic lesions within the ovary, classically forming 'chocolate cysts' due to the degradation of blood over time to a thick haemosiderin-rich fluid. Several variants on the implantation and metaplasia theories have been proposed to account for ovarian endometriomas. Thus, it has been suggested that superficial lesions on the ovarian cortex become inverted and invaginated, and that endometriomas are derived from functional ovarian cysts or metaplasia of the coelomic epithelium covering the ovary. Endometriomas have features in common with neoplasia such as clonal proliferation, which is consistent with the endometriosis disease theory. They are statistically associated with subtypes of ovarian malignancy, such as endometrioid and clear-cell carcinoma. However, it still remains uncertain whether such cancers arise from malignant transformation of benign endometriotic tissue.

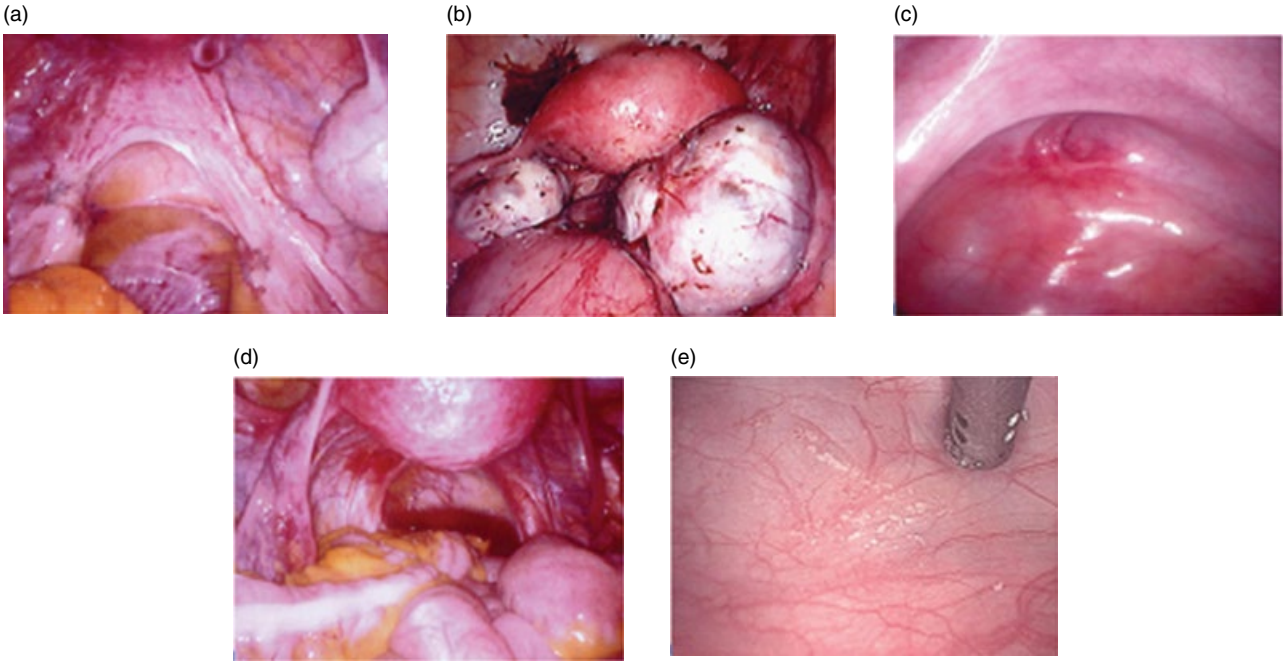

Fig. 53.1 Laparoscopic appearances of different endometriosis phenotypes: (a) peritoneal (typical) endometriosis adjacent to deep endometriosis of the left uterosacral ligament; (b) endometrioma of the right ovary; (c) peritoneal pocket in the anterior pouch of Douglas; (d) uterine adenomyosis and flame endometriotic lesion of left broad ligament; (e) subtle endometriosis vesicular lesions of the peritoneum. Images (a), (b), (d) and (e) kindly contributed by Dr Michael East, Gynaecologist, Oxford Women's Health, Christchurch, New Zealand. (*See also colour plate 53.1*)

Deep endometriosis

Now defined as lesions extending deeper than 5 mm under the peritoneal surface or those involving or distorting bowel, bladder, ureter or vagina [21], recognition of deep endometriosis may pose substantial difficulties for the inexperienced surgeon. Donnez *et al.* [22] suggested that these are a form of adenomyosis arising in Müllerian rests in the rectovaginal septum, and it has been proposed that deep endometriosis should be redefined as adenomyosis externa on pathological grounds [23]. However, deep endometriosis can be more widespread than this location. Numerous subtypes of deep endometriosis have even be described (Fig. 53.2), but such subclassifications become esoteric, as there is little consensus about the best treatment approaches for deep endometriosis [1] and more research focus needs to go into defining subtypes that actually predict response to different treatments, both surgical and medical.

Other phenotypes

Koninckx *et al.* [24] added three more lesion phenotypes to the three traditionally recognized phenotypes described. These were adenomyosis, peritoneal pocket lesions and subtle endometriosis. *Adenomyosis* is characterized by ectopically placed endometrial glands and stroma within the wall of the uterus itself, usually distributed through the endometrium and sometimes forming discrete myomas known as ademomyomas. *Peritoneal pocket lesions* were formerly assumed to reflect 'scarring from old endometriosis' but excision of such lesions usually reveals active endometriosis in the pocket margins. More recently recognized *subtle or atypical endometriosis* comprises red implants, polypoid lesions, and serous or clear vesicles. It remains unclear, however, whether these subtle lesions should be considered early disease, or whether they are transient physiological events without any clinical significance [25]. The 'most subtle' of all endometriotic lesions would be microscopic endometriosis [26], in other words the histological finding of endometriosis in macroscopically normal peritoneum. The significance of microscopic endometriosis is unclear but it seems likely that most endometriotic lesions would need to pass through this stage as they progress to macroscopic lesions.

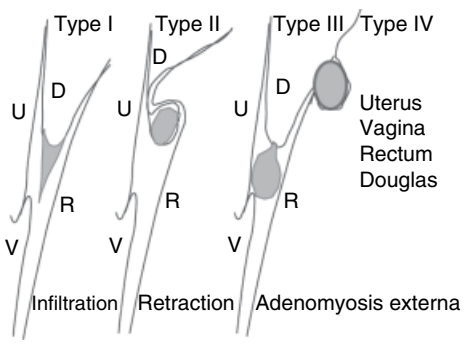

Fig. 53.2 Types of deeply infiltrating endometriosis. *Source:* Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? *Fertil Steril* 1992;58:924–928. Reproduced with permission of Elsevier.

Classification systems

The World Endometriosis Society consensus [21] identified three classification systems of value (from many proposed), although these still have limitations. There is an argument that all women with endometriosis undergoing surgery should have a Revised American Society of Reproductive Medicine (r-ASRM) score and stage completed [27], women with deep endometriosis should have an Enzian classification completed [28], and women for whom fertility is a future concern should have an Endometriosis Fertility Index (EFI) completed [29], and documented in the medical/surgical records (Fig. 53.3); that is, until better classification systems have been validated.

The most widely used classification is the r-ASRM classification [27], in which points are allocated for endometriotic lesions, periovarian adhesions and pouch of Douglas obliteration (Fig. 53.3a). The total score is then used to describe the disease as minimal (stage I), mild (stage II), moderate (stage III) or severe (stage IV). Stages I and II consist mainly of superficial lesions, and stages III and IV of endometriomas. The limitations of the r-ASRM classification system are that it does not describe deep endometriosis adequately, has poor correlation with fertility outcomes and very poor correlation with pain symptoms and quality of life, gives poor prognostic information, and has poor predictive accuracy with respect to treatment outcomes [21]. The main forces that perpetuate the r-ASRM classification system are its longevity, its widespread clinical use, its prevalence in the literature describing the operative appearance of endometriosis, and its incorporation into other classification systems of potentially greater value.

If the r-ASRM classification is to be used, the Enzian classification system [28] should be employed when deep endometriosis is also present to give a complete description of the operative findings (Fig. 53.3b). Enzian may also be used preoperatively based on findings on clinical examination, transvaginal ultrasound and MRI in order to assist planning of surgery by predicting the extent of deep endometriosis and the time required for surgery. However, the Enzian classification also has poor correlation with symptoms and infertility, and limited prognostic value for the

(a)

REVISED AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE CLASSIFICATION OF ENDOMETRIOSIS 1985

Patient's Name _____ Date: _____

Stage I (Minimal) 1-5 Laparoscopy_____Laparotomy_____Photography_____
Stage II (Mild) 6-15 Recommended Treatment _____
Stage III (Moderate) 16-40 _____
Stage IV (Severe) >40
Total _____ Prognosis _____

	ENDOMETRIOSIS	< 1 cm	1 – 3 cm	> 3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/3 Enclosure
Ovary	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____ Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

L R

To Be Used with Abnormal Tubes and/or Ovaries

L R

Fig. 53.3 Classification systems for endometriosis. (a) Revised American Society for Reproductive Medicine classification system. *Source:* Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817–821. Reproduced with permission of Elsevier. (b) Enzian classification system for women with deep endometriosis. *Source:* reproduced with permission from Professor Jörg Keckstein; www.endometriose-sef.de/dateien/ENZIAN_2013_web.pdf; accessed 30 June 2016) (*See also colour plate 53.3b*). (c) Endometriosis Fertility Index for women with endometriosis for whom future fertility is a consideration. *Source:* Adamson GD, Pasta DJ. Endometriosis Fertility Index: the new, validated endometriosis staging system. *Fertil Steril* 2010;94:1609–1615. Reproduced with permission of Elsevier.

(b)

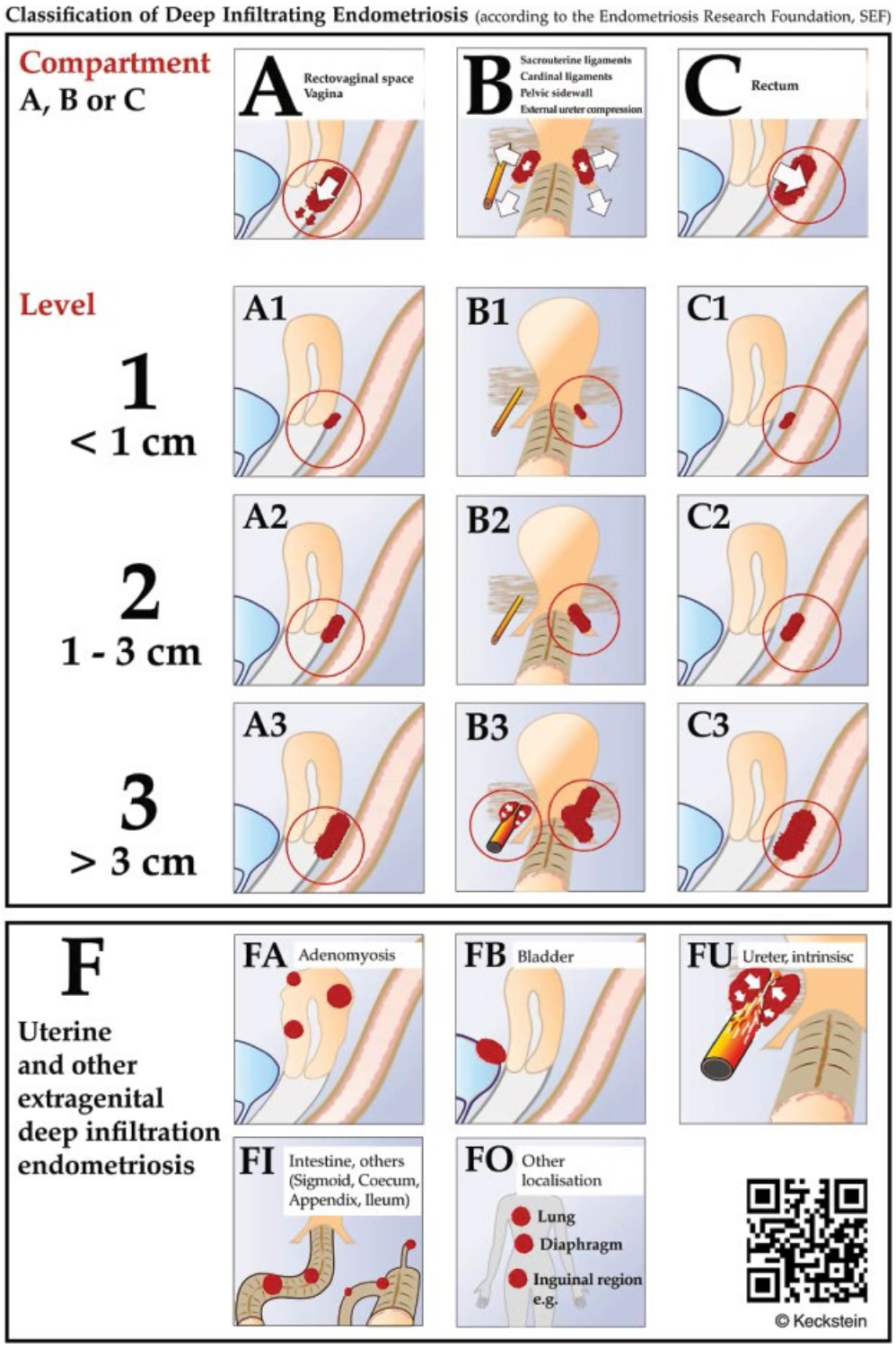

Fig. 53.3 (Continued)

(c)

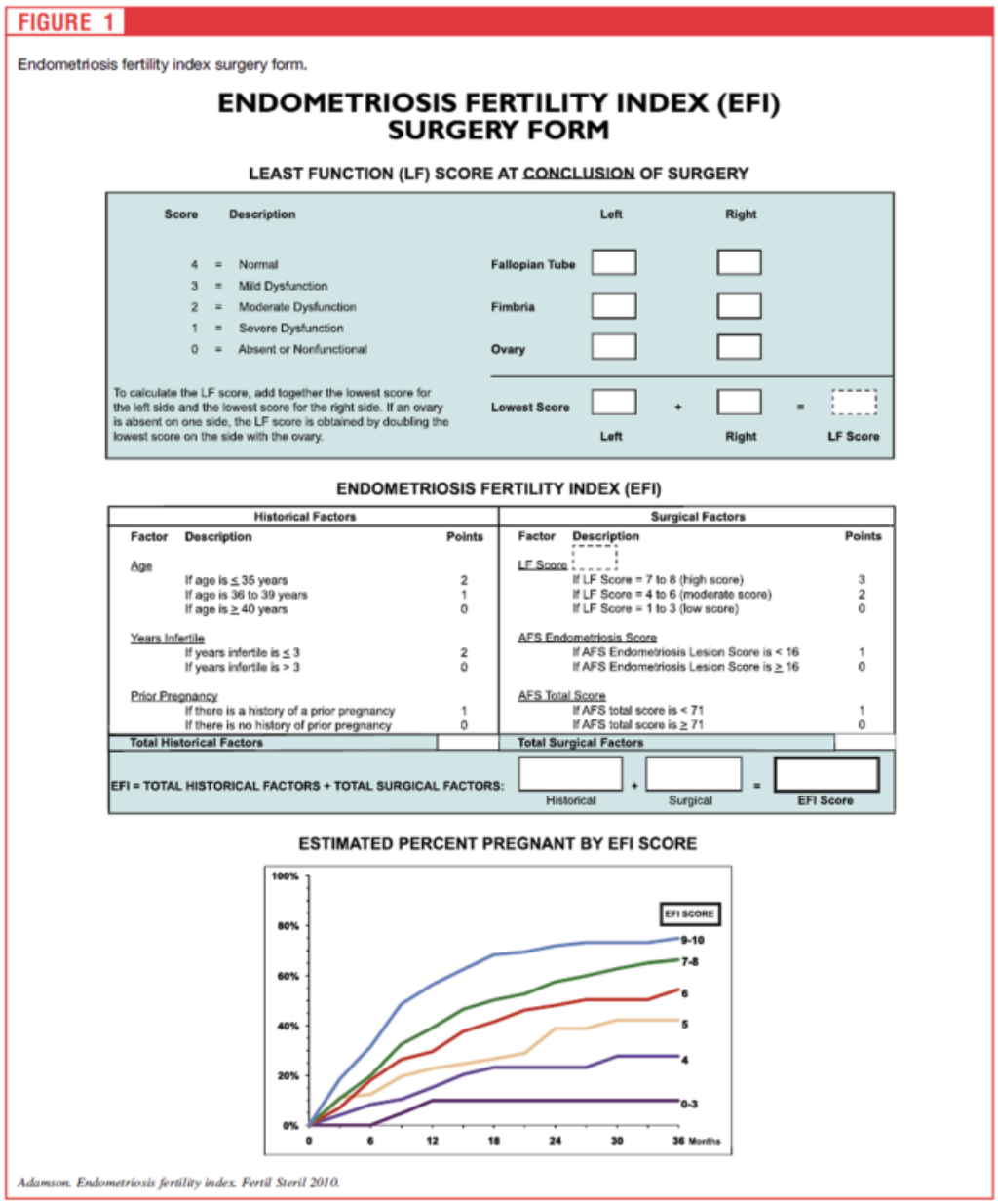

FIGURE 1

Endometriosis fertility index surgery form.

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube		
3	= Mild Dysfunction			
2	= Moderate Dysfunction	Fimbria		
1	= Severe Dysfunction			
0	= Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score: Left + Right = LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

Adamson. Endometriosis fertility index. Fertil Steril 2010.

Fig. 53.3 (Continued)

course of symptoms, quality of life and infertility, with an uncertain capacity to detect a woman's likely response to treatment for pain and/or infertility [21].

Adamson and Pasta [29] developed the EFI as a simple, robust and validated clinical tool that predicts fertility outcome for women following surgical staging of endometriosis (Fig. 53.3c) and it may have considerable utility in developing treatment plans for infertile women with endometriosis, now with extensive external validation [21]. It would be logical to develop an endometriosis classification system for pain and/or quality of life using a similar methodology to the EFI in order to combine the factors most predictive of pain and quality-of-life outcomes.

Symptoms of endometriosis

Endometriosis-associated pain symptoms

Severe dysmenorrhoea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual

symptoms – often bowel or bladder related, causing dyschezia or dysuria – with or without abnormal bleeding, and chronic fatigue have all been associated with endometriosis. Dyspareunia is the symptom that women often find most distressing and which usually has the biggest negative impact on their quality of life [30]. This is probably because, whilst other symptoms such dysmenorrhoea occur only for a limited time each cycle and are thus more manageable, dyspareunia can be present throughout the cycle and it may also have profound effects on a woman's relationship with her partner. The predictive value of any single symptom or set of symptoms is limited as each symptom can have other gynaecological or non-gynaecological causes. Interestingly, the symptom complex that most accurately predicts endometriosis from a woman's medical history is menstrual dyschezia and a history of benign ovarian cysts [31]. There is little correlation between disease stage and the type, nature and severity of pain symptoms, underscoring that the current classification systems are inadequate for women with pain related to endometriosis. It has long been accepted that typical lesions can cause moderate pain (although around half of all women with such lesions are pain-free), ovarian endometriomas tend to be associated with more severe pain (even though 10–20% of women are pain-free), and deep endometriosis can be associated with very severe pain (although, again, women sometimes have no pain at all). The association of other endometriosis phenotypes, including subtle lesions, with pain is less clear. The suggested causes for endometriosis-related pain include tissue damage and distorted anatomy, peritoneal inflammation, activation of nociceptors, and nerve irritation/invasion in deep endometriosis. If pain is persistent, it may become chronic and, through central sensitization, develop the hallmarks of a chronic pain syndrome [32]. Pain symptoms are usually assessed in clinical trials using a four-point verbal rating scale for three symptoms (dysmenorrhoea, dyspareunia and pelvic pain) and two examination signs (pelvic tenderness and induration). More recently, health-related quality of life has also been evaluated, as traditional outcome measures may not adequately assess what the patient considers important. The most useful patient-generated, disease-specific tool is the Endometriosis Health Profile (EHP)-30, a 30-item questionnaire that covers five dimensions: pain, control and powerlessness, emotional well-being, social support and self-image [33].

Endometriosis-associated subfertility

Endometriosis is associated with subfertility. The infertility associated with the anatomical distortion of fallopian tubes and ovaries, ovarian damage through endometrioma formation and tubal damage consequent on endometriosis is obvious. Most women do not have such severe endometriosis, but there is even an association between minimal/mild endometriosis and subfertility, with cohorts showing that fecundity is approximately halved and time to pregnancy doubled for women with these so-called milder forms of endometriosis [34,35]. Even women undergoing medically assisted reproduction, including *in vitro* fertilization (IVF), have poorer outcomes if they have endometriosis [36] or adenomyosis [37]. Numerous mechanisms have been proposed, including negative effects on ovarian reserve, ovulation dysfunction, sperm survival in the female genital tract and egg quality (and thus embryo quality). Potentially subtle effects on egg quality have variously been ascribed to abnormal folliculogenesis: the follicular fluid of women with endometriosis has been found to have increased levels of interleukin (IL)-6 and progesterone, and decreased levels of cortisol and insulin-like growth factor binding protein (IGFBP)-1; and granulosa cells express increased levels of tumour necrosis factor (TNF)-α, soluble Fas ligand and corresponding apoptotic activity. Intraperitoneal inflammation is also a feature of endometriosis, including evidence of increased phagocytosis of sperm by peritoneal macrophages, as well as inflammatory, proteolytic and angiogenic activity of the peritoneum and peritoneal fluid, involving IL-6, other growth factors (including vascular endothelial growth factors), cytokines and haptoglobins. Other proposed mechanisms have included reduced sexual frequency due to dyspareunia, luteinized unruptured follicle syndrome, luteal insufficiency and recurrent miscarriage. Whilst traditionally the biggest negative impact of endometriosis on a woman's fertility was thought to be mediated through egg quality, it is becoming more apparent that endometrial dysfunction, with the possibility of reduced endometrial receptivity, also seems likely. Women with endometriosis have reduced expression of integrins, the key receptivity molecules, in their endometrium at the time of the implantation window; they also overexpress osteopontin, a ligand that binds integrins.

Diagnosis

Diagnostic delay

The average delay of around a decade between symptom onset and a definitive diagnosis is well recognized. The key to avoiding diagnostic delay is improved education and awareness. This education and a willingness to consider endometriosis as a diagnosis extends not just to girls and young women and their families, but to

health professionals in primary care as well as gynaecologists. In the past, even the gynaecological community has been guilty of paternalistic attitudes regarding menstrual health and endometriosis. While a definitive laparoscopic diagnosis carries great importance for many women, many others would prefer to avoid a laparoscopic procedure if possible. Although a diagnosis is important, it is not a key end-point and can be viewed as an interim stage for a woman to regain wellness. What is crucial is that a possible diagnosis of endometriosis is considered at an early stage and that the woman (or adolescent) is offered appropriate management with that possibility in mind.

History and clinical examination

Making a diagnosis on the basis of symptoms alone is difficult as the presentation is so variable and other conditions such as irritable bowel syndrome, pelvic inflammation and pelvic congestion syndrome mimic endometriosis. Eliciting pelvic tenderness, a fixed retroverted uterus, tender uterosacral ligaments or enlarged ovaries on examination is suggestive of endometriosis, although examination findings can be normal. The diagnosis is likely if nodules are palpable in the uterosacral ligaments and pouch of Douglas, and is confirmed if lesions (which can be biopsied) are visualized on vaginal speculum examination.

Laparoscopy

Laparoscopic visualization of endometriotic lesions has long been held as the gold standard for diagnostic purposes, and this remains the case. However, Wykes *et al*. [38] showed in a systematic review including four studies with a total of 433 participants that, when compared with histological evaluation of visualized lesions, laparoscopic visualization alone has limited accuracy (94% sensitivity and 79% specificity). Histological confirmation of lesions seen at laparoscopy is therefore ideal, and mandatory if deep endometriosis or an endometrioma is present. The entire pelvis should be inspected systematically, and the findings documented in detail, preferably with the aid of standardized laparoscopic photographs or a video recording [39]. Whilst it has long been considered best practice to surgically remove endometriosis at the time of diagnostic laparoscopy (provided that adequate consent has been obtained and the surgeon's expertise is sufficient to deal with the extent of endometriosis diagnosed), Vercellini *et al*. [40] have made a yet stronger call to avoid 'low value care' (meaning interventions with uncertain benefits and/or defined harms, or whose effectiveness is comparable with less expensive alternatives). Hence they have argued that the concept of 'diagnostic laparoscopy' should disappear, with laparoscopy being reserved for those women likely to benefit from laparoscopic removal of their endometriosis.

Low-invasive tests

A low-invasive diagnostic test for endometriosis, through imaging or biomarkers (in urine, blood, endometrium or other body fluids or tissues) or some combination of these, has long been sought. This is partly related to the recognition that not all women who might have endometriosis will have a laparoscopy. In low-resource settings, access to laparoscopy may not be feasible. Even in developed countries, the availability of gynaecologists in relation to the number of women with endometriosis means that not all women with endometriosis can have a laparoscopic procedure, while some women elect to avoid laparoscopy. The concept of avoiding low-value care is inextricably interlinked to the aspiration of an accurate and reliable method of diagnosing endometriosis non-surgically.

Until recently, there was a dogma that laparoscopy was the only acceptable accurate method of diagnosing endometriosis and that imaging and biomarker tests were insufficiently accurate. In the case of many low-invasive tests this remains true, but we now have a comprehensive set of systematic reviews of low-invasive diagnostic tests for endometriosis [41–45]. Summary box 53.2 summarizes the evidence regarding the potential value of the low-invasive tests. A low-invasive diagnostic test might be considered suitable as a replacement test for laparoscopy if it equates to the accuracy attained by laparoscopic visualization itself (≥94% sensitivity and ≥79% specificity). Other tests might have utility as triage tests: those with very high sensitivity which, if negative, rule out endometriosis (so-called SnOUT triage tests); or those with high specificity that, if positive, can raise the suspicion of, or rule in, endometriosis (so-called SpIN triage tests).

Imaging tests have shown promise in diagnosing certain subtypes of endometriosis, such as endometriomas and deep endometriosis, and in mapping deep endometriosis to various sites (Summary box 53.2), although do not prove so accurate in making the actual diagnosis of endometriosis. Regarding biomarkers (measured in urine, blood and endometrial tissue), the accuracy of any one test has not been found to be sufficiently accurate to be a reasonable replacement, or even triage, diagnostic test. This is also true for the most widely used biomarker to date, serum CA125. The detection of endometrial nerve fibre antigens (protein gene product, PGP-9.5) showed promise as a replacement test in most studies but could not be reliably detected in all settings.

Summary box 53.2

Summary of evidence for low-invasive diagnostic tests for endometriosis [41–45].

	Candidate replacement tests	Candidate SnOUT triage tests	Candidate SpIN triage tests
Imaging	MRI for endometriomas, deep endometriosis and mapping deep endometriosis to various sites Multidetector CT enema for rectosigmoid and other bowel endometriosis*	–	Transvaginal ultrasound for endometriomas, deep endometriosis and mapping deep endometriosis to various sites (and almost for endometriosis) MRI for pouch of Douglas and rectosigmoid endometriosis Transrectal ultrasound for rectosigmoid endometriosis
Biomarkers			
Urine	–	–	–
Blood	–	–	–
Endometrium	PGP9.5 for endometriosis (but reliability of detection not confirmed in all settings)	–	–
Combined tests	Serum IL-6 + endometrial PGP9.5 for endometriosis Vaginal examination and transvaginal ultrasound for rectal endometriosis	–	Urine vitamin D-binding protein level corrected for creatinine (VDBP-Cr) × serum CA-125 (>2755) for pelvic endometriosis History (length of menses) + serum CA-125 (>35 U/mL) + endometrial leucocytes for pelvic endometriosis Transvaginal ultrasound + serum CA-125 or CA-19.9 (at various cut-offs) for ovarian endometrioma Vaginal examination + transvaginal ultrasound for mapping deep endometriosis at various sites

* Despite diagnostic utility, multidetector CT enema is not advised owing to its invasiveness and unacceptable radiation exposure.

The most promising approach for an accurate low-invasive diagnosis appears to be a combination of low-invasive tests. The diagnostic test accuracy research to date suggests utility of the combination of serum IL-6 with endometrial PGP9.5 to diagnose endometriosis, and of the combination of transvaginal ultrasound with serum CA-125 level (at cut-off >35 IU/L) to diagnose endometriomas. It should now be possible to develop a combination of the low-invasive diagnostic tests (including clinical history, examination findings, imaging and/or biomarkers) that most accurately diagnoses endometriosis. This would allow laparoscopy to be reserved for women most likely to benefit from laparoscopic removal of endometriosis.

General treatment issues

Patient participation in the decision-making process is essential, as multiple management options exist and endometriosis is potentially a chronic problem. Choosing which treatment to have will depend on a number of factors (Summary box 53.3). Summarizing how these factors influence decision-making is difficult because each patient is different and the decisions are often complex. Some women with endometriosis require long-term individualized care and their priorities may change over time consequent on the type and severity of their symptoms, the impact of those symptoms, current and future fertility wishes, and lifestyle factors. Hence there is value in an endometriosis centre of excellence, although this framework is now more appropriately considered as a network of expertise [1], as the concentrated locality of all facilities in a single centre is not mandatory. Through this, patients benefit from a multidisciplinary network of experts that typically includes gynaecologists, fertility specialists, gastroenterologists, colorectal surgeons, urologists, physiotherapists, psychologists and nutritionists. Networks of expertise require an adequate case mix with frequency of complex cases, a dedicated theatre team that facilitates management based on the best available knowledge, implemented by professionals with extensive experience and transparent records of outcome data [1]. An important link for a network of expertise is with an endometriosis organization (part of the function of which is a patient support group), which promotes education and information-sharing for women with endometriosis about the condition and its management [1].

Summary box 53.3

Factors influencing choice of treatment

- Woman's age.
- Fertility status.
- Nature of symptoms.
- Severity of disease.
- Previous treatments.
- Priorities and attitudes.
- Resource implications.
- Costs and side-effect profile.
- Risks of treatment.
- Other subfertility factors.
- Intended duration of treatment.
- Best available evidence.

Summary box 53.4

Treatment aims

- What are you treating (disease, symptoms or both)?
- Why are you treating?

Possible reasons to treat

- Improve natural fertility.
- Enhance chances of success at assisted reproductive technology.
- Pain relief as an alternative to surgery.
- Pain relief while awaiting surgery.
- Adjunct to surgery.
- Prophylaxis against disease occurrence.
- Symptom recurrence.

Treatment aims

The treatment aims should be agreed with the patient (Summary box 53.4). For surgery, the intended benefits and the major risks and complications should be explained and documented on the consent form. When medical treatment is initiated, ideal practice would be to document in the medical notes, and/or in a letter to the patient, what options were discussed, why the decision to treat was made, as well as the treatment aims and side effects/risks. Treatments may divided broadly into those designed to improve symptoms (primarily pelvic pain) and those designed to improve fertility. It is important to emphasize that a 30% placebo effect is common in endometriosis studies, hence the need for appropriately controlled randomized controlled trials (RCTs). The information on effective treatments which follows is drawn primarily from analysis of RCTs and systematic reviews of RCTs. Current information that is up to date is readily available in the Cochrane Library (http://www.cochranelibrary.com/), where an overview of all Cochrane reviews of endometriosis treatments is available, including 14 Cochrane reviews that examine pain outcomes and eight reviews that examine fertility outcomes in women with endometriosis [46], as well as key guidelines, such as the European Society for Human Reproduction and Embryology (ESHRE) guideline [47] and consensus statements such as the World Endometriosis Society consensus statement on current management [1].

Treatment for women with symptoms such as pain related to endometriosis

Lifestyle and dietary interventions

Women report positive effects from lifestyle and dietary interventions in managing their endometriosis, but few well-designed studies have examined lifestyle factors. RCTs have not been used to assess counselling and/or psychological support, cognitive–behavioural therapy, different types of exercise including yoga, and exclusion diets (especially gluten-free diets), all reported to have beneficial effects. Even in the context of positive RCT results, it has been difficult to establish consensus around the benefit of fish oil (omega-3 fatty acids) for dysmenorrhea, or of dietary intervention following endometriosis surgery in the form of vitamins, minerals, salts, lactic ferments and fish oil [1].

Empirical medical treatment

Many clinicians support empirical medical treatment of endometriosis either prior to or without laparoscopic confirmation of endometriosis. Time to surgery may delay appropriate treatment, there is a false-negative rate in laparoscopic diagnosis, and surgery is invasive, expensive compared with empirical therapies and carries a risk of morbidity. A full clinical evaluation that includes consideration of other causes of the symptoms and assessment of the disease impact for the individual woman is

required prior to empirical treatment. Management of pelvic pain should not be delayed in order to obtain surgical confirmation of endometriosis. First-line empirical treatment options that should be considered include non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics (paracetamol and opioids, although most clinicians would reserve opioid analgesics for second-line treatment), the combined oral contraceptive pill (OCP), traditional progestins such as medroxyprogesterone acetate and norethisterone, or newer progestins such as dienogest. Second-line medical treatment with gonadotrophin-releasing hormone (GnRH) agonists with add-back HRT, oral GnRH antagonists, the levonorgestrel-releasing intrauterine system (LNG-IUS) or opioid analgesics are sometimes also considered for empirical treatment for women who are not optimally treated with first-line empirical therapy whilst awaiting laparoscopic surgery (and some women successfully treated with second-line empirical medical treatment might not proceed to surgery). It is unclear whether medical treatment prior to laparoscopy might mask the diagnosis by reducing the appearance of endometriotic implants and hence may make endometriosis more difficult to diagnose and treat surgically. It is important to highlight that NSAIDs have important side effects, including peptic ulceration and an adverse impact on ovulation, and that analgesics, particularly opiates, if used inappropriately and without medical monitoring, carry a risk of abuse and/or addiction. All women receiving medical treatment should be carefully monitored for beneficial and harmful effects with regular follow-up consultations [1].

Surgical treatment

Crucial aspects in planning laparoscopic surgery are that surgery should be carried out in the most appropriate setting which can ensure adequate preoperative counselling, appropriate surgical expertise, adequate technical resources, and postoperative support care. Whenever possible, laparoscopic surgery should always be undertaken in preference to laparotomy for improved surgical visualization and for the benefits of speedier postoperative recovery. Laparoscopic surgical removal of endometriosis (through excision and/or ablation of endometriosis) is an effective first-line approach for treating pain related to endometriosis. The odds of overall pain reduction were significantly higher at 6 months following laparoscopic removal of endometriosis compared with diagnostic laparoscopy (OR 6.6, 95% CI 3.3–13.1, three RCTs, $N = 171$, $I^2 = 0\%$) (Fig. 53.4), an impact that was sustained at 12 months [48].

Although RCTs have failed to demonstrate benefit of excision over ablation for most endometriosis, there is unanimous consensus over the recommendation to excise lesions where possible, especially deep endometriotic lesions, which gives a more thorough removal of disease [1,49]. It is also acknowledged that, even after expert removal of endometriosis, there may be a recurrence rate of symptoms and endometriotic lesions that varies from 10 to 55% within 12 months [50], with recurrence affecting approximately 10% of the remaining women each additional year [51]. The risk of requirement for repeat surgery is higher in women younger than 30 years at the time of surgery [52]. First operations tend to produce a better response than subsequent surgical procedures, with pain improvements at 6 months in the region of 83% for first excisional procedures compared with 53% for second procedures [53]. Excessive numbers of repeat laparoscopic procedures should therefore be avoided.

It has been suggested that there may be an increased recurrence rate for surgery undertaken in the luteal phase (through reimplantation of retrograde-passing endometrial tissue at subsequent menses whilst the sites of surgically removed lesions are still healing). However, there remains insufficient evidence to necessitate the planning of surgery for a particular time of the cycle, although surgery in the follicular phase avoids the complicating factor of the presence of a haemorrhagic corpus luteum [1].

There is no place for adding laparoscopic uterine nerve ablation to laparoscopic removal of endometriosis. Although presacral neurectomy might provide benefit for a small number of women with central dysmenorrhoea, the benefits are likely to be outweighed by the potential for harmful effects (including presacral haematoma and dysfunction of bladder and/or bowel) and the technique is not usually recommended.

Laparoscopic excision (cystectomy) for endometriomas reduced the recurrence rate of the symptoms of dysmenorrhoea (OR 0.15, 95% CI 0.06–0.38), dyspareunia (OR 0.08, 95% CI 0.01–0.51) and non-menstrual pelvic pain (OR 0.10, 95% CI 0.02–0.56) compared with laparoscopic ablation (drainage and coagulation) (Fig. 53.5), and was also associated with a reduced rate of recurrence of the endometrioma (OR 0.41, 95% CI 0.18–0.93) [54]. Laparoscopic excision for ovarian endometriomas has therefore been preferred to ablation where possible to minimize recurrence of symptoms and of the endometriomas, although care must be taken to minimize damage to surrounding normal ovarian tissue. Endometrioma surgery is technically difficult and demanding owing to the risks of damaging the vasculature and surrounding ovarian tissue. For women with large endometriomas in whom ovarian reserve is a concern, there may be some value in a multiple-step procedure (with interval surgery that utilizes intervening medical suppressive treatment).

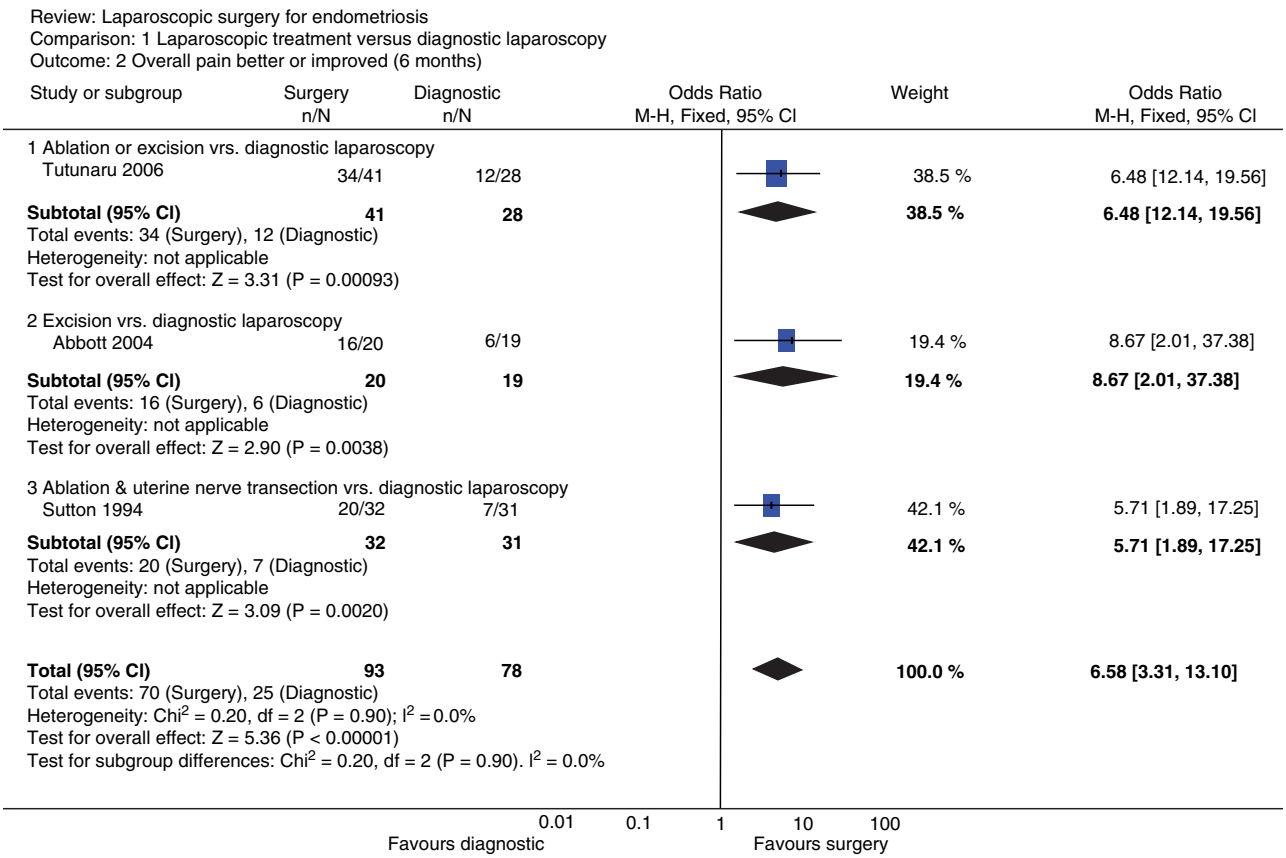

Fig. 53.4 Pain outcomes at 6 months after laparoscopic removal of endometriosis. *Source:* Duffy JM, Arambage K, Correa FJ *et al*. Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev* 2014;(4):CD011031. Reproduced with permission of John Wiley & Sons.

The OCP reduces the recurrence rate of endometriomas after ovarian cystectomy. Otherwise, evidence does not support the use of short-term preoperative or postoperative medical treatment in association with laparoscopic removal of endometriosis for improving pain outcomes or recurrence rates [1].

Different approaches have been taken in surgery for deep endometriosis. This surgery is among the most challenging in gynaecology. The dilemma is that incomplete resection may impact negatively on symptomatic outcome [55], but that radical interventions increase the risk of major complications such as ureteric and rectal injuries. Evidence is still lacking to guide the best surgical approach to deep endometriosis [1]. If the disease includes bowel endometriosis, the surgical options for the bowel include shaving, disc excision, or segmental excision and re-anastomosis. The low recurrence rates after shaving and disc excision suggest that, in most cases, it is possible to avoid removal of large segments of bowel, as segmental excision and re-anastomosis is associated with the highest complication rates, including post-anastomotic leak with the life-threatening complication of faecal peritonitis. Rather than undertake bowel surgery initially, the optimal approach is to first consider medical treatment. Bowel surgery should only proceed on the basis of shared decision-making after thorough consideration of risks versus benefits, ideally following multidisciplinary consultations that include provision of information for women on potential complications of surgery. Only then should bowel surgery be performed laparoscopically by expert surgeons, avoiding laparotomy whenever possible. What is clear is that highly specialized surgical expertise is required for excision of deep endometriosis and it should be undertaken only in centres of expertise. Evidence is emerging that triage of women due to undergo endometriosis surgery will allow almost all of them to receive appropriate treatment at their first surgical procedure. Triage methods include transvaginal ultrasonography, especially with the emergence of advanced gynaecological ultrasound [56], and MRI [57], which can predict the type of severe endometriosis that may involve ureters, bladder or bowel and which demands high-level surgical expertise.

Debate continues over the role of hysterectomy and of concurrent oophorectomy, with little reliable evidence to inform practice, but if such surgery is undertaken it

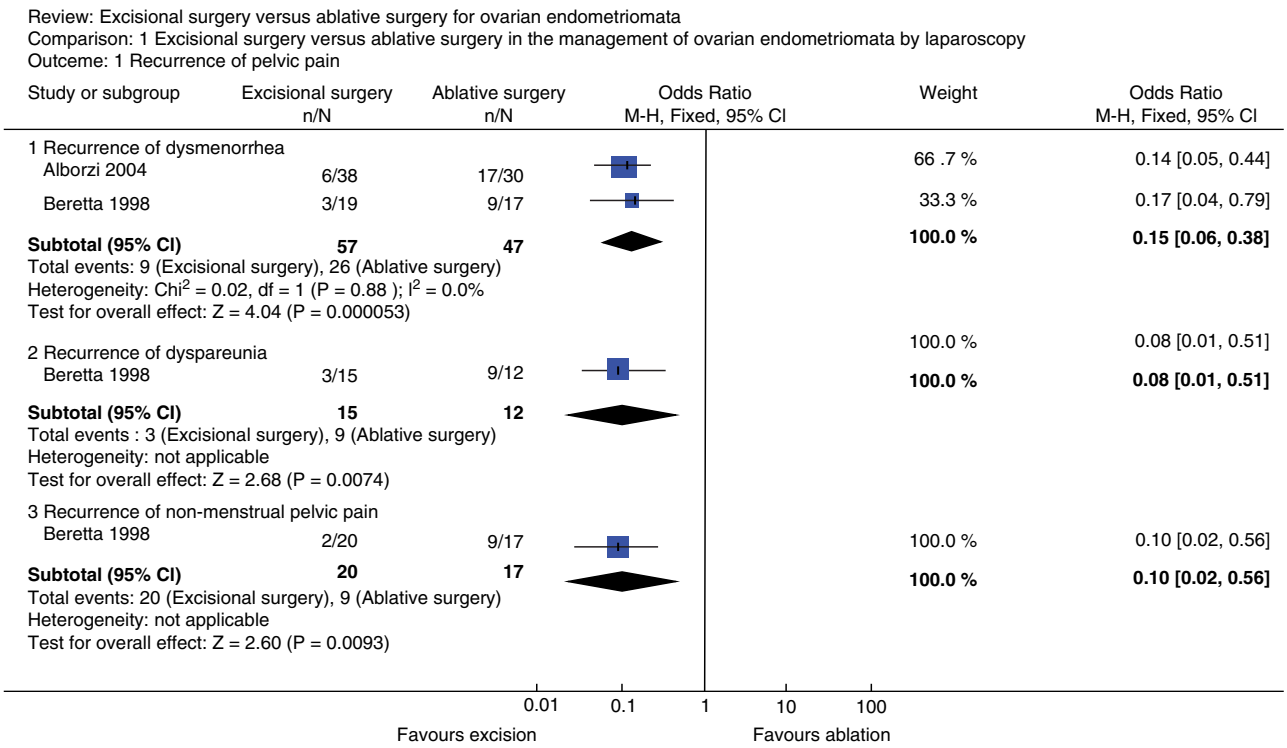

Fig. 53.5 Pain outcomes (dysmenorrhoea, dyspareunia and non-menstrual pelvic pain) following excisional versus ablative surgery for endometriomas. *Source:* Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008;(2):CD004992. Reproduced with permission of John Wiley & Sons.

should be performed laparoscopically where possible. Observational studies have suggested improved pain outcomes for women who undergo hysterectomy for r-ASRM stage IV endometriosis, but this may also be related to associated pathology such as adenomyosis. For young women who have undergone bilateral oophorectomy, it is wise to use HRT to avoid menopause symptoms and prevent loss of bone mass, preferably in a combined regimen including oestrogen and progestin, considering the possibility of unopposed oestrogen reactivating endometriosis that has not been fully removed. There is no evidence to justify delaying the start of HRT [1].

Medical management

Medical treatment may be given routinely as an adjunct to surgery preoperatively or postoperatively (although this is not recommended as discussed under surgical management), as a defined course of treatment remote from surgery, or as a longer-term strategy designed to prevent recurrence of endometriosis or endometriomas [58]. Hormonal treatments typically induce atrophy and/or decidualization of peritoneal deposits by suppressing ovarian function. Endometriomas rarely decrease in size with medical therapy and adhesions will be unaffected. Hypothetically, medical maintenance therapy might be an effective treatment option that could, in some cases, control the denervation and reinnervation changes that are believed to precede central sensitization and the development of a chronic pain syndrome. Whilst use of medical treatments such as OCP may be long term, specific studies are needed to investigate whether medical intervention may prevent development of a chronic pain syndrome. However, most medical agents are only effective for the duration of their use and symptoms often recur after treatment ceases.

As with empirical medical treatment, NSAIDs, other simple analgesics and OCPs can be considered for use as first-line medical treatment of laparoscopically proven endometriosis. Progestins with a proven effect in RCTs and with a specific indication for the treatment of endometriosis, such as medroxyprogesterone acetate, norethisterone and dienogest, can also be considered first-line treatments taking into consideration their different side-effect profiles. It is important to discuss potential side effects with the woman before treatment commences, and careful follow-up is required.

Second-line medical treatments could include GnRH agonists, which should be used with add-back HRT routinely (to alleviate hypo-oestrogenic side effects and prevent the loss of bone mass associated with GnRH agonist treatment), LNG-IUS (which is effective also for many

women with adenomyosis or deep endometriosis), orally active GnRH antagonists (elagolix) [59], depot progestins (although the side-effect profile and thus treatment burden is high), and opioid analgesics. Other possible second-line medical treatments include non-oral combined hormonal contraceptives such as transdermal patches and vaginal rings [60].

Danazol and gestrinone should not be used owing to the high treatment burden of androgenic side effects, other than for women established on these treatments in the absence of side effects for whom other treatments have proven ineffective.

Despite different modes of action, these hormonal medical treatments all appear to relieve symptoms even if deep endometriosis or endometriomas are present. Treatment response tends to be idiosyncratic, with women often responding to some medical treatments and not to others. There are no known markers that predict response to one agent rather than another, so treatment choice usually hinges on acceptability, likelihood of side effects and cost. If one hormonal treatment is ineffective, another may prove effective.

Emerging medical treatments

Preliminary studies have shown value from new orally active GnRH antagonists (relugolix), selective progesterone receptor modulators (ulipristal, mifepristone, asoprisnil and megestrol), melatonin, aromatase inhibitors (anastrozole, fadrozole, formestane, exemestane, letrozole), the thiazolidinedione rosiglitazone, and valproic acid, and further evaluation of these agents is ongoing. For the immunomodulator pentoxifylline and the anti-TNF-α agent infliximab, RCTs have not shown benefit to date. The selective oestrogen receptor modulator raloxifene was not found to be beneficial. As angiogenesis is a crucial activity for the normal processes of the reproductive tract and other organ systems, it is doubtful whether agents used for their anti-angiogenic properties (including cabergoline, endostatin, sirolimus, thalidomide and vascular endothelial growth factor inhibitors) will be useful clinically [1].

Complementary therapies

Complementary therapies may help women to cope better with their endometriosis and its treatment and are supported by some evidence from RCTs. Acupuncture appears to be moderately effective and safe but requires repeated treatments. High-frequency transcutaneous electrical nerve stimulation (TENS) has some effectiveness for short-term pain management. There is limited evidence in favour of Chinese herbal medicine that may be difficult to apply outside of the traditional Chinese medicine setting. For women with dysmenorrhoea only, there is limited evidence of benefit for vitamins B_1 and B_6 (with safety concerns associated with higher doses of vitamin B_6) and magnesium, and topical heat may be effective for low back pain, but there are no studies specifically examining endometriosis [1].

Treatment for women with endometriosis-related infertility

Surgery

The principles of laparoscopic surgery for subfertility are similar to those for other symptoms of endometriosis. Appropriate surgical training is again the key to the best outcomes. It is very important to consider ovarian reserve prior to laparoscopic surgery in the woman experiencing infertility, as evidence is growing that surgical treatment of endometriomas contributes to reduced ovarian reserve. The coexistence of pain will be an important factor to consider that will impact on the decision whether to proceed with surgery, although surgery and assisted reproductive techniques should be considered as complementary strategies.

Laparoscopic surgical removal of endometriosis is recognized as being effective in improving fertility in stage I and II endometriosis. The clinical pregnancy rate was significantly improved following laparoscopic removal of endometriosis compared with diagnostic laparoscopy (OR 1.9, 95% CI 1.3–2.9, three RCTs, $N = 528$, $I^2 = 0\%$) (Fig 53.6), which translated into a significantly increased live-birth rate in meta-analysis of two of these RCTs [48].

There is no RCT evidence to support excision over ablation, but it is recommended to excise lesions where possible, especially deep endometriosis where pain is present [1]. No RCTs have yet assessed whether surgery improves fertility in women with stage III and IV endometriosis and those with deep endometriosis. The functional appearance of the fallopian tubes and ovaries at the end of the laparoscopic procedure, gauged by the EFI, gives prognostic information that is helpful in counselling women postoperatively [29].

Laparoscopic excision (cystectomy) whenever possible for endometriomas greater than 4 cm in diameter improves fertility more than ablation comprising drainage and coagulation (spontaneous pregnancy OR 5.2, 95% CI 2.0–13.3) (Fig 53.7) [52]. However, much care needs to be taken in correct identification of tissue planes and careful dissection of the endometrioma to avoid damaging or removing normal ovarian tissue and thus impacting ovarian reserve. There is now also clear evidence that laparoscopic suturing for haemostasis

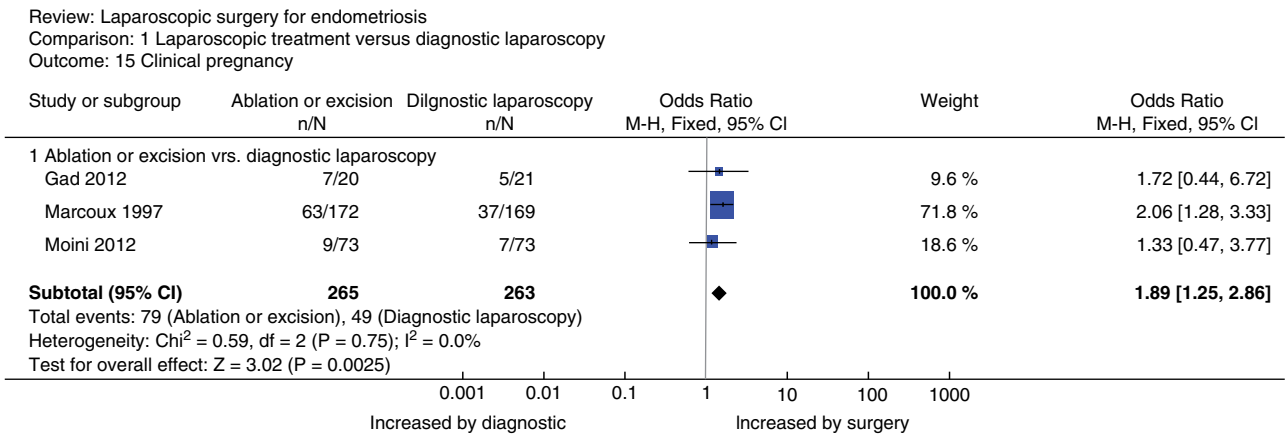

Fig. 53.6 Clinical pregnancy rate after laparoscopic removal of endometriosis. *Source:* Duffy JM, Arambage K, Correa FJ *et al.* Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev* 2014;(4):CD011031. Reproduced with permission of John Wiley & Sons.

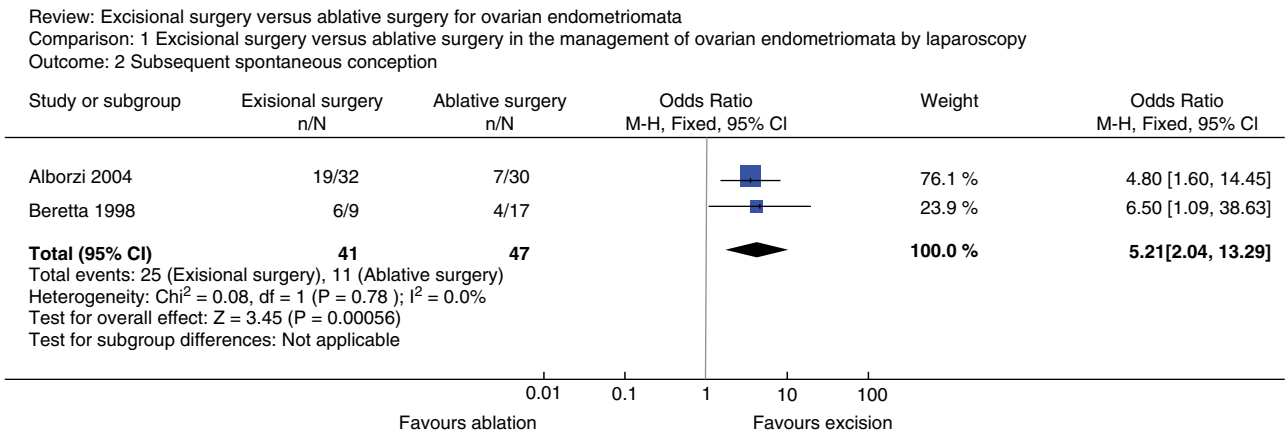

Fig. 53.7 Pregnancy rates following excisional versus ablative surgery for endometriomas. *Source:* Duffy JM, Arambage K, Correa FJ *et al.* Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev* 2014;(4):CD011031. Reproduced with permission of John Wiley & Sons.

preserves ovarian reserve more effectively than electrosurgical haemostasis [61] and thus minimal use of energy modalities in haemostasis is imperative. Young women for whom fertility is a consideration should have the benefit of discussion of the option of egg freezing prior to undergoing ovarian endometrioma surgery, especially if bilateral.

The best surgical approach for deep endometriosis in the context of endometriosis-related infertility remains unclear. Whilst observational studies suggest good fertility results in women who undergo laparoscopic excision [55,62], laparoscopic shaving [63] and colorectal excision [64,65], these data are far from confirmatory. These surgical approaches have not been assessed in RCTs and carry a high risk of complications. Laparoscopic surgery for deep endometriosis is usually considered a second-line treatment option after failed IVF (unless IVF is not feasible or the patient has severe pain symptoms).

The pregnancy rate after repeat surgery is lower, approximately half that after first surgery [50], and two cycles of IVF might be more effective in achieving pregnancy. However, surgery should be considered for women with endometriosis-related infertility who continue to be symptomatic, have enlarging endometriomas, or those who decline IVF and those for whom IVF is repeatedly unsuccessful.

Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to benefit fertility and is not recommended since postoperative medical adjunct therapy may delay pregnancy at a time when fertility has been improved by surgery [1].

Assisted conception for endometriosis-associated infertility

In terms of medically assisted reproduction, intrauterine insemination (IUI) combined with ovarian stimulation is

an effective option for women with minimal to mild endometriosis, if the fallopian tubes are normal. IUI plus ovarian stimulation is more effective than unstimulated IUI, gonadotrophin stimulation appears more effective than that with clomifene, and the role of unstimulated IUI is uncertain for women with endometriosis. Multiple pregnancy is a key hazard of ovarian stimulation and all reasonable steps should be employed to avoid this outcome. No consensus could be established over double insemination for IUI. However, IVF is commonly offered first line in preference to IUI when endometriosis is more severe, tubal function is impaired, or in the context of advanced female age and/or reduced sperm quality. It is unclear whether controlled ovarian stimulation alone provides fertility benefit for women with endometriosis and whether gonadotrophins provide benefit over, for example, letrozole [1].

The presence of endometriosis has a negative impact on IVF success rates compared with other causes of infertility [36]. Nonetheless, IVF is recommended as a fertility treatment for women with endometriosis, especially if fallopian tube function is compromised or if there are other infertility factors such as male factor. The chance of success is similar for GnRH antagonist versus GnRH agonist protocols [1]. IVF does not appear to increase the risk of recurrence of endometriosis [66].

Adjuvant therapy to assisted conception for endometriosis-associated infertility

Medical treatment (including GnRH agonists) and laparoscopic surgical treatment prior to IUI plus controlled ovarian stimulation is not recommended, since there are insufficient data demonstrating benefit [1].

The most dramatic improvement in the outcome of IVF appears to be through treatment with GnRH agonists for 3–6 months prior to IVF, as the systematic review of three RCTs showed a substantial benefit of this treatment in improving the chance of pregnancy (OR 4.3, 95% CI 2.0–9.2) (Fig 53.8) [67]. GnRH agonist treatment not only suppresses endometriosis, but the mechanism for fertility improvement in this case appears to be via the promotion of endometrial integrins, the expression of which is known to be much reduced in the endometrium of women with endometriosis.

There are insufficient data to recommend the use of OCP prior to IVF/ICSI and no data to compare the approach of pretreatment with OCP versus GnRH agonist. There is concern that the presence of an endometrioma may damage the ovary yet, on the other hand, ovarian response to stimulation in IVF might be reduced in some women who have had an endometrioma removed. The benefit of laparoscopic removal of endometriosis and/or endometriomas prior to IVF is unclear with respect to IVF outcome, although it may improve access to the ovaries and even reduce the chance of infection related to the egg collection procedure [1]. Whilst laparoscopic surgery following repeat failure of IVF treatment may improve the chance of natural conception, its role as an adjunct to IVF is unclear. Any decisions to perform surgery for endometriomas or deep endometriosis before assisted reproductive techniques should be made only after fully informed consent by surgeons with appropriate expertise. There should be discussion about the option of prior egg freezing with women contemplating such surgery.

Medical therapy

There is no evidence of fertility benefit from medical treatment – ovulation suppression may delay pregnancy and this is not recommended [1].

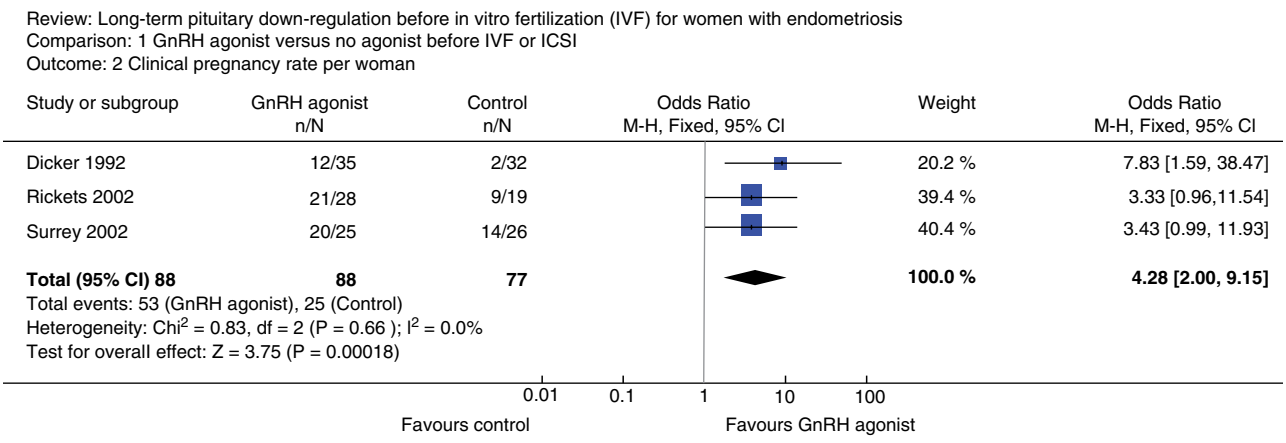

Fig. 53.8 Pregnancy rates following 3–6 months of GnRH analogue downregulation prior to IVF. *Source:* Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006;(1):CD004635. Reproduced with permission of John Wiley & Sons.

Emerging therapies

The most promising innovative fertility treatment for women with endometriosis-related infertility is lipiodol uterine bathing and tubal flushing. In an RCT evaluating fertility outcome from lipiodol among women with unexplained infertility attempting natural conception, a small subgroup of 62 women with endometriosis showed a dramatic significant improvement in pregnancy rate (RR 4.4, 95% CI 1.6–12.2) and live-birth rate (RR 3.7, 95% CI 1.3–10.5) following a lipiodol hysterosalpingogram versus no intervention [68]. The mechanism may be through an effect of lipiodol enhancing endometrial expression of uterine natural killer cells and downregulating endometrial osteopontin [69]. There is insufficient evidence to recommend the use of the following as fertility treatments: pentoxifylline, traditional Chinese medicine, vitamin C and E, mifepristone, rosiglitazone and valproic acid [1].

Ongoing research

The World Endometriosis Research Foundation (WERF) has evolved the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect), a global initiative aimed at facilitating and improving research in endometriosis. Publication of four papers recommending global standardization of data collection [39,70] and sample collection [71,72] in endometriosis research is intended to foster many new collaborations among existing centres and encourage other endometriosis centres that have not yet embarked on research to join. It is hoped that this endeavour will aid in the quest to improve the quality of life of millions of women affected by endometriosis worldwide.

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54

Chronic Pelvic Pain

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Pain perception is subjective, multifactorial and involves complex physical, biochemical, emotional and social interactions. Somatic pain is usually sharp and unilateral whereas visceral pain is duller, aching, bilateral or localized to the midline.

Chronic pelvic pain (CPP) is defined as non-cyclical pain lasting for more than 6 months, localized to the anatomical pelvis and anterior abdominal wall, at or below the umbilicus, or to lumbo-sacral back and buttocks of sufficient severity to cause functional disability or lead to medical intervention [1]. CPP is a broad term with varied presentations and has a significant impact on quality of life. It may present as dysmenorrhoea, dyspareunia, vulvodynia, non-specific pelvic pain, musculoskeletal pain, intestinal cramps or dysuria [2]. CPP is associated with long-standing mental health problems, with reported increased rates of anxiety, depression, somatic disorders, disturbed concentration and insomnia [3]. In primary care settings, CPP has a similar prevalence to migraine, back pain and asthma [4] and postmenopausal women have also reported a substantial burden of CPP [5]. In the literature the incidence and prevalence of CPP are reported in an inconsistent manner which makes comparison and discussion difficult. It is recognized that in England it can take several years for a patient's persistent chronic pain condition to be recognized and even longer before management is provided in a secondary care setting [6].

Chronic post-surgical pain may develop after any surgical procedure, and is a common feature after abdominal and pelvic surgery, with a prevalence varying between 10 and 40% [7].

CPP is a symptom and not a diagnosis but it has to be regarded as a disease in its own right and requires attention accordingly. This involves multidisciplinary care, which differs from the organ-centred view. Pain associated with a well-described disease process requires that the disease be treated as a priority. Pain management is therefore a vital component and may reduce chronicity.

In most instances the diagnosis is derived from clinical history rather than relying upon examination and investigations. An empathic consultation and acknowledging the presenting complaints can in themselves be therapeutic; furthermore, a comprehensive neurological, myofascial and postural assessment should be carried out. Overall, pain relief, though paramount, is not the only goal of treatment. Improvement in quality of life is also equally important.

Summary box 54.1

- Pain is a complex phenomenon.
- CPP is 6 months or more of non-cyclical pain in the pelvis.
- CPP is as common as migraine, back pain and asthma.
- CPP is a symptom and not a diagnosis.

Clinical history

Clinical history is an integral part of management as it not only helps to find the possible cause or predisposing factor but also helps in understanding the impact on quality of life and the patient's expectations from treatment. Table 54.1 presents a classification of causes of CPP that should be borne in mind while undertaking the clinical assessment.

Clinical history needs to include the onset and duration of symptoms, the location and radiation of pain, factors associated with exacerbation and relief, and the relationship of pain to the menstrual cycle. Dysmenorrhoea may be a separate or related symptom. The intensity of dysmenorrhoea can sometimes warn of the possibility of

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 54.1 Classification of the causes of chronic pelvic pain.

Inflammatory, infective: chronic salpingitis
Inflammatory, non-infective: endometriosis, vulvodynia with dermatosis
Mechanical: uterine retroversion, adhesions
Functional: pelvic congestion, irritable bowel syndrome
Neuropathic: post-surgical, dysaesthetic vulvodynia, vulval vestibulodynia ('vestibulitis')
Musculoskeletal: pelvic floor myalgia, abdominal and pelvic trigger points, postural muscle

specific pathology such as endometriosis. Dyspareunia may include pain during intercourse, but for many women a particularly unpleasant symptom is post-coital pain and a specific enquiry about this should be made.

One should also explore the temporal relationship of pain with events like labour and delivery, which could have damaged the pelvic floor, or surgery which could have caused adhesions or nerve damage leading to pain. A history of subfertility hints at a diagnosis of endometriosis. Earlier studies showed a history of sexual abuse in more than half of patients with CPP [8].

Many women with chronic abdominal or pelvic pain will turn out to have irritable bowel syndrome (IBS) as their primary problem [9]. These patients do not have good outcomes following (inappropriate) gynaecological referral and investigation [10]. Therefore, it is particularly important that a detailed history is taken of bowel symptoms. The Rome II criteria [11] for the clinical diagnosis of IBS in those with chronic pain include at least two of:

- relief of pain with defecation;
- change in the frequency of stool; and
- change in the appearance or form of stool.

Abdominal bloating in association with acute exacerbations of pain is indicative, but needs to be distinguished from menstrual cycle-related bloating. While dyspareunia is not likely to be due solely to IBS, bowel spasm may account for the experience of those patients who describe an interval between the end of intercourse and the onset of acute pain associated with the urge to defecate and abdominal distension [12].

Bladder symptoms also form an important part of the systems review. Urinary frequency and urgency, but most importantly exacerbation of pain associated with a full bladder, may indicate the presence of interstitial cystitis, a neurogenic inflammatory condition of the bladder associated with chronic pain. As with IBS, it has been suggested that a proportion of women with CPP seen by gynaecologists are in fact suffering from unrecognized interstitial cystitis on the basis of potassium chloride sensitivity testing [13].

As pain is subjective, attempts to quantify can be made using a number of validated pain assessment measures, such as a 10-cm visual analogue scale (VAS) where one end is marked 'no pain' and the other end is the 'worst imaginable pain' [14]. There are also specific questionnaires available from the International Pelvic Pain Society (https://pelvicpain.org/home.aspx).

Health-related quality of life can be measured using a generic instrument such as EuroQoL EQ-5D (measured on a scale of –0.59 to 1 based on responses to five questions about life quality) or the EQ-VAS scale (measured on a 0–100 scale) [15]. Other generic quality-of-life measures such as the SF-36 (http://www.sf-36.org/tools/sf36.shtml) or the shorter SF-12 can also be used.

Examination

Observing how a patient walks into the consulting room can provide a clue to the diagnosis. Pelvic pain that is predominantly secondary to musculoskeletal origins can lead to the typical pelvic pain posture, with lordosis and concomitant kyphosis. On examination, musculoskeletal symphysial tenderness may be noted in such women. Abdominal wall pain has been proposed as a defining new test, where there is abdominal wall tenderness with a positive Carnett test (i.e. tenderness that worsens or remains the same with abdominal wall contraction). The prevalence in women with pelvic pain was 67% and was independently associated with CPP (odds ratio, OR 13.8, 95% CI 3.71–51.2; P <0.001) but not with other symptoms including dysmenorrhoea, deep and superficial dyspareunia, or bowel and bladder symptomology. The women with abdominal wall pain were more likely to require opioids or pain adjuvants than women without it (P = 0.015 and P <0.001) [16].

Careful inspection of the abdomen can reveal previous surgical scars, which could suggest pain from adhesions or nerve entrapment. 'Trigger point' tenderness elicited by palpation with one finger suggests a nerve entrapment, often involving the ilioinguinal or iliohypogastric nerves. Hernial sites should be examined carefully. On palpation, abdomino-pelvic masses may be noted. It is useful to ask the patient to point to the area of maximum pain and encircle the area where the pain spreads. The diagnosis is confirmed by infiltration of local anaesthetic such as bupivacaine into the tender area. Interestingly, the duration of relief is often much longer than the action of the local anaesthetic, perhaps because surrounding muscles are induced to relax and are no longer pulling on the sensitive area.

Local examination of the perineum should be carried out after obtaining verbal consent and in the presence of a chaperone. Vulval erythema may suggest infection, whilst thinning is suggestive of lichen sclerosus. In cases of vulvar vestibulitis, there can be local redness near the vestibular gland. The presence of vulval or lower limb varicosities is associated with pelvic vein incompetence. During vaginal examination, tenderness on palpation of the pelvic floor muscles could suggest myofasciitis of the pelvic musculature, whereas deep fornicial tenderness with nodularity on palpation could suggest chronic inflammatory disease or endometriosis. The uterus should be palpated for size, mobility and tenderness. Palpation of the adnexa may reveal masses like endometriomas or there can be tenderness in the adnexa due to pelvic congestion syndrome (see later).

Investigations

Investigations largely depend on the diagnosis suggested by history and examination. A few basic tests may be required, such as urine microscopy and sensitivity to rule out infection and a full blood count to rule out anaemia and infection. Culture swabs to exclude sexually transmitted infections such as *Chlamydia* are useful. If symptoms suggest, tests may be required to rule out diabetes or hypothyroidism. An ultrasound examination may be useful in identifying uterine or adnexal pathology and has been shown to be an effective means of providing reassurance [17,18].

Laparoscopy has commonly been undertaken as the primary investigation for CPP. The aims are to give a diagnosis but also to provide 'one-stop' treatment for endometriosis and adhesions where these are identified. This approach is cost-effective for endometriosis treatment, as the expense of a second procedure or hormonal treatment is obviated [19]. This method is being challenged by a current study to assess if MRI can replace or triage the need for laparoscopy in women presenting with CPP (MEDAL study: http://www.nets.nihr.ac.uk/projects/hta/092250). The results are awaited.

Conscious pain mapping by laparoscopy has been used at some centres and found useful in cases where examination and imaging were inconclusive, with a majority of patients showing some improvement in VAS pain scoring [20–22]. However, these studies have been small and there are no randomized controlled trials to suggest that this technique should be implemented into routine practice.

Summary box 54.2

- A detailed comprehensive clinical history should differentiate between gynaecological and non-gynaecological pelvic pain.
- Cyclical pelvic pain is likely to be associated with endometriosis.
- Irritable bowel syndrome is a common non-gynaecological cause of CPP.
- Trigger points can indicate nerve entrapment.
- Ultrasound is a useful tool for excluding gross pelvic pathology and for providing reassurance.
- Laparoscopy is not recommended as a first-line investigation.

Management

Medical therapy

Medroxyprogesterone acetate (MPA) has been used extensively but is only effective after 4 months' treatment as reflected in pain scores (OR 2.64, 95% CI 1.33–5.25; $N = 146$] and a self-rating scale (OR 6.81, 95% CI 1.83–25.3; $N = 44$), but benefit was not sustained 9 months after treatment [23,24]. MPA plus psychotherapy was effective in terms of pain scores (OR 3.94, 95% CI 1.2–12.96; $N = 43$) but not the self-rating scale at the end of treatment. Benefit was not sustained following treatment. Venography scores, symptom and examination scores, mood and sexual function were improved to a greater extent 1 year after treatment with the GnRH analogue goserelin compared with progestogen [25].

No improvement in pain scores was seen in women taking the selective serotonin reuptake inhibitor sertraline compared with placebo. The SF-36 subscale 'health perception' showed a small improvement in the sertraline arm, while the 'role functioning–emotional' subscale showed a large fall in the sertraline arm [26].

Surgical therapy

Previously, laparoscopic uterosacral nerve ablation (LUNA) was commonly performed for the treatment of CPP. However, a large and well-designed randomized controlled trial showed that this technique did not lead to any improvement in pain, dysmenorrhoea, dyspareunia or quality of life [27].

Adhesiolysis

Intraperitoneal adhesions can form *de novo* or following a surgical procedure. Diamond *et al.* [28] distinguished

two types of postoperative peritoneal adhesions. Type 1, or *de novo* adhesion formation, involves adhesions formed at sites that did not have previous adhesions, and includes type 1A (no previous operative procedure at the site of adhesion) and type 1B (previous operative procedures at the site of adhesion). Type 2 involves adhesion reformation, with two separate subtypes: type 2A (no operative procedure other than adhesiolysis at the site of adhesion) and type 2B (other operative procedures at the site of adhesions). Each surgeon defines adhesions on an individual basis contingent on the surgeon's own experience and capability. A peritoneal adhesion index has been described and is based on the macroscopic appearance of adhesions and their extent in the different regions of the abdomen. The abdomen is divided into nine quadrants and bowel-to-bowel adhesions are also noted. Each area is given a grade: grade 0, no adhesions; grade 1, flimsy adhesions requiring blunt dissection; grade 2, strong adhesions requiring sharp dissection; and grade 3, very strong vascularized adhesions requiring sharp dissection with damage hardly preventable. Using specific scoring criteria, clinicians can assign a peritoneal adhesion index ranging from 0 to 30, thereby giving a precise description of the intra-abdominal condition [29].

There is no definite relationship between adhesions and pain. Usually, peritoneal adhesions, or flimsy adhesions which allow movement between two structures, cause little pain [30]. Traditionally, laparoscopy has been the only way of diagnosing and treating adhesions. Recently, transvaginal ultrasound has been suggested for the diagnosis of adhesions based on ovarian mobility [31,32].

It is controversial to surgically treat adhesions to decrease pain as adhesiolysis itself has an inherent risk of adhesiogenesis. A large Dutch trial randomizing both men and women to adhesiolysis or no treatment found no difference between the groups. There was a small possible difference in those undergoing adhesiolysis with dense vascular adhesions but the sample size was small for conclusive results [33]. A recent systematic review examining the efficacy of adhesiolysis for the treatment of chronic pain showed that the benefit of intervention varied from 16 to 88%, with the majority of studies reporting pain relief in more than 50% of cases. However, there was a high risk of bias in most of the studies [34,35]. Therefore, it is important to take steps to minimize adhesion formation in the first place. The use of hyaluronic acid derivatives, polyethylene glycol (PEG)-based derivatives and solid barrier agents derived from oxidized regenerated cellulose (Interceed) during laparoscopy or laparotomy in benign gynaecological surgery is supported by only limited evidence and their use should perhaps not be continued [36,37].

Summary box 54.3

- Progestogens and selective serotonin reuptake inhibitors are not useful for treating CPP.
- GnRH analogues have better efficacy but should only be used in the short term.
- LUNA and adhesiolysis should not be performed.

Other treatments

Despite all the options available, there are still thousands of women suffering from CPP. The experience of pain necessitates the involvement of the central nervous system (CNS) and there is increasing evidence that pain, no matter where it is perceived to originate from, can be both generated and perpetuated by the CNS itself. Currently, a double-blind, multicentre, randomized controlled trial (GaPP2) is evaluating the efficacy and mechanism of action of gabapentin for the management of CPP; 300 women with more than 3 months of pelvic pain, with no pathology found at laparoscopy within 36 months of trial entry, will be randomized to gabapentin and placebo. This treatment approach has already shown promise in a pilot study on 47 patients [38] which suggested that there is a central component to CPP that can be suppressed by the use of gabapentin.

While there are few data supporting the efficacy of treatments targeting the CNS in CPP specifically, there is good evidence to suggest that the underlying pain mechanisms and central changes associated with chronic pain are similar no matter where the pain is perceived to originate from and it is therefore reasonable to consider these treatment options for all women with CPP. Medical options such as antidepressant and anticonvulsant drugs are well tolerated and could therefore be started by a gynaecologist or primary care physician. Other more novel or invasive therapies are likely to require referral to a pain management team. However, it is important that gynaecologists are aware that such options exist so that referral can be considered for patients who are refractory to standard treatments prior to performing radical or fertility-removing surgery [39].

Acupuncture and Chinese herbal medicine may have roles to play in the treatment of CPP associated with dysmenorrhoea, endometriosis, IBS and pelvic inflammatory disease, either as an adjunct or as an alternative to conventional treatments. Unfortunately, the current evidence lacks rigour and the available trials are frequently small, poorly designed and inadequately reported [40].

Pelvic congestion syndrome

Pelvic congestion syndrome (PCS) is described as chronic pelvic pain arising from dilated and refluxing incompetent pelvic veins. The majority of studies cite pelvic pain, dilated ovarian veins and venous reflux or congestion as the principal features of PCS. There is no generally accepted, well-defined criteria for diagnosing PCS. It is predominantly observed in multiparous women of reproductive age, suggesting a mechanical and/or hormonal mechanism. The pain is typically described as dull pelvic pain that radiates to the upper thighs and is aggravated by prolonged standing and walking.

CPP affects 24% of women worldwide, and the cause cannot be identified in 40% despite invasive investigation. Pelvic vein incompetence is thought to be a possible cause of CPP. Taylor in 1949 first described how incompetent and distended pelvic veins might cause symptoms of pain/dyspareunia and menstrual dysfunction. There is some evidence to tentatively support this hypothesis, as there are data to suggest that women with pelvic vein incompetence experience more lower abdominal and pelvic pain than age-matched women with varicose veins or healthy controls [41]. The proportion of women found to have pelvic vein incompetence who report CPP varies from 39 to 91% [42]. Transvaginal Doppler and magnetic resonance venography are useful screening tools but the definitive diagnosis is made by venography.

Recent systematic reviews for evaluating pelvic vein occlusion in women suffering from CPP or PCS have shown that transvenous occlusion of the ovarian and internal iliac veins can be technically successful in 98–100%. The procedure is generally safe, with subjective improvement in pelvic pain frequency, dysmenorrhoea and dyspareunia lasting up to 5 years [43] (Figs 54.1–54.4). However, as there are significant methodological flaws with most of these studies, there is an urgent need for well-designed randomized controlled trials. A current study (Transvenous occlusion of pelvic vein incompetence, http://www.isrctn.com/ISRCTN15091500) is being conducted and the results are awaited. Until then, this procedure should not be routinely implemented in clinical practice.

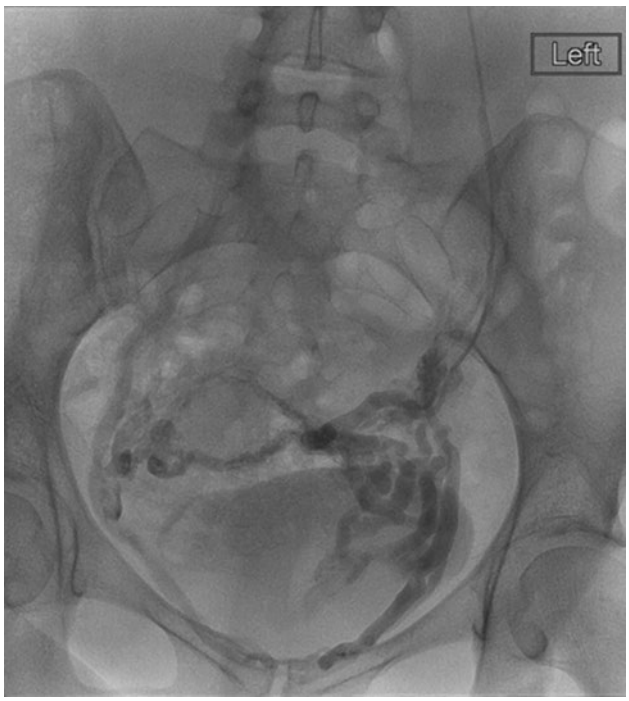

Fig. 54.1 Pre-embolization image of contrast injection from left ovarian vein demonstrating marked reflux into the deep pelvic veins and towards the vulval veins. Also note cross-filling into the left ovarian vein. *Source:* Dr Rob Jones. Reproduced with permission of Dr Rob Jones.

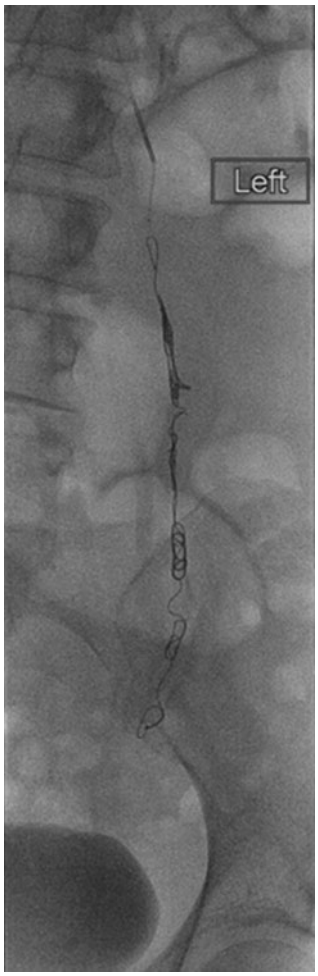

Fig. 54.2 Left ovarian vein post-coiling with multiple embolization coils. *Source:* Dr Rob Jones. Reproduced with permission of Dr Rob Jones.

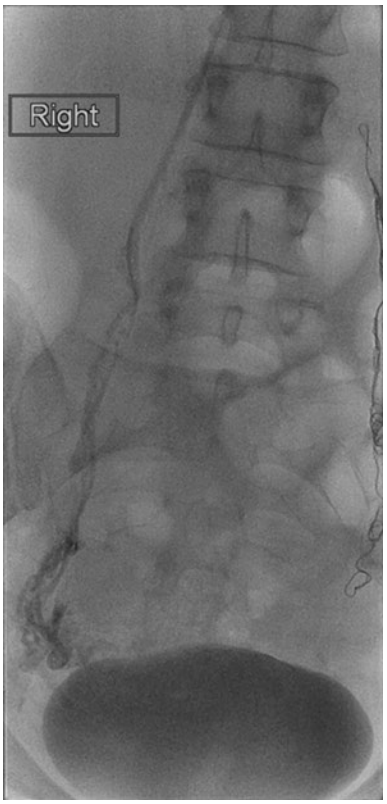

Fig. 54.3 Reflux as seen from injection into right ovarian vein. *Source:* Dr Rob Jones. Reproduced with permission of Dr Rob Jones.

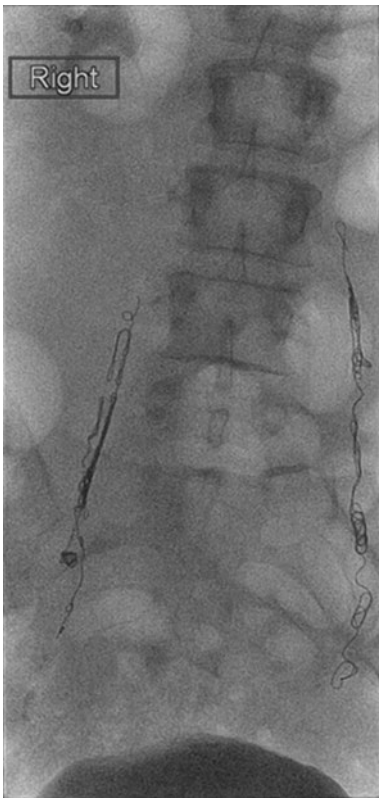

Fig. 54.4 Post-embolization of both ovarian veins. Note the parallel channels on the right side. In this case no reflux could be seen from injection into the internal iliac veins, therefore they were not embolized in this case. *Source:* Dr Rob Jones. Reproduced with permission of Dr Rob Jones.

Hysteroscopic sterilization

It is reported that women suffer from CPP after hysteroscopic sterilization. Patients with previous diagnoses of any chronic pain (CPPP, chronic low back pain, chronic headache and fibromyalgia) are more likely to report both acute pain (OR 6.81, 95% CI 2.95–15.73) and chronic pain (OR 6.15, 95% CI 2.10–18.10) after the procedure [44].

Myofascial pain

Myofascial pain usually arises from a trigger point, which is formed due to a metabolic crisis within the muscle. It is palpable as a taut, ropy band. Pain is movement related, aggravated by specific movement or activity and relieved by certain positions. Adjacent to the trigger point is a referral zone where the involved muscle displays weakness and restricted stretch. Trigger points involving the levator ani muscle and other pelvic floor muscles can cause CPP. Current guidelines by the Royal College of Obstetricians and Gynaecologists [39] and Cochrane database [45] suggest trigger point injections with local anaesthetic, corticosteroids and botulinum toxin A to treat myofascial CPP. Botulinum toxin A inhibits the release of acetylcholine from cholinergic nerve terminals, preventing the activation of muscle contraction and causing transient hypotonia and muscle weakness. It also provides long-term analgesia by retrograde axonal spread and blockade of neurotransmitter release from spinal cord. Studies have shown that botulinum toxin type A may be a useful agent in women with pelvic floor muscle spasm and CPP who do not respond to conservative physical therapy [46]. Self-limiting adverse effects like *de novo* urinary

Summary box 54.4

- Pelvic congestion syndrome is still being assessed as a potential cause for CPP.
- Treatment of pelvic vein incompetence with embolization has not been evaluated and should not be routinely performed until clinical trials have been completed.
- Myofascial pain arises from trigger points and can be treated with local anaesthesia, corticosteroids or botulinum toxin.

retention, faecal incontinence, and constipation and/or rectal pain have been reported with no obvious long-term adverse effects [47].

Conclusions

Chronic pelvic pain is a debilitating and distressing condition as in many cases diagnosis is uncertain and treatments unsatisfactory. A comprehensive clinical history and thorough examination can provide a diagnosis in many women. When no diagnosis can be reached, a treatment goal should be established. Some women are relieved by the fact that there is no sinister pathology and do not want further investigations and treatment, whereas pain relief is of paramount importance for others. A multidisciplinary team approach should evaluate such cases, especially in liaison with a chronic pain team. New avenues of research are ongoing in the field, such as assessment of the effects of pelvic vein occlusion, use of neuromodulators and complementary therapies.

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Part 13

Urogynaecology

55

Uterovaginal Prolapse

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Pelvic organ prolapse (POP) is defined as the downward displacement of pelvic organs from their original position into or beyond the vagina. An enormous variation exists in the clinical presentation, from minimal descent to complete eversion of the vagina along with the uterus, bladder and rectum. It can also occur in patients who have previously experienced a hysterectomy.

POP will affect a substantial number of women. Although it is a benign condition it can have a major impact on the quality of life. Skilful assessment and management is required to ensure appropriate treatment and improved outcome. Inappropriate treatment can leave women worse off than when they started.

Incidence and epidemiology

The lifetime risk of surgery for POP is 12–19%, with more than 300 000 women undergoing surgery a year in the USA. Approximately 8% of women in the UK report symptoms of prolapse [1–4].

On routine examination, loss of vaginal or uterine support will be seen in up to 30–70% of women who present for routine gynecological care. However, only a small proportion of these will report symptoms. Of this cohort, only about 3–6% will have descent beyond the hymenal margin and it is this group that will tend to be symptomatic [5]. In one large epidemiological study in the USA called the United States (US) National Health and Nutrition Examination Survey (NHANES), in response to the question 'Do you experience bulging or something falling out?', only 2.9% of women responded in the affirmative [6].

The most common form of prolapse is that of the anterior wall of the vagina (cystocele). Prolapse of the posterior wall (rectocele) is far less frequent and apical prolapse (descent of the uterus or vaginal vault if the patient has had a hysterectomy) the least common. Patients can present with one or more of the forms and in any combination.

The natural history of prolapse is not well known as long-term epidemiological studies are extremely rare. One study found that the incidence of prolapse to or beyond the hymen was 26% after 1 year of observation and 40% after 3 years. Over the same time period spontaneous remission rates at 1 and 3 years were 21% and 19% [7,8].

Summary box 55.1

- Most pelvic organ prolapse is asymptomatic.
- Anterior prolapse is the most common presentation.
- The natural progression of the condition is poorly understood.

Aetiology

The aetiology is poorly understood. Predisposing risk factors for the development of prolapse include vaginal childbirth, obesity, previous hysterectomy and age [9,10].

Vaginal birth is probably the principal risk factor, with avulsion injury to the levator ani during childbirth along with pudendal neuropathy and fascial damage the most common causes. There is no evidence that instrumental delivery increases the risk of developing POP [11–13]. Nulliparous women may also develop prolapse and a range of other conditions may contribute to the development of the disease [14]. Of these, age is the most significant contributor, with the incidence of prolapse doubling with every decade of life [5,8].

The genetic predisposition is less clear. There does seem to be an ethnic influence, with lower rates of POP reported in Black and Hispanic women compared with white women [5,15]. Twin studies have also

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

demonstrated a genetic component [16] and a familial association has been clearly identified [17]. Because of the protean nature of collagen diseases, it is more difficult to establish a clear link between collagen disorders and POP.

The influence of body mass index (BMI) is well established, which is of some concern given the 20% rise in obesity in the last 20 years [18]. There is no clear consensus that a prior hysterectomy (unless it was performed for prolapse) is a risk factor for subsequent vault or vaginal prolapse [19]. Conditions associated with chronically increased intra-abdominal pressure, such as chronic cough and heavy lifting, are also considered to be risk factors [15].

Summary box 55.2

Risk factors

- Childbirth
- Age
- Obesity
- Genetics
- Occupation

Pelvic anatomy

The bony pelvis provides the architectural framework for the supports of the organs of the pelvis. The organs are supported by the fibres of the paracolpium (direct support) and by the levator plate (indirect support). The fibres of the paracolpium arise from a broad area on the pelvic side wall over the fascia of the piriformis muscle, sacro-iliac joint and lateral sacrum. They insert into the lateral upper third of the vagina, with some fibres inserting anteriorly and posteriorly. These fibres are condensations of the endopelvic fascia and are composed of perivascular connective tissue and smooth muscle and contain blood vessels, lymphatics and nerves. They run in a predominantly vertical direction and their upper borders are continuous with the cardinal and uterosacral ligaments.

The levator ani comprises the pelvic diaphragm muscles: the pubococcygeus, iliococcygeus, puborectalis and coccygeus muscles. Together they form a thin broad muscle arising anteriorly from the posterior aspect of the pubic bone just lateral to the symphysis pubis and laterally from the white line of the obturator internus muscle fascia and ischial spine. The right and left muscle bellies swing backwards and downwards to fuse together behind the anal canal and anterior to the coccyx to form the levator plate between these two structures. The anal canal, lateral vagina and urethra gain some attachment of the medial margins to the levator ani. The levator plate provides indirect support for the vagina by acting as a platform against which the upper vagina and cervix are compressed during episodes of raised intra-abdominal pressure. Narrowing of the urogenital hiatus also occurs with rises in intra-abdominal pressure.

The supports of the vagina are divided into three zones: the upper, middle and the lower. The fibres in the upper are largely vertical in orientation while the fibres supporting the middle section are attached to the side wall. The fibres surrounding the lower third are almost fused with the surrounding structures [20]. This reflects the different embryological origins of the vagina and determines the surgical approach to the repair of each level.

Clinical presentation

The most consistent and specific symptom of POP is a feeling of a bulge in the vagina or a sensation of protrusion of tissue out of the vagina. In more advanced cases the prolapse can be seen and palpated outside the vagina with the patient complaining of a 'lump'. It is not uncommon for women to be asymptomatic in the early morning and then for the symptoms to develop or worsen throughout the day with activity and be relieved by lying down. While some women may present with a single symptom of prolapse, they typically have a more complex presentation that can include urinary symptoms of incontinence, frequency, nocturia and voiding dysfunction; faecal symptoms of incontinence and obstructed defecation; and sexual dysfunction. While these symptoms present commonly in association with prolapse, they are not usually caused by it and therefore are unlikely to be resolved by the surgery aimed at correcting the POP.

In a large study of women with symptomatic vaginal prolapse, 87% reported urinary frequency and urgency, 73% reported urinary incontinence and 50% had symptoms of voiding dysfunction [21]. As stated above this may be because of shared aetiological factors and may not be a direct causal link.

Bowel symptoms include the sensation of incomplete emptying and the need to manually assist defecation. The latter can include putting digital pressure on the perineum or splinting the posterior wall with the fingers during evacuation. Splinting is a mechanical means of improving defecation. In these cases obstructed defecation may be improved by surgery. Pressure on the perineum obviously has a different mechanism of action and there is no evidence that correction of a posterior wall prolapse in these cases will resolve the symptoms of obstructed defecation.

Sexual dysfunction is a common symptom in women attending a urogynaecology clinic [22]. A high percentage are not sexually active but cite the reason as lack of desire and arousal. Pain and discomfort only affect a small number.

The best way to record symptoms is with a validated quality of life (QOL) instrument. The pelvic floor distress inventories (PFDI-20, PFIQ-7) are well studied and validated [23]. The use of validated QOL instruments will help provide a more accurate reflection of the symptoms that bother a patient the most. One such system (e-PAQ, http://www.epaq.co.uk/) can be administered before the patient sees the doctor in clinic. Not only will this help with understanding what worries the patient most but can also be used for assessment of outcomes.

Summary box 55.3

Symptoms of POP

Symptoms likely to correlate with POP

- Bulge.
- Fullness.
- Dragging and deterioration with activity.
- Symptoms relieved by rest.

Symptoms unlikely to correlate with POP

- Backache.
- Pain.
- Urinary and/or bowel dysfunction.
- Sexual dysfunction.

Validated QOL instruments improve the accuracy of the history.

Evaluation

Patients presenting with a complaint of POP need to have a comprehensive history taken. This should include a full urinary, bowel and sexual history. It is also essential to establish which are the most worrisome symptoms and to clarify which symptoms the patient hopes will be corrected. The use of an objective QOL instrument can be very useful in establishing which symptoms are the most bothersome [24]. Because of a lack of understanding of the longitudinal history of prolapse, counselling about the need for intervention can be extremely difficult.

Because of the high incidence of asymptomatic POP, patients presenting to their practitioner with primary bladder or bowel dysfunction are often then referred on for management of the prolapse due to the mistaken belief that their bladder or bowel symptoms are the result of the prolapse noticed during the routine physical examination. Treatment of the prolapse in isolation will very often lead to disappointment with the outcomes achieved. This is a failure of expectation more than a failure of treatment and is a much-underestimated problem in the management of POP. Similarly, sexual dysfunction is seldom the result of POP in isolation. Other symptoms misappropriated to POP are backache and pelvic pain syndrome.

All women presenting with symptoms of POP should have a thorough examination. This should begin with palpation of the abdomen before proceeding to the pelvic examination to exclude an abdominal mass or ascites. For the pelvic examination the women should ideally be examined in the dorsal lithotomy position with Valsalva. This has been shown to be as effective as an examination in the standing position [25]. In cases where the symptoms do not correlate with the physical findings it may be worthwhile bringing the patient back for a late afternoon clinic and to perform the examination in the standing position [26]. A Sim's speculum is used to systematically identify each component of the prolapse. To assess for anterior prolapse the blade is used to retract the posterior wall while inspecting the degree of prolapse of the anterior wall. Conversely, for the posterior wall the blade is used to retract the anterior wall while assessing the degree of prolapse of the posterior wall. During this examination the position of the cervix, or in a post-hysterectomy patient the vault, is determined. The final part of the assessment is a bimanual pelvic examination. There are a range of methods that have been described to classify prolapse. Of these, the POP-Q method is the internationally accepted standard. The POP-Q system is the POP classification system of choice of the International Continence Society (ICS), the American Urogynecologic Society (AUGS) and the Society of Gynecologic Surgeons. It has proven inter-observer and intra-observer reliability and is the most commonly cited system in the medical literature (Fig. 55.1). Alternatively, the Baden–Walker Halfway Scoring System, which has five degrees/grades, is another commonly used POP staging system but it lacks accredited reproducibility (Table 55.1). The degree, or grade, of each prolapsed structure is described individually (e.g. grade 1 anterior vaginal wall prolapse or grade 3 uterine prolapse). The grade/degree is defined as the extent of prolapse for each structure noted on examination while the patient is straining. Because there are no clear demarcations among the cut-off stages, the Baden–Walker system lacks the precision and reproducibility of the POP-Q system.

There is no need for a routine rectal examination or a barrier test to look for urinary incontinence.

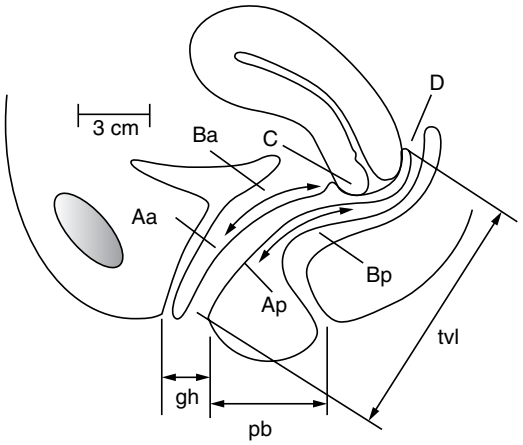

Fig. 55.1 The POP-Q system. Aa, anterior wall; Ap, posterior wall; Ba, anterior wall; Bp, posterior wall; C, cervix or cuff; D, posterior fornix; gh, genital hiatus; pb, perineal body; tvl, total vaginal length.

Table 55.1 Baden–Walker Halfway Scoring System.

0	Normal position for each respective site
1	Descent halfway to the hymen
2	Descent to the hymen
3	Descent halfway past the hymen
4	Maximum possible descent for each site

Investigation

Lower urinary tract symptoms should be evaluated independently with urinalysis, a urinary flow rate and assessment of the residual urine volume. In selected cases, where there are significant urinary symptoms, urodynamic testing may be helpful. Coexistent urinary incontinence should be investigated in the same way that it would be if the patient did not have POP.

The need to identify the patient at risk of developing urinary incontinence prior to surgery is more debatable. Women with POP without significant urinary incontinence have a 10–20% chance of developing incontinence after prolapse surgery. Because of this, some advocate the use of urodynamics after reduction of the prolapse to try to identify those at risk. They support the view that these patients should have an associated anti-incontinence operation at the time of their POP operation. This view is supported by the CARE study, which concluded that a prophylactic operation to prevent stress urinary incontinence was necessary at the time of sacrocolpopexy [27]. In an earlier study, researchers felt that preoperative testing overestimated the risk and resulted in a high proportion of women undergoing additional surgery when only a minority would develop the problem [28].

An anti-incontinence procedure should not be offered routinely. Patients are counselled about the risk and reassured that in the group that develop incontinence, spontaneous resolution will occur in more than 50% of the patients by 6 months. Only the remainder (5–8%) will need an additional incontinence procedure. A substantially lower number will undergo additional surgery than if one follows the CARE study protocol [27]. Because of the uncertainty surrounding this subject, very careful counselling of the patient is essential before embarking on surgery.

Patients with severe symptoms of bowel dysfunction, including obstructed defecation and faecal incontinence, should be seen by the colorectal team ahead of any surgical intervention.

There is little place for radiological investigations such as dynamic MRI and transperitoneal ultrasound (TPUS) in the routine management of POP. Dynamic MRI gives outstanding images but it is unlikely that it offers any advantages over a detailed clinical examination in the management of these patients. Likewise, TPUS does not seem to offer any advantages to clinical evaluation [29].

Summary box 55.4

Investigations

Essential
- Urinalysis.
- Flow study and measurement of residuals.

Unsure
- Urodynamics and barrier testing.

Of no value in routine management
- Radiological imaging.

Management

Conservative

It is always preferable to seek a conservative solution ahead of a surgical one. The condition is bothersome and can restrict normal activities but it is seldom life-threatening. The surgeon must be mindful that all surgical procedures carry inherent risks and should not proceed with a surgical procedure without first offering a trial of conservative treatment.

It is important to counsel the patient that progression is not inevitable. Unfortunately, a precise profile of risk factors for progression does not exist, further compounding the difficulties with counselling. An even more difficult group of patients to counsel are those who

present soon after pregnancy. The majority of them can expect to experience spontaneous resolution as time elapses from the delivery. Too hasty a recourse to surgical intervention is to be avoided and the patient should be encouraged to persist with conservative measures for at least 18 months before considering surgery.

Options for conservative therapy include pelvic floor muscle training (PFMT) and pessary use. Lifestyle advice such as weight loss and smoking cessation should be advised when relevant. The evidence supporting the role of weight loss in POP is limited. The Women's Health Initiative (WHI) study confirmed a higher rate of progression in women with raised BMI but did not demonstrate an improvement of POP after weight loss [7]. However, if the conservative measures fail, weight loss will improve their general health and reduce perioperative complication rates should surgery become an option. Weight loss will also reduce the risk of stress urinary incontinence.

Although PFMT has been recommended for the management of urinary incontinence, there is disagreement about its value for the management of POP, especially the more advanced stages. This was partly due to the paucity of literature in the area [30]. However, more recent studies have shown that PFMT can result in improvement in both POP symptoms and POP stage. Randomized trials have supported the benefit of PFMT especially when involving individualized training and supervision. In one study it was shown that symptom control was better than in controls but by 12 months there was no difference in the number of women who needed surgery [31]. The efficacy of PFMT beyond 12 months in unknown. However, as PFMT carries no risk to the patient, it should be offered to all patients who present with POP.

Vaginal pessaries are devices which are inserted into the vagina for the management of POP. They have been in use in various forms for hundreds of years. They offer an excellent non-surgical option for women with prolapse and there are virtually no contraindications to vaginal pessary use. A significant number of women express a preference for a non-surgical management of their prolapse. Pessaries can be used as a long-term solution or as a semi-diagnostic test to evaluate which symptoms are removed with reduction of the pessary. They can also be used as a temporary measure in women who want to delay surgery until they have completed their family or while waiting for surgery.

Patient acceptance of pessaries is variable ranging from 40 to 100%. The rate of acceptance is influenced by counselling and the enthusiasm of the healthcare practitioner. Patients who decline pessary use are usually younger, nulliparous and have severe symptoms of prolapse or incontinence. Women who have had prior prolapse surgery, more severe prolapse and more bothersome symptoms, especially those relating to bowel, bladder and sexual function, are more likely to choose surgical management. This is not surprising as this group will be desperate for a resolution of their problems. They need encouragement to try the pessary and be reminded that if it does not alleviate the symptoms, surgical treatment is still an option [32,33]. There are no direct contraindications apart from a possible allergy to the materials.

A wide variety of pessaries in a range of materials, shapes and sizes is available. They can be divided into support pessaries and space-filling pessaries. Support pessaries are further subdivided into those without a diaphragm (Fig. 55.2) (ring, Smith, Hodge, Gehrung) and those with (Falk and Schaatz). There is also a wide variety of space-occupying pessaries (Shelf, Gelhorn, Donut, Cube) although little to recommend one over another (Fig. 55.3).

The most commonly used pessary is the ring [34]. This has been shown to be very successful, with resolution of symptoms in a high percentage of patients. Ring pessaries have a smaller surface area than space-occupying pessaries and patients using rings are mostly able to have normal sexual intercourse. They are easily removed and inserted by the patient, which reduces the need for repeated pessary changes in the surgery. The common feature of all the pessaries is that they lack an evidence base for their use. Much of what we know is anecdotal and based on personal experience.

Fitting the pessary takes place after a careful examination. Using the length of the vagina (measured from

Fig. 55.2 Mediplus ring pessary. *Source:* Mediplus Ltd.
Reproduced with permission of Mediplus Ltd, United Kingdom.

Fig. 55.3 Other types of vaginal pessary. *Source:* Mediplus Ltd. Reproduced with permission of Mediplus Ltd, United Kingdom.

behind the symphysis pubis to the pouch of Douglas) as a guide, an estimate is made of the size of pessary. The pessary should be the largest size that fits into the vagina without the patient being able to feel it. Immersion of the pessary in hot water ahead of insertion will make it more malleable and easier to insert. Removal can be uncomfortable as it is difficult to alter the diameter ahead of extraction. Fitting the pessary is usually a process of trial and error. It is not uncommon to try two or three different sizes before getting the best fit. A ring pessary is usually trialled in the first instance. If this does not remain in place and there are no contraindications, a space-occupying pessary should be tried. Women must be counselled that the pessary may fall out, usually within the following 24 hours. This occurs most commonly in association with straining at stool. They are then advised to return for review. Patients are encouraged to remove their pessary fortnightly for cleaning and then reinsert. If the patient is unable to practise self-management, she should be seen for review every 3–6 months for a pessary change. Pessary changes can be very uncomfortable and this often becomes a greater problem with advancing age and progressive tightening of the introitus. Use of topical oestrogen can reduce this difficulty. Unless there is a contraindication to its use, patients should be encouraged to use topical vaginal oestrogen as a way of facilitating changes but also as a means of reducing discharge, granulation and bleeding. After an initial 2-week spell of daily insertion it is maintained with a twice-weekly regimen. There will be a group of patients unable to retain a pessary and the exact reasons for treatment failure remain elusive [35].

The most common side effects, which are also the major reasons for discontinuing use of a pessary, are vaginal discharge and the development of granulation tissue in the vagina. Granulation tissue can exacerbate the discharge and can lead to bleeding. The discharge is often anaerobic in nature, which suggests it occurs secondary to a change in the natural microbiome of the vagina or from the biofilm which can develop on the pessary. The change in pH in the vagina in association with the menopause, and further exacerbated by the presence of the pessary, may predispose to the development or recurrent urinary tract infections [36]. The discharge can be treated with the addition of intermittent courses of vaginal antibiotics usually containing metronidazole. Vaginal bleeding in postmenopausal patients is particularly bothersome and needs to be managed as for any other postmenopausal bleed. A transvaginal ultrasound will usually be able to rule out endometrial pathology. Persistence of discharge,

granulation tissue and bleeding are usually indications to consider surgical management.

Resolution of symptoms is experienced in a majority of women in the short term. However, there is a gradual reduction in satisfaction rates over time [35]. A study in Australia reported that pessary use dropped to 14% over 14 years [37].

There is no evidence that either systemic or topical oestrogen is effective therapy for POP. There is histological evidence that local oestrogen increases the development of mature collagen along with vaginal wall thickness but the clinical correlation is lacking [38]. However, the use of topical oestrogen may offer the patient some relief of symptoms caused by vaginal atrophy. Patients might otherwise have incorrectly attributed the hypo-oestrogenic symptoms to the presence of the prolapse. There is some evidence that use of the selective oestrogen receptor modulator raloxifene may reduce the need to undergo surgery [39], but the vasomotor side effects associated with this treatment are likely to preclude its use in clinical practice.

Summary box 55.5

Conservative management

Appropriate measures
- Weight loss.
- Pelvic floor muscle training.
- Vaginal pessary placement.

Invalid measures
- Hormone replacement therapy.

Surgery

Women with symptomatic POP who decline conservative treatment or experience no improvement with it may require surgical treatment. The aim of surgery is to restore anatomy, relieve symptoms and restore function. Before proceeding with surgery it is essential to understand the patient's expectations are. The surgeon must be convinced that the proposed procedure is appropriate and must also ensure that the patient knows what can be achieved with surgery and, more importantly, what cannot. Surgery should be reserved for patients who have at least stage 2 POP on examination and have bothersome symptoms attributable to the POP.

Surgery can be undertaken using vaginal or abdominal approaches. The abdominal approach can be through open abdominal surgery or minimal access surgery (MAS) undertaken either laparoscopically or robotically. There is no consensus on which approach is superior. Despite the major advances achieved in the field of MAS, the majority of surgeries are carried out via the vaginal approach. This may reflect the fact that MAS is technically more challenging. Comparison of different surgical procedures for POP is made more difficult by the lack of agreement on objective outcome measures. MAS has been shown to have significant advantages over open surgery, with a reduction in wound complications, postoperative pain, convalescent time and return to normal activity. Despite this only a minority of procedures are done in this fashion [40]. The increased adoption of robotically assisted surgery will enable more surgeons to utilize minimal access techniques for pelvic floor surgery. The da Vinci system is already available but other more versatile robotic platforms are under development by Transenterix, Medtronic and Cambridge Medical Robotics (CMR). The newer robots, like the CMR Versius, have a more versatile modular form that suits reconstructive pelvic surgery (Fig. 55.4).

Very few patients require surgery to a single compartment and will usually need some combination of the various approaches.

Surgery for apical prolapse

The abdominal approach usually involves sacrocolpopexy which involves suspending the vaginal apex to the anterior longitudinal ligament of the sacrum with a synthetic mesh. This can be carried out as an open procedure using a Pfannenstiel incision but more recently the majority are performed either as a laparoscopic sacrocolpopexy or a robotically assisted sacrocolpopexy.

Transvaginal apical support can also be achieved with a sacrospinous fixation. This involves suspending the vaginal vault to the sacrospinous ligament with sutures. Typically this is a unilateral extraperitoneal approach. There are descriptions of a bilateral approach, although this is often not possible in patients with reduced vaginal volume.

The uterosacral colpopexy also has good results but some series have reported high ureteric injury rates. The results after uterosacral suspension are similar to those achieved with a sacrospinous fixation. The 2013 Cochrane meta-analysis of randomized controlled trials on apical suspending surgery concluded that the abdominal approach was superior to vaginal-based sacrospinous colpopexy, with reduced recurrent vault prolapse, postoperative stress incontinence and dyspareunia. This was at a cost of longer operating time, longer time to recovery and greater expense. It would seem therefore that the abdominal supporting procedures should be reserved for the younger, fitter and more active patients while the vaginal procedures should be reserved for older and frailer patients.

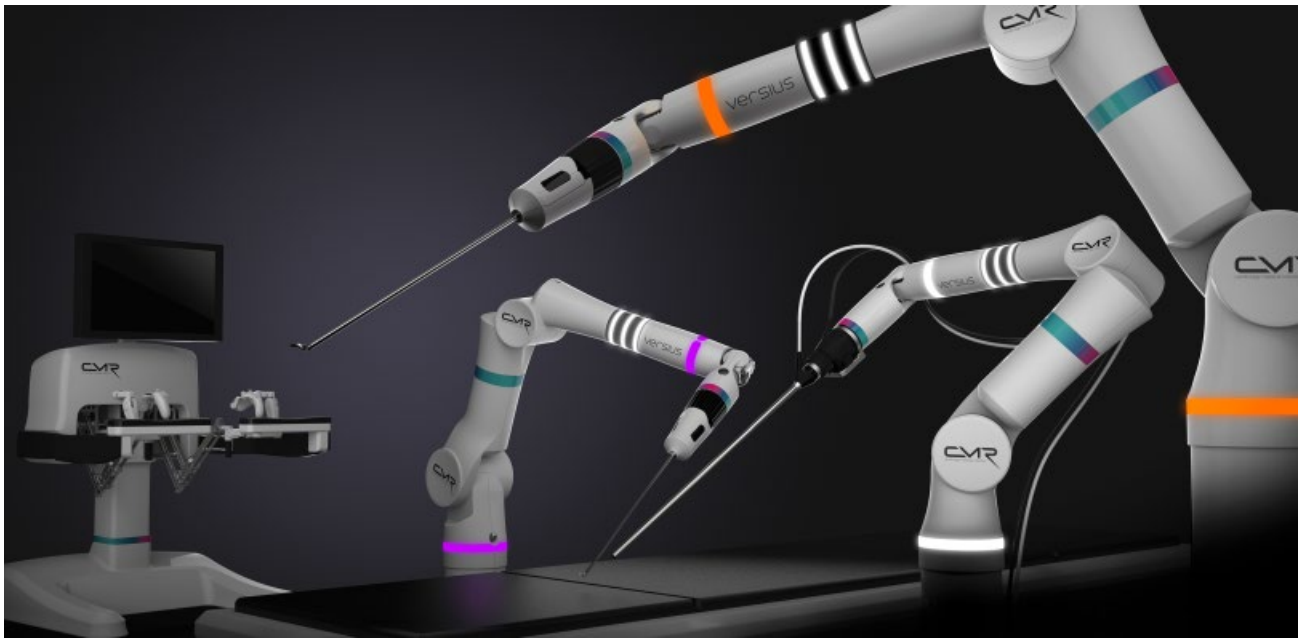

Fig. 55.4 The Versius® Surgical Robot by Cambridge Medical Robotics. *Source:* Cambridge Medical Robotics, Ltd. Reproduced with permission of Martin Frost.

Surgery for anterior compartment prolapse

Anterior vaginal wall defects rarely occur in isolation and are often accompanied by descent of the vaginal apex (cervix or vaginal vault) or posterior wall. The need to repair other anatomic sites should usually be decided under anaesthesia when the patient is fully relaxed and a detailed examination can be carried out. The apical support must be very carefully evaluated as it is increasingly believed that anterior compartment prolapse rarely occurs in isolation. This is borne out by significantly better surgical outcomes when an anterior repair is performed concurrently with an apical support repair [41].

Traditionally, the anterior repair involves the midline plication of the vaginal fascia followed by excision of the redundant vaginal wall epithelium and then suture of the epithelium. Repair of the anterior wall may also involve correction of lateral wall defects. This can be performed vaginally or abdominally and has similar success rates to the midline technique.

Anterior wall surgery has success rates in the range of 40–60% [42]. Because of these poor results, surgeons have started to use artificial grafts to try to improve outcomes. In a study of 2756 women it was shown that the addition of an apical supporting procedure to an anterior repair significantly reduced the need for reoperation from 20% to 11% [43]. Native tissue repair is the dominant method of repair; perhaps the addition of apical support procedures will lead to improved outcomes.

Surgery for posterior compartment prolapse

Posterior repair is associated with much higher rates of anatomical success, with outcomes as high as 80–95% [44]. The operation involves a midline plication of the rectovaginal fascia, excision of redundant epithelium and reconstruction of the epithelium. The use of mesh has never been shown to have advantages over native tissue repair. Improvement in bowel symptoms has been demonstrated in the majority of women after posterior colporrhaphy [45].

Patients who present with significant prolapse of the anterior and posterior walls often have concomitant loss of apical support. Some believe that if the apex or uterus is poorly supported, there is a lower chance of supporting the anterior and posterior wall defects.

Obliterative surgical procedures

Obliterative procedures are reserved for women who have failed conservative therapy but who have significant comorbidities and are therefore not candidates for extensive surgery and who do not plan for future vaginal intercourse. The most common procedure is a colpocleisis. This can be done in women who have had a hysterectomy and those who have not.

The procedure involves removal of strips of vagina from the anterior and posterior vaginal epithelium, leaving a small strip of lateral epithelium on each side. The anterior and posterior walls are then sutured together. The main purpose of the side strips is to allow for vaginal or uterine secretions to be discharged. The procedure is associated with excellent results and very low complications [46].

Role of synthetic materials

Grafts may be biological (allograft, autograft or xenograft) or synthetic. Synthetic materials are further defined according to the type of polymer (absorbable or non-absorbable, monofilament or multifilament), pore size and weight. These features will determine how the graft will behave in the body, especially the way these various materials will integrate in the tissues. The best grafts are monofilament, with a pore size greater than 75 µm. Microporous and multifilamentous grafts cause an over-exuberant inflammatory reaction with subsequent tissue damage [47].

Early data suggested that traditional repair was associated with more postoperative prolapse as seen on examination and also as reported by patients [44]. This led to a rapid introduction of multiple operations (kits) utilizing mesh and tools for the insertion of the mesh. These were marketed very aggressively and with little regard to whom they were being sold. Consequently, reports soon appeared with mesh complications, including extrusion, infection, shrinkage and fibrosis.

Multiple law suites materialized all over the world, which led many manufacturers to withdraw their products from the market. In 2016, the US Food and Drug Administration (FDA) reclassified surgical mesh for transvaginal POP as a class III device, requiring manufacturers to submit premarket approval applications to support the safety and effectiveness of the synthetic mesh [48]. Consequently, the use of mesh in transvaginal surgery has dropped from a high of 27% of surgeries in 2008 to less than 2% by 2011.

Summary box 55.6

Surgical options

Restorative

Vaginal

- Anterior colporrhaphy.
- Posterior colporrhaphy.
- Vaginal hysterectomy.
- Sacrospinous fixation.
- Sacrospinous hysteropexy.
- Uterosacral plication.

Abdominal

- Sacrocolpopexy (open/laparoscopic/robotic).
- Sacrohysteropexy (open/laparoscopic/robotic).

Obliterative

- Colpocleisis.

The future

With an ageing population with an increasingly sedentary lifestyle and endemic levels of obesity, the number of patients presenting for treatment is likely to rise. Investment in POP research is required so that we can better delineate the problems and hopefully develop more effective solutions. There needs to be more effort directed towards the accurate measurement of outcomes. This will involve the monitoring of operative morbidity as well as long-term functional outcomes. Improved outcome data will allow us to understand the natural history of the condition, which in turn will help us counsel our patients and so hopefully better manage expectations.

The urogynaecology community must learn from the lessons of the mesh debacle and ensure that we always demand evidence ahead of fashion and fad. Hopefully there will be newer and better graft materials to help augment surgical repair. These may or may not include a contribution from stem cell technology.

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56

Urinary Incontinence

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Urinary incontinence has a major impact on the quality of life of women and urgency incontinence has been found to be associated with increased mortality [1]. Through ignorance, embarrassment and a belief that loss of bladder control is a 'normal' result of childbirth and ageing, many women suffer for years before seeking help [2]. An accurate diagnosis can be made and many women can be cured or improved by the use of various management strategies.

Urinary incontinence is defined as the complaint of any involuntary loss of urine [3], whereas continence is the ability to retain urine at all times except during micturition. Both continence and micturition depend on a structurally and functionally normal lower urinary tract.

Urinary incontinence is best classified according to aetiology, as shown in Table 56.1. There are a number of additional causes of urinary incontinence in elderly woman (Table 56.2), many of which can be reversed by appropriate intervention.

Clinical presentation of urinary incontinence

Symptoms of lower urinary tract dysfunction fall into three main groups: (i) incontinence; (ii) overactive bladder (OAB) symptoms; and (iii) voiding difficulties.

Stress urinary incontinence (SUI) is the most common complaint. It may be a symptom or a sign but it is not a diagnosis. Apart from stress incontinence, women may complain of urge incontinence, dribble or giggle incontinence, or incontinence during sexual intercourse. Nocturnal enuresis (bed wetting) may occur on its own or in conjunction with other complaints. Symptoms of voiding difficulty include hesitancy, a poor stream, straining to void and incomplete bladder emptying.

Apart from the symptoms of lower urinary tract dysfunction, it is important to take a full history from all women who present with urinary incontinence. Other gynaecological symptoms such as prolapse or menstrual disturbances may be relevant. A fibroid uterus may compress the bladder and can cause urinary frequency and urgency. There is an increased incidence of stress incontinence amongst women who have had large babies, particularly following instrumental vaginal delivery, so an obstetric history may be helpful. Information regarding other urological problems, such as recurrent urinary tract infections, episodes of acute urinary retention or childhood enuresis, should be sought.

Urinary incontinence is sometimes the first manifestation of a neurological problem (such as multiple sclerosis) so it is important to enquire about neurological symptoms. Endocrine disorders such as diabetes may be responsible for symptoms of lower urinary tract dysfunction and should therefore be recorded.

Some drugs affect urinary tract function, especially diuretics, which increase urine output. In older people they may cause urinary incontinence where only urgency existed previously. Other drugs that affect detrusor function include tricyclic antidepressants, major tranquillizers and α-adrenergic blockers.

Unfortunately, clinical examination is usually unhelpful in cases of female urinary incontinence. General examination should include the subject's mental state and mobility as well as the appearance of local tissues. Excoriation of the vulva will indicate the severity of the problem and atrophic changes may reveal long-standing hormone deficiency. A gynaecological/urological examination should be carried out and although stress incontinence may be demonstrated, this will only confirm the patient's story; it will not actually indicate the cause. If a neurological lesion is suspected, then the cranial nerves and sacral nerve roots S2–S4 should be examined.

The bladder has been described as an 'unreliable witness'. The correlation between clinical diagnosis and

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 56.1 Causes of urinary incontinence in women.

Urodynamic stress incontinence (urethral sphincter incompetence)
Detrusor overactivity (neurogenic detrusor overactivity)
Overactive bladder
Retention with overflow
Fistulae: vesicovaginal, ureterovaginal, urethrovaginal, complex
Congenital abnormalities, e.g. epispadias, ectopic ureter, spina bifida occulta
Urethral diverticulum
Temporary, e.g. urinary tract infection, faecal impaction
Functional, e.g. immobility

Table 56.2 Causes of incontinence in the elderly, many of which may be transient.

Infection (e.g. urinary tract infection)
Confusional states (e.g. dementia)
Faecal impaction
Oestrogen deficiency
Restricted mobility
Depression
Drug therapy (e.g. diuretics)
Endocrine disorder (e.g. diabetes)
Limited independence

urodynamic diagnosis is poor, and therefore it is unusual to be able to make an accurate diagnosis based on history and examination alone. Urodynamic stress incontinence is the commonest cause of urinary incontinence in women and detrusor overactivity is the second most common cause. These two diagnoses account for over 90% of cases of female urinary incontinence. As their treatment differs it is important to make an accurate initial diagnosis.

Summary box 56.1

Urinary incontinence

- Defined as the complaint of any involuntary loss of urine.
- Often under-diagnosed and under-treated.
- The incidence increases with age.
- Known to have a significant effect on quality of life.
- Stress urinary incontinence, overactive bladder (with or without incontinence) and mixed incontinence are the commonest types of urinary incontinence.

Table 56.3 Investigations of female urinary incontinence.

General practitioner/outpatient
Mid-stream specimen of urine
Frequency–volume chart
Pad test
Basic urodynamics
Uroflowmetry
Cystometry
Videocystourethrography
Specialized
Urethral pressure profilometry
Cystourethroscopy
Ultrasound
Cystourethrography
Intravenous urography
Electromyography
Ambulatory urodynamics

Investigations

Investigations range from the very simple to the highly sophisticated and complex and are outlined in Table 56.3.

GP/outpatient tests

Midstream urine sample

A midstream urine (MSU) specimen should always be sent for culture and sensitivity prior to further investigation. Although the patient's symptoms are unlikely to be caused by a urinary tract infection, they can be altered by one.

Frequency–volume charts

It is often helpful to ask women to complete a frequency–volume chart or urinary diary (Fig. 56.1). This is informative for the doctor as well as the patient and may indicate excessive drinking or bad habits as the cause of lower urinary tract symptoms. The frequency–volume chart (urinary or bladder diary) provides an objective assessment of a patient's fluid input and urine output.

As well as the number of voids and incontinence episodes, the mean volume voided over a 24-hour period can also be calculated, as well as the diurnal and nocturnal volumes. Frequency–volume charts have the advantage of assessing symptom severity in the everyday situation.

Pad test

Incontinence can be confirmed (without diagnosing the cause) by performing a pad weighing test. Many different types of pad test have been described based on the method for filling the bladder or length of the test.

	Day 1			Day 2			Day 3			Day 4			Day 5		
Time	In	Out	W	In	Out	W	In	Out	W	In	Out	W	In	Out	W
6 am															
7 am							200	150						300	
8 am 8.30	200 200	350		200	250		200				350		200		
9 am										400	50		200	150	
10 am 10.45	200	50			75										
11 am								50		200					
12 pm				200	60		200				50			50	
1 pm	200	100						25					200		
2 pm				200	60					200	100			175	
3 pm	100				100					100					
4 pm		75					200	100							
5.30 pm	100			50	150			300		100					
6.15 pm		150									100		40		
7 pm		100			50									100	
8 pm							200	175		200	150				
9 pm		250			100					150			50	100	
10 pm	200				50		200				100				
11.30 pm		200 100						325			100			150	
12 am							100								
1.30 am		100		100	50						100				
2 am								50							
3 am		75													
4 am					150										
5 am											150			200	

Fig. 56.1 A frequency–volume chart showing frequent small voided volumes.

Urodynamics

Urodynamic studies comprise several investigations that are employed to determine bladder function.

Uroflowmetry

Uroflowmetry, the measurement of urine flow rate, is a simple test that can exclude the presence of outflow obstruction or a hypotonic detrusor, but on its own will not differentiate between the two. In order to obtain a flow rate, the patient is asked to void onto the flowmeter, in private, when her bladder is comfortably full. The maximum flow rate and volume voided are recorded. In women, the normal recording is a bell-shaped curve with a peak flow rate of at least 15 mL/s for a volume of 150 mL of urine voided (Fig. 56.2a). A reduced flow rate in an asymptomatic woman may be important if she is to undergo incontinence surgery as she is more likely to develop voiding difficulties in the postoperative period (Fig. 56.2b).

Cystometry

Cystometry, which measures the pressure–volume relationship within the bladder, can differentiate between

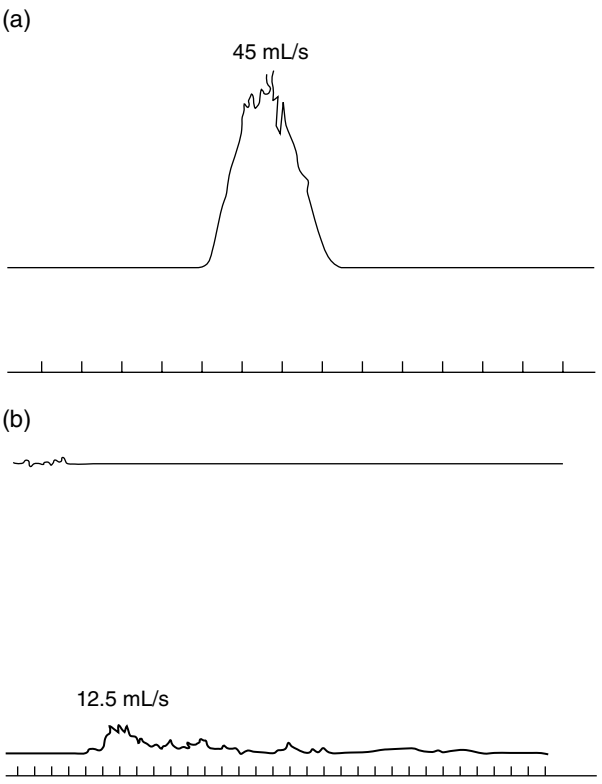


Fig. 56.2 (a) Normal uroflowmetry (maximum flow 45 mL/s, voided volume 330 mL); (b) reduced flow rate (maximum flow rate 12.5 mL/s, voided volume 225 mL).

urodynamic stress incontinence and detrusor overactivity in the majority of cases. The bladder is filled with physiological saline via a urethral catheter. During bladder filling the intravesical (total bladder) pressure and the intra-abdominal pressure are measured. The rectal (or vaginal) pressure is recorded to represent intra-abdominal pressure and this is subtracted from the bladder (intravesical) pressure to give the detrusor pressure. This is called subtracted cystometry (Fig. 56.3).

The information obtained from a subtracted cystometrogram includes sensation, capacity, contractility and compliance (Fig. 56.4). The urinary residual volume is normally less than 50 mL, the first sensation of desire to void is normally at 150–250 mL and the cystometric bladder capacity is normally 400–600 mL. Under normal circumstances, the detrusor pressure does not rise by more than 0.03 cmH_2O for 1 mL of bladder volume and there are no detrusor contractions during bladder filling. Ideally, the bladder is filled with the woman sitting or standing and the filling catheter removed once capacity is reached. She is asked to cough several times and to heel bounce and any rise in detrusor pressure or leakage per urethram is recorded. She is then asked to pass urine and the detrusor pressure is measured and any urinary residual volume can be noted (Fig. 56.5).

Videocystourethrography

Videocystourethrography with pressure and flow studies, which combines cystometry, uroflowmetry and radiological screening of the bladder and urethra, can be a most informative investigation (Fig. 56.6). It is relatively expensive and time-consuming and is only available in tertiary referral centres. Abnormal bladder morphology can be assessed as well as the presence of vesico-ureteric reflux, trabeculation or diverticula. Occasionally, a urethral diverticulum or vesicovaginal fistula may be identified (Fig. 56.7).

Special investigations

Urethral pressure profilometry

The resting urethral pressure profile (UPP) is a graphical record of pressure within the urethra at successive points along its length. Of particular interest are the maximum urethral closure pressure and functional urethral length (Fig. 56.8). In addition, stress pressure profiles can be performed if the patient coughs repeatedly during the procedure. This enables the pressure transmission ratio (the increment in urethral pressure, on stress, as a percentage of the simultaneously recorded increment in intravesical pressure) to be calculated. Urethral instability or relaxation can also be identified. Although urethral pressure profilometry is not useful in the diagnosis of urodynamic stress incontinence, it is helpful in women whose incontinence operations have failed and also in those with voiding difficulties [4].

Imaging of the urinary tract

Imaging of the urinary tract is mainly through ultrasound, X-rays or MRI [5]. Intravenous urography has now largely been replaced by ultrasound of the upper urinary tract. However, a CT urogram is important in cases of haematuria (Fig. 56.9). Additional pathology may be diagnosed, such as the presence of a ureteric fistula, a transitional cell carcinoma or calculi.

Ultrasound is now routinely used for assessing bladder volumes [6] and assessing the upper urinary tracts. Transvaginal ultrasound does allow clear visualization of the urethra and urethral diverticula. Bladder wall thickness of an empty bladder can be measured transvaginally giving a reproducible and sensitive method of screening for detrusor overactivity (a mean bladder wall thickness >5 mm gave a predictive value of 94% in the diagnosis of detrusor overactivity) [7]. Measurement of bladder wall thickness has also been shown to have a role as an adjunctive test in those women whose lower urinary tract symptoms are not explained by conventional urodynamic investigations [8].

MRI is useful in diagnosing urethral diverticula and imaging the pelvic floor muscles [9].

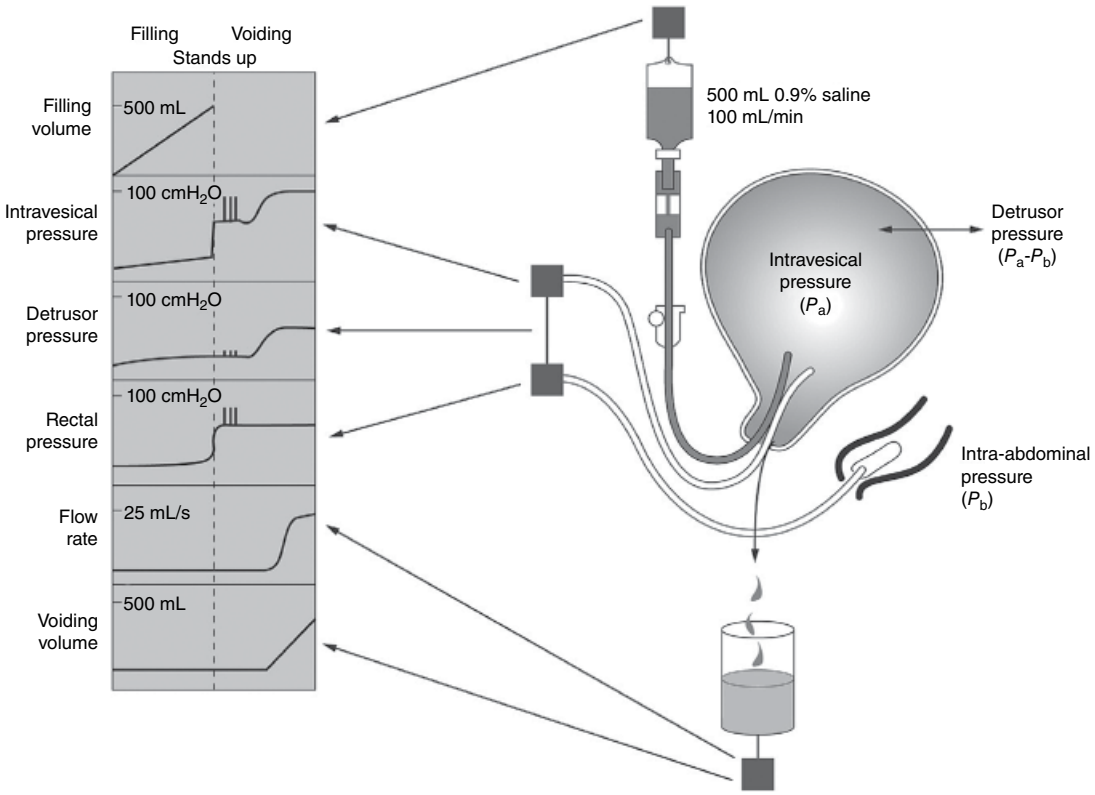


Fig. 56.3 Subtracted cystometry.

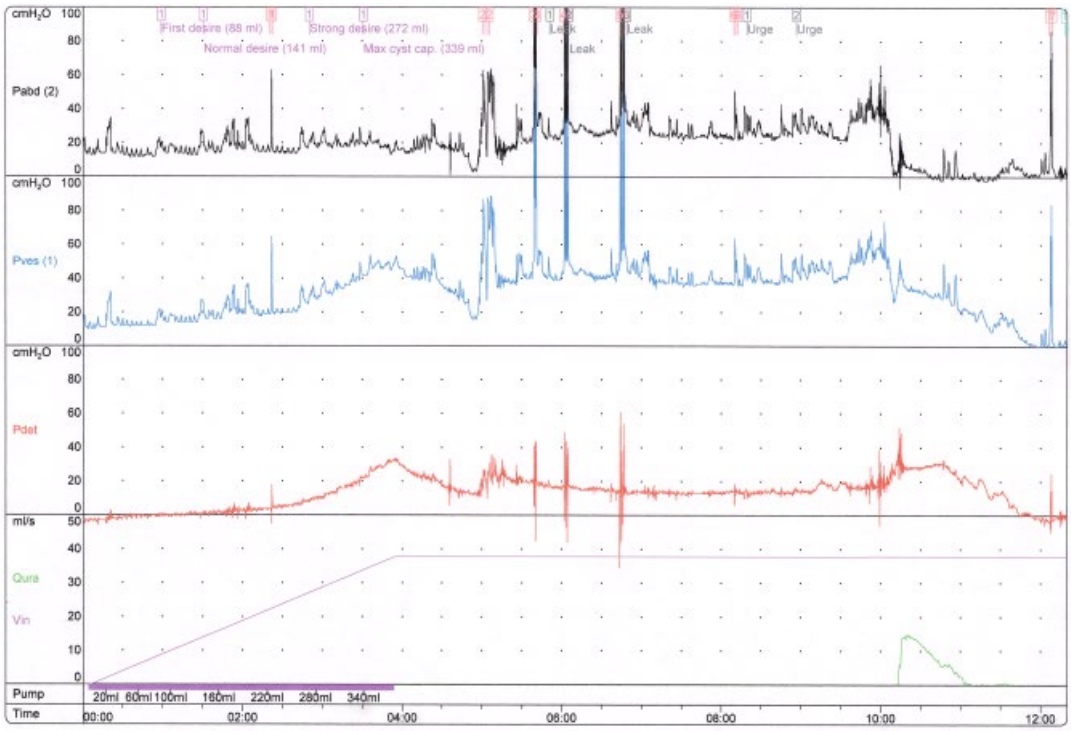


Fig. 56.4 Subtracted cystometrogram trace showing a picture of low compliance.

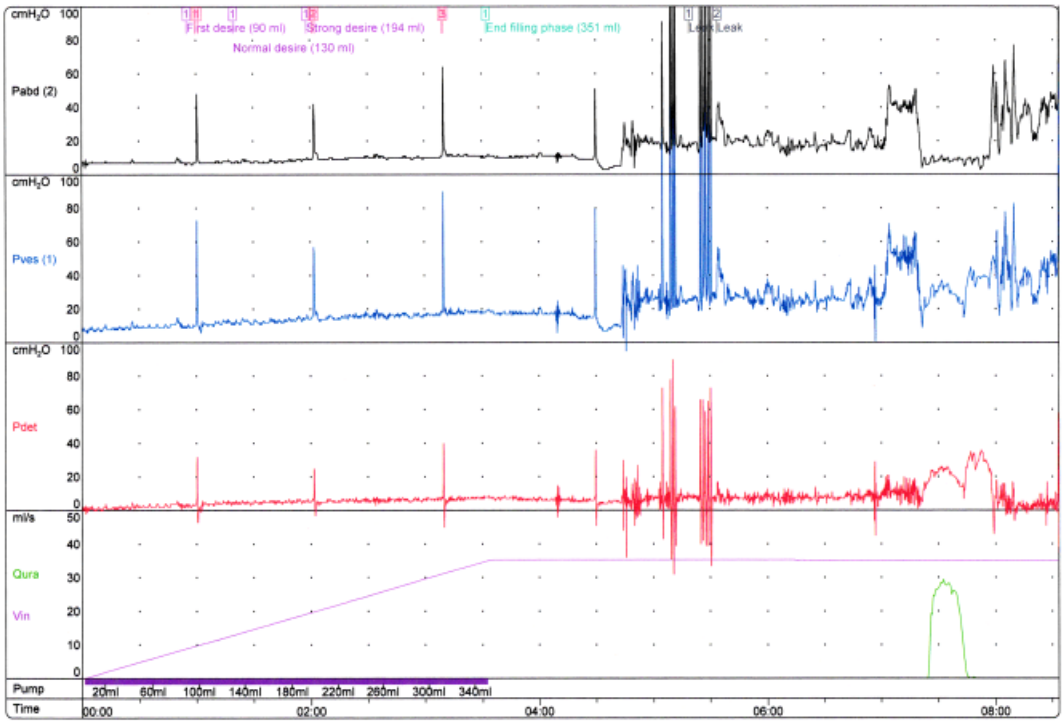


Fig. 56.5 A normal cystometrogram trace (the bottom line represents the flow rate, which is normal).

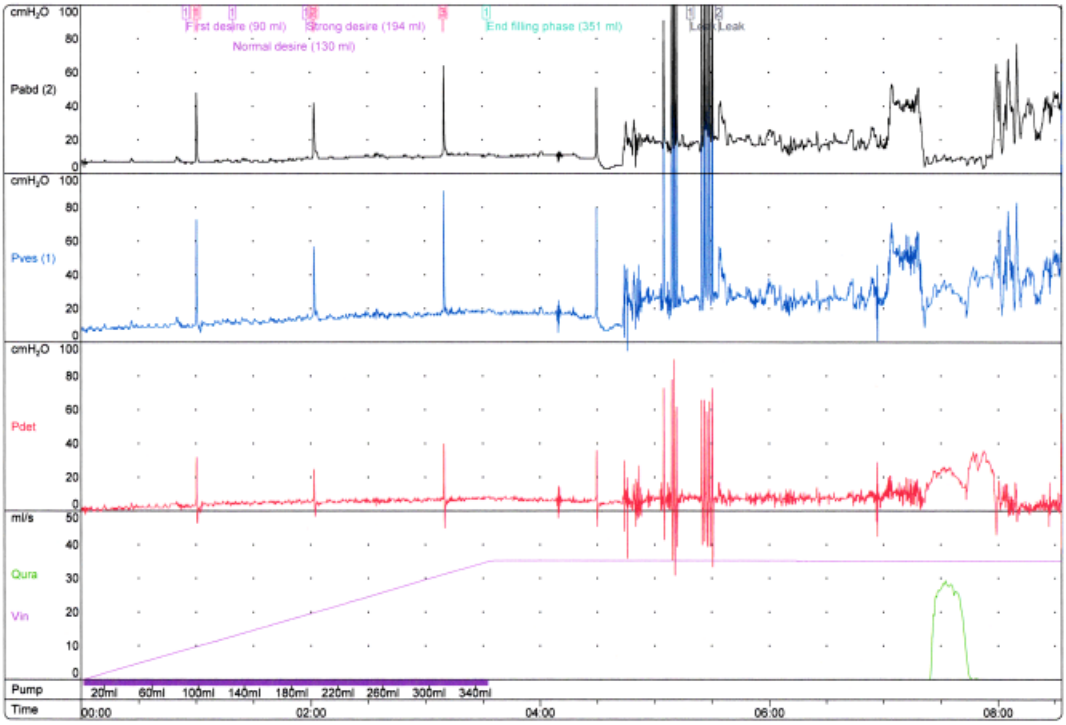


Fig. 56.6 Videocystourethrography demonstrating urodynamic stress incontinence. Subtracted filling cystometry showing no evidence of detrusor overactivity and synchronous screening demonstrating urethral sphincter incompetence on coughing.

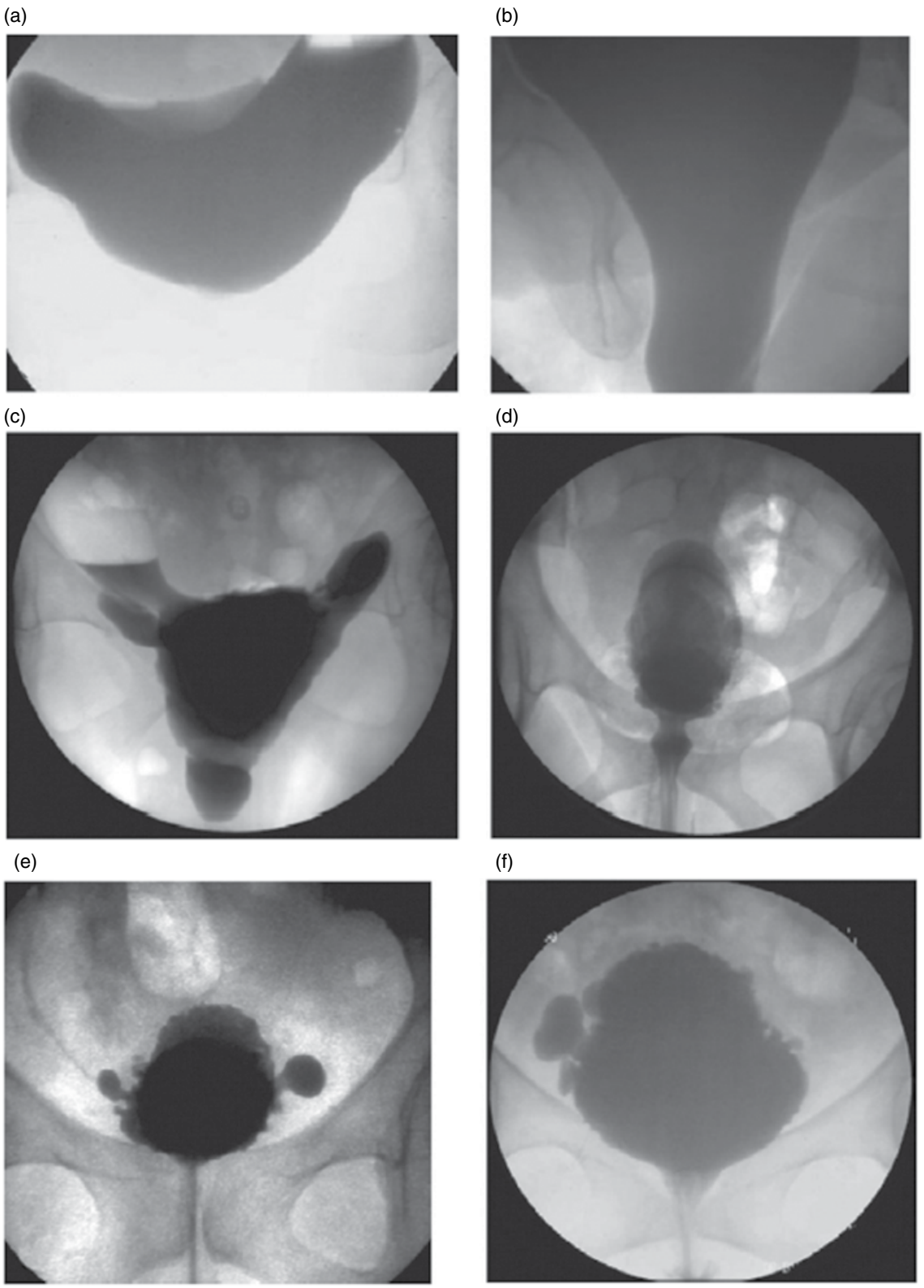


Fig. 56.7 Videocystourethrography images. (a) Extrinsic compression of the bladder by uterine fibroids; (b) large cystocele; (c) multiple bladder diverticula; (d) neurogenic bladder with uninhibited detrusor contraction and associated leakage; (e) bladder trabeculation, diverticula and right-sided vesico-ureteric reflux; and (f) multiple diverticula, bladder trabeculation and an unprovoked contraction with leakage.

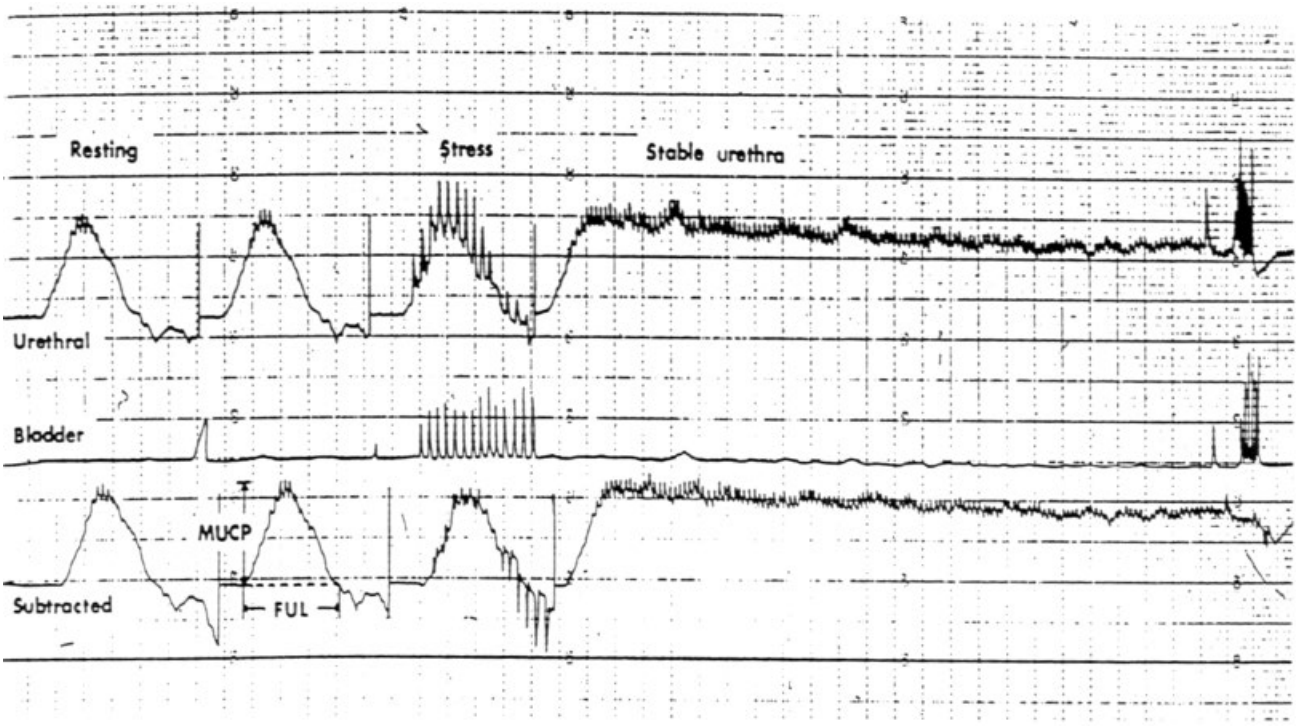


Fig. 56.8 Urethral pressure profilometry: normal trace.

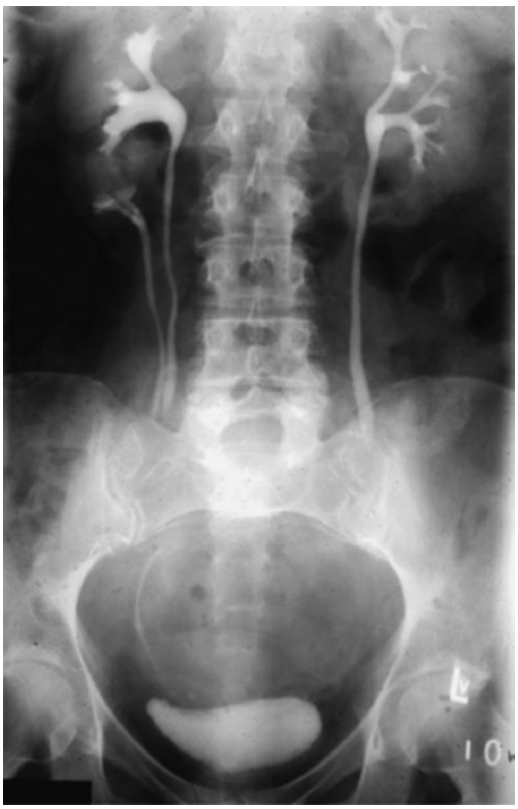


Fig. 56.9 Intravenous urogram showing a right duplex ureter.

Electromyography

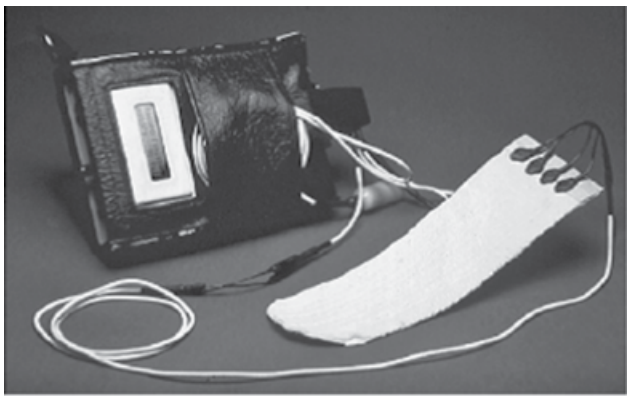
Electromyography can be employed to assess the integrity of the nerve supply to a muscle [10]. The electrical impulses to a muscle fibre are measured following nervous stimulation. Two main types of electromyography are employed in the assessment of lower urinary tract dysfunction. The pudendal nerve is stimulated and potentials measured via the electrode. This is inaccurate as the muscular activity of the levator ani is not necessarily representative of that of the rhabdosphincter urethrae [11]. Single-fibre electromyography is more accurate as it assesses the nerve latency within individual muscle fibres of the rhabdosphincter. Electromyography may be useful in the assessment of women with neurological abnormalities or those with voiding difficulties and retention of urine [12].

Ambulatory urodynamics

All urodynamic tests are unphysiological and most are invasive. Various authors have suggested that long-term ambulatory monitoring may be more physiological as the assessment takes place over a prolonged period of time and during normal daily activities. Ambulatory urodynamics is defined as a functional test of the lower urinary tract utilizing natural filling and reproducing the subject's everyday activities [13].

Ambulatory urodynamics is useful in cases where the clinical and conventional urodynamic diagnoses differ,

(a)



(b)

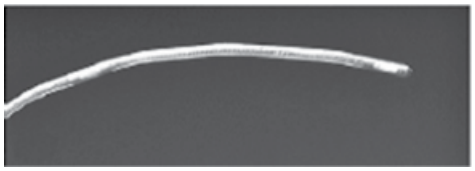


Fig. 56.10 Ambulatory urodynamic equipment demonstrating (a) the digital recording unit and Urilos pad and (b) microtip pressure transducer.

or when no abnormality is found on laboratory urodynamics [14] (Fig. 56.10). Ambulatory urodynamics has been shown to be more sensitive than laboratory urodynamics in the diagnosis of detrusor overactivity but less sensitive in the diagnosis of urodynamic stress incontinence [14], although its role in clinical practice remains controversial [15].

Summary box 56.2

Investigation of urinary incontinence

- Diagnosis may be based on symptoms or urodynamic studies.
- All women should have a full history and clinical examination.
- Frequency–volume charts are useful in making a diagnosis.
- Infection and voiding difficulties should be excluded.
- Subtracted cystometry should be considered in those patients who fail conservative therapy.
- Women with recurrent incontinence or who may have neurological problems should be investigated with videocystourethrography.
- Ambulatory urodynamics may be useful in women with symptoms not explained by conventional cystometry.
- All women with haematuria and bladder pain require cystoscopy.

Causes of urinary incontinence

Urethral incontinence will occur whenever the intravesical pressure involuntarily exceeds the intraurethral pressure. This may be due to an increase in intravesical (or detrusor) pressure or a reduction in urethral pressure or a combination of the two. Thus, the fault which leads to incontinence may lie in the urethra or the bladder or both.

Urodynamic stress incontinence

Urodynamic stress incontinence is defined as the involuntary leakage of urine during increased abdominal pressure in the absence of a detrusor contraction [3]. There are various different underlying causes that result in weakness of one or more of the components of the urethral sphincter mechanism (Table 56.4).

Urodynamic stress incontinence is associated with vaginal delivery due to denervation of the urethral sphincter mechanism or damage to the urethral sphincter [16,17]. Snooks *et al.* [18] employed electromyography to reveal evidence of pelvic floor denervation in women who had delivered vaginally but not in those who had undergone caesarean section. A long active second stage of labour was the only factor associated with severe damage.

If a woman complains of stress incontinence as her sole symptom and stress incontinence can be demonstrated on coughing, there is a 95% chance that the diagnosis is urodynamic stress incontinence. However, Haylen *et al.* [19]

Table 56.4 Causes of urodynamic stress incontinence.

Urethral hypermobility
Urogenital prolapse
Pelvic floor damage or denervation
Parturition
Pelvic surgery
Menopause
Urethral scarring
Vaginal (urethral) surgery
Incontinence surgery
Urethral dilatation or urethrotomy
Recurrent urinary tract infections
Radiotherapy
Raised intra-abdominal pressure
Pregnancy
Chronic cough (bronchitis)
Abdominal/pelvic mass
Faecal impaction
Ascites
(Obesity)

Table 56.5 Conservative treatment for urodynamic stress incontinence.

Pelvic floor muscle training (PFMT)
Perineometry
Vaginal cones
Maximum electrical stimulation
Duloxetine

have shown that only 2% of women who present for urodynamic assessment fall into this category.

Conservative treatment

Types of conservative treatment for urodynamic stress incontinence are listed in Table 56.5. Conservative treatment is indicated as first-line therapy if the patient is medically unfit for surgery or does not wish to undergo an operation, or in women who have not yet completed their families.

Pelvic floor muscle training

Pelvic floor muscle training (PFMT) and pelvic floor physiotherapy remain the first-line conservative measures since their introduction in 1948 [20]. PFMT appears to work in a number of different ways:

- women learn to consciously pre-contract the pelvic floor muscles before and during increases in abdominal pressure to prevent leakage ('the knack');
- strength training builds up long-lasting muscle volume and thus provides structural support; and
- abdominal muscle training indirectly strengthens the pelvic floor muscles [21].

Cure rates varying from 21 to 84% have been reported [22,23]. Success appears to depend on the type and severity of incontinence treated, the instruction and follow-up given, the compliance of the patient and the outcome measures used. However, the evidence would suggest that PFMT is more effective if patients are given a structured programme to follow rather than simple verbal instructions [24] and it appears that pelvic floor exercises increase the size of the urethral sphincter on three-dimensional ultrasound measurement [25]. The results are not superior to continence surgery [26].

Weighted vaginal cones

These are currently available as sets of five or three [27], all of the same shape and size but of increasing weight (20–90 g). When inserted into the vagina, a cone stimulates the pelvic floor to contract to prevent it from falling out and this provides 'vaginal weight training'. A 60–70% improvement rate has been reported using this technique [27] and two studies have shown that cones are as effective as more conventional forms of pelvic floor re-education and require less supervision [28].

Maximal electrical stimulation

Maximal electrical stimulation can be carried out using a home device that utilizes a vaginal electrode through which a variable current is passed. The woman is able to adjust the strength of the stimulus herself and is instructed to use the device for 20 min daily initially for 1 month. Maximum electrical stimulation has been employed in both the management of urodynamic stress incontinence and detrusor overactivity, although it has not gained popularity [29].

Vaginal devices

There are many women who, for various reasons, are not suitable for, or who do not wish to undergo, active treatment of their incontinence. However, they do require some sort of 'containment' of their leakage and vaginal devices may be suitable for use during exercise on a short-term basis [30].

Medical therapy

Although various agents such as α_1-adrenoceptor agonists, oestrogens and tricyclic antidepressants have all been used anecdotally in the past for the treatment of stress incontinence, duloxetine is the first drug to be specifically developed and licensed for this indication.

Duloxetine is a potent and balanced serotonin (5-hydroxytryptamine) and noradrenaline reuptake inhibitor (SNRI) that enhances urethral striated sphincter activity via a centrally mediated pathway [31]. Duloxetine was associated with significant and dose-dependent decreases in incontinence episode frequency. Reductions were 41% for placebo and 54, 59 and 64% for the 20, 40 and 80 mg groups, respectively. Discontinuation rates were also dose dependent: 5% for placebo and 9, 12 and 15% for the 20, 40 and 80 mg groups, respectively; the most frequently reported adverse event was nausea [32].

Surgery

Surgery is usually the most effective way of curing urodynamic stress incontinence, and a 90% cure rate can be expected for an appropriate, properly performed primary procedure. Traditional surgery for urodynamic stress incontinence aims to support the bladder neck and proximal urethra and in some cases to increase the outflow resistance. Undoubtedly, the results of suprapubic operations such as Burch colposuspension or the Marshall–Marchetti–Krantz procedure are better than those for the traditional anterior colporrhaphy with bladder neck buttress [33–35]. Numerous operations

Table 56.6 Operations for urodynamic stress incontinence.

Vaginal
Retropubic mid-urethral tape procedures
Transobturator mid-urethral tape procedures
Urethral bulking agents
Urethrocliesis
Anterior colporrhaphy ± Kelly/Pacey suture
Abdominal
Burch colposuspension
Marshall–Marchetti–Krantz procedure
Laparoscopic
Colposuspension
Combined
Sling
Endoscopic bladder neck suspension, e.g. Stamey, Raz
Complex
Neourethra
Artificial sphincter
Urinary diversion

have been described and many are still performed today. Common operations for urodynamic stress incontinence are listed in Table 56.6.

Anterior colporrhaphy

Anterior colporrhaphy is only rarely performed for urodynamic stress incontinence. Although it is usually the best operation for a cystourethrocele, the cure rates for urodynamic stress incontinence are poor compared with those from suprapubic procedures [36]. As prolapse is relatively easier to cure than stress incontinence, it is appropriate to perform the best operation for incontinence when the two conditions coexist.

Marshall–Marchetti–Krantz procedure

The Marshall–Marchetti–Krantz procedure is a suprapubic operation in which the paraurethral tissue at the level of the bladder neck is sutured to the periostium and/or perichondrium of the posterior aspect of the pubic symphysis. This procedure elevates the bladder neck but will not correct any concomitant cystocele. It has been largely superseded by Burch colposuspension because its complications include osteitis pubis in 2–7% of cases.

Colposuspension

The Burch colposuspension has been the operation of choice in primary urodynamic stress incontinence as it corrects both stress incontinence and a cystocele. The operation is performed via a low transverse suprapubic incision. The bladder, bladder neck and proximal urethra are dissected medially off the underlying paravaginal fascia and three or four pairs of non-absorbable or long-term absorbable sutures are inserted between the fascia and the ipsilateral iliopectineal ligament. Haemostasis is secured and the sutures are tied, thus elevating the bladder neck and bladder base (Fig. 56.11). Postoperatively, a suction drain is left in the retropubic space and a suprapubic catheter is inserted into the bladder. Colposuspension is now well recognized as an effective procedure for stress incontinence but complications include detrusor overactivity, voiding difficulties or exacerbated recto-enterocele. There have been studies comparing open and laparoscopic colposuspension, with similar results if surgeons are trained adequately [33].

Sling procedures

Sling procedures are normally performed as secondary operations where there is scarring and narrowing of the vagina. The sling material can be either biological (autologous rectus fascia, porcine dermis, cadaveric fascia) or synthetic (Prolene® and Mersilene®, Ethicon, Somerville, NJ, USA). The sling may be inserted either abdominally or vaginally, or by a combination of both. Sling procedures are associated with a higher incidence of side effects and complications, especially after the insertion of inorganic material but mid- to long-term continence outcomes are superior to open colposuspension [33] but there are increased rates of irritative symptoms [37].

Retropubic mid-urethral tape procedures: tension-free vaginal tape

The tension-free vaginal tape (Gynecare®, Ethicon, Somerville, NJ, USA), first described by Ulmsten in

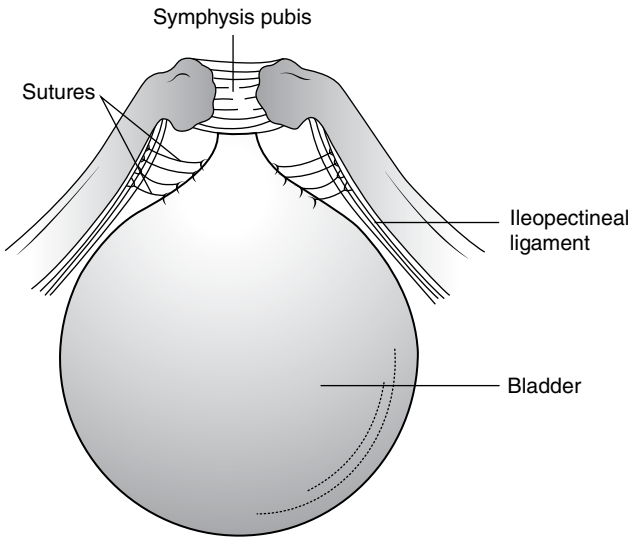


Fig. 56.11 Suture placement for the Burch colposupension between the paravaginal tissue and the ileopectineal ligament.

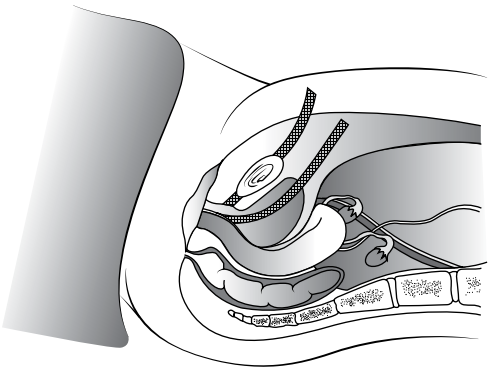


Fig. 56.12 Tension-free vaginal tape *in situ* under the mid-urethra and exiting suprapubically.

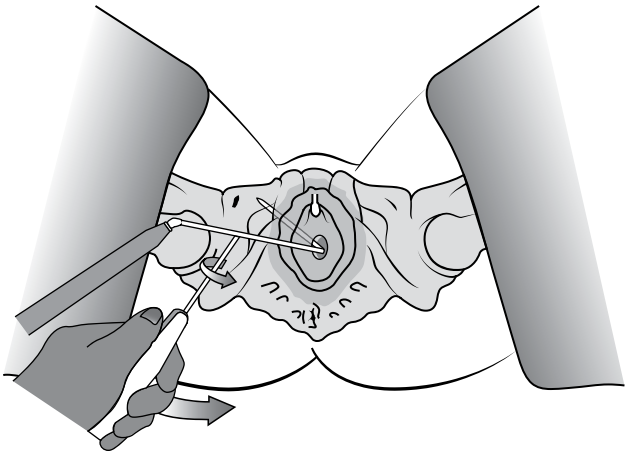


Fig. 56.13 Transobturator tape: 'inside out' procedure.

1996 [38], is now the most commonly performed procedure for SUI in the UK, and more than 2 million procedures have been performed worldwide. A knitted 11 mm × 40 cm polypropylene mesh tape is inserted transvaginally at the level of the mid-urethra, using two 5-mm trocars (Fig. 56.12). The procedure may be performed under local, spinal or general anaesthesia. Most women can go home the same day, although some do require catheterization for short-term voiding difficulties (2.5–19.7%). Other complications include bladder perforation (2.7–5.8%), *de novo* urgency (0.2–15%) and bleeding (0.9–2.3%) [34]. It has comparable outcomes to Burch colposuspension [33].

Transobturator mid-urethral sling procedures

The transobturator route for the placement of synthetic mid-urethral slings was first described in 2001 by Delorme [39] (Fig. 56.13). However, the transobturator route may be associated with damage to the obturator nerve and vessels; in an anatomical dissection model, the tape passes 3.4–4.8 cm from the anterior and posterior branches of the obturator nerve, respectively, and 1.1 cm from the most medial branch of the obturator vessels [40]. Consequently, nerve and vessel injury, in addition to bladder injury and vaginal erosion, remain a potential complication of the procedure. Also the success rate has been found to be lower than retropubic tape in randomized studies [41].

Bladder neck suspension procedures

Endoscopically guided bladder neck suspensions [42–44] are simple to perform but are less effective than open suprapubic procedures and are now seldom used.

Urethral bulking agents

Urethral bulking agents are a minimally invasive surgical procedure for the treatment of urodynamic stress incontinence and may be useful in the elderly and those women who have undergone previous operations and have a fixed, scarred and fibrosed urethra.

Although the actual substance injected may differ, the principle is the same. It is injected either periurethrally or transurethrally on either side of the bladder neck under cystoscopic control, and is intended to 'bulk' the bladder neck and mid-urethra in order to stop premature bladder neck opening, without causing outflow obstruction. The procedure may be performed under local, regional or general anaesthesia. There are now several different products available (Table 56.7). The use of minimally invasive

Table 56.7 Urethral bulking agents.

Urethral bulking agent	Application technique
Glutaraldehyde cross-linked bovine collagen (Contigen*)	Cystoscopic
Polydimethylsiloxane (Macroplastique†)	Cystoscopic MIS implantation system
Pyrolytic carbon-coated zirconium oxide beads in β-glucan gel (Durasphere‡)	Cystoscopic
Ethylene vinyl copolymer in dimethyl sulfoxide (DMSO) gel	Cystoscopic
Calcium hydroxylapatite in carboxymethylcellulose gel (Coaptite§)	Cystoscopic
Copolymer of hyaluronic acid and dextranomer	Cystoscopic Implacer system
Polyacrylamide hydrogel (Bulkamid¶)	Cystoscopic

* Bard, Covington, GA, USA.
† Uroplasty, Minnetonka, MN, USA.
‡ Coloplast, Peterborough, UK.
§ Boston Scientific, Marlborough, MA, USA.
¶ Gynecare, Somerville, NJ, USA.

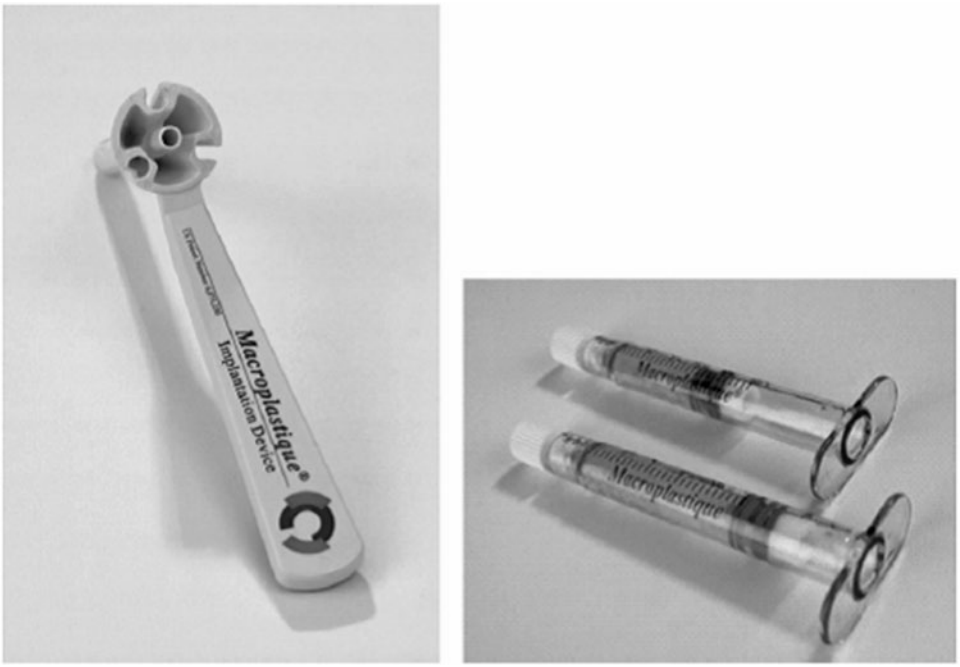


Fig. 56.14 Macroplastique urethral bulking agent and implantation device.

implantation systems (Fig. 56.14) has also allowed some of these procedures to be performed in the office setting without the need for cystoscopy. Long-term follow-up studies give a greater than 50% objective cure rate at 2 years but a subjective improvement rate of about 70% [45–47].

Although success rates with urethral bulking agents are generally lower than those with conventional continence surgery, they are minimally invasive and have lower complication rates, meaning that they remain a useful alternative in selected women.

Artificial urinary sphincter

An artificial sphincter is a device that may be employed when conventional surgery fails [48]. It is implantable and consists of a fluid-filled inflatable cuff that is surgically placed around the bladder neck. A reservoir containing fluid is sited in the peritoneal cavity and a small finger-operated pump is situated in the left labium majus. The three major components are connected via a control valve. Under normal circumstances the cuff is inflated and thus obstructs the urethra. When voiding is desired the pump is utilized to empty the fluid in the cuff back into the balloon reservoir so that voiding may occur. The cuff then gradually refills over the next few minutes. Artificial sphincters are associated with many problems [49]: they are expensive, the surgery required to insert them is complicated and the tissues around the bladder neck following previous failed operations may be unsuitable for the implantation of the cuff. In addition, mechanical failure may occur, necessitating further surgery. However, there is a place for these devices and their technology is likely to improve in the future.

National Institute for Health and Care Excellence guidelines

In the UK, the management of SUI has recently been reviewed by the National Institute for Health and Care Excellence (NICE) [50]. A trial of supervised PFMT of at least 3 months' duration should be offered as first-line treatment to all women with stress or mixed urinary incontinence.

Retropubic mid-urethral tape procedures using a 'bottom-up' approach with macroporous (type 1) polypropylene meshes are recommended as treatment options for SUI in cases where conservative management has failed. Open colposuspension and autologous rectus fascial sling procedures are recommended alternatives where clinically appropriate. Synthetic slings using materials other than polypropylene that are not of a macroporous (type 1) construction are not recommended for the treatment of SUI.

Intramural bulking agents (glutaraldehyde cross-linked collagen, silicone, carbon-coated zirconium beads} should be considered for the management of SUI if conservative management has failed, although women should be made aware that repeat injections

may be required and that efficacy diminishes with time and is inferior to that of a retropubic suspension or sling.

Laparoscopic colposuspension is not recommended as a routine procedure for the treatment of SUI in women and should only be performed by an experienced laparoscopic surgeon. Anterior colporrhaphy, needle suspension procedures, paravaginal defect repair and the Marshall–Marchetti–Krantz procedure are not recommended.

Conclusions: stress incontinence

It is important to remember that the first operation for stress incontinence is the most likely to succeed. Most suprapubic operations in current use produce a cure rate in excess of 85–90% in patients undergoing their first operation for correctly diagnosed urodynamic stress incontinence. The colposuspension has long been recognized as the 'best' first operation, although mid-urethral tape procedures would now appear to be as efficacious. Repeat continence surgery is often less efficacious than primary surgery and subsequent surgery may have to be performed on a vagina that is less mobile and in which there is fibrosis of the urethra. In such cases, insertion of a urethral bulking agent may be easier to perform and more effective. Ultimately, it is important that the operative procedure performed is tailored to the needs of the individual.

Summary box 56.3

Stress urinary incontinence

- SUI is a symptom.
- Urodynamic stress incontinence is a urodynamic diagnosis.
- SUI is the commonest form of incontinence in women.
- All women should be treated conservatively with PFMT initially.
- Duloxetine may be useful in addition to PFMT.
- Women who fail to improve with conservative measures may be suitable for surgery.
- Mid-urethral tapes are currently the most commonly performed operation for SUI.

Detrusor overactivity

Detrusor overactivity is defined as a urodynamic observation characterized by involuntary contractions during the filling phase that may be spontaneous or provoked [3]. It is the second commonest cause of urinary incontinence in women and accounts for 30–40% of cases. The incidence is higher in the elderly and after failed incontinence surgery. The cause of detrusor overactivity remains uncertain and in the majority of cases it is idiopathic, occurring when there is a failure of adequate bladder training in childhood or when the bladder escapes voluntary control in adult life. In some cases detrusor overactivity may be secondary to an upper motor neurone lesion, especially multiple sclerosis. In such cases it is known as neurogenic detrusor overactivity. In men, detrusor overactivity may be secondary to outflow obstruction and may be cured when the obstruction is relieved. However, outflow obstruction in women is rare.

Low compliance is said to exist when there is a sustained rise in detrusor pressure without actual detrusor contractions during bladder filling. There is a variety of causes, including radical pelvic surgery, radiotherapy, recurrent urinary tract infections and interstitial cystitis, but the symptoms associated with phasic detrusor overactivity and with low compliance may be indistinguishable without cystometry (Fig. 56.15).

Detrusor overactivity and overactive bladder

The symptoms of OAB are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle (termed detrusor overactivity). However, OAB is not synonymous with detrusor overactivity as the former is a symptom-based diagnosis whereas the latter is a urodynamic diagnosis. It has been estimated that 64% of patients with OAB have urodynamically proven detrusor overactivity and that 83% of patients with detrusor overactivity have symptoms suggestive of OAB [51].

Clinical symptoms

Most women with an OAB exhibit a multiplicity of symptoms, including urgency, urgency incontinence, stress incontinence, enuresis, frequency and especially nocturia and sometimes incontinence at orgasm [52]. There are no specific clinical signs and the diagnosis can only be made urodynamically when there is a failure to inhibit detrusor contractions during cystometry.

Treatment for detrusor overactivity aims to re-establish central control or to alter peripheral control via bladder innervation (Table 56.8). The fact that so many different types of treatment are available for this condition shows that none is universally successful. Various behavioural interventions (habit retraining) have been successfully

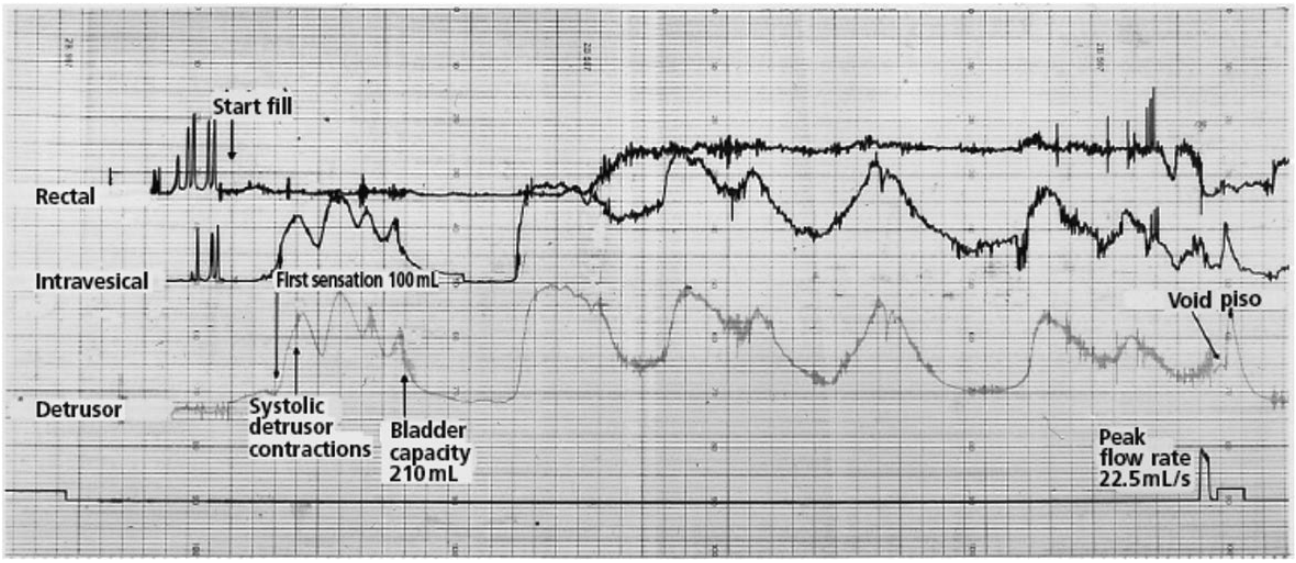


Fig. 56.15 Cystometrogram recording showing phasic detrusor overactivity.

Table 56.8 Treatment of detrusor overactivity

Psychotherapy
Bladder drill
Biofeedback
Hypnotherapy
Acupuncture
Drug therapy
Inhibit bladder contractions
Anticholinergic agents
Musculotrophic relaxants
Tricyclic antidepressants
Improve local tissues
Oestrogens
Reduce urine production
DDAVP (synthetic vasopressin)
Intravesical therapy
Capsaicin
Resiniferatoxin
Botulinum toxin
Neuromodulation
Peripheral: posterior tibial nerve stimulation (PTNS)
Central: sacroneuromodulation (SNS)
Cystoplasty
Clam ileocystoplasty
Detrusor myectomy
Other
Maximum electrical stimulation
Acupuncture

used to treat idiopathic detrusor overactivity and have been shown to improve symptoms in up to 80% of women [53,54]. Unfortunately, these types of therapy are time-consuming and require the patient to be highly motivated. However, it is always appropriate to instruct patients with detrusor overactivity regarding the use of bladder drill, which is timed voiding, often as an adjunct to drug therapy.

Drug therapy

Drug therapy is the most widely employed treatment for detrusor overactivity (Table 56.9). From the number of preparations studied it is clear that there are no ideal drugs and very often the clinical results have been disappointing, this being partly due to poor efficacy and side effects [55].

Drugs that have a mixed action

Oxybutynin The effectiveness of oxybutynin in the management of patients with detrusor overactivity is well documented. A double-blind placebo-controlled trial found oxybutynin to be significantly better than placebo in improving lower urinary tract symptoms, although 80% of patients complained of significant adverse effects, principally dry mouth or dry skin [56]. Similar results have also been demonstrated in further placebo-controlled trials [57,58]. These can be mitigated by slow-release preparations or alternative methods of administration (e.g. topical or intravesical).

Propiverine Propiverine (Detrunorm, Amdipharm UK Ltd, London) has been shown to combine anticholinergic and calcium channel blocking actions [59]

Table 56.9 Drugs used in the management of detrusor overactivity.

	Level of evidence	Grade of recommendation
β_3-Adrenoceptor agonist		
Mirabegron	1	A
Antimuscarinic drugs		
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Fesoterodine	1	A
Propantheline	2	B
Atropine, hyoscamine	3	C
Drugs acting on membrane channels		
Calcium channel antagonists	2	D
Potassium channel openers	2	D
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Alpha-antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Beta-agonists		
Terbutaline	3	C
Salbutamol	3	C
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Prostaglandin synthesis inhibitors		
Indometacin	2	C
Flurbiprofen	2	C
Vasopressin analogues		
Desmopressin	1	A
Other drugs		
Baclofen	3	C (intrathecal)
Capsaicin	2	C (intravesical)
Resiniferatoxin	2	C (intravesical)
Botulinum toxin (idiopathic)	1	A (intravesical)
Botulinum toxin (neurogenic)	1	A (intravesical)

Source: Andersson KE, Chapple CR, Cardozo L *et al*. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A (eds) *Incontinence*, 5th edn. Paris: Health Publication Ltd, 2012.

and may be useful in women who have troublesome adverse effects with other antimuscarinic agents. An extended-release preparation has also recently been launched. In a study by Stohrer *et al.* [60], dry mouth was experienced by 37% in the treatment group as opposed to 8% in the placebo group, with drop-out rates being 7% and 4.5%.

Antimuscarinic drugs

Tolterodine Tolterodine is a competitive muscarinic receptor antagonist with relative functional selectivity for bladder muscarinic receptors [61] and although it shows no specificity for receptor subtypes, it does appear to target the bladder over the salivary glands [62]. The drug is metabolized in the liver to the 5-hydroxymethyl derivative, which is an active metabolite having a similar pharmacokinetic profile and is thought to significantly contribute to the therapeutic effect [63].

Several randomized, double-blind, placebo-controlled trials on patients with both idiopathic detrusor overactivity and neurogenic detrusor overactivity have demonstrated a significant reduction in incontinent episodes and micturition frequency [64–66]. Further studies have confirmed the safety of tolterodine and at the recommended daily dosage the incidence of adverse events was no different to that in patients taking placebo [67].

Trospium Trospium chloride (Specialty European Pharma, London, UK) is a quaternary ammonium compound that is non-selective for muscarinic receptor subtypes and shows low biological availability [68]. It crosses the blood–brain barrier to a limited extent, and hence would appear to have few cognitive effects [69]. Overall, trospium chloride was associated with a significant improvement in urinary frequency, incontinence episodes, urgency severity and volume voided when compared with placebo. The most common side effect was dry mouth (trospium 8.7% vs. placebo 3%) and constipation (trospium 9.4% vs. placebo 1.3%).

Solifenacin Solifenacin (Astellas, Chertsey, Surrey, UK) is a potent M_3 receptor antagonist that has selectivity for the M_3 receptors over M_2 receptors and has much higher potency against M_3 receptors in smooth muscle than it does against M_3 receptors in salivary glands [70].

The evidence would appear to suggest that solifenacin may offer superior efficacy to the other currently available antimuscarinic agents and that switching from tolterodine to solifenacin offers improved efficacy rates [71]. Pooled data from the phase III studies have demonstrated equal efficacy in the elderly [72] while phase IV studies have shown little cognitive effect, a synergistic effect with conservative therapy [73] and improvement in quality-of-life and patient-reported outcome measures [74].

Darifenacin Darifenacin (Warner Chilcott, Rockaway, NJ, USA) is a tertiary amine with moderate lipophilicity and is a highly selective M_3 receptor antagonist that has been found to have a fivefold higher affinity for the human M_3 receptor relative to the M_1 receptor [75].

A review of the pooled darifenacin data from three phase III, multicentre, double-blind clinical trials in 1059 patients with OAB has been reported [76]. Darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week. Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation.

Fesoterodine Fesoterodine (Pfizer, Sandwich, Kent, UK) is a derivative of 3,3 diphenylpropylamine, which is a non-selective antimuscarinic agent that has recently been developed for the management of OAB. It is rapidly and extensively converted by ubiquitous esterases to its active metabolite 5-hydroxymethyl tolterodine (5-HMT) [77]. The pharmacokinetic profile of 5-HMT is dose proportional at doses up to 12 mg, and thus allows for flexible dosing [78]. Although tolterodine is also converted to 5-HMT, this occurs primarily in the liver via cytochrome P450 (CYP) 2D6, and hence is more dependent on the metabolizer status of the patient. Consequently, the potential benefit of fesoterodine over tolterodine is that it allows a more predictable dose–effect relationship. The current evidence would suggest that fesoterodine may offer some advantages over tolterodine in terms of efficacy and flexible dosing regimens.

Antidepressants

Imipramine Imipramine has been shown to have systemic anticholinergic effects and blocks the reuptake of serotonin. Some authorities have found a significant effect in the treatment of patients with detrusor overactivity [79], although others report little effect [80]. In light of this evidence and the serious adverse effects associated with tricyclic antidepressants, their role in detrusor overactivity remains of uncertain benefit, although they are often useful in patients complaining of nocturia or bladder pain.

Antidiuretic agents

Desmopressin Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) (Ferring Pharmaceuticals, Copenhagen, Denmark) is a synthetic vasopressin analogue. It has strong antidiuretic effects without altering blood pressure. The drug has been used primarily in the treatment of nocturia and nocturnal enuresis in children [81] and adults [82]. Desmopressin is safe for long-term use; however, the drug should be used with care in the elderly owing to the risk of hyponatraemia.

Intravesical therapy

Botulinum toxin Botulinum toxin interferes with neural transmission by blocking the calcium-dependent release of the neurotransmitter acetylcholine, causing the affected muscle to become weak and atrophic. The affected nerves do not degenerate, but as the blockage is irreversible only the development of new nerve terminals and synaptic contacts allows recovery of function.

The role of botulinum toxin has been established in the treatment of neurogenic and idiopathic detrusor overactivity using 200 units and 100 units of botulinum toxin A respectively. The main complications are urinary retention and the need for intermittent self-catheterization and urinary tract infection [83].

At present, the evidence would suggest that cystoscopic administration of botulinum toxin may offer an alternative to surgery in those women with intractable detrusor overactivity, although the effect lasts for up to 9 months.

Neuromodulation

Peripheral neuromodulation

Stimulation of the posterior tibial nerve in patients with urge incontinence was first reported in 1983 [84] and has also been proposed for pelvic floor dysfunction [85]. The tibial nerve is a mixed nerve containing L4–S3 fibres and originates from the same spinal cord segments as the innervation to the bladder and pelvic floor. Consequently, peripheral neuromodulation may have a role in the management of urinary symptoms.

Peripheral neuromodulation may offer an alternative therapeutic option for those patients with intractable OAB who have failed to respond to medical therapy, although it remains less cost-effective than treatment with antimuscarinic agents.

Sacral neuromodulation

Stimulation of the dorsal sacral nerve root using a permanent implantable device in the S3 sacral foramen has been developed for use in patients with both idiopathic and neurogenic detrusor overactivity (Fig. 56.16). The sacral nerves contain nerve fibres of the parasympathetic and sympathetic systems providing innervation to the bladder as well as somatic fibres providing innervation to the muscles of the pelvic floor. The latter are larger in diameter and hence have a lower threshold of activation, meaning that the pelvic floor may be stimulated selectively without causing bladder activity. Prior to implantation, temporary cutaneous sacral nerve stimulation is performed to check

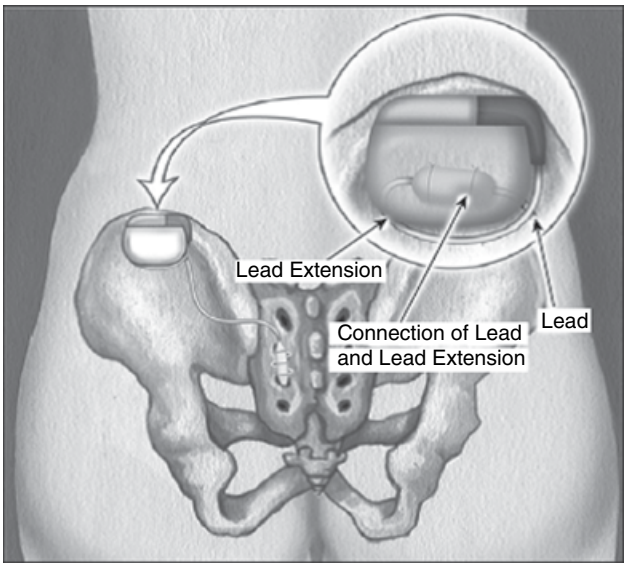


Fig. 56.16 Sacral neuromodulation.

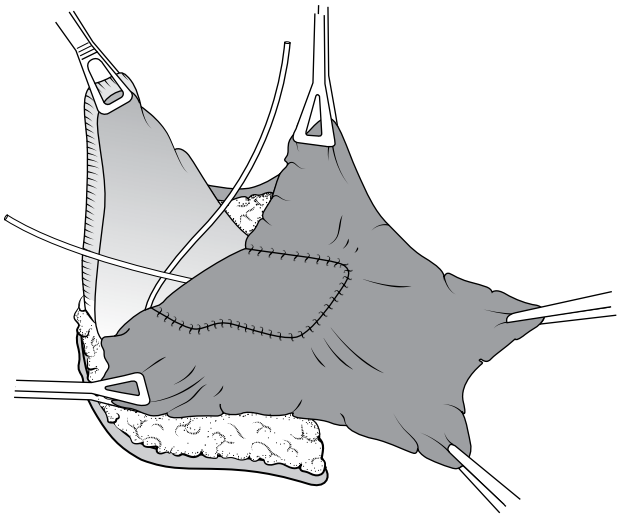


Fig. 56.17 Clam ileocystoplasty.

for a response and, if successful, a permanent implant is inserted under general anaesthesia. Initial studies in patients with detrusor overactivity refractory to medical and behavioural therapy have demonstrated that, after 3 years, 59% of 41 urinary urge incontinent patients showed a greater than 50% reduction in incontinence episodes, with 46% of patients being completely dry. However, up to 50% of implanted patients will require reoperation and the stimulators need replacing after 10 years.

Although neuromodulation remains an invasive and expensive procedure, it offers a useful alternative to medical and surgical therapies in patients with severe intractable detrusor overactivity.

Surgery

For those women with severe detrusor overactivity that is not amenable to simple types of treatment, surgery may be employed.

Clam cystoplasty

In the clam cystoplasty [86] the bladder is bisected almost completely and a patch of gut (usually ileum) equal in length to the circumference of the bisected bladder (about 25 cm) is sewn in place (Fig. 56.17). This often cures the symptoms of detrusor overactivity [87] by converting a high-pressure system into a low-pressure system, although inefficient voiding may result. Patients have to learn to strain to void, or may have to resort to clean intermittent self-catheterization, sometimes permanently. In addition, mucus retention in the bladder may be a problem, but this can be partially overcome by ingestion of 200 mL of cranberry juice each day [88] in addition to intravesical mucolytics such as acetylcysteine. The chronic exposure of the ileal mucosa to urine may lead to malignant change [89]. In addition, metabolic disturbances such as hyperchloraemic acidosis, vitamin B_{12} deficiency and occasionally osteoporosis secondary to decreased bone mineralization may occur.

Urinary diversion

As a last resort for those women with severe detrusor overactivity or neurogenic detrusor overactivity who cannot manage clean intermittent catheterization, it may be more appropriate to perform a urinary diversion. Usually this will utilize an ileal conduit to create an abdominal stoma for urinary diversion. An alternative is to form a continent diversion using the appendix (Mitrofanoff) or ileum (Koch pouch), which may then be drained using self-catheterization.

National Institute for Health and Care Excellence guidelines

The medical management of OAB has been reviewed by NICE [50]. In the first instance, bladder retraining lasting for a minimum of 6 weeks should be offered to all women with mixed or urge incontinence. In those women who do not achieve satisfactory benefit from bladder retraining alone, the combination of an antimuscarinic agent and bladder retraining should be considered.

When considering drug therapy, immediate-release non-proprietary tolterodine should be offered to women with OAB or mixed urinary incontinence as first-line drug treatment if bladder retraining has been ineffective. If immediate-release tolterodine is not well tolerated, darifenacin, solifenacin, trospium or an extended-release

formulation of tolterodine should be considered as alternatives. In addition, women should be counselled regarding the adverse effects of antimuscarinic drugs.

Propiverine should be considered as an option to treat frequency of micturition but is not recommended for the treatment of urinary incontinence. Flavoxate, propantheline and imipramine should not be used for the treatment of OAB. Although desmopressin may be considered specifically to reduce nocturia in women, it is currently outside marketing authorization and hence informed consent must be obtained.

When considering the role of oestrogens, systemic hormone replacement therapy should not be recommended, although intravaginal oestrogens are recommended for the treatment of OAB in postmenopausal women with urogenital atrophy.

Summary box 56.4

Overactive bladder and detrusor overactivity

- OAB is a symptomatic diagnosis.
- Detrusor overactivity is a urodynamic diagnosis.
- All women benefit from conservative measures and bladder retraining.
- Antimuscarinics are the most commonly used drugs.
- Patients refractory to drug therapy may benefit from botulinum toxin.
- Neuromodulation may be useful in refractory cases.
- Reconstructive surgery should only be considered when all other therapy has failed.

Mixed incontinence

Those women with both detrusor overactivity and urodynamic stress incontinence pose a difficult management problem. The detrusor overactivity is initially treated with antimuscarinic agents but if there is persistent SUI once the urgency and urgency incontinence is treated, then continence surgery is performed. However, if urge incontinence still predominates, surgery may aggravate the woman's symptoms.

Retention with overflow

In women, chronic retention with resultant overflow incontinence is uncommon and often no cause can be found. It is one manifestation of the wide range of voiding difficulties which may occur, the major causes of which are shown in Table 56.10.

Table 56.10 Causes of voiding difficulties leading to overflow incontinence in women.

Neurological
Lower motor neurone lesion
Upper motor neurone lesion
Inflammation
Urethritis, e.g. 'honeymoon cystitis'
Vulvitis, e.g. herpes
Vaginitis, e.g. candidiasis
Drugs
Tricyclic antidepressants
Antimuscarinic agents
Ganglion blockers
Epidural anaesthesia
Patient-controlled analgesia
Obstruction
Urethral stenosis/stricture
Oedema following surgery or parturition
Fibrosis due to repeated dilatation or irradiation
Pelvic mass, e.g. fibroids, retroverted uterus, ovarian cyst, faeces
Urethral distortion due to large cystocele
Myogenic
Atonic detrusor secondary to over-distension
Functional
Anxiety

Women with overflow incontinence present in a variety of ways. They may complain of dribbling urine or of voiding small amounts at frequent intervals, or of stress incontinence. Alternatively, they may notice recurrent urinary tract infections. The diagnosis is usually made by the discovery of a large bladder on clinical examination. This can be confirmed by a post-micturition ultrasound scan to assess the residual urine volume or by catheterization, which will reveal a residual volume of more than 50% of bladder capacity. There may, in addition, be a reduced peak flow rate of less than 15 mL/s.

Clinical examination will rule out many of the causes, such as a pelvic mass or a cystocele. It is important to investigate cases of urinary retention thoroughly in order to exclude any treatable underlying pathology. An MSU specimen should be sent for culture and sensitivity, and the appropriate swabs (urethral, vaginal and cervical) should also be sent. Radiological investigations should include intravenous urography, an X-ray of the lumbosacral spine and an MRI scan where indicated. It is particularly important to identify diabetes so that treatment can be undertaken before permanent damage occurs.

Treatment for overflow incontinence will depend on the underlying pathology. If the detrusor is hypotonic, cholinergic agents such as bethanechol 25 mg three

times a day may be helpful. If there is outflow obstruction, urethral dilatation or urethrotomy may be required. In cases where no cause can be found, clean intermittent self-catheterization is the best long-term method of management for these patients.

Fistulae

Urinary fistulae may be ureterovaginal, vesicovaginal, urethrovaginal or complex, and can occur following pelvic surgery or in cases of advanced pelvic malignancy, especially when there has been radiotherapy. The most common varieties in the UK are lower ureteric or bladder fistulae occurring after an abdominal hysterectomy. In developing countries, poor obstetrics with obstructed labour resulting in ischaemic necrosis of the bladder base is more likely to be the cause of a vesicovaginal or urethrovaginal fistula.

Fistulae give rise to incontinence that is continuous, occurring both day and night. They are usually visible on speculum examination but cystoscopy and intravenous urography may be required to confirm the diagnosis.

Treatment is surgical. Ureterovaginal fistulae should be repaired as quickly as possible to prevent upper urinary tract damage. Vesicovaginal fistulae are usually treated conservatively, initially with bladder drainage and antibiotics, during which time some will close spontaneously. Abdominal or vaginal repair is normally performed 2 or 3 months after the initial injury, although there is now a trend towards earlier repair; if a fistula is detected within a very short period of time after the initial operation, it can often be closed immediately.

Urethral diverticulum

Urethral diverticula are becoming more common, presumably because of the increased incidence of sexually transmitted infections. They are found in women of any age and lead to various complaints including pain, particularly after micturition, post-micturition dribble and dyspareunia. Diagnosis can be made either radiologically on a micturating cystogram or videocystourethrogram or by urethroscopy. In addition, MRI may be useful. Urethral diverticula should be managed conservatively, initially with intermittent courses of antibiotics if necessary; if there are severe symptoms, then surgical excision of the diverticulum may be required. It is usual to perform a subtotal diverticulectomy in order to avoid urethral stricture formation, and following the procedure a urethral catheter is left in place for 2 weeks, acting as a stent to allow the urethra to heal.

General conservative measures

All incontinent women benefit from simple measures such as the provision of suitable incontinence pads and pants. Those with a high fluid intake should be advised to restrict their drinking to 1 L a day, particularly if frequency of micturition is a problem. Caffeine-containing drinks (such as teas, coffee and cola) and alcohol are irritant to the bladder and act as diuretics, so should be avoided if possible. Anything that increases intra-abdominal pressure will aggravate incontinence, so patients with a chronic cough should be advised to give up smoking, and constipation should be treated appropriately.

Women with long-standing severe incontinence, especially the elderly, may be more comfortable and easier to manage with a regularly changed indwelling suprapubic catheter; for the young disabled, urinary diversion should be considered earlier rather than later. It is not always possible to cure urinary incontinence but it is usually possible to help the sufferer and thus improve her quality of life.

Oestrogens in the management of incontinence

From the available evidence oestrogen alone does not appear to be an effective treatment for SUI. There was some evidence suggesting that the use of local oestrogen therapy may improve urgency incontinence (relative risk, RR 0.74, 95% CI 0.64–0.86) and overall there were one or two fewer voids in 24 hours and less frequency and urgency [90]. The authors concluded that local oestrogen therapy for incontinence may be beneficial, although there was little evidence of long-term effects. The evidence would suggest that systemic hormone replacement using conjugated equine oestrogens may make incontinence worse. In addition, the authors comment that there are too few data to comment reliably on the dose, type of oestrogen and route of administration.

Other lower urinary tract disorders

Urethral lesions

Urethral caruncle

A urethral caruncle is a benign red polyp or lesion covered by transitional epithelium usually found on the

posterior aspect of the urethral meatus. It is commonly seen in postmenopausal women and although usually asymptomatic, it may cause pain, bleeding and dysuria. The cause is unknown. Treatment is by excision biopsy and local vaginal oestrogens.

Urethral mucosal prolapse

Prolapse of the urethral mucosa also occurs in the postmenopausal woman but, in addition, is sometimes seen in girls (usually Black) between the ages of 5 and 10 years. It is a reddish lesion that encompasses the whole circumference of the external urethral meatus, thus differentiating it from urethral caruncle. Urethral mucosal prolapse is not painful but may cause bleeding, dysuria or urethral discharge. It may be treated by excision or cautery.

Urethral stenosis or stricture

Outflow obstruction due to urethral stenosis or stricture is rare in women. Such lesions usually present after the menopause and are found in the distal urethra. They are often the result of chronic urethritis or may follow fibrosis from repeated urethral dilatations or other surgery to the urethra. The most common symptoms are of voiding difficulties, but recurrent urinary tract infections may occur. Diagnosis can be made using uroflowmetry in conjunction with cystometry or by videocystourethrography. Urethral pressure profilometry or cystourethroscopy will help to localize the lesion. Urethrotomy, either Otis or open, is the treatment of choice, and local oestrogen therapy may be helpful in postmenopausal women.

Urinary frequency and urgency

Definitions [2]

- *Diurnal frequency*: the complaint that micturition occurs more frequently during waking hours than previously deemed normal.
- *Nocturia*: the complaint of interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep.
- *Urgency*: the complaint of a sudden compelling desire to pass urine, which is difficult to defer.
- *Urgency incontinence*: the complaint of involuntary leakage accompanied by or immediately preceded by urgency.

Causes and assessment

There are many different causes of frequency and urgency of micturition; the more common ones are shown in Table 56.11.

Clinical examination will exclude many of the causes. This is important before expensive time-consuming investigations are undertaken. As one of the commonest causes of frequency of micturition is a lower urinary tract infection, it is important to send an MSU specimen for culture and sensitivity. If negative in persistent symptomatic women, then fastidious organisms such as *Mycoplasma hominis* and *Ureaplasma urealyticum* or *Chlamydia trachomatis* should be tested for. If there is a history of haematuria, loin or groin pain, and a urinary tract infection cannot be identified, intravenous urography and cystoscopy should be performed.

The investigations performed should be organized around the patient's precise symptomatology. However, a frequency–volume chart is often useful as it may identify excessive drinking as the cause of urinary frequency or diagnose nocturnal polyuria. For women with incontinence in addition to frequency with or without urgency, it is best to organize urodynamic studies prior

Table 56.11 Causes of urgency and frequency in women.

Urological
Urinary tract infection
Urethral syndrome
Detrusor overactivity
Bladder tumour
Bladder calculus
Small capacity bladder
Interstitial cystitis
Radiation cystitis/fibrosis
Chronic retention/residual
Urethral diverticulum
Gynaecological
Cystocele
Pelvic mass, e.g. fibroids, ovarian cyst
Previous pelvic surgery
Genital
Urethritis ('honeymoon cystitis')
Vulvovaginitis
Urethral caruncle
Herpes
Warts
Sexually transmitted infections
Atrophy (hypo-oestrogenism)
Medical
Upper motor neurone lesion
Impaired renal function
Diabetes mellitus
Diabetes insipidus
Hypothyroidism
Congestive cardiac failure
Diuretic therapy
Faecal impaction
General
Excessive drinking habit
Anxiety
Pregnancy

to cystoscopy as the latter is usually unrewarding. Subtracted cystometry detects detrusor overactivity, which is a major cause of urgency and frequency and also reveals chronic retention of urine with an atonic bladder, which may lead to frequency or recurrent urinary tract infections. For women with frequency, urgency and dysuria without incontinence, a cystourethroscopy may be more helpful than a urodynamic assessment.

Treatment

As for detrusor overactivity, treatment should be directed to the underlying cause if one has been identified.

Painful bladder syndrome

Painful bladder syndrome is the complaint of suprapubic pain related to bladder filling accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology [3]. A cause of painful bladder syndrome in women is interstitial cystitis.

Interstitial cystitis

Interstitial cystitis produces severe symptoms that include frequency, dysuria and lower abdominal and urethral pain. It affects individuals of both sexes, although only about 10% of sufferers are men. The peak age is 30–50 years [91]. There is growing evidence that interstitial cystitis is an autoimmune disease. Histological changes in bladder wall biopsies are consistent with a connective tissue disorder. The most common marker is mast cell infiltration of the muscularis layer of the bladder.

Diagnosis

The diagnosis of interstitial cystitis can be difficult. Pain is the most common presenting complaint and occurs in 70% of sufferers. This is usually suprapubic, although urethritis, loin pain and dyspareunia are also frequently encountered. A long history of a combination of frequency, urgency and dysuria in the absence of proven infection is often present. Other urinary complaints may coexist. Many of the women have previously undergone hysterectomy, although it is difficult to know if this represents a true relationship or just reflects desperate attempts on the part of the doctor to relieve the patient's symptoms.

Clinical examination is usually unrewarding and the diagnosis is often based on the finding of sensory urgency (painful catheterization, urgency and the absence of a rise in detrusor pressure and a bladder capacity of less than 300 mL) at dual-channel subtracted cystometry. Cystoscopy needs to be undertaken under general anaesthesia in order to obtain a good-sized bladder biopsy. Terminal haematuria at either urodynamic investigation or cystoscopy is suggestive of interstitial cystitis (Fig. 56.18). Characteristically, the cystoscopic findings include petechial haemorrhages on distension, especially with a second fill, reduced bladder capacity and rarely Hunner's ulcers. There is still confusion because of the lack of conformity in diagnostic parameters commonly used. Table 56.12 lists the criteria for excluding a diagnosis of interstitial cystitis.

Treatment

Interstitial cystitis is the final common pathway of a multifactorial disease process and therefore many different types of treatment have been proposed. Many patients benefit from simple self-help measures and the avoidance of caffeine-containing compounds (tea, coffee and cola) and dietary changes.

Both non-steroidal and steroidal anti-inflammatory agents such as azathioprine, sodium cromoglycate and chloroquine have been tried [91]. Sodium pentosan polysulfate is believed to decrease the bladder wall permeability, and variable success rates have been quoted, from 27% [92] to 83% [93]. Heparin, which is thought to reduce the available cations and have a similar effect to sodium pentosan polysulfate, has also been employed [94].

Those who prefer an infective hypothesis of causation have employed long-term antibiotics. Norfloxacin can be given 400 mg nightly for 3 months or, alternatively, a bladder antiseptic such as hexamine hippurate may be used.

Dimethyl sulfoxide (DMSO) has also been instilled into the bladder with some success [95] and recent randomized studies have shown a superior outcome using iAluril over DMSO. Tricyclic antidepressants are used in low doses as an adjunct to treatment to help relieve pain [96].

Although bladder distension has been used for the treatment of sensory bladder disorders, there is no evidence to support the use of this technique in interstitial cystitis. Short-term benefit may be reported, but repeated distensions can lead to an exacerbation of symptoms. There is still a place for either substitution cystoplasty or urinary diversion in severely affected patients but augmentation cystoplasty is rarely effective as pain continues to be a problem.

The majority of women who suffer with interstitial cystitis do so for many years until they either find ways of coping with their symptoms or eventually undergo surgery. Fortunately, the symptoms tend to wax and wane and it is often possible to provide support and intermittent therapy until a remission occurs [97].

For postmenopausal women, failure of adequate lubrication during sexual intercourse may be a problem so a

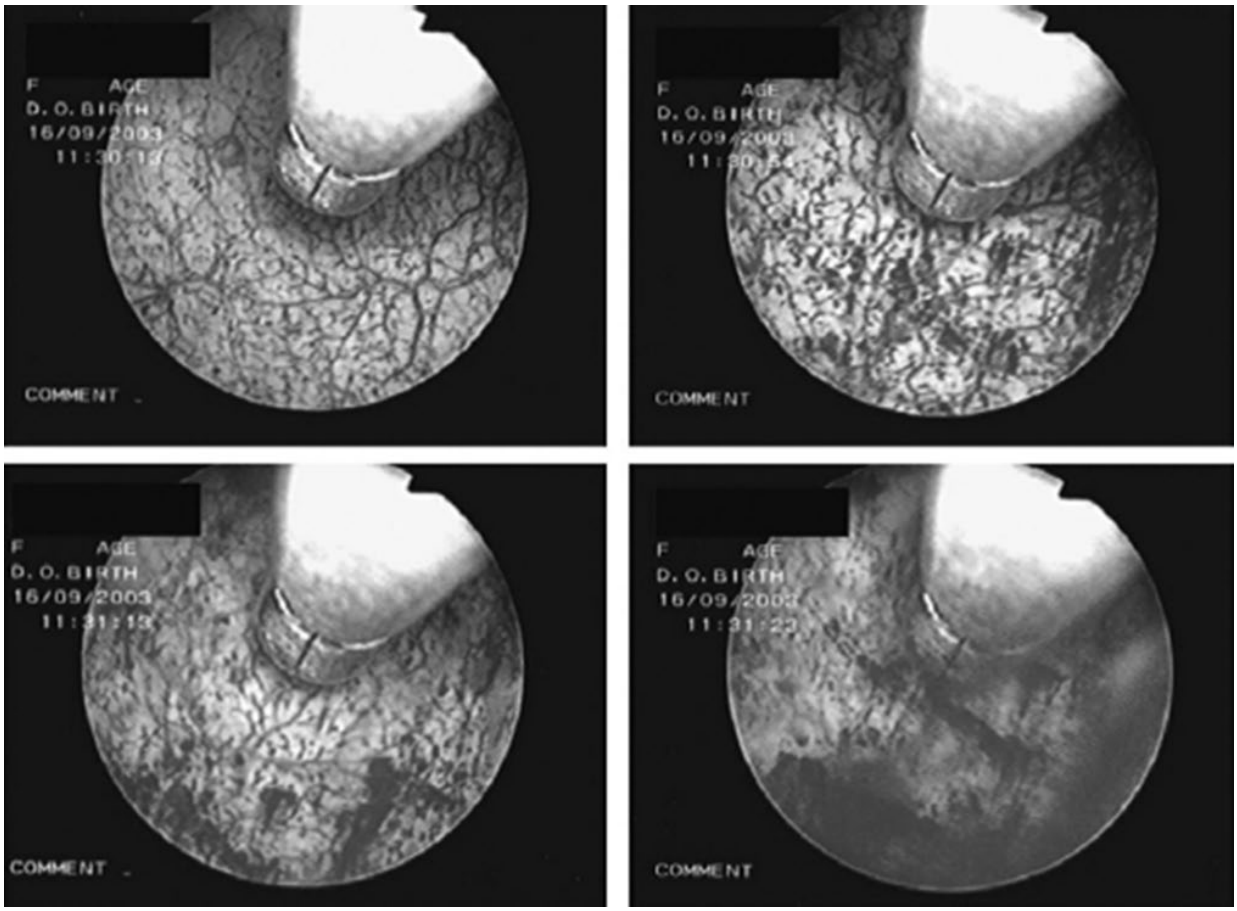


Fig. 56.18 Series of cystoscopic images showing gradual cystodistension with haemorrhage in a young woman with interstitial cystitis.

Table 56.12 Criteria for excluding a diagnosis of interstitial cystitis.

Bladder capacity >350 mL on awake cystometry
Absence of an intense desire to void at 150 mL during medium-fill cystometry (30–100 mL/min)
Demonstration of phasic involuntary bladder contractions on cystometry
Symptomatology of <9 months' duration
Absence of nocturia
Symptoms relieved by antimicrobials, urinary antiseptics, antimuscarinics or antispasmodics
Urinary diurnal frequency <9 times
Diagnosis of bacterial cystitis within the last 3 months
Bladder calculi
Active genital herpes
Gynaecological malignancy
Urethral diverticulum
Chemical cystitis
Tuberculosis
Radiation cystitis
Bladder tumours
Vaginitis
Age <18 years

lubricant gel or preferably vaginal oestrogen replacement should be prescribed [98]. For premenopausal women who develop recurrent urinary tract infections associated with sexual intercourse, post-coital antibiotic prophylaxis with trimethoprim, nitrofurantoin or cephalexin has been shown to be highly effective.

Conclusion

Urinary incontinence is common and, though not life-threatening, is known to have a significant effect on quality of life. Appropriate investigation and management allow an accurate diagnosis and avoid inappropriate treatment. Although many forms of conservative therapy may be initiated in primary care, continence surgery, and the investigation of more complex and recurrent cases of incontinence, should be performed in specialist secondary and tertiary referral units. Ultimately, an integrated pathway utilizing a multidisciplinary team approach including specialist nurses, continence advisers, physiotherapists, urologists and colorectal surgeons will ensure the best possible outcomes in terms of 'cure' and patient satisfaction.

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Part 14

Benign Gynaecological Disease

57

Benign Diseases of the Vulva

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Many women who present with vulval symptoms may have a dermatological problem rather than an infective or gynaecological complaint. It is therefore important that all healthcare professionals who see these patients learn to recognize the common skin conditions that affect the vulva and to refer for dermatological advice and management appropriately. Many clinics with a multidisciplinary team have been established to provide a specific service for women with vulval disorders.

This chapter gives an overview of the common skin problems that affect the vulva and the basic principles of initial management.

History-taking

A good history is the initial step in making an accurate diagnosis in any patient who presents with vulval symptoms. A clear method of history-taking should be used, and a proforma can be helpful to ensure that the key areas are covered.

The interview should take place in a sympathetic environment and it is often helpful to enquire about the general history initially before moving on to the more personal questions related to vulval disease.

The following areas should all be covered, but sometimes more detail is required about specific symptoms depending on the presenting problem.

- Presenting symptoms: is it itch or pain? Patients may report 'irritation' but this should always be qualified, as irritation is not always synonymous with itching. It is helpful to ask if they want to scratch to alleviate the symptoms, as if they say no, then itch is not the problem. Is the itching constant or intermittent and are there any provoking or alleviating factors?
- Previous treatments: what has been used (prescribed and over-the-counter medication) and what was the response? What regimen was used?
- Dermatological history: ask about a personal and family history of atopy and psoriasis. Ask about any other skin problems, either past or present, and also specifically about oral and ocular symptoms. Do they have any known allergies?
- Gynaecological history: is there any relationship of the symptoms with menstruation? If the patient has been pregnant, were deliveries straightforward or complicated resulting in trauma to the vulva? The history relating to cervical smears and any abnormalities or treatment is important, particularly in patients with vulval intraepithelial neoplasia, where cervical intraepithelial neoplasia is frequently associated.
- Sexual history: is there any history of sexually transmitted infections, vaginal discharge or dyspareunia? If appropriate, ask about risk factors for HIV infection. Loss of libido is common with any dermatological condition of the vulva, and psychosexual factors frequently complicate vulval conditions.
- General medical history: underlying medical conditions can be relevant to some vulval problems, i.e. inflammatory bowel disease, other autoimmune conditions.
- Medication: some drugs can be associated with vulval ulceration, e.g. nicorandil, foscarnet.
- Social history: details on the smoking history, alcohol intake and travel history where appropriate.

Examination

The examination should always be carried out with a trained chaperone present. Good lighting and appropriate magnification is essential. The vulva can be adequately

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

examined with the patient in the dorsal and left lateral position. Again, the examination should be approached systematically. The vulva is first examined overall but the labia majora need to be separated in order to adequately visualize the internal structures of the vulva.

General view

- Hair
- Skin colour, texture and surface.

Specific areas to be inspected

- Mons pubis
- Labia majora
- Labia minora
- Interlabial sulci
- Clitoris
- Vestibule
- Hymen
- Perianal skin.

The vagina and cervix should be examined in all patients with erosive disease (e.g. erosive lichen planus, autoimmune bullous disease) and vulval intraepithelial neoplasia, as well as in patients complaining of a vaginal discharge. An examination of the skin at extragenital sites will often give valuable diagnostic information and inspection of the oral mucosa, eyes, scalp, nails and other flexural sites is important.

Normal variants

There are some very common and important normal variants seen on examination of the vulva. These should be easy to recognize and the patient reassured. There are also physiological changes that vary with age and hormonal status.

Angiokeratomas

These are common and are usually seen on the labia majora. They are often multiple and appear as small red or purple vascular lesions with overlying hyperkeratosis (Fig. 57.1).

Hart's line

This demarcates the junction of the keratinized and non-keratinized epithelia of the labia minora and vestibule, respectively (Fig. 57.2). It can be very prominent in some women.

Vestibular papillae

A common finding is the presence of tiny filiform projections on the inner labia minora and vestibule (Fig. 57.3).

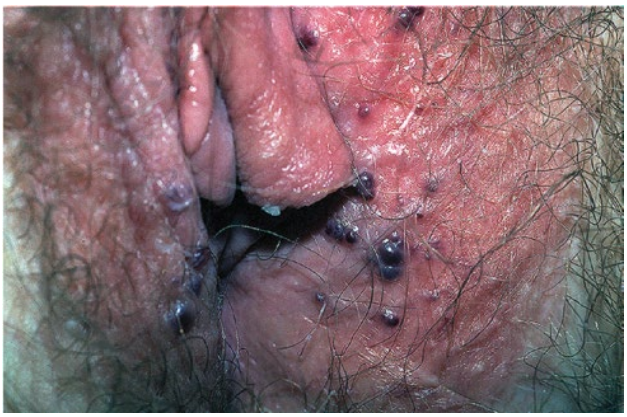

Fig. 57.1 Angiokeratomas: dark-red papules seen on the labia majora. (*See also colour plate 57.1*)

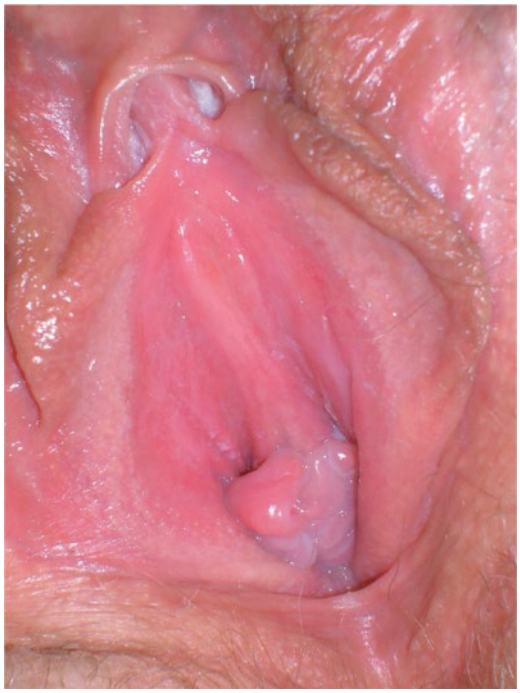

Fig. 57.2 Hart's line demarcating the junction between the keratinized skin of the labia minora and the non-keratinized mucosa of the vestibule. (*See also colour plate 57.2*)

Originally, it was thought that these were related to human papillomavirus (HPV) but there is good evidence that this is not the case. They are a normal variant and do not require any treatment.

Fordyce spots

These are small sebaceous papules found on the inner surfaces of the labia minora (Fig. 57.4). They can be very prominent in some women and may also be seen on the buccal mucosa.

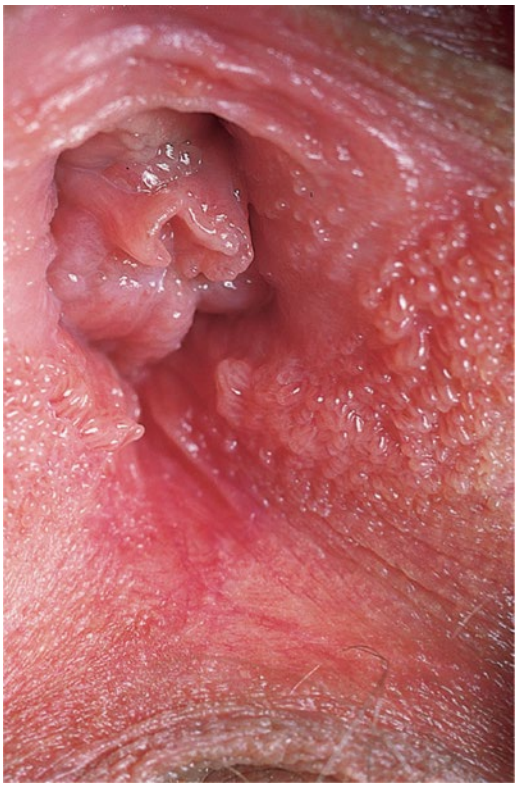

Fig. 57.3 Vestibular papillae: filamentous projections of the vestibular epithelium. (*See also colour plate 57.3*)

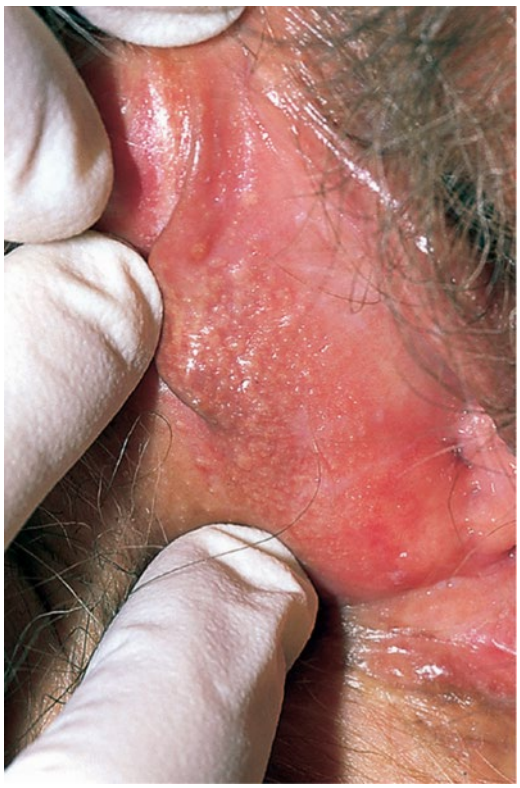

Fig. 57.4 Fordyce spots: tiny yellow papules on the inner labium minus. (*See also colour plate 57.4*)

Normal physiological changes

Childhood

In the first few weeks of life, the vulva is under the influence of maternal hormones. The clitoral hood and labia minora are relatively prominent and may be seen without separation of the labia majora. Labial adhesions are common and usually resolve with time. Topical oestrogens may be helpful.

Puberty

Deposition of fat increases the size of the labia majora and mons pubis, and pubic hair appears. The rims of the labia minora may become pigmented. The clitoris enlarges and the vestibular glands become active.

Pregnancy

The vulva can be engorged and varicosities are common. Hyperpigmentation can be significant.

Post menopause

The labia majora become less prominent and there is a reduction in hair growth.

Investigations

In some cases, a firm diagnosis can be made on the clinical appearances alone, but in others a variety of investigations are needed to confirm the diagnosis.

Biopsy

This is a very simple procedure that can be performed in the outpatient clinic under local anaesthesia. A 4–6 mm punch biopsy is taken after infiltrating the area with lidocaine. Topical EMLA (lidocaine 2.5%, prilocaine 2.5%, Astra Zeneca, London, UK) may be used before injecting the lidocaine but care must then be taken in interpreting the histological appearances as subepidermal cleavage can be induced by this agent [1]. Clinicopathological correlation is vital in all cases of vulval dermatoses, and review by a dermatopathologist is very helpful. In cases where an autoimmune bullous disorder is suspected, a biopsy should also be taken for direct immunofluorescence.

Microbiological investigation

Appropriate swabs and transport media for bacterial, yeast and viral culture may be needed. If a sexually transmitted infection is suspected, the patient should be referred to a genitourinary clinic for full investigation and contact tracing.

Skin scrapings to look for fungi can be taken in the clinic and direct examination of the skin under Wood's lamp may be helpful to confirm erythrasma, where the affected skin will fluoresce pink.

Patch testing

This is performed where an allergic contact dermatitis is suspected, either as a primary problem or where it is a secondary phenomenon caused by an allergy to treatment. Patients need to be referred to a dermatologist for these tests, which should include specific allergens that may cause problems on the vulva.

Inflammatory diseases of the vulva

Lichen sclerosus

Lichen sclerosus is an inflammatory dermatosis with a predilection for the anogenital skin [2]. It is significantly more common in women than men. Extragenital lesions may be seen in about 10% of women with genital involvement. They present as ivory white plaques, often at sites of trauma or friction (Fig. 57.5).

Aetiology

The aetiology remains unclear but it is thought that it is mediated by a lymphocyte reaction. Immunohistochemical alterations of the epidermis and dermis support an autoimmune cause and circulating IgG antibodies to extracellular matrix proteins have been demonstrated. There is an association in both the patient and their first-degree relatives with other autoimmune diseases, particularly thyroid disorders.

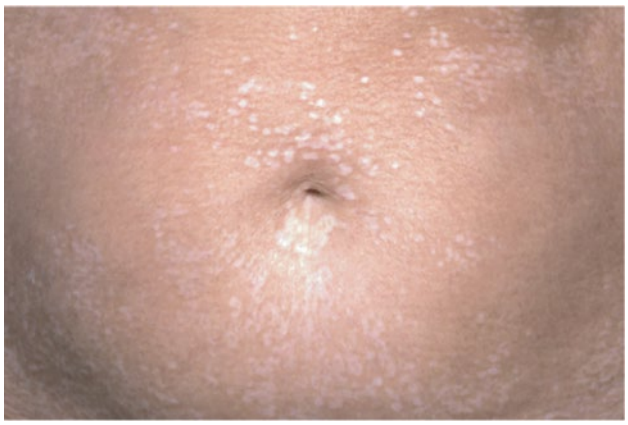

Fig. 57.5 Extragenital lichen sclerosus: 'white spot disease'. Flat white lesions which can coalesce into plaques. Follicular plugging may be seen. (*See also colour plate 57.5*)

Clinical features

There are two peaks of presentation: in childhood and around or after the menopause. The predominant symptom is that of pruritus but soreness and dyspareunia will be experienced in the presence of ulceration, erosions and fissures. In children, constipation is a frequent feature if the perianal area is affected.

The early lesions are white ivory papules that may coalesce to form plaques. Ecchymosis due to rupture of dermal vessels is common, as is oedema (Fig. 57.6). Ecchymosis is common in children and often leads to the erroneous diagnosis of sexual abuse. Extension of disease around the perianal area presents as a 'figure of eight' pattern. As the disease progresses, scarring occurs with loss of the labia minora, which become fused to the labia majora. The clitoral hood can seal over and the clitoris may be buried (Fig. 57.7). Introital narrowing can lead to difficulties with intercourse and dyspareunia if the skin splits. The vagina is not involved in lichen sclerosus and this may be a useful distinguishing feature from lichen planus. The only exception to this is where there is a significant vaginal prolapse, where the epithelium becomes keratinized and lichen sclerosus can then develop on this vaginal mucosa.

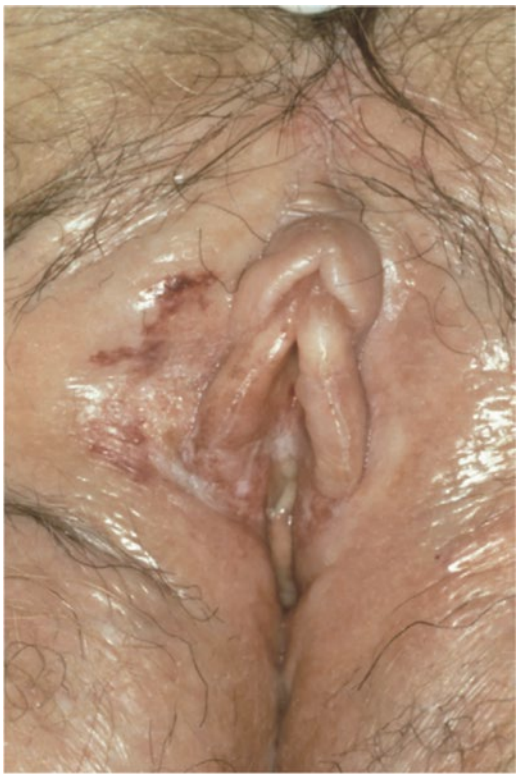

Fig. 57.6 Vulval lichen sclerosus: early established disease showing rubbery oedema of labia minora and clitoral hood and stark whitening extending to perianal skin. Note currently healing fissure at 6 o'clock position. (*See also colour plate 57.6*)

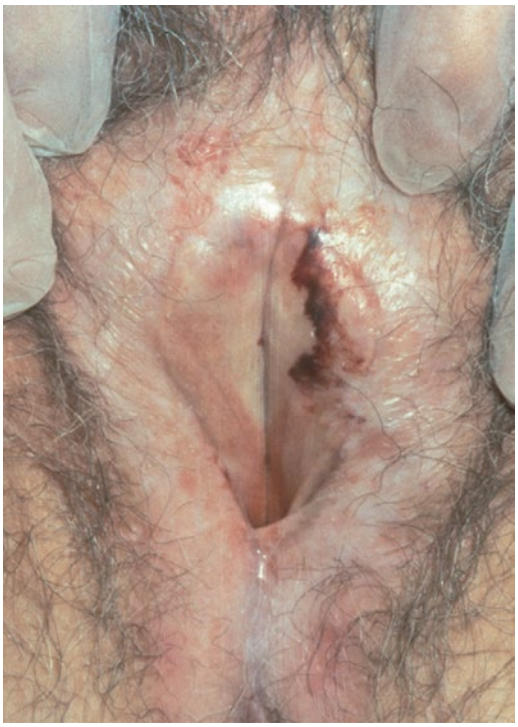

Fig. 57.7 Advanced vulval lichen sclerosis: white sclerotic change, complete burying of the clitoris and total replacement of architecture with 'plastering' down and resorption of labia. Gross ecchymoses and narrowing of vaginal introitus. (*See also colour plate 57.7*)

Histology shows a thinned epidermis overlying a homogenized band of collagen in the upper dermis with a lymphocytic inflammatory cell infiltrate underlying this (Fig. 57.8).

Lichen sclerosus and malignancy

Squamous cell carcinoma (SCC) is a rare complication of lichen sclerosus, occurring in about 4% of patients [3]. This may present as a small persistent erosion or ulcer, a hyperkeratotic area or fleshy friable papule or nodule (Fig. 57.9). Any suspicious lesions must be biopsied. If vulval intraepithelial neoplasia (VIN) is found in association with lichen sclerosus, it is usually the differentiated form where there is basal atypia but normal maturation of the epidermis. It is less common to have undifferentiated VIN.

Treatment

There is good evidence that the treatment for lichen sclerosus, in adults and children, is a super-potent topical steroid such as clobetasol propionate 0.05% ointment [4,5]. This is applied once daily for a month, on alternate days for the second month and then twice weekly for the third month. Emollients are used as a soap substitute. Ongoing treatment may be required by some patients to maintain control. Patients whose disease is difficult to control or those with any history of VIN or SCC need long-term follow-up in specialized clinics.

There is no role for the use of topical testosterone. Surgery is only required to treat the scarring complications

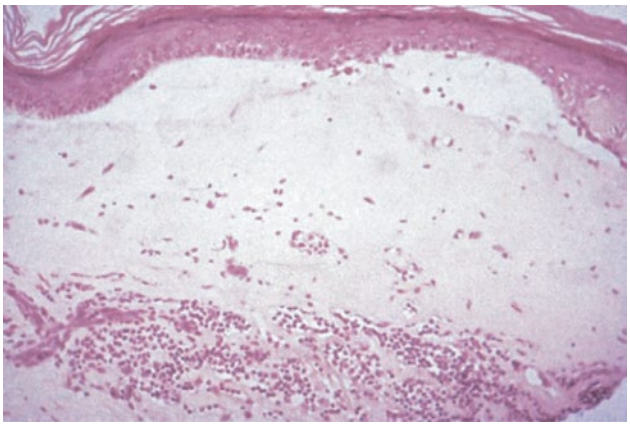

Fig. 57.8 Histology of lichen sclerosus: an atrophic epidermis is seen over the homogenized band of collagen and, below this, a lymphocytic infiltrate. Haematoxylin and eosin × 40. (*See also colour plate 57.8*)

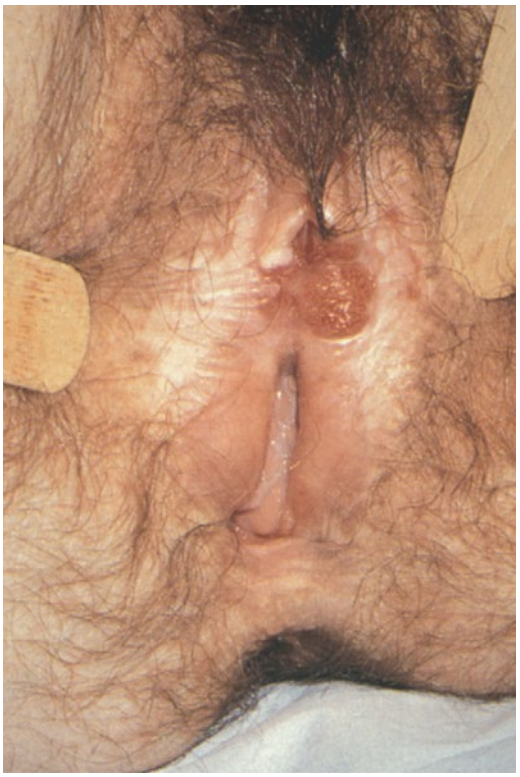

Fig. 57.9 Lichen sclerosus complicated by squamous carcinoma. Note the classical cigarette-paper scarring and background whitening. Here the squamous cell carcinoma presents as a fleshy nodule, but persistent erosion should also prompt biopsy. (*See also colour plate 57.8*)

or if there is neoplastic or pre-neoplastic change. Topical calcineurin inhibitors are increasingly popular but should not be used first line as there are concerns about their long-term safety in relation to the development of malignancy.

In those with resistant symptoms, it is important to exclude an allergic contact dermatitis to treatment, irritant dermatitis due to urinary incontinence, or an additional problem such as herpes simplex or candidiasis. A proportion of patients will develop vulvodynia after their lichen sclerosus is well controlled. Treatment must be targeted at this rather than increasing the use of topical steroids.

Summary box 57.1

Lichen sclerosus

- Lichen sclerosus is an inflammatory dermatosis that commonly affects the anogenital skin.
- There are two peaks of presentation: prepubertal girls and postmenopausal women.
- It presents with itchy, white, atrophic lesions, often with ecchymosis and oedema.
- Scarring will occur if untreated.
- An ultra-potent topical steroid is the first-line treatment.
- Patients require long-term follow-up as there is a small risk of malignancy developing.
- Any resistant areas, ulcers or hyperkeratotic lesiors should be biopsied.

Lichen planus

Lichen planus (LP) is an inflammatory disorder, which can affect both skin and mucous membranes. The characteristic cutaneous lesions are small purplish papules, which may exhibit a fine lace-like network over their surface known as Wickham's striae. These can also be seen on mucosal lesions. The papules commonly occur on flexor surfaces and can koebnerize at sites of trauma. The nails can show pterygium formation and scalp lesions can result in a scarring alopecia.

Histology shows irregular acanthosis with a saw-toothed pattern, basal cell degeneration and a dense band-like dermal infiltrate of lymphocytes. There is often pigmentary incontinence, which is responsible for the marked hyperpigmentation sometimes seen clinically (Fig. 57.10).

Aetiology

The cause is unknown but it is likely that it is a T-lymphocyte-mediated inflammatory response to some form of antigenic insult. Lichenoid eruptions can be seen in graft-versus-host disease and secondary to medications such as non-steroidal anti-inflammatory drugs (NSAIDs). Although there has been interest in the association of hepatitis C infection and LP, there is only evidence for this in certain populations and it is not relevant in northern Europe. There is an association of LP and other autoimmune disorders.

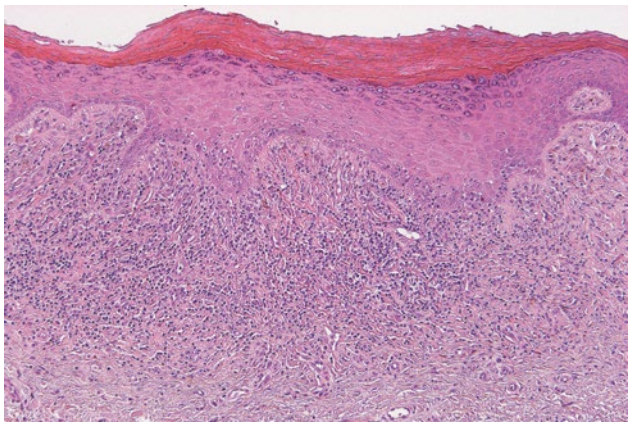

Fig. 57.10 Histology of lichen planus showing saw-toothing of the epidermis, with a dense lymphocytic infiltrate and liquefactive degeneration of the basement membrane. *Source:* Eduardo Calonje. Reproduced with permission of Eduardo Calonje. (*See also colour plate 57.10*)

There are three major clinical patterns of LP affecting the anogenital skin: erosive, classic and hypertrophic. These may occur in isolation without the presence of disease at other sites.

Erosive lichen planus

Erosive LP is the commonest form to affect the genital skin [6]. There is a specific subtype of erosive mucosal LP, the vulvovaginal–gingival (VVG) syndrome affecting the vulva, vagina and gingival margins [7], with specific genetic associations. The lacrimal duct, external auditory meatus and oesophagus can also be involved and disease at these sites needs a multidisciplinary approach to management.

The vulval lesions mainly affect the inner labia minora and vestibule where erythema and erosions occur (Fig. 57.11). A lacy white edge is seen and this is the best site for a confirmatory biopsy (Fig. 57.12). There may be marked scarring with significant architectural change, which can be impossible to differentiate from lichen sclerosus in some cases. Symptomatically the condition is itchy and painful and dyspareunia is a common feature. If there is vaginal involvement, there may be a blood-stained discharge and episodes of post-coital bleeding. It is important to recognize vaginal disease as scarring at this site can result in complete vaginal stenosis. Glazed erythema and erosions occur on the gingivae (Fig. 57.13), buccal mucosa and also the tongue.

The disease tends to fluctuate with a relapsing and recurring pattern.

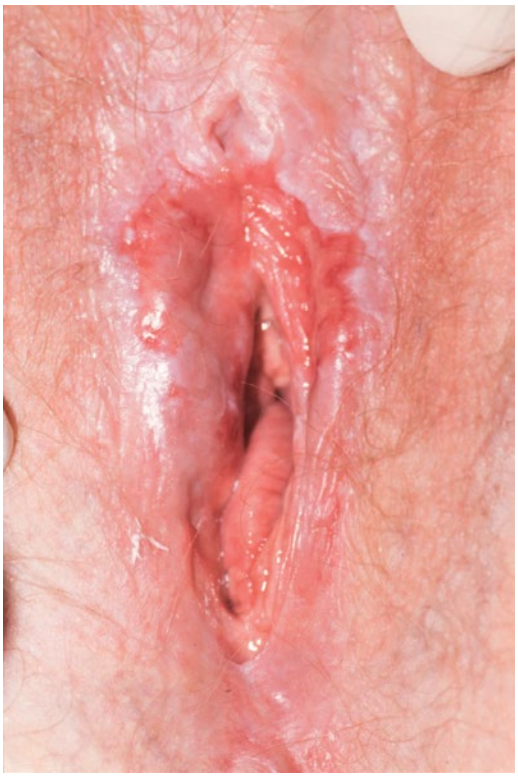

Fig. 57.11 Erosive lichen planus: there is scarring with loss of the labia minora. Wickham's striae are seen at the edge of the erosions. (*See also colour plate 57.11*)

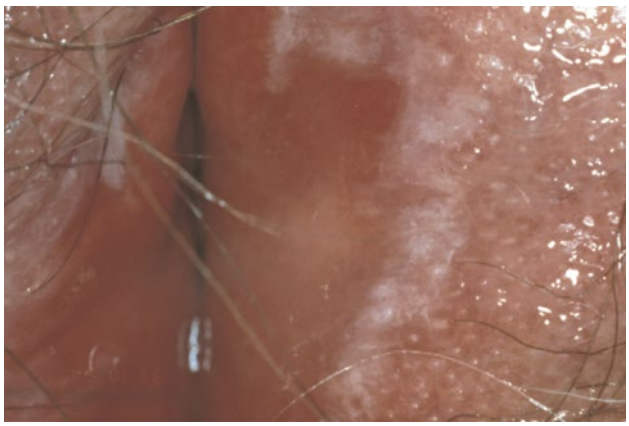

Fig. 57.12 The lacy white edge of the eroded area is seen. This is the best site for biopsy. (*See also colour plate 57.12*)

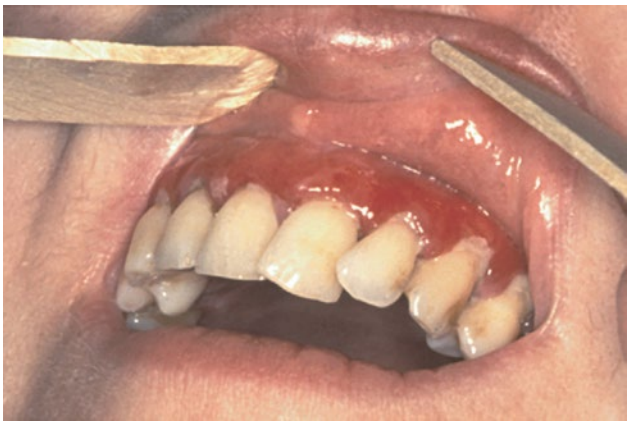

Fig. 57.13 Erosive lichen planus with gingival involvement. Erythema and erosions are seen at the gingival margins. Similar lesions may be seen on the buccal mucosa and tongue. (*See also colour plate 57.13*)

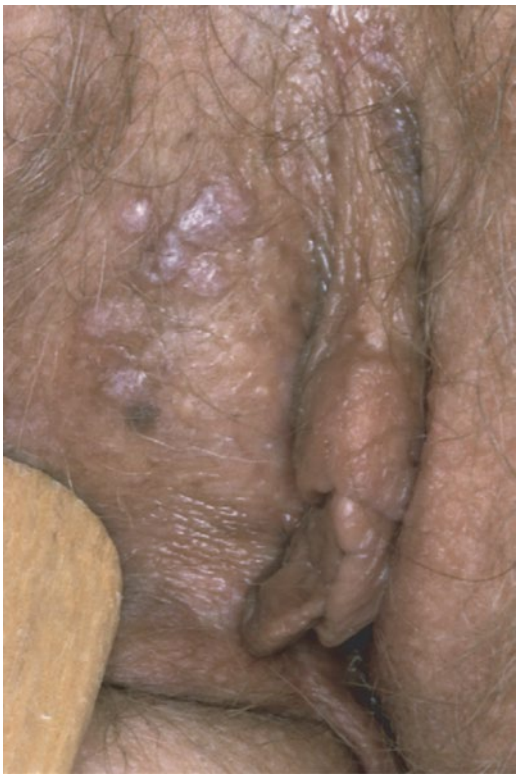

Fig. 57.14 Papular lichen planus: typical coalescing flat-topped papules showing white Wickham's striae. They are violaceous in colour and are usually also found on the inner wrist and elsewhere. (*See also colour plate 57.14*)

Classic lichen planus

Papules, very similar to the cutaneous lesions, are found on the vulva (Fig. 57.14) and perianal skin. They may be asymptomatic in over 50% of patients [8]. Wickham's striae can also be seen associated with the lesions. Flexural hyperpigmentation can be significant even many months after the disease has resolved.

Hypertrophic lichen planus

Hypertrophic lesions are less common and mainly affect the perineum and perianal skin. They can become ulcerated and painful. They can be resistant to topical treatment.

Lichen planus and malignancy

Squamous cell carcinoma and SCC *in situ* have been reported in classic and hypertrophic types but not in the VVG syndrome. In studies of patients with vulval malignancy, LP has been seen in the surrounding epithelium [9].

Management

The main treatment is a super-potent topical steroid ointment. In general, clobetasol propionate 0.05% ointment is applied in a similar regimen to that used for lichen sclerosus for 3 months, then reducing to be used as needed. Bland emollients can be helpful as a soap substitute. Petroleum jelly used as a barrier will help symptomatically. For vaginal disease, some of the foam preparations used in inflammatory bowel disease can be useful, for example hydrocortisone acetate. This is inserted via the applicator into the vagina at night. Dilators may also be required to keep the vagina patent.

There is some evidence for the use of the topical calcineurin modulators tacrolimus and pimecrolimus in the treatment of LP. There are small case series that support their use but there is also concern with long-term safety, particularly with regard to the development of malignancy. It is therefore recommended that they are not used as first-line treatment but for short periods in those who do not respond to potent topical steroids. They are not tolerated well on the anogenital skin, which also limits their use.

Several systemic treatments have been used in LP but no controlled trials exist [10].

Summary box 57.2

Lichen planus

- Lichen planus can affect the skin and oral and genital mucosae, but also the scalp and nails.
- The erosive subtype, VVG syndrome, can also involve the lacrimal ducts, oesophagus and external auditory meatus. These sites should be examined.
- Scarring can occur with marked functional sequelae.
- The management should be multidisciplinary and it is very important to involve other specialties early, e.g. for oesophageal involvement.
- The first-line treatment is an ultra-potent topical steroid.
- There is a small risk of SCC in the classic and hypertrophic types.

Eczema

The terms 'eczema' and 'dermatitis' are used synonymously for an epidermal inflammation that has many forms. It is characterized histologically by spongiosis where the keratinocytes lose cohesion and vesicles may form. Many different inflammatory cells infiltrate the dermis. The skin becomes scaly secondary to parakeratosis and fluid may ooze onto the surface and dry to a crust. In chronic cases, the skin becomes thickened and lichenified. Vulval eczema is often over-diagnosed and there is a significant overlap with vulval psoriasis, which is much more common.

Seborrhoeic eczema

This is a common type of eczema, with peaks in childhood (cradle cap and nappy rash) and early adulthood. There is evidence that it is caused by the yeast *Pityrosporum ovale*. The lesions are erythematous with a greasy scale and particularly affect the naso-labial folds, eyebrows, forehead, scalp and behind the ears. The anogenital skin may be involved together with other flexural sites, including the inguinal folds and gluteal cleft. The skin shows erythema and a build-up of keratinous debris.

It is often very difficult to distinguish seborrhoeic eczema from flexural psoriasis. Characteristic lesions at other sites may help and the histology may be similar. The management of seborrhoeic eczema is the same as that of psoriasis.

Irritant eczema

The anogenital skin is very susceptible to an irritant eczema as it is a site that is occluded and often exposed to many irritant substances. There is diffuse erythema and fissuring and the skin may become thickened and macerated in areas. Deodorants, bubble baths, soaps and irritant topical treatment (e.g. wart preparations) are common causes. It is a particular problem in those suffering from urinary or faecal incontinence.

Allergic contact dermatitis

Allergic contact dermatitis is a delayed type IV hypersensitivity reaction and in the genital area is much more likely to occur on perianal skin than on the vulva. Relevant positive patch-test reactions are found and the most common culprits are topical medicaments, local anaesthetics, cosmetics and fragrances [11]. Dermatological advice on patch testing should be sought. In addition to the standard patch-test series, extended testing is often necessary to find the causative allergen.

Lichen simplex

'Lichenification' is the term used to describe a thickening of the skin with accentuation of the skin markings. It is a response to chronic scratching and rubbing of the skin and is usually seen on a background of eczema or psoriasis. 'Lichen simplex' is the term used to describe an isolated area of lichenification without an obvious background dermatitis. It is common in areas that the patient can easily reach. The thickened plaques may be

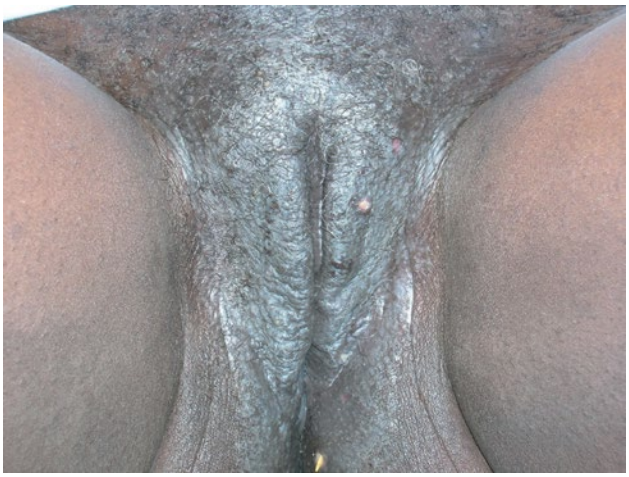

Fig. 57.15 Vulval lichen simplex: the outer labia majora are significantly lichenified with accentuated skin markings and loss of hair from rubbing. (*See also colour plate 57.15*)

hypopigmented or hyperpigmented and the common sites are the outer labia majora and mons pubis. There may also be loss of hair from rubbing (Fig. 57.15). A potent topical steroid applied on a reducing regimen over a 3-month period can be very helpful and in many cases will resolve the problem. However, in others, it is considered to be a sensory problem and treatment needs to be directed towards breaking the itch–scratch cycle.

Management of vulval eczema

The management of all eczematous processes is similar. All potential irritants and allergens should be withdrawn. Bland emollients (e.g. emulsifying ointment) are used as a soap substitute. A topical steroid, combined with an antimicrobial if appropriate, can be used once daily initially and then as needed as the problem improves. If the eczema is acute and the skin is oozing and wet, then potassium permanganate soaks (1 in 10 000 dilution) are helpful. Gauze is soaked in the solution and applied to the affected areas for 15 min once or twice a day. Patients with lichen simplex may require a potent topical steroid to gain control of their symptoms. The frequency of application can slowly be reduced as the lichenification resolves. Antihistamines may help at night to reduce scratching.

Psoriasis

Psoriasis is one of the commonest skin conditions, affecting about 2% of the population in some form. The characteristic lesions are silvery white scaly plaques on the extensor aspects of the limbs, but generalized disease may occur with scalp and nail involvement. The aetiology is unknown but there is a genetic predisposition and the disease may be triggered by streptococcal infection and trauma (Koebner phenomenon). Psoriasis may also be exacerbated by some drugs, for example beta-blockers, lithium and chloroquine.

Histology shows marked epidermal thickening (acanthosis) with deep epidermal ridges projecting into the dermis. Spongiosis with a neutrophil infiltrate of the epidermis may be seen.

Genital flexural psoriasis is common and may occur in isolation [12]. There is little scaling because of the moist occluded environment of the anogenital skin. The lesions present on the inner and outer aspects of labia majora as well-demarcated erythema or salmon-pink patches that are usually symmetrical (Fig. 57.16). The genito-crural inguinal folds may also be affected. Perianal involvement is common with extension into the gluteal cleft (Fig. 57.17). Itching and burning are common symptoms but as maceration and fissuring is often seen, women

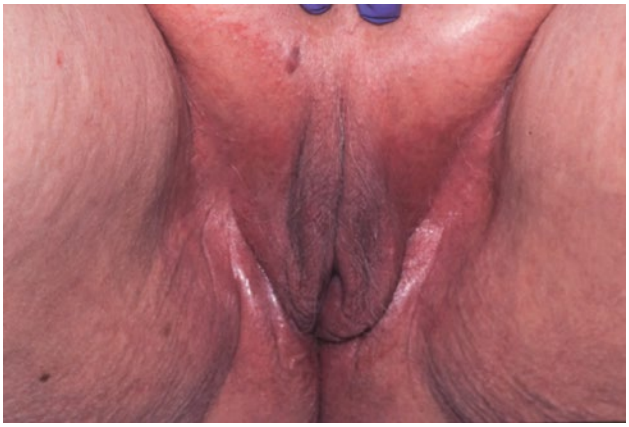

Fig. 57.16 Vulval psoriasis: erythema and maceration with extension into the inguinal folds. The edge is still well defined. (*See also colour plate 57.16*)

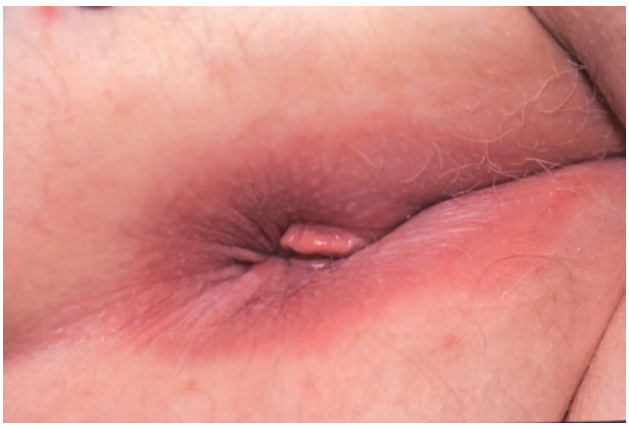

Fig. 57.17 Perianal psoriasis: well-demarcated erythema with extension into the natal cleft. (*See also colour plate 57.17*)

may also complain of soreness. It is helpful to examine the rest of the skin to look for other signs: the scalp may show scaling and the nails in psoriasis display thimble pitting, onycholysis and subungual hyperkeratosis.

The use of an emollient as a soap substitute is helpful. The traditional treatments for psoriasis (e.g. tar, dithranol, calcipotriol) are too irritant to be used in the flexures and therefore a mild to moderately potent topical steroid is used. This can be applied once daily and then reduced in frequency to be used as needed. In patients with severe disease, systemic treatment may be required but these patients should be under specialist dermatological supervision. Oral therapy with methotrexate, cyclosporin and acitretin can be used and the new biological therapies may be considered in very extensive, resistant cases.

Reiter's disease is an inflammatory response to an enteric or lower genital tract infection, with arthritis, uveitis and skin lesions that are very similar to those of psoriasis. The vulva may be affected with a circinate ulcerative vulvitis similar to the balanitis that commonly occurs in men with this syndrome. The histology is similar to that of pustular psoriasis.

Hidradenitis suppurativa

Hidradenitis suppurativa is an inflammatory disorder affecting areas where apocrine glands are present. The basic pathology is not in the gland itself but in the follicular epithelium, where an infundibular inflammation, possibly triggered by antimicrobial peptides produced after injury, leads to abscess formation and deep sinus tracts [13].

Anogenital involvement is common, with painful nodules, sinuses and scarring (Fig. 57.18). Bridged comedones are characteristic. SCC has been reported in chronic disease.

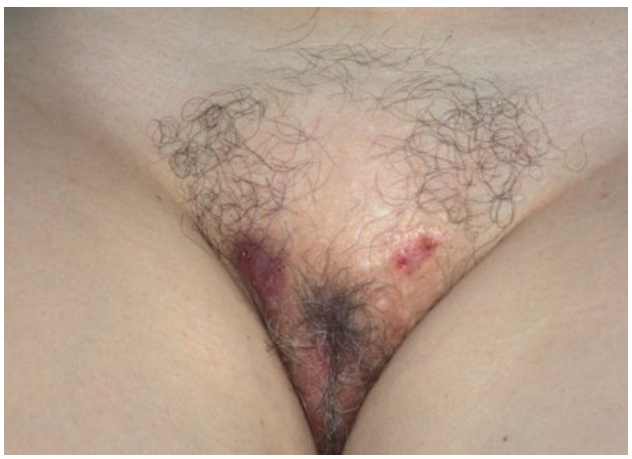

Fig. 57.18 Hidradenitis suppurativa: oozing inflamed lesions are seen on the mons publis with bridged comedones. (*See also colour plate 57.18*)

The management of this condition can be difficult. Topical antibiotics can be used in mild disease together with other measures such as stopping smoking and weight reduction. In moderate to severe disease, long-term oral tetracyclines are the first-line treatment. Oral clindamycin has been used in some cases with success. Second-line treatments include surgery, anti-androgen therapies and, now, anti-tumour necrosis factor (TNF) biological agents.

Bullous diseases

Genetic causes

Epidermolysis bullosa

Epidermolysis bullosa is used to describe a group of inherited conditions (dominant or recessive) characterized by skin fragility and bullae. The junctional and dystrophic types involve the vulva and scarring may result. These children must be cared for in specialist centres with access to expert nursing care.

Benign familial chronic pemphigus (Hailey–Hailey disease)

This is rare autosomal dominant condition where moist red plaques in the flexures and genital areas develop in the second to fourth decades. Friction worsens the problem and the plaques may fissure and become secondarily infected. Histology shows extensive intraepidermal acantholysis described as a 'dilapidated brick wall'. Treatment is unsatisfactory but topical steroids and prompt treatment of any infection can be helpful. Photodynamic therapy has had limited success in a few patients.

Bullous drug eruptions

Fixed drug eruption

Fixed drug eruptions occur at the same cutaneous or mucosal site each time the causative drug is ingested. Vulval involvement usually presents with swelling that may then form blisters and erode. As this is intermittent, the patient rarely associates it with medication and challenge tests may be needed. There are many drugs that can cause this problem, the most relevant for the vulva being co-trimoxazole, fluconazole, aciclovir and NSAIDs. Resolution frequently results in post-inflammatory hyperpigmentation.

Erythema multiforme

Erythema multiforme is an acute reaction pattern where mucosal erosions and ulcers occur, often with

cutaneous 'target' lesions. Stevens–Johnson syndrome is a severe form of erythema multiforme where bullous lesions occur which may scar. Vaginal involvement can lead to stenosis and it is important to perform a vaginal examination and treat this site if it is involved, otherwise permanent stenosis can occur secondary to the inflammation and erosion. Erythema multiforme and Stevens–Johnson syndrome may be induced by herpes simplex infection or medications, especially antibiotics and NSAIDs. However, no cause is found in up to 50% of cases.

Toxic epidermal necrolysis (Lyell's syndrome)

This is a dermatological emergency where severe and widespread epidermal loss occurs. It carries a significant mortality. Drug hypersensitivity is the usual cause (most commonly antiepileptics, NSAIDs and antibiotics), but idiopathic cases may be seen.

There is sudden onset of painful areas of erythema which rapidly become eroded or blistered, usually of the genitalia, mouth and eyes. Vulvovaginal scarring and stenosis may occur as erosions heal. The triggering drug must be stopped and the patient transferred to a specialist dermatology centre or burns unit experienced in the management of these cases. Treatment is mainly supportive, with the role of steroids and immunoglobulin still undecided. In the early stages, the differential diagnosis is that of staphylococcal scalded skin. In this latter condition, there is very superficial desquamation caused by staphylococcal exotoxins. Treatment is with high-dose antibiotics such as flucloxacillin.

Autoimmune bullous disorders

Bullous pemphigoid

Bullous pemphigoid is the commonest autoimmune bullous disorder and mainly affects the elderly, although cases have been reported in children. IgG antibodies are directed against the basement membrane and these are demonstrated in a linear fashion on direct immunofluorescence studies. Circulating IgG antibodies may be found. Histology shows subepidermal blisters. The mucous membranes may be involved with tense blisters which rupture to form superficial erosions.

These patients need to be managed by a dermatologist. Potent topical steroids may be used but systemic steroids and immunosuppressive drugs are usually required.

Mucous membrane pemphigoid (cicatricial pemphigoid)

This is a rare autoimmune bullous disorder but mucosal involvement is prominent, with the vulva, vagina, eyes, mouth and larynx being affected. Scarring is common and can cause problems with the vulva and eyes. It generally affects older women. The histological and immunofluorescence findings are similar to those of bullous pemphigoid, but there are often less eosinophils present. Treatment can be difficult but steroids, mycophenolate and other immunosuppressive treatments are used [14]. These patients are at risk of ophthalmological and oesophageal complications and management should involve dermatologists and any other relevant specialists. These patients share many of the clinical features of the VVG form of lichen planus.

Pemphigus

Pemphigus vulgaris is a rare bullous disorder affecting the skin and mucous membranes. IgG antibodies are directed against keratinocytes. The bullae are flaccid and erosions are more commonly seen. The patients are often younger and cases have been reported in children. Histology shows intraepidermal bullae. IgG is seen in the intercellular spaces on direct immunofluorescence and circulating IgG antibodies are found.

This disease carries a high degree of morbidity and patients should always be under the care of a dermatologist. Treatment includes high-dose systemic steroids, azathioprine cyclophosphamide and mycophenolate mofetil.

Vulval ulceration

Aphthous ulcers

Oral aphthae are common but similar lesions can occur on the vulva and are frequently mistaken for herpetic infection. The vulval ulcers measure a few millimetres and have a yellow base surrounded by an erythematous rim, but major aphthae may be larger than this. Histology is non-specific. Treatment is difficult but topical steroids, tetracyclines and local anaesthetic agents can be helpful.

Acute ulcers associated with infection

Lipschutz described acute painful ulcers in young women in 1913. They are now known to be a reaction to systemic infection and have been reported most commonly in association with Epstein–Barr virus infection [15]. They typically occur in teenagers and present as rapidly enlarging painful ulcers, often occurring in apposition in a 'kissing' pattern. They usually heal without scarring after a few weeks but a short course of prednisolone can speed resolution if severe. Topical steroids and local anaesthetic agents such as 5% lidocaine ointment are helpful symptomatically.

Manifestations of underlying disease

Inflammatory bowel disease

Although anogenital lesions can occur in ulcerative colitis, they are rare. They are commoner in Crohn's disease, affecting up to 30% of patients, and they may precede the onset of bowel disease by some years [16]. Where there is no continuity with bowel disease or distant sites are involved, the lesions are termed metastatic and most vulval lesions are of this type. Typical presentation includes unilateral or bilateral oedema (Fig. 57.19) lymphangiectasia and classic 'knife-cut' fissures in the interlabial sulci (Fig. 57.20). Sinus tracts and fistulae may also occur. Perianal ulceration or oedematous tags are also often present.

Histology shows granulomatous inflammation but may be non-specific. The main differential diagnosis is hidradenitis suppurativa and the two may coexist.

Treatment can be challenging and ideally should involve a multidisciplinary team. Potent topical steroids are used initially but systemic treatment is often needed and include steroids, immunosuppressive agents, antibiotics, especially metronidazole, and the biological TNF-α blockers; these may be successful in improving the condition [17].

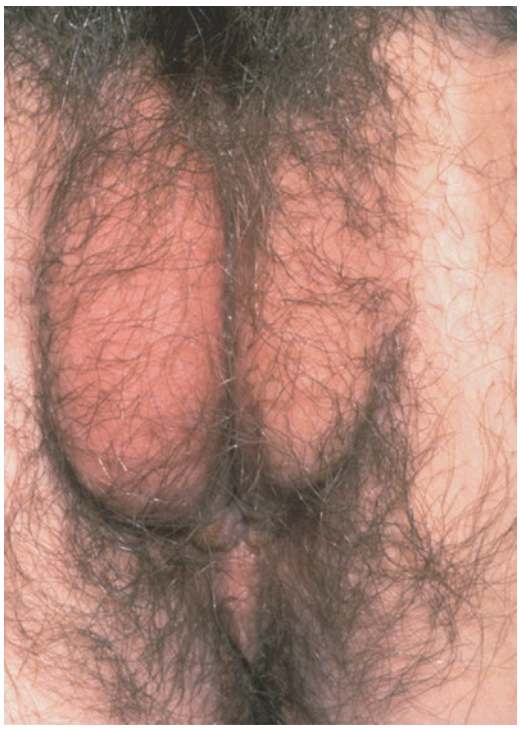

Fig. 57.19 Unilateral vulval oedema: Crohn's disease. Sometimes vulval oedema, usually unilateral, can accompany Crohn's disease of the gastrointestinal tract. (*See also colour plate 57.19*)

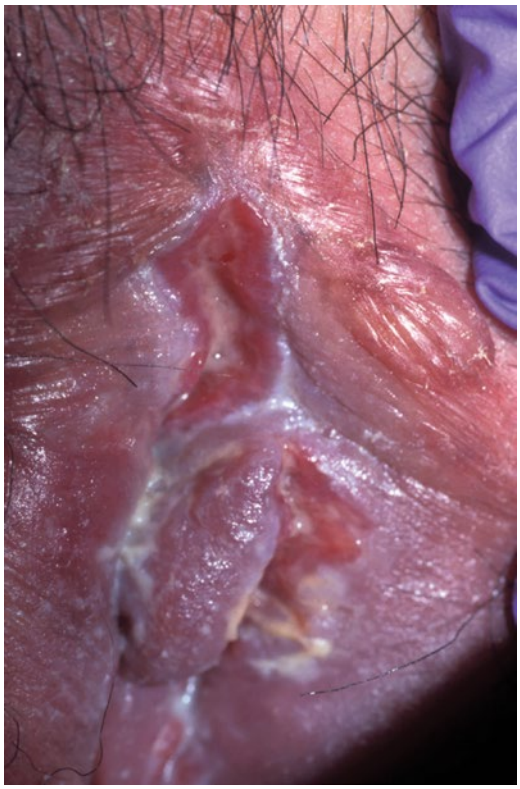

Fig. 57.20 Vulval Crohn's disease: deep 'knife-cut' fissures are seen in the inter-labial sulci. (*See also colour plate 57.20*)

Pyoderma gangrenosum

Pyoderma gangrenosum is an aggressive ulcerative disorder of unknown aetiology but with a strong association with an underlying inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease and myeloproliferative disorders.

Purulent ulcers with a prominent violaceous edge are most commonly seen on the lower limb but the vulva may be involved. The initial lesion is sometimes pustular, which then ulcerates rapidly to form single or multiple ulcers with an indurated edge.

Histology is inflammatory but non-specific and the diagnosis is usually clinical. Early recognition is important as there is often a prompt response to systemic steroids or cyclosporin. Other agents such as dapsone, azathioprine or minocycline may be needed. Surgery should be avoided at all costs as the lesions koebnerize and so debridement is often followed by disease progression.

Behçet's syndrome

The original description by Behçet was a triad of oral and genital ulceration with uveitis. It is now known as a multisystem disorder and the diagnostic criteria have been refined [18]. The diagnosis is made on the clinical

features, with a score of 4 or more points when a patient has recurrent oral ulceration (2 points), recurrent genital ulceration (2 points), ocular lesions (2 points), cutaneous lesions (erythema nodosum, folliculitis, pyodermatous plaques, all scoring 1 point), vasculitis (1 point) and a positive pathergy test (where pustulation occurs at the site of minor skin trauma, such as venepuncture).

The syndrome usually starts before the age of 50. The oral ulcers are similar to common aphthae but the vulval ulcers are usually larger, more painful and tend to heal with scarring. The labia minora are most commonly affected (Fig. 57.21). The histology is rather non-specific but thrombosed arterioles may be seen.

The management of these patients should be multidisciplinary as many organ systems may be involved. Neurological and ophthalmological complications can be serious and must be actively treated. Several drugs are used including steroids, colchicines, dapsone and thalidomide. Topical steroids may be used for the genital ulcers. There may be a role for the use of biological agents.

Necrolytic migratory erythema (glucagonoma syndrome)

This is a rare syndrome, of unknown cause, where cutaneous changes are seen secondary to a pancreatic islet cell tumour. The eruption is erosive and can migrate with a spreading serpiginous edge. The perineum is most severely affected but perioral lesions may also be seen. Glossitis and diabetes are usually associated. The diagnosis is made by finding a raised glucagon level. The rash often responds well to surgical removal of the primary tumour.

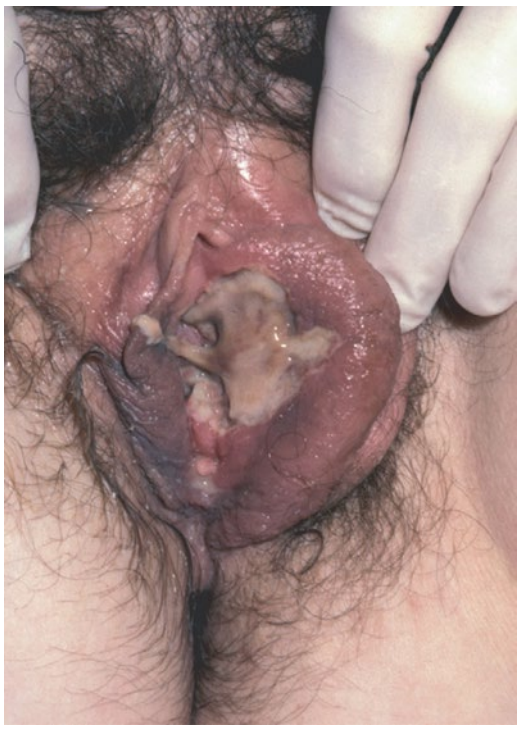

Fig. 57.21 Behçet's syndrome. Extensive deep ulcers, here penetrating the labia in a 45-year-old Turkish woman. (*See also colour plate 57.21*)

Acrodermatitis enteropathica

This is related to zinc deficiency and may be inherited as an autosomal recessive condition or acquired secondary to parenteral nutrition, malabsorption, severe eating disorders or penicillamine. The erythematous and pustular lesions affect the genitalia and also the perioral skin. Diagnosis is made on a low zinc level and treatment is with oral supplementation.

Disorders of pigmentation

The pigmentation of the vulval skin can vary widely with ethnicity and hormonal status. Dark areas can result from deposition of haemosiderin or melanin. Haemosiderin pigmentation tends to be red/brown and occurs after an inflammatory dermatosis such as lichen planus. Melanin pigmentation is usually darker brown or black and any new pigmented areas where the diagnosis is not clinically obvious must be biopsied.

Hyperpigmentation

The most common cause of pigmented patches on the vulval skin is post-inflammatory hyperpigmentation. It most frequently occurs after lichen planus but can be seen after other inflammatory dermatoses and fixed drug eruptions.

Vulval melanosis

Areas of pigmentation may be seen without any preceding history of inflammation (Fig. 57.22). These can be very irregular and must always be biopsied to confirm their benign nature. Histology shows an increased number of melanocytes and some pigmentary incontinence. Similar lesions may be found in the oral cavity and there is no evidence that they become malignant at either site.

Acanthosis nigricans

Velvety, thickened and hyperpigmented plaques are seen symmetrically spreading form the labia majora to the inguinal folds and may extend perianally. Similar lesions can be seen on the neck and in the axillae. Multiple skin tags are often seen on the surface of the plaques. The condition is most frequently seen in overweight individuals and it is associated with insulin resistance. Some cases, particularly those of sudden onset and in thin patients,

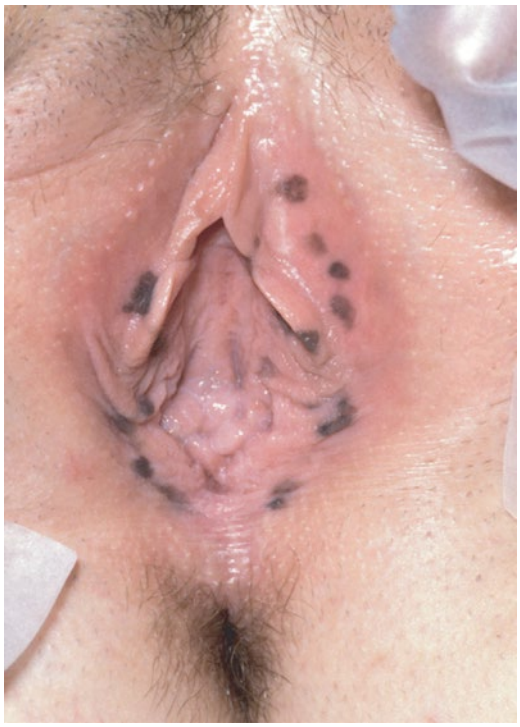

Fig. 57.22 Vulval melanosis: irregular areas of pigmentation without any preceding inflammation. (*See also colour plate 57.22*)

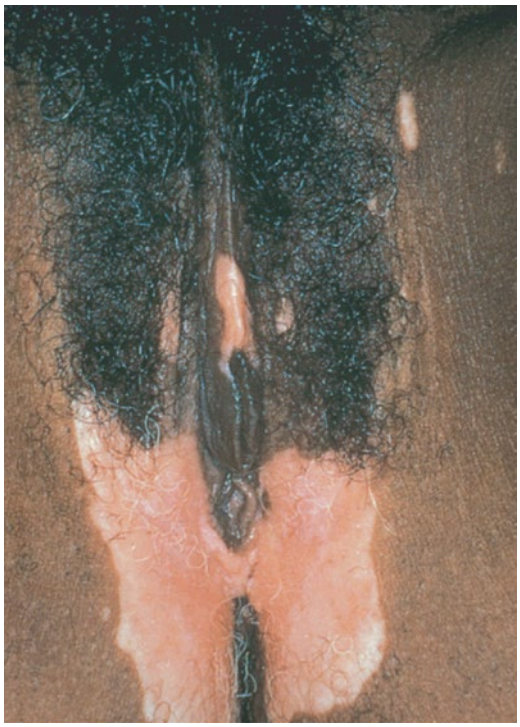

Fig. 57.23 Vitiligo, showing symmetrical loss of pigmentation. (*See also colour plate 57.23*)

can be associated with an underlying malignancy and appropriate investigations should be performed.

Hypopigmentation

Hypopigmentation can occur as a post-inflammatory change and is most clearly seen in darker skin. It resolves spontaneously after the inflammation is treated.

Vitiligo

This is a common autoimmune disorder where complete depigmentation of the skin occurs. It is patchy but symmetrical and peri-oroficial sites including the genitalia are often involved. The main differential diagnosis is lichen sclerosus and indeed the two diseases may coexist. However, in vitiligo there is no ecchymosis or architectural change and the texture of the skin is normal (Fig. 57.23). There is no effective treatment, and ultraviolet phototherapy that is occasionally helpful at other sites is not suitable for use on the vulval skin.

Pigmented lesions

Benign pigmented lesions can occur on the vulva. However, any pigmented lesion should be subjected to histological examination to exclude pigmented variants of VIN or malignant melanoma of the vulva.

Seborrhoeic keratoses

These may be heavily pigmented and have a 'stuck-on' appearance. They are usually found on the outer labia majora and in the groins. No treatment is generally required but cryotherapy or curettage and cautery are effective if they become troublesome. If there is any suspicion of HPV infection or cervical intraepithelial neoplasia, the lesions should be biopsied to exclude undifferentiated VIN.

Melanocytic naevi

Vulval naevi are not common. Some have atypical features and are regarded as atypical genital naevi [19] rather than variants of 'dysplastic' naevi. The unwary pathologist may report a malignant melanoma as there is cytological atypia but the lesions are symmetrical with normal cellular maturation. Naevi seen with lichen sclerosus can also mimic malignant melanoma clinically and histologically but there are case reports of true malignant melanoma developing in association with lichen sclerosus.

Benign tumours

Skin tags (acrochordia)

These small lesions are very common, particularly at flexural and frictional sites such as the axillae, eyelids

and groins. No treatment is needed but if they enlarge and become painful, they can be removed by cryotherapy or cautery.

Cysts

Epidermoid cysts are the most common type of cyst found on the vulva and are usually seen on the labia majora. They present as small, painless, yellow lumps. No treatment is needed but surgical excision is effective if they become symptomatic (Fig. 57.24).

Bartholin's cysts occur due to an obstruction in Bartholin's ducts and are therefore seen on the lower third of the inner labia majora. They can become infected and enucleation is the treatment of choice. Rarely, a carcinoma of Bartholin's glands can present as a cyst and any recurrent lesions should be excised to exclude this.

Hidradenoma papilliferum

These arise from anogenital mammary glands and are therefore usually found in the inter-labial sulcus or on the perineum. They are painless but excision is needed for histological examination.

Syringomata

Syringomata are eccrine duct tumours that are most commonly found on the face. They present as small papules which may be itchy on the genitalia. They occur on the labia majora most frequently but the labia minora can be involved. Treatment is unsatisfactory but laser ablation is used in those who are highly symptomatic.

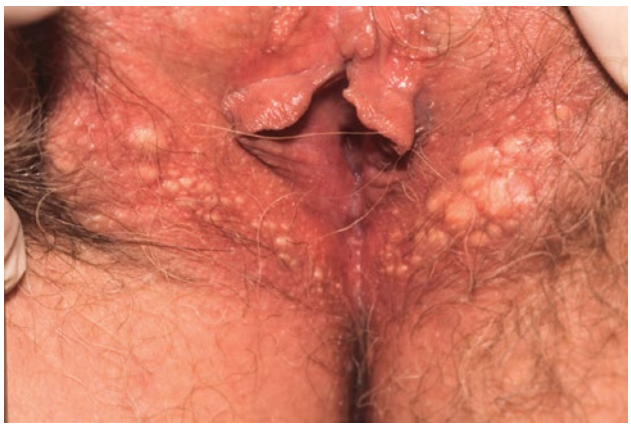

Fig. 57.24 Multiple epidermoid cysts on outer labia majora. These are usually asymptomatic. (*See also colour plate 57.24*)

Vascular lesions

Angiokeratoma

See section Normal variants.

Haemangiomas

Capillary haemangiomas are present at birth and do not fade. They are asymptomatic and cause no functional problems. Although laser treatment can be used, this is only done to improve the cosmetic appearance.

Cavernous haemangiomas (strawberry naevi) develop within the first few weeks of life and may grow rapidly. When present on the vulva, the labia majora are the most common sites involved but the perianal area and buttocks may also be affected. Occasionally, they break down and cause painful areas of ulceration that often become infected. Early assessment by a paediatric dermatologist is helpful, as propranolol is now commonly used to treat the lesions. They do spontaneously resolve over a period of years but, if troublesome, may require ablative treatment such as laser or excision.

Varicosities

Vulval varicosities are common during pregnancy and some thrombose spontaneously after delivery. They are usually associated with varicosities on the lower limbs, but if isolated to the genitalia the patient should be further investigated to exclude an obstructive pelvic lesion.

Disorders of lymphatics

Acute lymphoedema

Some swelling may occur in diseases such as candidiasis or acute eczema but resolves quickly with appropriate treatment of the condition. Urticaria and angioedema may involve the vulva. The history is that of acute swelling, sometimes related to intercourse where it may be pressure induced.

Type I hypersensitivity contact urticarial reactions to latex are an increasing problem. There is immediate swelling of the labia after using latex condoms and it can also occur if healthcare workers wear latex gloves for examination. In severe cases, the reaction may be life-threatening if full anaphylaxis follows. Contact urticaria to seminal fluid has also been described but is rare. The symptoms are completely abolished if condoms are used. Desensitization may be successful and a

successful pregnancy can be achieved by artificial insemination after removing the allergenic components of the seminal fluid.

Chronic lymphoedema

Lymphoedema may follow chronic inflammation (such as hidradenitis suppurativa or Crohn's disease), infection, malignancy, surgery or radiotherapy. The vulva becomes thickened and indurated and may be more prone to attacks of cellulitis. Prophylactic penicillin may be required.

Lymphangiectasia

Small lymphatic vesicles (lymphangiectasia) may develop on a background of chronic lymphoedema. They may be primary, due to an inherited defect, or secondary, due to Crohn's disease or following radiotherapy for cervical or vaginal cancer. The lesions have a verrucose appearance and are often incorrectly diagnosed as viral warts.

Treatment with CO_2 laser can be used in symptomatic cases where there is leakage of lymph. Congenital lesions may need imaging studies to identify if there are deeper lymphatic abnormalities.

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58

Benign Diseases of the Vagina, Cervix and Ovary

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Vagina

The vagina is the lowest part of the female internal genital tract. Clinical examination of the vagina is often limited as it is obscured during the use of a speculum and digital examination does not allow assessment. It is therefore only examined in detail in circumstances where there are specific symptoms to prompt vaginal examination.

The vagina consists of a non-keratinized squamous epithelial lining supported by connective tissue and surrounded by circular and longitudinal muscle coats. The muscle is attached superiorly to the fibres of the uterine cervix, and inferiorly and laterally to the pubococcygeus, bulbospongiosus and perineum. The lower end of the epithelium joins, near the hymen, the mucosal components of the vestibule and superiorly extends over the uterine cervix to the squamocolumnar junction. The vaginal epithelium has a longitudinal column in the anterior and posterior wall, and from each column there are numerous transverse ridges or rugae extending laterally on each side. The squamous epithelium during the reproductive years is thick and rich in glycogen. It does not change significantly during the menstrual cycle, although there is a small increase in glycogen content in the luteal phase and a reduction immediately premenstrually. The prepubertal and postmenopausal epithelium is thin or atrophic.

The vagina has a varied bacterial flora in oestrogenized women, and knowledge of what is normal and abnormal is important for determining infection. The main organisms are listed in Table 58.1.

Vaginal infection

Between puberty and the menopause the vaginal lactobacilli maintain a pH between 3.8 and 4.2 which protects against infection. Before puberty and after the menopause, the higher pH level and urinary and faecal contamination increase the risks of infection. Vaginal atrophy may also occur in the postpartum period with the hypo-oestrogenic state during lactation. Normal physiological vaginal discharge consists of a transudate from the vaginal wall, squames containing glycogen, polymorphs, lactobacilli, cervical mucus and residual menstrual fluid, as well as a contribution from the greater and lesser vestibular glands. Vaginal discharge varies according to oestrogen levels during the menstrual cycle and is a normal physiological occurrence. Vaginal discharge does not normally have an unpleasant odour, and if this occurs in the presence of change in colour or copiousness, then it may indicate infection. Non-specific vaginitis may be associated with sexual trauma, allergy to deodorants or contraceptives, and chemical irritation from topical antimicrobial treatment. Non-specific infection may be further provoked by the presence of foreign bodies, for example ring pessary, continual use of tampons and the presence of an intrauterine contraceptive device.

Bacterial vaginosis

Bacterial vaginosis has been previously associated with the organism *Gardnerella vaginalis* but a wide range of organisms, including *Mobiluncus* spp., *Bacteroides* spp. and *Peptostreptococcus*, are also implicated. Some 50% of infected women are asymptomatic and the vagina is not usually inflamed, and therefore the term 'vaginosis' is used rather than vaginitis [1]. Examination will reveal a thin grey–white discharge and a vaginal pH increased to greater than 5. A Gram stain of collected material will show 'clue' cells, which consist of vaginal epithelial cells covered with microorganisms and the absence of lactobacilli. The diagnosis can also be confirmed by adding a drop of vaginal discharge to saline on a glass slide and adding one drop of 10% potassium hydroxide. This

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 58.1 Normal frequency.

	100%	50%	<5%
Staphylococccus epidermidis	+	–	–
Lactobacillus	+	–	–
Staphylococcus aureus	–	+	–
Staphylococcus mitis	–	+	–
Enterococcus faecalis	–	+	–
Streptococcus pneumoniae	–	–	+
Streptococcus pyogenes	–	–	+
Neisseria sp.	–	+	–
Neisseria meningitidis	–	+	–
Escherichia coli	–	+	–
Proteus sp.	–	+	–
Bacteroides sp.	–	–	+
Corynebacterium	–	+	–
Mycoplasma	–	+	–
Candida albicans	–	–	+

releases a characteristic fishy amine smell. Bacterial vaginosis may be associated with increased risk of preterm labour [2], pelvic inflammatory disease and postoperative pelvic infection [3,4]. The treatment of bacterial vaginosis is with metronidazole, either as 200 mg three times a day for 7 days or as a single 2-g dose. Alternatively, clindamycin can be used as a vaginal cream.

Trichomoniasis

Trichomoniasis is a sexually transmitted disease caused by the parasite *Trichomonas vaginalis*. Symptoms usually appear 5–28 days after exposure and include a yellow–green vaginal discharge, often foamy, with a strong odour, dyspareunia and vaginal irritation. Of women infected, 10% also manifest a 'strawberry' cervix on examination (Fig. 58.1). *Trichomonas vaginalis* is a flagellated organism that can damage the vaginal epithelium, increasing a woman's susceptibility to infection by human immunodeficiency virus (HIV). This is caused by lysis of the epithelial cells. Treatment is with metronidazole 400 mg three times daily for 7 days or tinidazole 2 mg as a single dose. As this is a sexually transmitted disease, diagnosis should prompt the gynaecologist to refer the patient to a genitourinary medicine clinic for contact tracing.

Vaginal candidiasis

This is a fungal infection commonly referred to as 'thrush'. It is caused by any of the species of *Candida*, of which *Candida albicans* is the most common. This is an infection that causes vaginal irritation and vaginitis, which leads to itching, burning, soreness and a classic

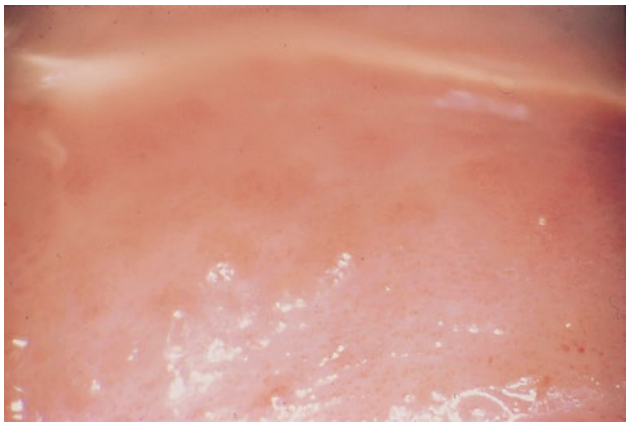

Fig. 58.1 Trichomoniasis with 'strawberry' vaginitis. (*See also colour plate 58.1*)

whitish or whitish-grey cottage cheese-like discharge. The irritation and inflammation spreads across the vulva and may also involve the perianal skin. *Candida* can be transmitted to a sexual partner, in whom it can cause red patchy sores near the head of the penis or on the foreskin, causing a severe itching and burning sensation. *Candida albicans* usually causes infection when production of lactic acid by lactobacilli is disturbed, resulting in a change in the pH in the vagina and subsequent overgrowth of *Candida*. Diabetics and patients using antibiotics for other infections have an increased incidence of candidiasis. This, in conjunction with other treatments (e.g. steroids) or conditions including HIV, leads to a weakening in the immune response, allowing *Candida* to thrive. *Candida* is frequently found in the vagina but it may also be part of the intestinal flora. The diagnosis is usually made on inspection, but a swab from the infected area will confirm the diagnosis in culture. Treatment for vaginal candidiasis is primarily with antifungal pessaries or cream inserted high into the vagina. Single-dose preparations offer the advantage of compliance, and imidazole drugs (clotrimazole, econazole and miconazole) are effective in short courses of 1–14 days according to the preparation. Oral medication is also available in the form of fluconazole or itraconazole and these treatments are usually extremely effective at eradicating the disease. Some 10% of women who contract candidiasis will develop recurrent disease – this is particularly likely if there are predisposing factors, such as pregnancy, diabetes or oral contraceptive use. It is important to consider partner treatment in those patients who suffer recurrent disease and in those patients who are resistant to two courses of imidazoles. If bacteriological confirmation of recurrent disease is made, a number of long-term treatments can be prescribed. These include fluconazole 100 mg orally every week for 6 months, clotrimazole 500-mg pessary weekly for 6 months or itraconazole

400 mg every month for 6 months. There is extensive alternative medicine literature on the treatment of *Candida* but there is very little scientific evidence to prove its efficacy.

Summary box 58.1

Vaginal infection

- It is important to differentiate between infection and normal flora in diagnosing vaginal infection.
- Bacterial vaginosis may be associated with preterm labour.
- Recurrent vaginal candidiasis needs systemic investigation prior to long-term treatment.

Syphilitic lesions of the vagina

Syphilis is uncommon among women in the UK. However, unusual vaginal lesions must raise suspicion, particularly if the patient or partner has recently travelled overseas.

The primary lesion may be in the vagina or on the vulva or cervix. There is usually a single, painless, well-demarcated ulcer with indurated edges, associated with lymphadenopathy. Secondary lesions include condylomata lata, mucous patches and snail-track ulcers.

Diagnosis is based on identification of the causative organism, *Treponema pallidum*, on dark-ground microscopy, or by serological examination for syphilis, for example using enzyme-linked immunosorbent assay (ELISA). For further details and specifics of treatment with Bicillin (i.e. procaine penicillin with benzylpenicillin sodium), see Chapter 64.

Gonococcal vaginitis

Gonorrhoea may infect the cervix or Bartholin's gland but not the vaginal epithelium, except in prepubertal girls or postmenopausal women. If there is suspicion of sexual abuse in a young child with a vaginal discharge, a swab for culture for *Neisseria gonorrhoeae* (see Chapter 64) should be taken.

Bartholin's gland diseases

These paired glands close to the introitus are responsible for mucus secretion that keep the vagina moist and lubricated during sexual arousal. If the duct becomes blocked, mucus is unable to escape and therefore a cyst will form. If this becomes infected, abscess formation occurs and this can be extremely painful. The most common organisms causing this are *Staphylococcus* and *Escherichia coli*, although other organisms may be encountered including *Neisseria gonorrhoeae* or *Chlamydia*. Bartholin's cysts or abscesses occur in about 3% of women, most commonly between the age of 20 and 30 years.

Bartholin's cysts may require no treatment unless troublesome, but abscesses almost always do. These may spontaneously rupture and resolve but recurrence rates are high. There are a number of surgical options, including incision and treatment with silver nitrate, marsupialization (which involves wide excision, drainage and eversion of the cyst mucosa to the vaginal skin), fistulization (incision, drainage and insertion of a catheter for 2–4 weeks), carbon dioxide laser incision and drainage, and needle aspiration of cysts.

A meta-analysis in 2009 failed to identify a best treatment approach [5]. Recurrence rates vary but are around 5%.

Viral infections

Lesions due to human papillomavirus (HPV) and herpes simplex virus can be seen in the vagina. Further information is given in Chapter 64.

Vaginal atrophy

This is seen not only following the menopause, but also prior to puberty and during lactation. Examination shows loss of rugal folds and prominent subepithelial vessels, sometimes with adjacent ecchymoses. The patient may present with vaginal bleeding, vaginal discharge or vaginal dryness and dyspareunia but also with urinary symptoms including frequency, nocturia, dysuria and recurrent urinary infection. Superficial infection, with Gram-positive cocci or Gram-negative bacilli, may be associated. Vaginal atrophy is symptomatic in 45% of postmenopausal women.

Treatment requires oestrogen to restore the vaginal epithelium and pH level. This is usually by topical oestrogen cream, and some of the oestrogen will be absorbed systemically. The endometrial safety of long-term use is uncertain. Preparations vary in length of recommended treatment, but this is usually for 3 months and then the effect is assessed. Repeated applications over time may be needed depending on symptoms returning. Alternatively, in postmenopausal women hormone replacement therapy can be used.

Vaginal trauma

This may follow coitus, with damage to the epithelium or less frequently the vaginal muscle wall, or the breakdown of adhesions at the vault following vaginal surgery (Fig. 58.2). It may be associated with parturition or be iatrogenic, for example ulceration associated with the use of a ring pessary. Trauma may be associated with significant haemorrhage and occasionally will leave vesical or rectal fistulae.

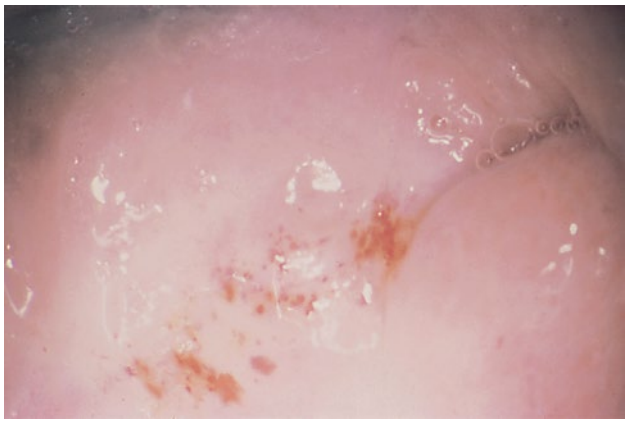

Fig. 58.2 Bleeding and adhesions at the vaginal vault. (*See also colour plate 58.2*)

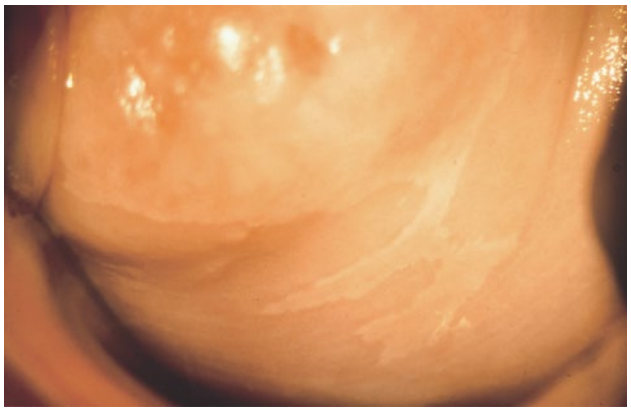

Fig. 58.3 Vaginal intraepithelial neoplasia as an extension of a cervical lesion. (*See also colour plate 58.3*)

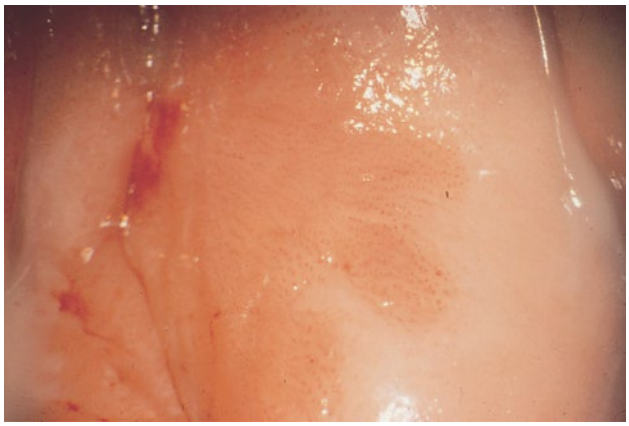

Fig. 58.4 Vaginal intraepithelial neoplasia in post-hysterectomy vaginal angle. (*See also colour plate 58.4*)

Fistula

A fistula may result from trauma, as described in the previous section, or it may be due to carcinoma or Crohn's disease. Fistula of the anterior wall is now uncommon in association with childbirth, but rectovaginal fistula may follow an obstetric tear or extension of an episiotomy, and an incomplete or inadequate repair. Fistulae involving ureter, bladder or rectum may follow gynaecological surgery.

Endometriosis

Occasionally, deposits of endometriosis can be found beneath the vaginal epithelium in patients with rectovaginal endometriosis or following surgery or episiotomy. They may cause abnormal vaginal bleeding or pain. They are most easily identified while bleeding but have a blueish appearance at other times. Treatment can be by laser vaporization or excision, or by drug therapy as for endometriosis elsewhere.

Vaginal intraepithelial neoplasia

Vaginal intraepithelial neoplasia (VAIN) is seen in about 10% of patients with cervical intraepithelial neoplasia (CIN) (Fig. 58.3). It is almost always in the upper vagina and confluent with the cervical lesion [6]. It is uncommon to find VAIN in the presence of a normal cervix, but Lenehan *et al.* [7] reported that 43% of their patients with VAIN after hysterectomy had a history of negative cervical smears and benign cervical pathology. VAIN may be present in the vaginal vault or suture line after hysterectomy (Fig. 58.4) (this may be residual after CIN has been treated) or may be distant from the vault and associated with multicentric intraepithelial neoplasia. Hummer *et al.* [8] reported a series of 66 patients with VAIN and showed that one-third of cases had developed within 2 years of treatment of the previous cervical lesion. The longest time interval between the diagnosis of CIN and VAIN was 17 years; the age of patients with VAIN in that series ranged from 24 to 74 years, with a mean age of 52 years.

The aetiology of VAIN is similar to that of CIN, with HPV found in 98% of cases and HPV-16 being found in 68% [9]. Extension of the transformation zone into the fornices would seem to be responsible, even though no abnormality was recognized when the cervical lesion was treated. A higher incidence of VAIN has been noted in patients on chemotherapy or immunosuppressive therapy. The role of radiotherapy for carcinoma of the cervix some 10–15 years prior to the development of VAIN has been noted, particularly when a subsequent lesion is in the lower vagina. It is thought by some [10] that a sublethal dose of radiation may induce tumour transformation and that VAIN or vaginal sarcoma may result.

As for cervical lesions, VAIN I is equivalent to mild dysplasia, VAIN II to moderate dysplasia and VAIN III to severe dysplasia or carcinoma *in situ*. The disease is normally recognized as a result of abnormal cytology seen in a vaginal vault smear specimen. Townsend [11] recommended that vault smears should be performed annually for women after hysterectomy performed for CIN, and every 3 years if the hysterectomy was for benign disease. Current teaching discourages the need for any subsequent smears in this latter group but recommends follow-up of patients who have had hysterectomy for cervical lesions. Gemmell *et al.* [12] recommend that vault smears should be taken 6 months, 12 months and 2 years after hysterectomy; the patient should then return to 5-yearly screening.

Colposcopic assessment of patients with abnormal vault smears will delineate areas of aceto-white epithelium. Punctuation may be apparent in more than 50%, and areas of abnormality will often fail to stain following the application of Lugol's iodine solution (Fig. 58.5). However, atrophic changes within the vagina may lead to extensive areas of non-Lugol's staining and difficulty in defining the limits of lesions. A preliminary 2-week course of oestrogen cream to correct oestrogen deficiency and then colposcopic examination 2 weeks following this will improve the definition of lesions. Problems may be encountered in interpreting or gaining access to areas of change disappearing into post-hysterectomy vaginal angles or suture line. Vaginal biopsies from the vault can usually be taken without anaesthesia, but occasionally difficult access into vaginal angles may require the use of general anaesthesia and appropriate vaginal retractors.

No adequate study on the progression of VAIN to invasive disease has been reported. Among the series of patients reported by McIndoe *et al.* [13] were patients who had abnormal smears following hysterectomy; some of these patients were followed up for almost 20 years before developing invasive carcinoma while others progressed more rapidly.

There has been a wide variety of treatments for VAIN. Surgical excision remains the mainstay of treatment, including excision biopsy for smaller lesions, partial vaginectomy for mutifocal disease and, rarely, total vaginectomy for extensive or persistent high-grade VAIN. The difficult patient to treat is the one who has already undergone a hysterectomy for a cervical lesion and returns with an area of abnormality in the suture line. Whether leaving the vault open at the time of hysterectomy avoids sequestration of the vaginal mucosa above the usual suture line has not been proven. Ireland and Monaghan [14] found that 9 of 32 patients with VAIN had invasive carcinoma in the area of the suture line, and they emphasized both the difficulty in assessing the vaginal vault and the need for obtaining adequate tissue for histological examination. They therefore advocated partial vaginectomy whenever abnormal epithelium is seen at the angles or suture line of the vault. This procedure requires an abdominal approach after packing the vaginal vault and involves the mobilization of the ureters down to their insertion into the bladder, dissection of bladder and rectum from the vagina, and sufficient mobilization to allow removal of the upper 1–2 cm from the top of the vagina. The definition of just how much to remove is usually best achieved by commencing a mucosal dissection from below prior to packing the vagina. Occasionally, more extensive disease will require total vaginectomy followed by either skin grafting or mobilization of a loop of bowel to reconstruct the neovagina. There are some who advocate a vaginal approach [15], but access may not be easy and occasionally brisk bleeding from vaginal arteries may be encountered.

Use of the carbon dioxide laser is more likely to be successful in treating those women who have not had

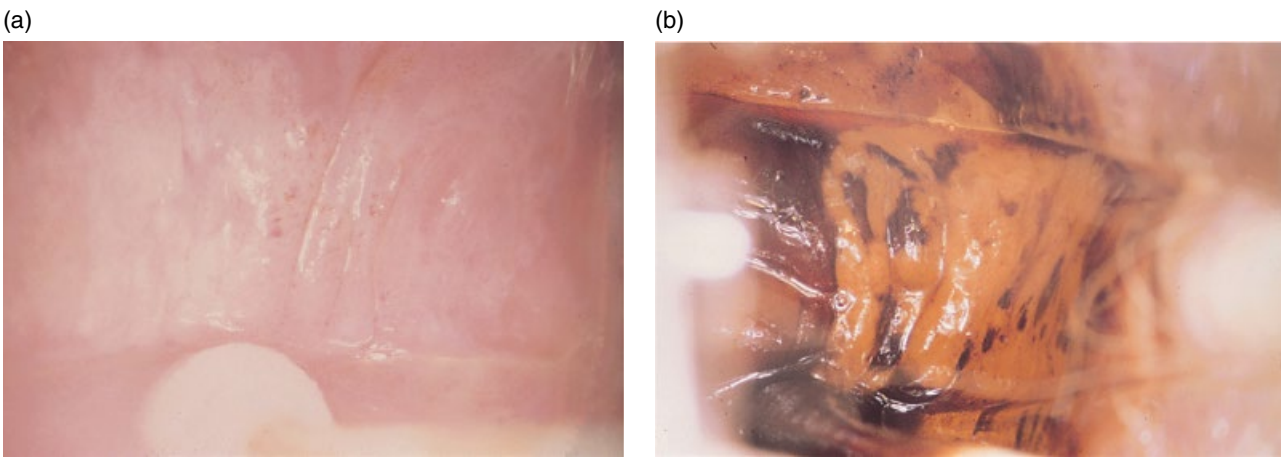

Fig. 58.5 (a, b) Area of vaginal intraepithelial neoplasia before and after the application of iodine solution. (*See also colour plate 58.5*)

hysterectomy and where the full extent of the lesion can be demarcated. It must be noted that the vaginal wall may be thin in postmenopausal women and the bladder and rectal mucosa less than 5 mm away. The advantage of the carbon dioxide laser over other forms of selective ablation, for example diathermy or loop excision, is that there should be greater control of the area and depth of laser vaporization. Techniques using high-power density and rapid beam movement minimize carbonization and adjacent thermal necrosis to allow recognition of tissue architecture with removal of lesional epithelium down to the underlying stroma, thereby reducing the risk of bladder or bowel damage [16].

Medical treatment has also been used. Imiquimod 5% cream is commonly used and a recent review reported complete response rates in VAIN I–III of 57–86% [17]. Experience with the use of 5-fluorouracil has been less extensive in the UK than in the USA. Caglar *et al.* [18] claimed that the subsequent denudation of epithelium was specific for only abnormal epithelium. However, sometimes epithelial ulceration is extensive, accompanied by severe vaginal burning, and subsequent healing may take several months. Treatment failure is common. A recent study by Rhodes *et al.* [19] examined the role of intravaginal oestrogen alone and in combination with other therapies. In the group treated with oestrogen alone, 90% had regression or cure; of those who had combined therapy, a cure rate of 81.3% was reported. In contrast, those treated without oestrogen had a cure rate of only 71%.

The other option is to use radiotherapy by the intravaginal approach [20]. Such treatment may produce vaginal narrowing and interfere with coitus, and so this should be reserved for highly selected difficult cases and in older women in whom sexual activity has ceased. Local damage to the bladder and rectum are risks of brachytherapy.

Summary box 58.2

- VAIN coexists with CIN in up to 6% of patients.
- Colposcopic assessment and follow-up is mandatory.
- Treatment is either by excision or local ablative therapy.

Diethylstilbestrol and related vaginal lesions

Diethylstilbestrol (DES) was used from the mid-1940s for the treatment of recurrent or threatened abortion and unexplained fetal loss late in pregnancy, predominantly in the north-eastern states of the USA (where it is estimated that 2 million women were treated) and also in Canada, Mexico, Western Australia and western Europe.

Herbst and Scully [21] reported seven cases of clear cell adenocarcinoma of the vagina seen and treated in Massachusetts General Hospital, Boston, in young women aged between 14 and 22 years. A retrospective study by them linked these carcinomas with the intrauterine exposure of the patients to DES given to their mothers during pregnancy. The more extensive survey [22] looked at 346 cases of clear cell adenocarcinoma of the cervix and vagina. The maternal history was available in 317 patients and it was found that two-thirds of the patients had been exposed *in utero* to DES or a similar non-steroid oestrogen given to the mothers during pregnancy. In a further 10%, drugs of doubtful origin were given but in 25% no history of maternal hormone therapy could be obtained. The authors found that the age incidence for clear cell adenocarcinoma of the vagina in young women began at 14 years, peaked at 19 years and then subsequently declined. They estimate that the probable risk of development of clear cell carcinoma in women exposed to DES *in utero* is 0.14–1.4 per 1000 women. DES produced various other vaginal and cervical lesions. Vaginal adenosis was often seen in combination with cervical eversion or ectropion. The patients often had a ridge between the vaginal and cervical tissue referred to as a collar, a rim or a 'cock's comb cervix'. Such appearances occurred in approximately 25% of exposed patients. The adenosis can affect the anterior and posterior vaginal walls and lateral vaginal fornices, but is usually restricted to the upper third of the vagina. Sometimes there will be cytological abnormality, extensive immature metaplasia and CIN. Originally it was recommended that women who were known to have been exposed to DES *in utero* should be screened from the age of 14 years with both cytology and colposcopy. DES exposure was uncommon in the UK and associated vaginal changes will be seen infrequently. Such patients should be managed by annual cervical and vaginal cytological surveillance and colposcopic assessment. It is still not known if the risk of adenocarcinoma persists, for example after the menopause.

Benign vaginal tumours

These are uncommon but occur within the vaginal wall and include myoma, fibromyoma, neurofibroma, papilloma, myxoma and adenomyoma.

Cystic lesions may be found within the vagina, usually laterally and occasionally extending from the fornix down to the introitus. These are usually of Gartner's or Wolffian duct origin. They may increase to such a size as to interfere with coitus or tampon use. They can usually be managed by de-roofing, but care must be taken in the fornices to avoid large uterine and vesical vessels.

Cervix

Benign lesions

Position of the squamocolumnar junction and changes within the transformation zone

It is known that the uterine cervix increases in size in response to oestrogens; because the cervix is anchored at the fornices, the end result of any enlargement is eversion to expose the columnar epithelium of the endocervical canal. This occurs dramatically in the neonate and under the influence of maternal oestrogens, at puberty under the influence of rising oestrogen levels, during the use of the combined oral contraceptive pill and during the first pregnancy (Fig. 58.6). Ectopy is the preferred term for this display of columnar epithelium (rather than 'erosion'); colposcopic examination demonstrates the folding of the epithelium into villi (Fig. 58.7). Upon withdrawal of oestrogen, for example in the puerperium or at the menopause, the squamocolumnar junction approaches the external os once more and indeed may be found within the endocervical canal.

In approximately 5% of women there will be extension of the squamocolumnar junction into the anterior and posterior fornices so that on subsequent examination an extensive area of change will be noted, the so-called congenital transformation zone. The presence of this may not be apparent to the naked eye but can be demonstrated following the application of iodine. Biopsy will show no evidence of intraepithelial neoplasia but delayed or immature metaplasia.

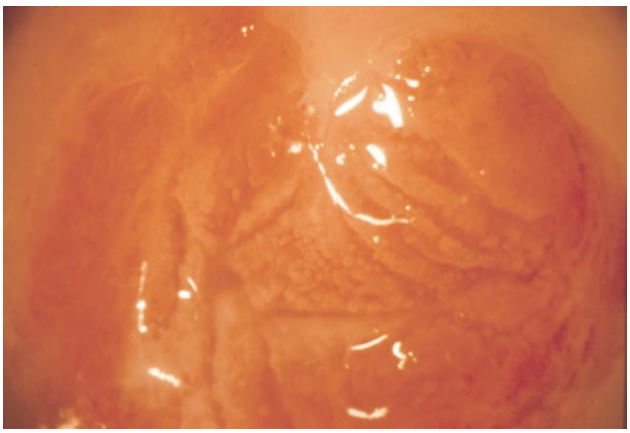

Fig. 58.6 Eversion of the cervix during pregnancy. (*See also colour plate 58.6*)

Cervical metaplasia

Exposure of the columnar epithelium to low pH as found within the vagina promotes a series of physiological changes, known as metaplasia. It is believed that reserve cells lying within the monolayer of columnar epithelium will proliferate, producing a multilayered epithelium with the columnar cells left exposed on the surface (Fig. 58.8). These cells will initially appear immature and undifferentiated, but with the passage of time will show the usual differentiation to resume a squamous epithelium with glycogenation of the superficial squamous cells. This process occurs at the squamocolumnar junction, or transformation zone, starting in the neonate and continuing until well after the menopause. Examination of the endocervix will show a series of longitudinal ridges with columnar cells lining both the tops of the ridges and extending down into the depths or crypts (Fig. 58.9). Metaplasia usually occurs initially in the ridges and may well bridge over these, leaving a squamous cover with columnar epithelium remaining within the crypts. If a crypt cannot expel the mucus produced from the columnar epithelium, a retention cyst or Nabothian follicle will occur (Fig. 58.10); sometimes these follicles are large and

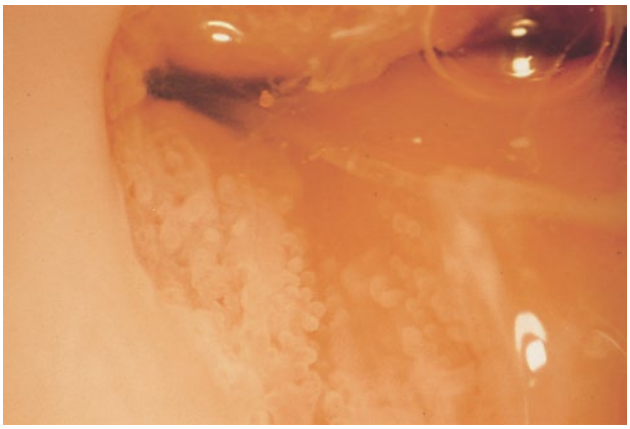

Fig. 58.7 Columnar villi at the squamocolumnar junction. (*See also colour plate 58.7*)

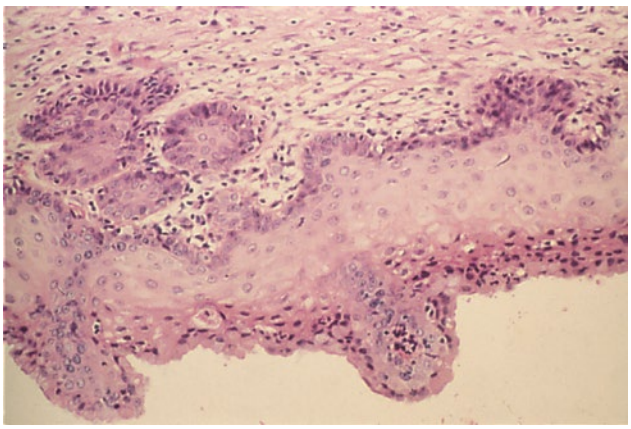

Fig. 58.8 Photomicrograph of columnar and multilayered immature metaplastic epithelia. (*See also colour plate 58.8*)

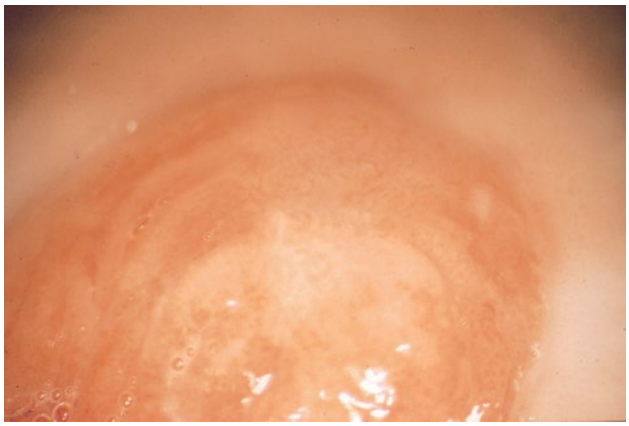

Fig. 58.9 Squamous metaplasia of the cervix. (*See also colour plate 58.9*)

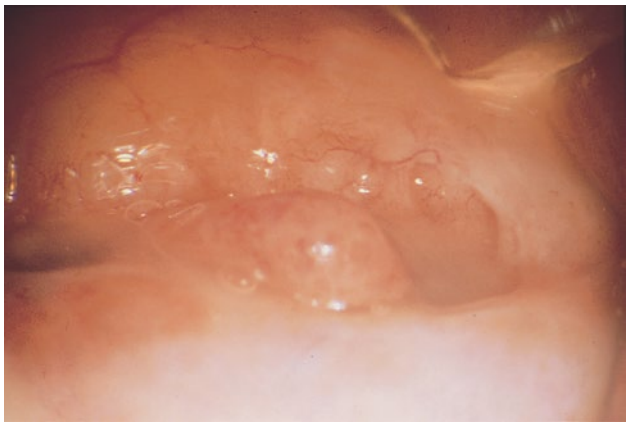

Fig. 58.11 A small endocervical polyp. (*See also colour plate 58.11*)

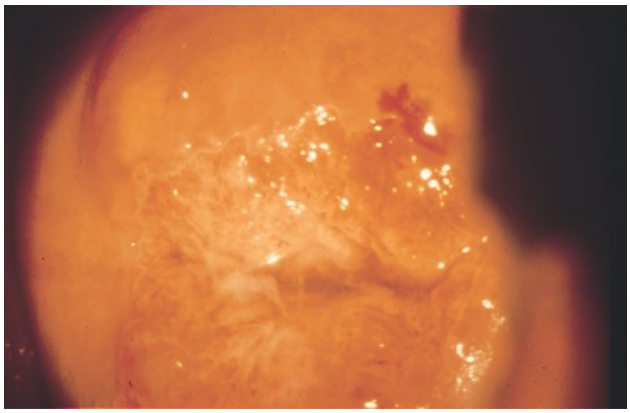

Fig. 58.10 A typical transformation zone with a mucus-filled Nabothian follicle at 11 o'clock. (*See also colour plate 58.10*)

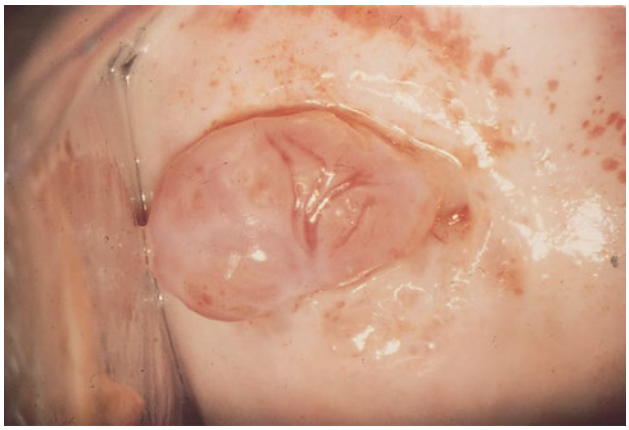

Fig. 58.12 A large polyp with adjacent atrophic epithelium and ecchymoses. (*See also colour plate 58.12*)

extensive across the transformation zone. They are entirely benign and are not associated with infection, i.e. they are not a sign of cervicitis and require no treatment.

Endocervical polyps

The recognition of endocervical polyps at the time of taking a cervical smear is common and usually increases with age up to and beyond the menopause (Figs 58.11 and 58.12). Occasionally these polyps will be symptomatic, producing some increase in vaginal discharge or bleeding on coital contact. Histology of these polyps will show that they consist of columnar epithelium, sometimes with metaplastic squamous epithelium across the tip. Malignant change is most unusual. However, if these polyps are removed, for example by polypectomy, tissue should be sent for histology, recognizing that some 15% of uterine tumours will be polypoidal and occasionally will extrude through the external os.

Chronic cervicitis

There was previous enthusiasm for treating by cautery or diathermy those patients who complained of chronic watery vaginal discharge and were found to have an 'erosion'. As already explained, these areas of ectopy or everted columnar epithelium are not pathological and the term 'cervicitis' is not appropriate.

However, some women with *Chlamydia trachomatis* (and rarely with *Neisseria gonorrhoeae*) will present with symptoms of discharge and an abnormal cervix will be noted. Brunham *et al.* [23] described 'mucopurulent cervicitis' in association with *Chlamydia*, and Hare *et al.* [24] described the colposcopy appearances of 'follicular cervicitis'. Providing these organisms have been excluded by appropriate microbiology, 'cervicitis' does not require treatment except by increasing vaginal acidity to promote squamous metaplasia.

Summary box 58.3

Cervical disease

- The squamocolumnar junction can be found in a number of clinical sites across the cervix and occasionally reaches the vault of the vagina.
- Cervical metaplasia is a normal phenomenon.
- Endocervical polyps can be removed in an outpatient setting.
- Chronic cervicitis requires no treatment.

Ovaries

Benign disorders

Anatomy

The ovaries are attached to the lateral pelvic side walls by the suspensory ligament containing the ovarian vessels, and to the cornua of the uterus by a ligamentous condensation of the broad ligament. Each ovary is $3 \times 2 \times 1$ cm in size in the resting or inactive state, but will increase in size during physiological stimulus; they shrink after the menopause. The surface is covered by a flattened monolayer of epithelial cells, and beneath this are the ovarian follicles, with oocyte, granulosa layer and surrounding theca. Beneath this cortical layer are a stromal medulla and a hilum where the vessels enter through the mesovarium. The events associated with follicular development and ovulation are described in Chapter 46. The size and position of the ovaries varies between puberty and menopause – the mean volume, as assessed by transvaginal ultrasound scan of a premenopausal ovary, is 6.8 cm^3 (upper limit of normal 18 cm^3) compared with a mean postmenopausal size of 3 cm^3 (upper limit 8 cm^3).

Ovarian enlargement

Ovarian enlargement will occur in response to follicle stimulating hormone and luteinizing hormone. Follicular and luteal cysts can occur, and theca lutein cysts up to 15 cm in size will develop in response to very high levels of chorionic gonadotrophin, as occurs with trophoblastic disease. Hyperstimulation syndrome can occur, with massive enlargement of the ovaries and development of ascites, in response to therapeutic gonadotrophin stimulation during fertility treatment (see Chapter 52).

Polycystic disease

Polycystic enlargement of the ovaries has been described under a variety of names. Stein and Leventhal [25] described seven cases of amenorrhoea or irregular menstruation with enlarged polycystic ovaries demonstrated by 'pneumoroentgenography' and restoration of normal physiological function after wedge resection. Judd *et al.* [26] demonstrated that the mildly elevated androgen levels found in this syndrome were of ovarian origin. The changes in gonadotrophin ratios and androgen levels are not always consistent with the appearances of the ovaries, and increasingly the diagnosis of polycystic ovarian disease is based on ultrasound findings of peripheral distribution of 10 or more follicles of 2–8 mm in diameter, with increased ovarian volume and associated endocrine criteria (see Chapter 47).

Ovarian pregnancy

Ovarian ectopic pregnancy is uncommon, with an estimated incidence of 1 per 25 000 of all pregnancies. Patients usually present with features of an extrauterine pregnancy or bleeding from a corpus luteum. Preoperative diagnosis is difficult.

Treatment is surgical removal, which may require removal of the ovary. This can usually be achieved laparoscopically (see Chapter 43).

Ovarian endometriosis

Ovarian enlargement may be found secondary to endometriosis (i.e. endometriomas). Endometriomas vary in size considerably and although medical management is possible with smaller cysts, larger endometriomas require surgical treatment (see Chapter 53).

Ovarian tumours

There are five main groups of ovarian tumour as classified by the World Health Organization. However, the benign tumours are as follows:

- Epithelial: serous cystadenoma, mucinous cystadenoma, Brenner tumour.
- Germ cell: teratoma (Fig. 58.13).

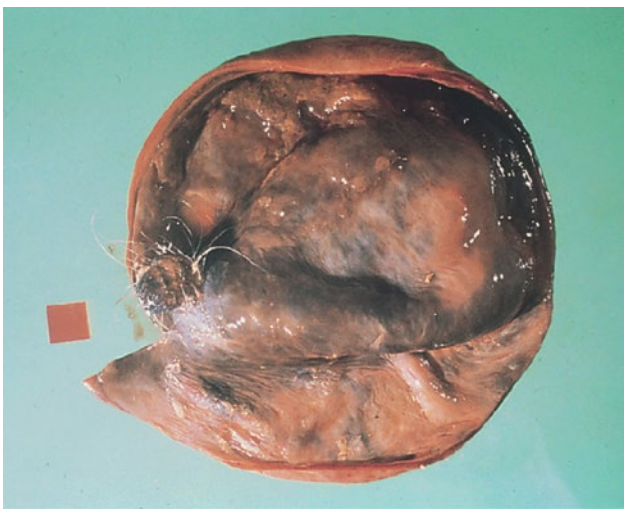

Fig. 58.13 A benign cystic teratoma of the ovary showing hair and skin. (*See also colour plate 58.13*)

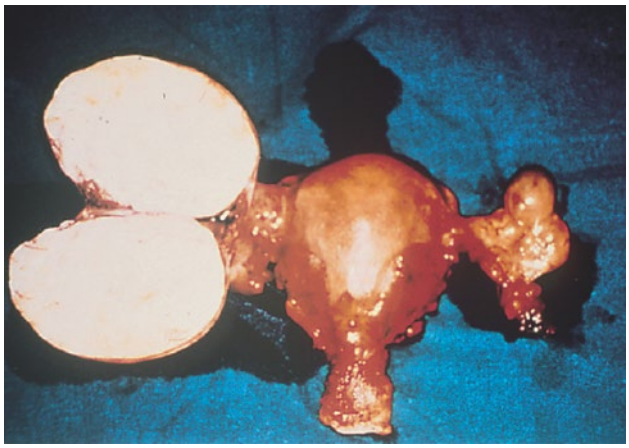

Fig. 58.14 An ovarian fibroma. (*See also colour plate 58.14*)

Benign tumours comprise about 85% of all ovarian neoplasms, mucinous cystadenomas contributing 50% and serous 25%, with teratomas occurring in about 10%. There are other soft tissue tumours that are not specific to the ovary, such as fibromas (Fig. 58.14).

Corpus luteum

The corpus luteum is a physiological development following ovulation, and in a normal menstrual cycle may reach 3 cm in diameter. Occasionally, the corpus luteum may persist in the absence of pregnancy and may increase in size to up to 5 cm in diameter. It is usual at this point that regression begins and the corpus luteum cyst spontaneously resolves. These cysts are often seen incidentally on ultrasound in asymptomatic women or in women who have mild abdominal pain. The management is conservative. In 95% of cases, repeat ultrasound at 6–8 weeks will show that the structure has disappeared and normal ovarian function ensues. It is extremely important that a conservative approach is adopted in these circumstances and these cysts only need to be removed laparoscopically if they persist or increase in size over time.

Mature cystic teratomas (dermoid cysts)

Dermoid cysts are cystic teratomas that contain elements of ectoderm, endoderm and mesoderm which may include skin, hair follicles and sweat glands; occasionally, hair can be quite prolific. There can also be pockets of sebum, blood, fat, bone, nails, teeth and cartilage and occasionally thyroid tissue. Dermoid cysts usually present with abdominal discomfort or acute pain due to torsion, in women between the ages of 18 and 25 years. Diagnosis may be made on ultrasound, where there are classic features (see Chapter 36), and if there is any doubt as to the aetiology, an MRI scan can be performed although is rarely necessary. Dermoid cysts can vary in size and grow over time until diagnosis is made. Occasionally, dermoid cysts may be diagnosed for the first time during pregnancy and here clinical decisions – about whether to adopt a conservative approach with management of the cyst postnatally – need to be made in the light of clinical symptoms and size. Dermoid cysts are bilateral in 10–15% of cases.

The management of dermoid cysts is surgical in cases where the patient is symptomatic. Ovarian cystectomy can be performed by laparotomy or laparoscopy. With larger cysts (i.e. >6 cm), the preferred method is laparotomy; smaller cysts may be removed laparoscopically. There is some controversy about the laparoscopic approach due to the risk of spillage of the contents leading to chemical peritonitis. The risk is small (0.2%) but it is a serious complication when it does occur [27]. Spillage has been reported as occurring in 13–100% of cases [28,29]. There is also debate about the incidence of recurrence after laparoscopic surgery. There would seem little doubt that the recurrence rate is higher in the laparoscopic group, probably about 10%, compared with 0.1% in the laparotomy group [28].

Ovarian cystectomy is always the preferred surgical option as most of these patients will not have tested their fertility. In the majority of cases, the finding of a dermoid cyst is incidental and so expectant management may be an option, particularly if the cyst is small. Data on this strategy are lacking at present but this would seem a logical approach.

Serous cystadenomas

These account for approximately 25% of all benign ovarian neoplasms and their peak incidences are in the fourth and fifth decades of life. Symptoms are usually rather non-specific but can include pelvic pain or discomfort or occasionally a pelvic mass is discovered at routine examination. Approximately 20% of cystadenomas are bilateral and they are benign. Treatment is by either salpingo-oophorectomy or ovarian cystectomy depending on whether the patient is keen to preserve her fertility. Recurrence is extremely rare.

Mucinous cystadenomas

These comprise 50% of benign ovarian epithelial neoplasms and tend to occur most often between the third and sixth decades of life, with a mean age of around 50 years. Small tumours are often found incidentally, whereas the larger tumours present as an obvious pelvic or abdominal mass. They are rarely bilateral. Treatment

is by ovarian cystectomy or oophorectomy, which may be performed either laparoscopically or by laparotomy.

Ovarian cyst accidents

Ovarian cysts may present acutely, and here pain may be severe following rupture, haemorrhage or torsion of the cyst. Haemorrhage can be dramatic and severe bleeding can cause hypovolaemia and a haematoperitoneum. Patients present in a collapsed state and the differential diagnosis is often of a ruptured ectopic pregnancy. Treatment is by emergency laparotomy to stop the bleeding, followed by assessment and salvage of the ovary if possible. Torsion of an ovarian cyst presents as intermittent acute abdominal pain, usually in the iliac fossa associated with the ovary. The pain is colicky in nature and the pain may be referred to the sacro-iliac joint or to the upper medial thigh. It is important that ultrasound imaging, including Doppler assessment for blood flow, is performed although torsion will only be diagnosed in 60% of cases. Episodes of torsion may be spread over quite long periods of time and it is important for the clinician to recognize the pattern of symptoms of acute presentation if multiple torsion is to be avoided or it will result in ovarian ischaemia. Sadly, failure to recognize this sequence of events may lead to an acute situation with surgery resulting in salpingo-oophorectomy as salvage of the ovary is not possible. However, treatment is usually by detorsion even if the ovary appears necrotic, with removal of the ovarian cyst either at the time or as an interval procedure. Detorsion alone is insufficient as rates of recurrent torsion are high [30].

Summary box 58.4

Benign disease of the ovary

- Cysts of the corpus luteum should be monitored and will resolve spontaneously in 95% of cases.
- Mature cystic teratomas should be removed surgically.
- Cyst accidents are common and careful diagnosis and management will avoid loss of an ovary.

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59

Benign Disease of the Uterus

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Benign disease of the uterus includes uterine fibroids, adenomyosis and endometrial polyps. These pathologies may remain asymptomatic or cause considerable morbidity. Uterine fibroids are the most prevalent benign lesions of the uterine corpus. Benign focal intracavitary lesions are present in-one third of premenopausal women and in almost half of postmenopausal women with abnormal uterine bleeding. In premenopausal women, focal intracavitary lesions, including intracavitary fibroids and endometrial polyps, become more prevalent with advancing age [1].

This chapter discusses each of these conditions and considers their aetiology, pathogenesis, presenting symptoms, diagnosis and treatment with inclusion of new developments, particularly in the treatment of symptomatic fibroids.

Adenomyosis

Definition

Adenomyosis is defined as the presence of endometrial tissue, including endometrial glands and stroma, in the myometrium and is associated with smooth muscle proliferation in the inner myometrium [2]. It may be either diffuse or focal. Adenomyosis typically results in uterine enlargement and an irregular endo-myometrial border or junctional zone. The histological definition of adenomyosis usually includes a depth of penetration between 2.5 and 5 mm [3].

Incidence

The reported incidence of adenomyosis in hysterectomy specimens varies considerably, ranging from 9 to 62% [4]. This wide range is likely to reflect the varying diagnostic methodologies used by different pathologists.

Aetiology

The ectopic endometrium is responsive to steroid hormones. In addition, gene polymorphisms have been identified in the oestrogen receptor, with mutations of oestrogen receptor alpha [5]. This ectopic tissue may respond to the cyclical hormone changes of the menstrual cycle, contributing to the symptoms of heavy menstrual bleeding (HMB) and dysmenorrhoea. Abnormal prostaglandin production also occurs and this could exacerbate both pelvic pain and heavy bleeding.

Clinical presentation

The commonest presentation is HMB and dysmenorrhoea, the latter being worse in deep infiltrating disease [6]. However, adenomyosis is often diagnosed in women without bleeding or pain symptoms, leading Weiss *et al.* [4] to challenge the causative relationship between adenomyosis and symptoms. The condition is reportedly characteristic of the fifth decade of life, with 45 years being the commonest age of presentation. It is uncommon in nulliparous women and occurs less frequently in smokers [7].

Diagnosis

The diagnosis is made on histological examination of the uterus after hysterectomy but the preoperative diagnosis may be suggested on ultrasound examination. Typical ultrasound features of adenomyosis include an asymmetrical thickening of the myometrium or a globular uterus, myometrial cysts, myometrial echogenic islands, fan-shaped shadowing, subendometrial echogenic lines and buds, translesional vascularity and an irregular or interrupted junctional zone [8,9] (Fig. 59.1).

On MRI, adenomyosis has historically been linked with a thickened junctional zone [10]. According to Brosens

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

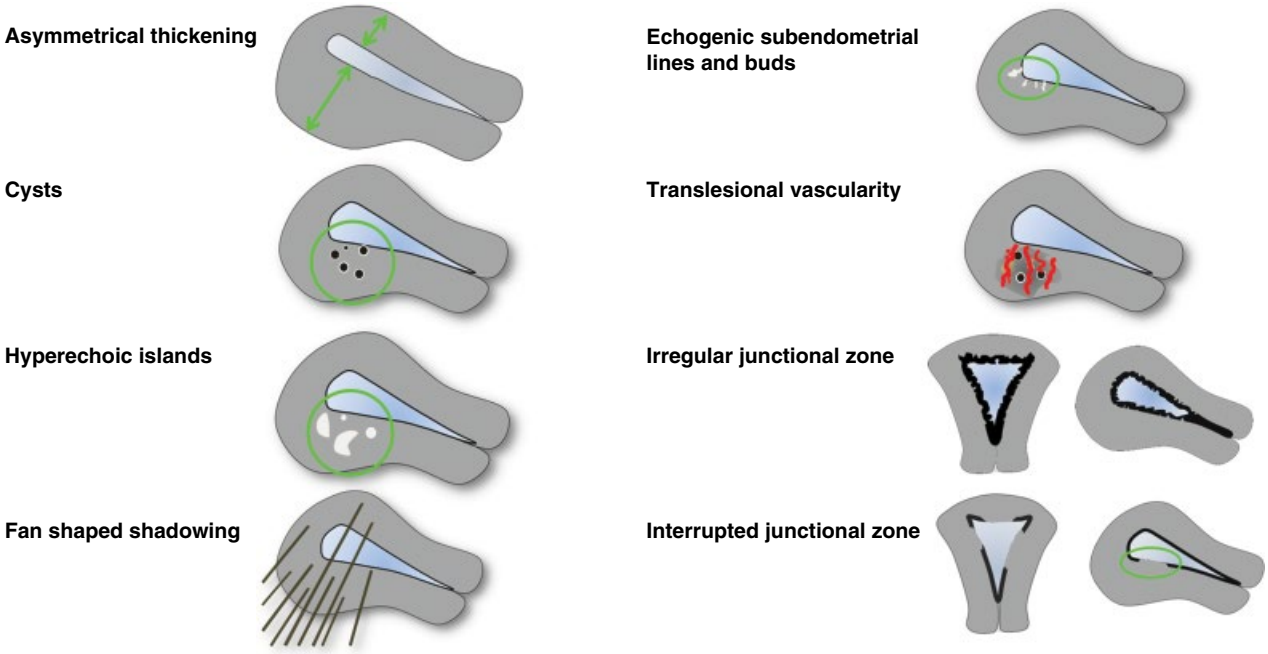


Fig. 59.1 Ultrasonographic features of adenomyosis. *Source:* Van den Bosch T, Dueholm M, Leone FP *et al.* Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. *Ultrasound Obstet Gynecol* 2015;46:284–298. Reproduced with permission of the International Society of Ultrasound in Obstetrics and Gynaecology.

et al. [11], the thickening seen on MRI relies on the disruption of the inner myometrial architecture secondary to smooth muscle hyperplasia but, unlike the ultrasound features, does not evidence mucosal invasion of the myometrium.

Treatment

The treatment is mainly symptomatic, and aims to relieve HMB and dysmenorrhoea. Various medical and minor surgical techniques have been shown to be of some benefit in the short term. Antifibrinolytics, non-steroidal anti-inflammatory drugs, the oral contraceptive pill and progestins may be considered as first-line methods of treatment. The levonorgestrel-releasing intrauterine system (LNG-IUS) has been shown to be effective for reducing uterine volume and relief of adenomyosis-related symptoms at 1 year, but the efficacy of this device declines with time [12]. Endometrial ablation is not used as a first-line treatment of adenomyosis as it fails to remove deeply infiltrating endometrial glands. It has been shown to improve menorrhagia and dysmenorrhoea in some women, and those with superficial disease have good results from this treatment option. Those with deeply infiltrating disease, however, tend to have persistent symptoms and, if conservative therapy fails, should be offered hysterectomy if fertility is not an issue [13].

The minimally invasive radiological technique of uterine artery embolization (UAE) is used in some centres for the treatment of symptomatic adenomyosis. It has been shown to be effective in the short term, but there is a high rate of symptom recurrence within 2 years of treatment [14].

Summary box 59.1

- Adenomyosis is a cause of menorrhagia, dysmenorrhoea and uterine enlargement.
- Its true prevalence is unknown, but it has been reported in 9–62% of hysterectomy specimens.
- Transvaginal ultrasonography is the primary diagnostic tool.
- Symptomatic medical treatment is the first-line management.
- Hysterectomy is the definitive treatment.

Endometrial polyps

Definition

Endometrial polyps are discrete outgrowths of the endometrium containing a variable amount of glandular tissue, stroma and blood vessels. Polyps may be pedunculated

or sessile, single or multiple. They are relatively insensitive to cyclical hormonal changes and thus are not shed at the time of menstruation. Hyperplastic or malignant foci within a polyp are infrequent. The incidence of cancer in asymptomatic women and in women with postmenopausal bleeding diagnosed with a polyp is 0.1–1.5% and 1.0–4.5%, respectively [15,16].

Epidemiology

In symptomatic women the prevalence of polyps is reported as ranging between 6 and 32% [17]. In the general population aged 20–74 years, Dreisler *et al.* [17] reported the presence of endometrial polyps in 7.8%, the occurrence being very low below age 30. In their study they did not find an association between the presence of polyps and abnormal bleeding.

Presentation

Postmenopausal uterine bleeding, HMB, intermenstrual bleeding, dysmenorrhoea and subfertility have been related to endometrial polyps.

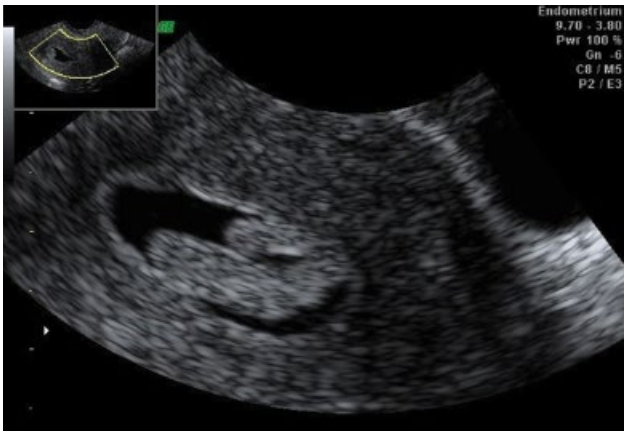
Diagnosis

Both fluid instillation sonography and hysteroscopy have a comparable diagnostic accuracy in detecting focal intracavitary lesions [18].

On transvaginal ultrasound examination a polyp typically is a relatively hyperechogenic lesion with or without small and regular internal cysts. The interface between the endometrium and the lesion often appears as a bright echogenic edge. On colour imaging a dominant vessel is often visible [19]. In a premenopausal woman with a spontaneous menstrual cycle, an echogenic polyp is more readily detected in the proliferative phase of the cycle, when the endometrium is more hypoechogenic (three-layer pattern). In women on hormonal therapy or who are postmenopausal, where timed examination is not feasible, instillation of fluid into the uterine cavity will create a negative contrast against which focal intracavitary lesions are easily visualized (fluid instillation sonography) (Fig. 59.2). Both saline infusion sonography and gel instillation sonography may be used [20].

Hysteroscopy enables direct visualization of the uterine cavity and is often considered the reference test. On hysteroscopy, polyps can be distinguished from pedunculated fibroids as they have fewer vessels over their surface. Malignant polyps are more likely to be irregular, vascular and/or friable. Hysteroscopic-guided biopsy

(a)



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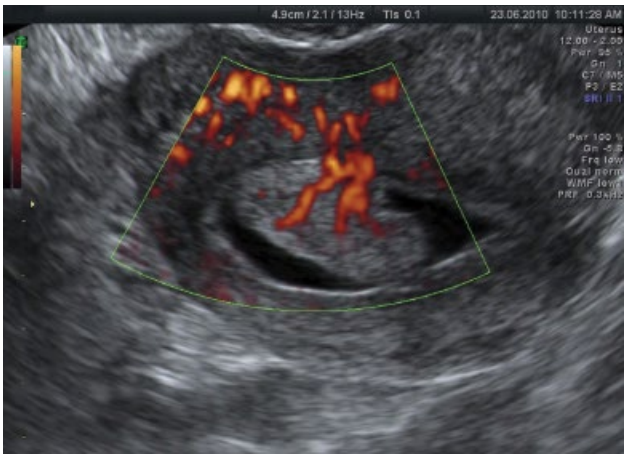


Fig. 59.2 (a, b) Fluid instillation sonography demonstrating endometrial polyps. On power Doppler imaging (b) the vascular pedicle is visible. (*See also colour plate 59.2*)

(preferably total excision of the lesion) and pathological analysis confirm the diagnosis, as visual appearance alone is insufficient.

Endometrial polyps are frequently missed with blind endometrial sampling, including dilation and curettage. There is no place for blind sampling without imaging in modern gynaecology [21,22].

Treatment

There is consensus that symptomatic women with endometrial polyps should undergo hysteroscopically guided removal under direct vision. In the vast majority this will result in cessation of the abnormal uterine bleeding [23]. The resection may be performed either under general anaesthesia or in an outpatient setting with or without local anaesthesia or sedation [24].

Summary box 59.2

- Endometrial polyps occur in about 25% of women who present with unscheduled vaginal bleeding.
- The most accurate tests for diagnosing polyps are fluid instillation sonography and hysteroscopy.
- There is no place for blind sampling in the diagnosis of focal intracavitary lesions.
- Treatment involves excision under direct vision (using hysteroscopy).

Uterine leiomyomata (fibroids)

Definition

Uterine leiomyomata or fibroids are the most common benign tumours of the female genital tract, arising from neoplastic transformation of single smooth muscle cells of the myometrium. They usually appear as well-circumscribed firm tumours with a characteristic white-whorled appearance on cross-section. Fibroids are paler than the surrounding myometrium and there is usually a very sharp line of demarcation between the tumour and the normal uterine muscle (Fig. 59.3).

Histologically, they are typically composed of varying proportions of spindled smooth muscle cells and fibroblasts. The size of fibroids varies greatly. The vast majority of fibroids are found in the corpus (body) of the uterus, but they may also occur in the cervix, uterine ligaments and ovary. Fibroids may be single but are commonly multiple and should be reported using the FIGO classification [25] (Fig. 59.4):

0 pedunculated intracavitary;
1 submucosal, <50% intramural;
2 submucosal, ≥50% intramural;
3 100% intramural, but in contact with the endometrium;
4 intramural;
5 subserosal, ≥50% intramural;
6 subserosal, <50% intramural;
7 subserosal pedunculated;
8 other (e.g. cervical, parasitic).

Incidence

The incidence of fibroids increases with age: it has been reported to occur in 20–40% of women during reproductive life and in as many as 70% of uteri removed at the time of hysterectomy [7]. Especially in postmenopausal women, conservative treatment including myomectomy, myoma morcellation, UAE or endometrial ablation [26] should be considered only after malignancy has been excluded [27,28].

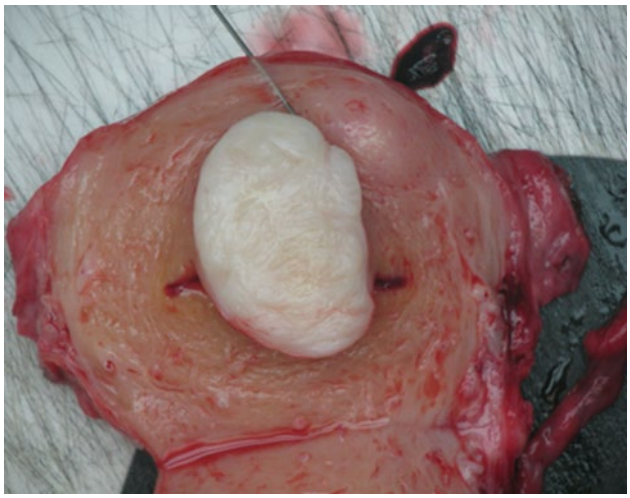


Fig. 59.3 Macroscopy: transverse section through the uterine corpus, with a fibroid. Figure courtesy of Ann Cornelis. (*See also colour plate 59.3*)

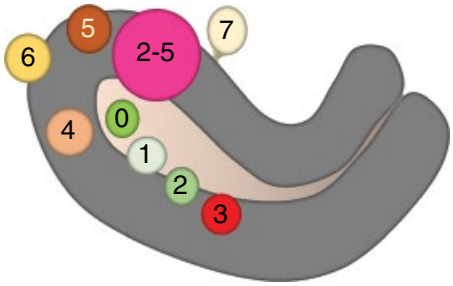


Fig. 59.4 FIGO classification for fibroid localization. *Source:* Van den Bosch T, Dueholm M, Leone FP *et al.* Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. *Ultrasound Obstet Gynecol* 2015;46:284–298. Reproduced with permission of the International Society of Ultrasound in Obstetrics and Gynaecology.

The incidence of malignancy (leiomyosarcoma) is 0.64 per 100 000 women per year and is extremely uncommon in women below the age of 40. Unlike a fibroid, which consists of spindled cells arranged in fascicles with abundant eosinophilic cytoplasm and uniform nuclei, a leiomyosarcoma is hypercellular and consists of atypical smooth muscle cells with hyperchromatic enlarged nuclei and shows increased mitotic activity and tumour cell necrosis [29]. However, the pathogenesis of leiomyosarcomas remains unclear and no evidence exists to suggest that fibroids undergo neoplastic change.

There are significant racial differences in the incidence of fibroids, with Afro-Caribbean women having a twofold to ninefold greater risk. In addition, they tend to present at a younger age compared with Caucasian women and have multiple fibroids and higher uterine weights and are more prone to both anaemia and severe pelvic

pain [30,31]. Reproductive factors also influence the risk of fibroids, with a reduction in incidence with increasing parity (beyond 24 weeks' gestation) and the prolonged use of the oral contraceptive pill [31,32]. Environmental factors also influence the risk of fibroid development. Independent of body mass index, smoking appears to decrease the risk of fibroid development [33,34].

Aetiology

The pathophysiology of fibroids remains poorly understood. Clonality studies using the homozygosity of glucose 6-phosphate dehydrogenase forms show that multiple tumours in the same uterus are derived from individual myometrial cells rather than occurring through a metastatic process. This, together with their high prevalence, suggests that initial development arises from a frequently occurring event, the nature of which is currently unknown. Growth of fibroids is partly dependent on the ovarian steroids that act through receptors present on both fibroid and myometrial cells. It is likely that the control of growth is due, in part, to alterations in apoptosis. Bcl-2, an inhibitor of apoptosis, is significantly increased in cultured leiomyoma cells. It is also influenced by the steroid hormone milieu.

Cytogenetic abnormalities occur in 40% of uterine fibroids. Most commonly, these involve translocation within or deletion of chromosome 7, translocations of chromosomes 12 and 14, and occasionally structural aberrations of chromosome 6 [35]. These cytogenetic abnormalities are not observed in normal myometrial tissue and may not be present in all the fibroids in a single uterus [36]. Abnormalities in uterine blood vessels and angiogenic growth factors are also involved in the pathophysiology of uterine fibroids. The myomatous uterus has increased numbers of arterioles and venules and is also associated with venule ectasia or dilatation. It has been noted that there are no mature vessels running through uterine fibroids despite the fact that they have a well-developed blood supply.

Control of growth

More information is available on the control of uterine fibroid growth than on the aetiology of these benign tumours. Growth factors are of importance in controlling the growth of fibroids and their composition. Higher concentrations of the angiogenic fibroblast growth factor have been found in fibroids than in the surrounding myometrium. In addition, the functions of transforming growth factor-β, granulocyte–macrophage colony-stimulating factor and epidermal growth factor (EGF), amongst others, have been shown to differ between fibroid and normal myometrial tissue [36].

As fibroids have not been identified in prepubertal girls and usually shrink at the time of the menopause, it has long been assumed that these lesions are dependent on the presence of the sex steroids, oestrogen and progesterone. The sex steroids act via receptors. The steroid combines with the receptor, which is then translocated to the nucleus of the cell. Studies have identified that steroid receptors are present in higher concentrations in fibroids than in the surrounding myometrium and that the concentration of receptors is significantly affected by the administration of agents which alter circulating estradiol concentration. Further work has centred on the relationship between steroid hormones and growth factors, such as EGF and insulin-like growth factor (IGF), which would appear to be important, possibly as mediators for oestrogen action. The number of progesterone receptors is greater in fibroids than in the surrounding myometrium. Like oestrogen, it has an impact on EGF receptor content and also suppresses apoptosis. Progesterone stimulates and inhibits fibroid growth, the former by upregulating EGF and Bcl-2 and downregulating tumour necrosis factor-α expression, the latter by downregulating IGF-1 [37].

Symptoms associated with uterine fibroids

It is estimated that only 20–50% of women with one or more fibroids will experience symptoms that are directly attributable to them. However, it is not always clear why some produce symptoms and others do not [7]. In the case of small fibroids, it is often the assumed that only those impinging on the uterine cavity cause symptoms. This may be a result of the presence of surface vessels on the fibroid and/or the resultant increased surface area of the uterine cavity.

Symptoms associated with fibroids may be variable, ranging from mild to severe, causing distress and impinging significantly on health-related quality of life. Women commonly present with menstrual problems, particularly HMB [38]. Dysmenorrhoea may be an additional problem leading to a further negative impact on a woman's health. Not all women will present with a menstrual problem, some experiencing symptoms related purely to the size of the fibroid. This may be a dragging sensation or feeling of pressure in the pelvis, abdominal swelling or urinary symptoms. Table 59.1 highlights the commonly encountered symptoms associated with fibroids. The relationship between fibroids and fertility is discussed in Chapters 51 and 52.

Diagnosis

The uterus is often found to be enlarged and presents as a pelvic mass (often central and mobile) on both abdominal and vaginal examination. However, it may

Table 59.1 Presenting symptoms of uterine fibroids.

Menstrual upset: menorrhagia and/or dysmenorrhoea
Abdominal discomfort
Sensation of pelvic pressure or backache
Abdominal distension
Urinary frequency, difficulty in micturition, incomplete bladder emptying or incontinence
Bowel problems such as constipation
Reproductive dysfunction: difficulty in conceiving, pregnancy loss, postpartum haemorrhage

be difficult to distinguish between an enlarged uterus and an ovarian mass and so further imaging is mandatory. Ultrasonography, especially transvaginal, is very useful as a first-line diagnostic test (Fig. 59.5). Fibroids are typically well-defined round or lobulated myometrial lesions. The echogenicity is highly variable: it may be uniform hypoechogenic, isoechogenic or hyperechogenic as compared with the surrounding myometrium, or non-uniform due to mixed echogenicity, internal hyperechogenic spots or calcifications. These calcifications may cause intense shadowing. On colour Doppler a fibroid typically has circumferential vascularization, and sometimes some internal vascularization.

Abdominal ultrasound and MRI may be of additional value in the case of larger fibroids. MRI is useful for examining large fibroids or in obese women where adequate imaging on transvaginal or transabdominal ultrasonography is precluded, or in cases of suspected malignancy. There are no pathognomonic features for a leiomyosarcoma on any imaging technique. A large (≥8 cm), solitary, oval-shaped, heterogeneous myometrial tumour, with strong and irregular vascularization, central necrosis/degenerative cystic changes and absence of calcifications should raise the suspicion of a leiomyosarcoma. Rapid increase in size has been reported in leiomyosarcoma. MRI with gadolinium enhancement gives an indication of the vascularity and may prove helpful in differentiating between a leiomyosarcoma and a fibroid. Total lactate dehydrogenase (LDH) and LDH isozyme 3 are reportedly elevated in leiomyosarcoma. Elevated CA125 levels are seen in advanced-stage leiomyosarcoma only [27,28].

Treatment of uterine fibroids

The management of fibroids depends on the symptoms, the type and size of the fibroid, the patient's age and the desire to preserve fertility. Surgical treatment includes hysterectomy and myomectomy. Medical treatments do not eradicate fibroids but are designed to provide symptomatic relief.

Medical treatment

Gonadotrophin-releasing hormone agonists

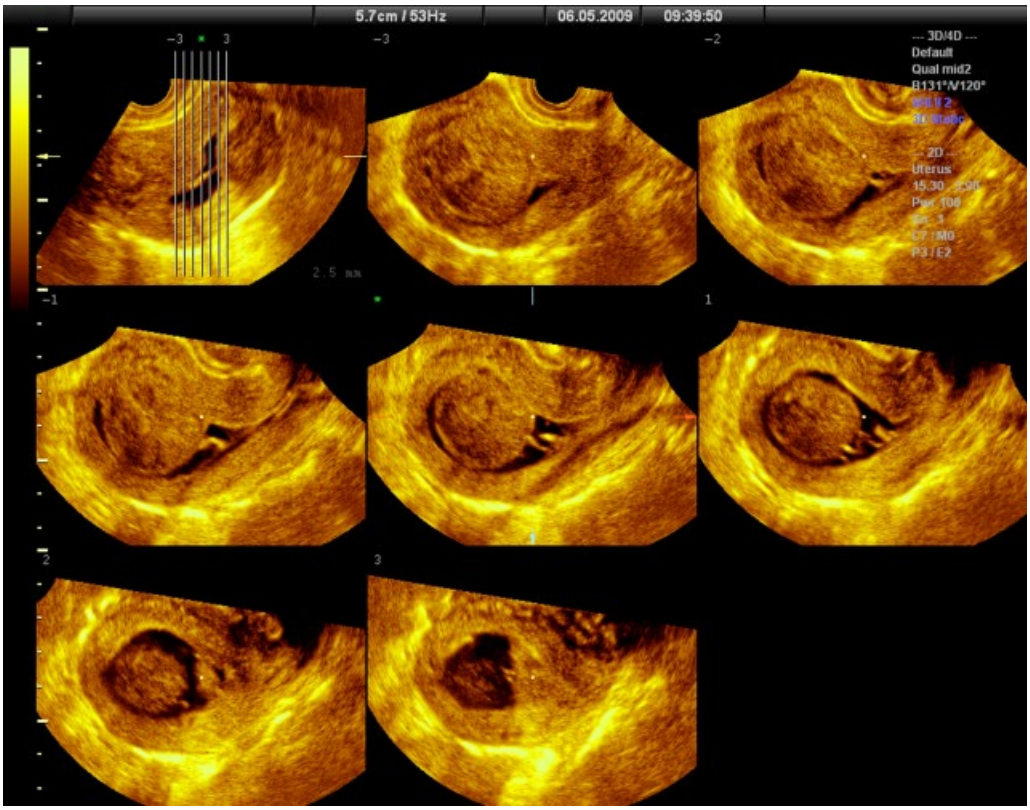
The most established medical option is administration of a gonadotrophin-releasing hormone (GnRH) agonist. These drugs lead to the downregulation of pituitary receptors that result initially in stimulation of gonadotrophin release, followed by gonadotrophin output reduction and consequent reduction in ovarian steroid production within 2–3 weeks of commencing treatment. The decreased output of ovarian steroids continues while treatment is ongoing. These analogues are given as 1- or 3-monthly depot injections or as nasal spray. Fibroid shrinkage occurs rapidly in the first 3 months but then tends to slow down with little further decline. Most studies suggest a fibroid volume reduction of 40% [39]. The principal disadvantages of GnRH analogue administration are that the fibroids regrow when treatment has stopped. In addition, they are associated with postmenopausal side effects consisting of hot flushing, vaginal dryness and, with prologed use, significant bone loss. An 'add-back' therapy by administering low-dose oestrogen replacement therapy counteracts these side effects without inducing fibroid regrowth.

GnRH agonists have a licence for use in the UK in women with severe anaemia. Their administration results in amenorrhoea, which is associated with a significant increase in haemoglobin. Agonists are also useful prior to surgery [40,41], for example enabling a hysterectomy to be carried out vaginally, with or without laparoscopic assistance. GnRH agonists have also been used prior to myomectomy for similar reasons. However, it is important to note that the plane of cleavage between the fibroid and the surrounding myometrium can be masked after preoperative use, making the surgery significantly more difficult.

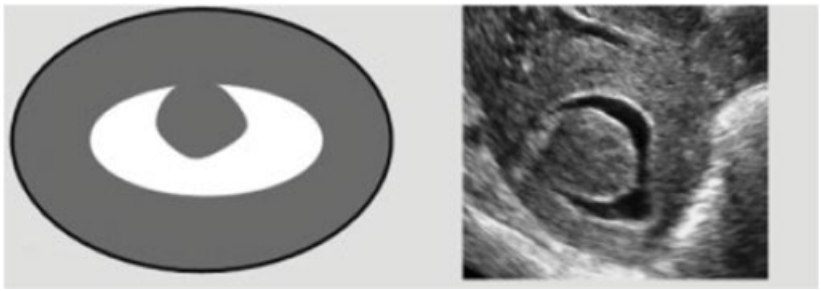
Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are effective in reducing pain, bleeding and fibroid size, and are associated with an improvement in quality of life [37,42]. Unlike GnRH analogues, SPRMs do not lead to oestrogen deficiency and do not cause hot flushes, nor osteoporosis. Short-term administration appears to be safe and these preparations may influence the way we treat symptomatic fibroids in the future [43].

The SPRM ulipristal acetate reduces the proliferation of leiomyoma cells and induces apoptosis [44]. Moreover, it inhibits neovascularization, cell proliferation and cell survival in the fibroid but not in the normal surrounding myometrium. Side effects include headache and breast tenderness. The progesterone antagonist action may lead to unopposed oestrogen stimulation of the endometrium. Administration for a longer period may lead to endometrial thickening. Progesterone



(a)



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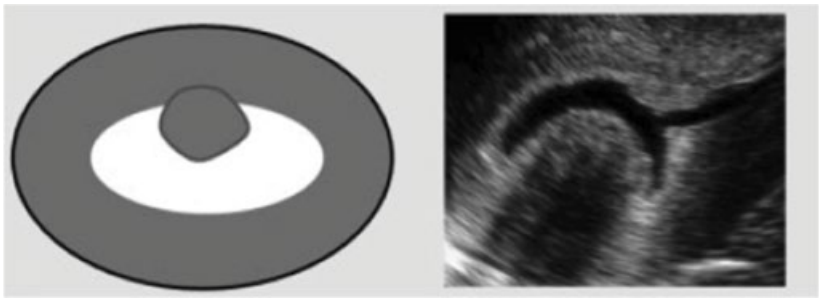

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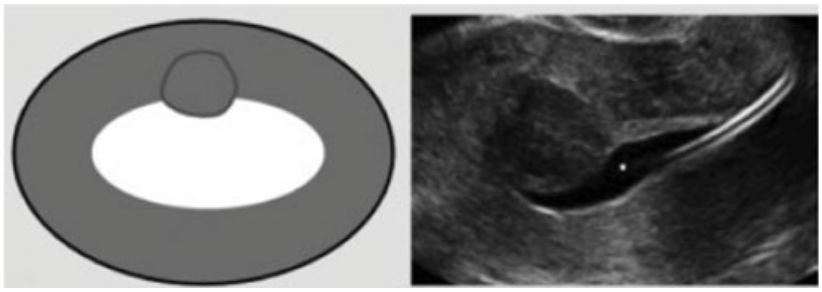

Fig. 59.5 Fluid instillation sonography showing an intrauterine fibroid [44]. Reproduced with permission of John Wiley and Sons. (*See also colour plate 59.5a*)

receptor modulator-associated endometrial changes (PAEC) characterized by cystic glandular dilatation should be distinguished from endometrial hyperplasia. Long-term studies are needed to evaluate outcomes after prolonged use.

Levonorgestrel-releasing intrauterine system

LNG-IUS has revolutionized the treatment of dysfunctional uterine bleeding and may be one of the reasons why the hysterectomy rate has declined over recent years. However, the use of this system in women with fibroids is considered to be a relative contraindication, partly because the device is more likely to be expelled during a very heavy bleeding episode and because the presence of a distorted uterine cavity may make insertion of the device more difficult and increase the expulsion risk.

Intuitively, if the cavity is regular, a trial with an LNG-IUS system may be appropriate. However, coil placement should be checked after a very heavy bleeding episode to exclude expulsion.

Other medical treatments tending to reduce menstrual bleeding without effect on fibroid size include progestogens, the oral contraceptive pill and tranexamic acid.

Surgical treatment

Hysterectomy

Hysterectomy remains the most common surgical treatment option for uterine fibroids. It ensures immediate and definitive resolution of fibroid-associated symptoms. However, it also guarantees infertility, which may not be an appropriate option for some women. Moreover, it is associated with significant morbidity, a relatively long inpatient hospital stay and prolonged recovery period. Major complications occur with hysterectomy and data from a large UK audit (the VALUE study) suggest that complications are all increased in the presence of uterine fibroids [46].

Myomectomy

In women who wish to retain their fertility, uterine-sparing options must be considered. The first of these is myomectomy, which involves the selective removal of the fibroid. This can be carried out as an open/abdominal, laparoscopic or hysteroscopic procedure. Intracavitary fibroids (FIGO type 0, 1 and some type 2) lend themselves to hysteroscopic removal, which decreases blood loss and improves fertility. The feasibility of hysteroscopic resection depends on fibroid location (FIGO classification), size and number and on the surgeon's skills. Complications during hysteroscopic myomectomy include uterine perforation and the associated potential for visceral damage, haemorrhage, infection and fluid overload.

Some of these issues are likely to be even more significant when laparoscopic myomectomy is performed. Rupture of the uterus in labour is also a risk after myomectomy if the cavity is breached during the myomectomy.

Uterine artery embolization

UAE is a minimally invasive radiological technique. Pelvic arterial embolization has been used in the treatment of massive obstetric haemorrhage for more than three decades, and was first reported by the French gynaecologist Ravina [47]. UAE involves the cannulation of the common femoral artery with a small plastic tube that is fed around the aortic arch, through the iliac vessels and thereafter into the contralateral internal iliac artery and corresponding uterine artery. Multiple particulate material (usually in the form of polyvinyl alcohol) is then injected into the circulation to effect embolization and thus cease flow beyond the level of the uterine artery. Visualization of the latter is facilitated by the use of a contrast medium and digital fluoroscopy. The procedure may be performed under local anaesthesia, or under intravenous conscious sedation. Opiate analgesia is usually required up to 24 hours following treatment and most women are managed thereafter with oral analgesia, returning to normal activities within 2 weeks of the procedure.

For poorly understood reasons, the blood supply to the normal myometrium renews itself via the rich pelvic collateral circulation, with contributions from ovarian and vaginal arteries. However, the fibroids do not usually revascularize to a significant extent. This leads to shrinkage of the fibroids and subsequent relief of fibroid-related symptoms. In contrast to the effects of GnRH agonists, where shrinkage of fibroids is maintained only as long as treatment continues, embolization results in sustained shrinkage.

There has been much discussion in the literature regarding the pros and cons of UAE [48]. Observational data suggest that there is a significant beneficial effect on menstrual blood loss and bulk-related symptoms [48,49]. Patient satisfaction rates following the procedure are also high and comparable to those found after hysterectomy. More recent data suggest that in addition to the shorter hospital stay and recovery period associated with UAE, improvements in health-related quality of life are also sustained in the long term after UAE [51]. Another significant benefit of embolization is uterine conservation, and thus preservation of fertility.

The average uterine shrinkage is 40%, although in some instances this can be greater. A cervical or submucosal fibroid may also pass vaginally in the weeks or months following treatment, resulting in an anatomically normal uterus. However, variable recurrence rates for fibroids have been reported after embolization as occurs with myomectomy [52]. Unlike hysterectomy, there is no

guarantee that the procedure will eliminate all menstrual symptoms and revascularization with subsequent regrowth of fibroids does occur in some women. Nonetheless, most case series report improvements in HMB of 85–88% at 1 year [52]. More recently, longer-term data from randomized trials have been published, stating that health-related quality-of-life measures improve significantly and remain stable at 5-year follow-up evaluation [53].

Some women may require further treatment with hysterectomy, myomectomy, endometrial ablation or a repeat embolization. Importantly, with increasing long-term follow-up, it appears that such reinterventions associated with UAE occur more often than previously suggested, with rates of 28% being reported at 5 years [53].

A number of complications (Table 59.2) may be associated with embolization and these may be serious, particularly if severe sepsis occurs.

In approximately 10% of women, the post-embolization syndrome occurs 7–10 days after the procedure. It consists of a flu-like illness and is characterized by general malaise and pelvic pain in association with a mild pyrexia and raised white cell count. This is not as a result of infection but is thought to be due to cytokine release at the time of necrosis of the fibroid. The syndrome is often very difficult to distinguish from infection and is treated with a combination of analgesia, adequate hydration, prophylactic antibiotics and reassurance.

Another significant problem resulting from embolization is infection. Most women require a simple course of antibiotics but, rarely, sepsis may occur, a complication that may lead to the patient's death.

There is a radiation penalty to the ovaries associated with the procedure which occurs during digital fluoroscopy. This, in combination with disruption of uterine blood flow and with non-target embolization, may increase the risk of premature ovarian failure. Reassuringly, however, recent studies demonstrate that there is no evidence for UAE accelerating a decline in ovarian function at 1 year following treatment when compared with surgery, irrespective of age [54,55].

Table 59.2 Complications of uterine artery embolization.

Groin injury: haematoma, infection
Contrast allergy
Radiation exposure to ovaries
Non-target or mis-embolization: ovary, bowel or bladder
Fibroid expulsion
Persistent vaginal discharge
Amenorrhoea: secondary to premature ovarian failure, endometrial atrophy or intrauterine adhesions
Ovarian failure
Post-embolization syndrome
Infection
Sepsis requiring emergency hysterectomy (occurs in <1%)
Death (rare)
Treatment failure: failed cannulation, revascularization or regrowth of fibroids

There are some studies reported in the literature of pregnancies. While some suggest that the outcome is not adversely affected [56], others report increased rates of miscarriage, intrauterine growth restriction, preterm delivery, malpresentation and postpartum haemorrhage following embolization [57].

While a few non-randomized studies have assessed UAE versus myomectomy [58], a randomized study suggests that of the two treatment options, myomectomy is associated with superior reproductive outcomes in the first 2 years after treatment in terms of miscarriage, pregnancy and labour rates. Perinatal outcomes were similar [59].

The cost-effectiveness of UAE versus surgery has been studied. Short-term data reported embolization to be more cost-effective at 1 year [60], but more recent unpublished studies suggest that owing to reintervention and return visits to hospital after UAE, both embolization and surgery are cost-neutral in the long term.

Ablation procedures

Endometrial ablation may be performed with or without myomectomy and is associated with a high rate of amenorrhoea. Provided that the uterine cavity is not too enlarged or distorted, ablation appears to be a successful option. It would seem that microwave and bipolar radiofrequency endometrial ablation may be the best of the second-generation techniques, although randomized data looking at fibroids in particular are not available [61].

A new transcervical device (VizAblate®) is currently available, allowing radiofrequency ablation of fibroids under real-time sonographic guidance. The first reports have shown a significant reduction in fibroid size, together with symptomatic relief in the first 12 months after the procedure [62].

High-intensity focused ultrasound

With high-intensity focused ultrasound (HIFU), an extracorporeal source of focused ultrasonic energy is used to induce coagulative necrosis in the fibroid, without damaging the surrounding tissues. The procedure is MRI-guided to monitor the exact anatomical location of the target lesion and the temperature within the lesion as well as in the surrounding tissues [63]. Recently, sonographically guided HIFU has also been introduced [64]. HIFU of the target lesion causes tissue destruction by a thermal effect, cavitation and direct damage to the lesion's blood vessels. Unlike UAE, HIFU

is not associated with an infarction-like syndrome. Quality-of-life symptom severity scores are similar to those associated with UAE, but the impact of treatment on HMB is less than for embolization [65]. This modality is neither suitable for large fibroids nor large numbers of fibroids, and its impact on the recurrence rate of these benign tumours is unclear.

Summary box 59.3

- Fibroids occur in 25% of women during reproductive life.
- Aetiology is poorly understood.
- Symptoms include menorrhagia, bulk-related problems and reproductive dysfunction.
- Diagnosis is by clinical examination and transvaginal ultrasound.
- Abdominal ultrasound and MRI may be of additional value in the case of larger fibroids.
- GnRH analogues with add-back therapy or SPRMs may be used in the short term or as a useful adjunct to surgery in the presence of large fibroids or associated anaemia.
- The LNG-IUS or endometrial ablation may considered in the presence of a fibroid uterus which is no more than 14 weeks in size in the absence of significant uterine cavity distortion.
- Myomectomy permits uterine conservation but is associated with fibroid regrowth and subsequent adhesion formation.
- Hysterectomy remains a good treatment option for some women but is associated with significant morbidity, a prolonged hospital stay and recovery, and induces infertility.
- UAE is an alternative to surgery for symptomatic fibroids.

Conclusions

Benign gynaecological disease is common and may cause women many problems, some of which can have a significant impact on quality of life. The treatment options for uterine fibroids include hysterectomy, myomectomy, minimally invasive modalities (e.g. UAE, ablation techniques, HIFU) and medical treatment (e.g. GnRH analogues, SPRMs). The treatment choice will be made together with the patient according to fibroid characteristics, the symptoms, the patient's age and the wish to preserve fertility.

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Part 15

Gynaecological Cancer

60

Malignant Disease of the Vulva and the Vagina

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Background

Vulval carcinoma is uncommon. In 2013, just over 1300 cases were registered in the UK, making it the twentieth most common malignancy (Table 60.1). The lifetime risk of developing vulval cancer is now estimated at 1 in 275. Age-specific incidence rates rise gradually from around age 35–39, and more sharply from around age 65–69, reaching the highest rates in the 90+ age group [1]. The age-standardized incidence of vulval squamous cell carcinoma is 2.5 per 100 000 women per year in England and 2.4 per 100 000 in the USA [2].

There appears to be an association between vulval cancer incidence and social deprivation. The estimated deprivation gradient in vulval cancer incidence between females living in the most and least deprived areas in England has widened in the period 1996–2010 [1]. It has been estimated that there would have been around 240 fewer cancer cases each year in England during 2006–2010 if all females experienced the same incidence rates as the least deprived [1].

Vulval cancer mortality rates have decreased in the UK, an observation noted since the early 1970s. European age-standardized mortality rates decreased by 43% between 1971–1973 and 2010–2012, with most of this decline occurring before the late 1990s. This trend can mainly be attributed to improvements in treatment and earlier diagnosis [3,4]. Over the last decade (between 2001–2003 and 2010–2012), European age-standardized mortality rates have remained stable [5]. The West Midlands Cancer Registry UK, which covers a population of 5.6 million, has reported rates for cases registered between 2001 and 2005, with a 5-year relative survival of 80.5% in women aged under 65 at diagnosis and 61.6% in older women; the corresponding figures from the SEER programme for cases diagnosed in the USA in 2004 were 81.6% and 70.6% [6]. In neither dataset is there evidence of an increase in relative survival over time in these age groups.

There has been a significant increase in rates of vulval cancer in younger women. The proportion of cases diagnosed in those under the age of 50 years rose from 6% in 1975 to 15% in 2006 [1]. A similar trend has been documented in other countries [7,8]. These tumours appear to be more frequently associated with vulval intraepithelial neoplasia (VIN), human papillomavirus (HPV) infection, and immunosuppression. In older women they are more frequently associated with non-neoplastic epithelial disorders such as lichen sclerosus. This suggests that there are at least two oncogenic pathways for the development of this cancer.

The overall increase in vulval cancer might be explained by the rise in the average age of the female population and possibly because of an increase in HPV infection in younger women.

Risk factors

The following are recognized as risk factors for developing vulval cancer.

- Lichen sclerosus: 4–7% risk of developing cancer [9,10].
- Vulval cancer develops in 9% of women with untreated high-grade VIN, 1–8 years after their VIN diagnosis, a systematic review suggested [11].
- Paget's disease [12].
- Melanoma *in situ* [13–15].
- Smoking [16].
- Immunosuppression.
- Advanced age.
- Cohort studies have shown that vulval/vaginal cancer risk is four to eight times higher in cervical cancer survivors [17–19]. Other cohort studies have shown

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 60.1 Vulval cancer (C51), number of new cases, crude and European age-standardized incidence rates per 100 000 population, females, UK, 2013 (Cancer Research UK).

	England	Wales	Scotland	Northern Ireland	UK
Cases	1061	78	142	32	1313
Rate per 100 000	3.9	5	5.2	3.4	4
Age-standardized rate per 100 000	4 (3.7–4.2)	4.8 (3.7–5.8)	5.1 (4.3–5.9)	3.8 (2.5–5.2)	4.1 (3.9–4.3)

that vulval cancer risk is two to six times higher in women with previous cervical intraepithelial neoplasia (CIN) [20].
- A cohort study showed that vulval cancer risk is higher in women whose sister or mother has/had cervical squamous cell carcinoma [21]. The association between cervical and vulval cancers is probably mainly due to shared risk factors (e.g. HPV).

Aetiology

The aetiology of vulval cancer remains unknown. However, oncogenic HPVs are strongly associated with some vulvar cancers [22] and non-neoplastic epithelial disorders (lichen sclerosus) with others. Currently available data suggest two hypotheses. First is the classic *de novo* neoplasm in the elderly that is frequently seen in association with conditions such as lichen sclerosus. The second type is more often associated with VIN, particularly multifocal disease and disease elsewhere in the lower genital tract. This 'infectious-like' type is presumed to be linked to HPV.

Recently it has been suggested that non-HPV VIN or differentiated VIN might be the precursor lesion associated with lichen sclerosus and therefore non-HPV squamous cell cancers. Previously it had been thought that differentiated VIN was found only in association with established cancers, but it has now become clear that this type of VIN can and does occur without contemporaneous cancers but usually with lichen sclerosus. This observation provides additional support for the two oncogenic pathways hypotheses [22]. Recent studies have focused on the genetic, epigenetic and molecular changes in vulval squamous cell carcinoma and associated lichen sclerosus [23]. Many studies have reported significantly higher incidences of somatic mutations in HPV-negative tumours compared with their positive counterparts, *TP53* being the most frequent. Epigenetic changes have also been identified and hypermethylation appears to be a common event in lichen sclerosus [24].

An understanding of premalignant epigenetic changes offers the opportunity of either reducing or even reversing the dysplastic process in vulvar epithelium.

Histology

The majority of vulvar cancers are squamous in origin. The various histotypes include:

- squamous cell carcinomas;
- malignant melanoma;
- Paget's disease;
- Bartholin's gland carcinoma;
- adenocarcinomas;
- sarcomas (dermatofibrosarcoma protuberans, Kaposi's sarcoma); and
- metastatic malignant disease and lymphomas.

Verrucous cancer and basal cell cancer are variants of squamous cell carcinomas. Non-squamous cancers of the vulva account for 10% of all vulval cancers. Histology does have a bearing on management, largely because of the different risks of nodal metastases and the predilection for distant spread (Fig. 60.1 and Table 60.2).

Summary box 60.1

- Vulval carcinoma is an uncommon tumour that is most common in the elderly.
- There is evidence suggesting a gradual increase in the number of younger women with this disease.
- There are likely to be two distinct carcinogenic processes, one linked to oncogenic papillomaviruses and the other to conditions such as lichen sclerosus.
- The majority of vulval cancers are squamous.

Presentation

Most squamous cancers primarily involve the medial aspects of the labia majora, with the labia minora being involved only one-third as often. Other sites of predilection include the clitoral and periurethral areas. Small lesions may be asymptomatic and go unnoticed by the patient, and even now there would appear to be excessive delay in diagnosis for some women. A recent review of practice in the West Midlands suggests that up to one- third of patients apparently report symptoms for over a year.

Fig. 60.1 Histological variants of vulval cancer.

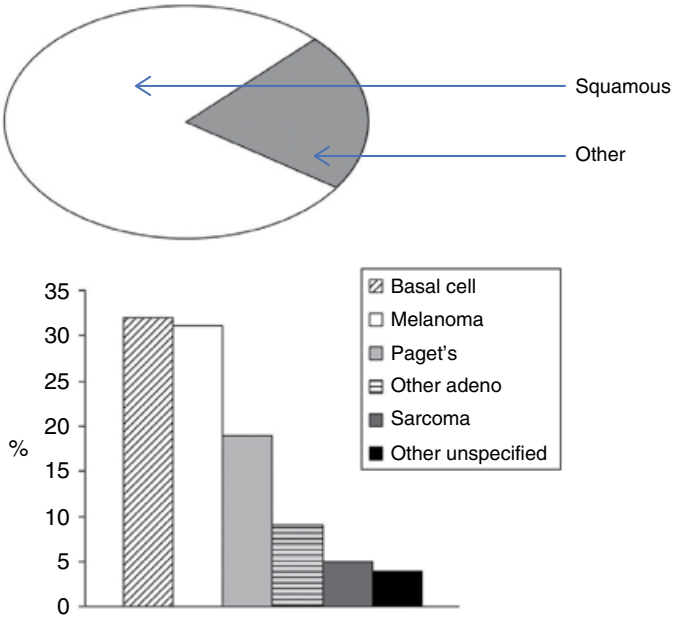


Table 60.2 Summary of histological variants.

Histotype	Comments
Squamous cell carcinomas	Account for 90% of malignant vulval neoplasms
	Metastasize to the local lymph nodes, primarily the superficial and deep inguinal nodes, and they may be involved bilaterally. The risk of nodal disease varies with location and degree of invasion
	Usually present with a nodule or ulcer and may cause pruritus or soreness and pain. Bleeding and an offensive odour may be present with larger lesions
Veruccous and basal cell carcinomas	Squamous variants and rarely, if ever, metastasize locoregionally
	Verrucous carcinomas present as slow-growing wart-like lesions with a tendency to recur locally after excision
	Basal cell carcinomas usually present as an ulcerated nodule on the labia. They do not metastasize and can be managed by local excision or radiation. Up to 20% recur locally after treatment
Malignant melanoma	Has a poor prognosis and is generally managed as for cutaneous melanomas at other sites
	The overall 5-year survival ranges between 8 and 50% and appears to be worse than for cutaneous melanomas elsewhere
	Three patterns of vulval melanoma are identified: mucosal lentinginous (commonest), superficial spreading and nodular. Breslow's thickness of invasion (invasion >1.75 mm has a high risk of recurrence), ulceration and amelanosis are significant prognostic factors. Surgical excision of the lesion with wide margins remains the mainstay of treatment. c-Kit expression another valuable predictor of prognosis and survival
Adenocarcinomas	Exceedingly rare and are more likely to represent metastases from another site. There is an association with vulval Paget's disease
Carcinoma of Bartholin's gland	Also rare and may be squamous, adenocarcinoma or an adenoid cystic carcinoma. They occur more often in younger premenopausal women and overall have a survival rate of about 35% at 5 years
	They usually present as a solid mass in the region of Bartholin's gland with intact overlying skin. Surgical management is similar to that for squamous cell carcinoma
Sarcomas	Very uncommon and in general are biologically similar to soft-tissue sarcomas at other sites. Generally there is poor prognosis after the appearance of regional or distant relapse. Wide local excision appears to offer the best chance of preventing local recurrence. Elective treatment of the regional nodes is not indicated and there is no advantage in resecting metastatic nodes. The role of adjuvant radiation and chemoradiation has not been assessed, largely because of its rarity
Metastatic tumours	Rare and account for about 8% of all vulval neoplasms. Cervix, endometrium and renal carcinomas have been the most frequently documented primary sites
Paget's disease	Presents as a crusty, erythematous, dark pink/red eczematous 'glazed' area on the vulva. It is an intraepithelial malignancy in 90%. Up to 10–15% of vulval Paget's disease is associated with underlying adenocarcinoma, which may be of the breast, stomach, bowel and bladder. Fluorescein dye has been used to detect the lateral extent of disease spread. Wide local excision with closure of large defects with advancement flaps is required to manage this condition

Table 60.3 Presenting symptoms in vulval carcinoma.

Symptoms	Frequency (%)
Pruritus	71
Vulval lump or swelling	58
Vulval ulceration	28
Bleeding	26
Pain or soreness	23
Urinary tract symptoms	14
Discharge	13

This may reflect patients' attitudes in seeking medical attention or, as suggested by Stroup *et al.* [25], a lack of awareness of the disease in both patients and clinicians. This study also suggested that older patients were more likely to be diagnosed with advanced disease. A more recent US-based study [26] came to similar conclusions, with advancing age and social deprivation both being associated with more advanced stage at diagnosis.

As squamous cell carcinoma of the vulva often progresses slowly, early disease presentation should be feasible and could enable diagnosis to be made at a less advanced stage. Both younger patient age and early disease stage are associated with favourable disease outcome. Therefore, efforts should be considered that improve both patient and primary care awareness. This observation is not new – Monaghan reported that 32 of 335 patients delayed seeking medical attention for more than 24 months, and only 35 of 335 presented within 3 months of noticing symptoms [27]. Similar delays ranging from 1 to 36 months, with a mean of 10 months, were noted by Hacker *et al.* [28]. Whether this is due to fear or ignorance on the part of the patients or to delay in clinical examination by the primary carer is unknown. A recent study, based on the first English National Audit of Cancer Diagnosis in primary care, analysed the patient and primary care interval in 10 953 patients covering 28 different cancer sites, including vulval cancer. The mean patient referral interval (patient time to present to GP) was 59 days, the fifth longest for the study cohort. The mean interval from consulting a GP to referral was 16 days, the third shortest referral interval [29]. These data imply that a significant burden of the delay lies in women not presenting to their GPs and thus a fairly robust case can be made for improved lay education. The reasons for presenting have been analysed by Podratz *et al.* [30] (Table 60.3).

Other indications for suspecting malignancy include pigmentation disorders relating to potential melanoma and melanoma *in situ*. This appears to be increasing although evidence so far is only anecdotal, but could reflect the growing awareness by the public of moles and other pigmented skin lesions and their association with malignant melanoma.

Assessment

There are two phases of investigation. First, confirming the diagnosis and histotype. The initial disease assessment should also include the clinical and histopathological extent of disease (stage). Second, the patient's fitness needs to be assessed, as does the possibility of concurrent disease, which might influence management. Although not disease focused the second phase is equally important, as the age range of patients with this disease makes comorbidity and frailty important variables when designing management strategies.

Examination

The clinical assessment of a vulval malignancy should document both the size and location(s) of all the lesions and the characteristics of the adjacent skin. Care should be taken to assess any involvement of the vagina, urethra, and base of bladder or anus. Palpation is important with large tumours to determine whether the tumour is infiltrating deep to the pubic and ischial bone. The integrity of the anal sphincter can only be reliably assessed by a combined rectal and vaginal examination.

Discomfort and tenderness are often associated with large tumours, necessitating examination under general anaesthesia. The presence or absence of groin lymphadenopathy or discrete skin metastases should also be noted.

Diagnosis

Diagnosis is based on a representative biopsy of the tumour that should include an area where there is a transition of normal to malignant tissue. Biopsies should be of a sufficient size to allow differentiation between superficially invasive and frankly invasive tumours and orientated to allow quality pathological interpretation. Occasionally an alternative strategy might be considered. In certain situations where the clinical diagnosis is apparent and the patient is very symptomatic (i.e. experiencing heavy bleeding and/or pain), definitive surgery to the vulval lesion may be performed. However, biopsy with frozen section is recommended before performing any radical procedure.

Because of the potential for other genital tract malignancy, the vagina and cervix should also be thoroughly assessed and biopsied as necessary.

Spread

The major histotype will determine, to a certain extent, how the tumour invades and metastasizes. The following comments relate to the most common squamous variant.

The tumour spreads both locally and via the lymphatics to the regional lymph nodes. Local spread may involve the vagina, perineum and anal canal, urethra and clitoris and, in

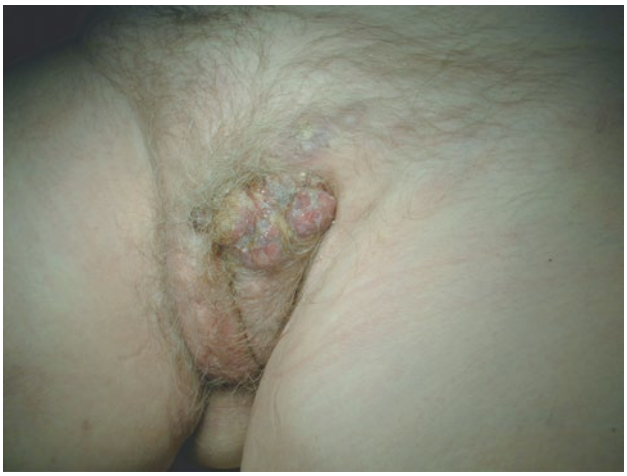


Fig. 60.2 Large anterior vulval cancer with satellite skin deposits. (*See also colour plate 60.2*)

late disease, involvement of bone may occur. The sites and extent of spread as well as the involvement of structures where function may be impaired (anal sphincter, urethra, clitoris, etc.) are of extreme importance when planning treatment. Skin beyond the vulva may also become involved (Fig. 60.2), particularly over the mons onto the lower abdominal wall and laterally to involve the skin of the thighs. Lymphatic drainage of the vulva is initially to the superficial inguinal nodes, thence to the deep inguinofemoral chain and on to the pelvic (iliac) nodes. In general, central vulvar structures are believed to drain bilaterally whereas lateral structures drain to the ipsilateral nodes primarily. Deep pelvic node involvement in the absence of inguinal node disease is rare. Overall, about 30% of operable patients have nodal spread, 10–15% with tumours measuring 4 cm or less in diameter and more for higher-stage tumours [31–33]. Haematogenous spread can also occur but is uncommon and tends to be associated with large tumours that have already involved the regional nodes.

Premalignant and malignant change in the vagina and cervix is not infrequently seen in association with vulvar cancers. This is not necessarily a metastatic process but may indicate a common aetiological event such as oncogenic HPV infection that can render the whole lower genital tract vulnerable to neoplastic transformation.

Staging

Vulval cancer is staged surgico-pathologically using the FIGO staging system, last updated in 2009 [34]. FIGO staging employs the familiar four categories with substages but now takes into account the number of positive nodes and type of nodal positivity. It also recognizes that tumour size on its own has little discriminatory value in terms of survival, large node-negative tumours having almost as good an outcome as small node-negative tumours (Table 60.4). An alternative is the tumour node metastasis (TNM) system, which is a composite of primary tumour, nodal and metastatic status (Table 60.5). Both systems employ nodal status to allocate stage.

Table 60.4 International Federation of Gynecology and Obstetrics (FIGO) staging of vulval cancer (2009).

Stage I	Tumour confined to the vulva
Ia	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1 mm. No nodal metastasis
Ib	Lesions >2 cm in size or with stromal invasion >1 mm confined to the vulva or perineum. No nodal metastasis
Stage II	Tumour of any size with extension to adjacent perineal structures (lower third of urethra; lower third of vagina; anus) with negative nodes
Stage III	Tumour of any size with or without extension to adjacent perineal structures (lower third of urethra; lower third of vagina; anus) with positive inguinofemoral nodes
IIIa	With one lymph node metastasis (≥5 mm), or one or two lymph node metastases (<5 mm)
IIIb	With two or more lymph node metastases (≥5 mm), or three or more lymph node metastases (<5 mm)
IIIc	With positive nodes with extracapsular spread
Stage IV	Tumour invades other regional (upper two-thirds of urethra; upper two-thirds of vagina) or distant structures
IVa	Tumour invades any of the following: upper urethral and/or vaginal mucosa; bladder mucosa; rectal mucosa or fixed to pelvic bone; or fixed or ulcerated inguinofemoral lymph nodes
IVb	Any distant metastasis including pelvic lymph nodes

Groin node assessment

Given that most surgically managed vulval cancers will not have metastatic involvement of the lymph nodes and that surgical exploration of the groin will be associated with short- and long-term morbidity, it is understandable that continuing efforts are being made to identify node-positive and node-negative cases prior to surgical intervention. The more accurate the prediction, the more that unwanted morbidity can be avoided. The last 10 years has seen considerable effort in this area, initially with imaging but also with selective node resection. Table 60.6 lists the various methodologies that have been assessed in this role.

Sentinel lymph node biopsy

This technique has quickly become the most adopted as an adjunct to surgical treatment, particularly in earlier cancers. The sentinel node is defined as the first node in the lymphatic chain draining an anatomical area. If the sentinel node from the suspected lesion is negative for disease, then the remainder of the nodes should also be

Table 60.5 TNM classification system.

Primary tumour (T)	
Tis/0	Pre-cancer stage: carcinoma *in situ* or vulval intraepithelial neoplasia (VIN)
T1	There is a tumour and it is confined to the vulva and/or perineum
T1a	Tumour has grown no more than 1 mm into underlying stromal tissue and no more than 2 cm wide
T1b	Tumour is >2 cm wide or it has grown more than 1 mm into stromal tissue
T2	Tumour is any size and is growing into the lower third of the vagina or urethra or anus
T3	Tumour is any size and cancer is spreading to the upper urethra, rectum, bladder or pubic bone
Regional lymph nodes (N)	
N0	Cancer has not spread to lymph nodes
N1	One to two lymph nodes have become infected in the groin area. Either:
N1a	One or two lymph nodes affected and area of cancer spread in both <5 mm
N1b	One lymph node is affected and area of cancer spread >5 mm
N2	Cancer has spread to the lymph nodes in the groin with one of the following features:
N2a	Three or more lymph nodes affected but each area of spread <5 mm
N2b	Two or more lymph nodes affected, all with area of spread 5 mm or more
N2c	Cancer has spread to lymph nodes and has started to grow through the outer covering of a least one node (known as extracapsular spread)
N3	Cancer has spread to the lymph nodes causing the development of open sores (ulcerations). The lymph nodes become stuck to the tissue near it
Distant metastasis (M)	
M0	Cancer has not spread to distant sites (no metastasis)
M1	Cancer has spread to distant sites, metastasis. This includes spread to pelvic lymph nodes

Table 60.6 Imaging techniques for groin node assessment and sensitivities.

Technique	Sensitivity	Reference
Magnetic resonance imaging	40–50%	Barton *et al.* [35]
Magnetic resonance lymphography	55–89%	Sohaib & Moskovic [36]
Ultrasonography*	58%	Heaps *et al.* [37]; Moskovic *et al.* [38]
Computed tomography scan	Poor	Lin *et al.* [39]; Andersen *et al.* [40]
Positron emission tomography	Poor	Kamran *et al.* [41]

*With and without fine needle aspiration.

free of the disease (Fig. 60.3). The sentinel node for vulval lesions can be identified by injecting methylene blue dye into the tumour edge and/or using immunoscintigraphy where a radiolabelled marker (technetium-99) is injected into and around the margins of the lesion. A hand-held gamma camera is used to identify the radioactive tracer uptake in the regional lymph nodes [42,43]. Identification during surgery is further enhanced by the use of blue dye, which, along with the raised radiation count, allows the sentinel node to be clearly seen (Fig. 60.4).

Three recent systematic reviews [44–46] all indicate that the sentinel node technique using the combined method (technetium-99 and blue dye) is sufficiently sensitive and specific to be regarded as the standard of care for women with unifocal tumours measuring 4 cm or less where there is no evidence of clinically enlarged nodes. The technique may be enhanced using preoperative SPECT/CT imaging, which might also help in the identification of aberrant sentinel nodes [47]. Data are still required as to the effectiveness of the technique when the primary lesion has been removed (post excision biopsy). In one study of 32 women, slightly more sentinel nodes were identified when performed after diagnostic biopsy when compared with those following excision biopsy [48]. In a cohort of 106 patients in whom one-third had undergone primary excision with a secondary resection of the nodes performed on average 30 days later, no compromise in accuracy was noted [49]. Our own data and those of others indicate that surgical morbidity is significantly reduced, with shortened length of hospital stay, reduced wound breakdown, and reduced lymphoedema and lymphocyst.

Table 60.7 compares the most frequently seen complications in a routine audit comparing women who had complete lymphadenectomy versus sentinel node. Both groups had similar tumours in terms of size and stage. Importantly, patient-reported outcomes are favourable as well [49] and the technique has been shown to be significantly cost-effective when compared with complete lymphadenectomy [50].

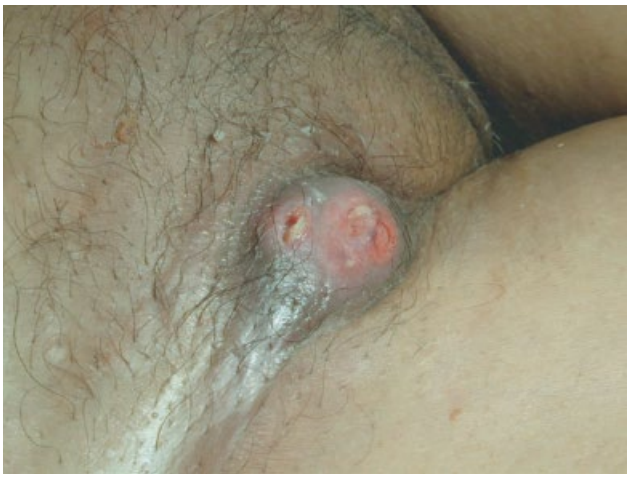
As with inguinofemoral lymphadenectomy, there is a risk of a false-negative outcome (2–3%). However, the difference between the false-negative rates is not significant and given the potential huge benefit in morbidity avoidance is a small risk outweighed by benefit.

One observer has raised a potential negative effect of this technique: although based on the observation of only two patients, there was concern that in patients who are node positive, the technique might increase the risk of extranodal metastasis by a direct effect on the lymphatics [51].

Summary box 60.2

- Most vulval cancers present with soreness, pruritus or the presence of a mass or ulcer.
- All suspicious lesions should be subjected to a diagnostic biopsy.
- Primary spread is both local and to the inguinofemoral nodes.
- The status of the lymph nodes has a major bearing on clinical outcome.
- Invasion >1 mm in depth is associated with increasing rates of lymph node involvement.
- Clinical examination of the lymph nodes is unreliable.
- Staging of vulval cancer is surgical and clinical.
- Sentinel node sampling is proving to be the most accurate method of assessing lymph node spread.

(a)



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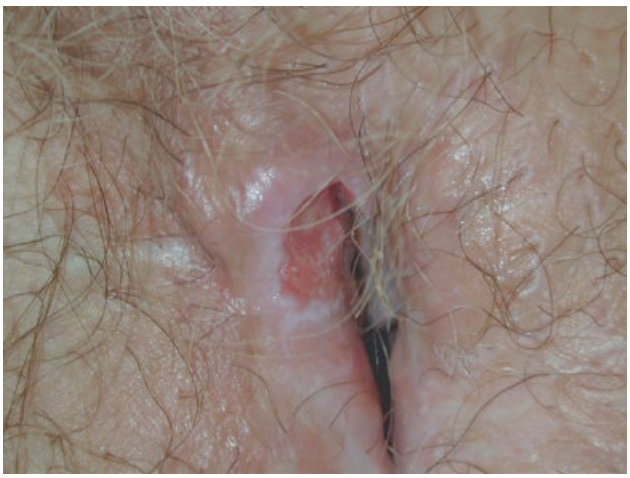

Fig. 60.3 (a) Reccurence in the right groin after previous simple vulvectomy. (b) Anterior local recurrence after radical vulvectomy. (*See also colour plate 60.3*)

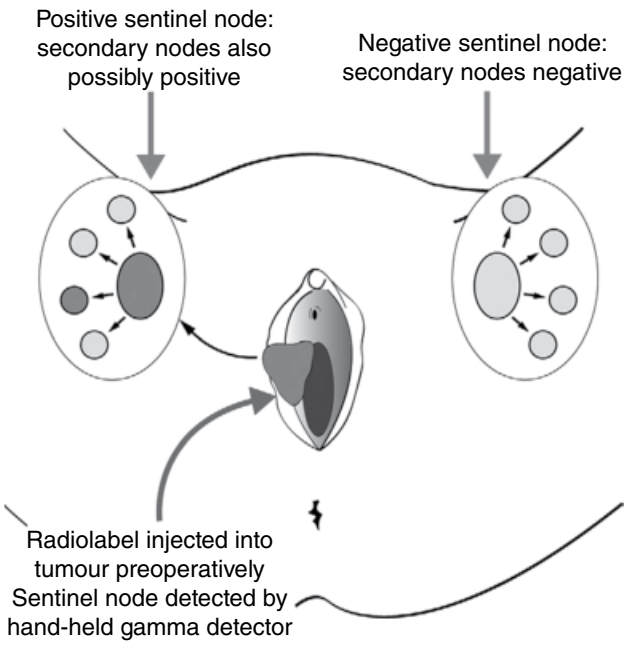

Fig. 60.4 Schematic demonstrating the rationale of sentinel lymph node sampling.

Table 60.7 Complication rate by groin node dissection type.

	Sentinel lymph node only (*N* = 89)	Sentinel lymph node biopsy plus full groin node (*N* = 18)
Lymphocyst	5.5%	44%
Lymphoedema	2.7%	33%
Recurrence	2%	0%
Average length of stay	2 (1–17) days	7 (5–25) days

Surgical management of the primary vulvar lesion

The site, size and relation of the lesion to important functional structures will determine the most appropriate method for treating the vulvar lesion. Similarly, the clinical presence or absence of nodal or distant disease will affect the management strategies. It would, for instance, be illogical to embark upon radical local treatment for the primary cancer in the presence of distant untreatable metastases unless there was no other suitable form of palliation. Two broad categories of patient can be identified at the outset:

1) those who have small unifocal vulvar lesions with no clinical evidence of nodal involvement;
2) those who have more advanced vulvar disease and/or have clinical evidence of nodal involvement.

For the purposes of further discussion, these will be termed as early and late disease, respectively.

Surgical management of early vulvar cancer

Radical vulvectomy is excessive treatment for the majority of unifocal and early cancers. Wide local excision is usually sufficient for the majority of lesions between 1 and 10 mm in depth. Until recently the general consensus was that the most important factor governing local recurrence was the margin of excision. Two publications have underpinned this management principle for 20 years [37,52]. Current guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) still endorses the principle of wide resection margins in order to guarantee a post-fixation maximum clearance of 8 mm on all margins. One large single institution retrospective cohort has recently questioned this approach [53]. This cohort contained 102 consecutive patients and the authors did not find any significant increased risk of recurrence in relation to the margin of excision, as long as the tumour was completely excised. A similar but larger cohort from the West Midlands [54] has reached similar conclusions. The latter included over 200 patients followed up for over 5 years. In addition, the histopathology of the adjacent epithelium and HPV status was also included in the multivariate analysis. There would appear to be ample evidence to revisit the concept of wide excision margins as this could have a significant impact on local surgical morbidity.

The excision should be taken to the depth of the fascia lata, which is coplanar with the fascia of the urogenital diaphragm. Even when adequate excision has been achieved, there may be other variables identified after examination of the specimen that some have suggested indicate a high risk of relapse. These include tumour thickness (or invasiveness) and capillary lymphatic space involvement, and perineural infiltration [55]. In addition the adjacent epithelium, which may reflect the underlying oncogenic process, may influence recurrence. Differentiated VIN appears to have a higher rate of recurrence than basaloid or warty VIN, although this is based on a very small case series [56].

As one would expect, the local recurrence rate for wide local excision compares favourably with that following radical vulvectomy. Hacker and van der Velden [52] have collated data from 12 published series including 530 patients, of whom 165 were treated by radical local excision and 365 by radical vulvectomy. The local recurrence rates were 7.2% and 6.3%, respectively.

Surgical management of advanced vulvar lesions

The reader should appreciate that 'advanced' in vulvar terms indicates that wide local excision would either be a radical vulvectomy and/or would compromise function. The same principles apply here as with the smaller unifocal lesions in that the objective is to obtain adequate clearance on all the resection margins. As subsequent function and cosmesis are more likely to be affected, consideration should also be given to adjunctive treatment. It is important to consider the woman and her feelings when constructing the management plan. An elderly woman with extensive or multifocal disease with an associated symptomatic non-neoplastic epithelial disorder such as lichen sclerosus may well gain an overall benefit from radical vulvectomy with subsequent grafting. Conversely, a young woman with a clitoral cancer may be managed initially by radiotherapy, reserving surgery for failed local control. These types of cases form the basis for local management of advanced vulvar lesions. The prime objective is to maximize local control, closely followed by consideration of further function and cosmesis in that particular woman.

Lymph node disease

Patients with superficially invasive vulval cancer are at minimal risk of nodal disease (Table 60.8). This is defined as a depth of invasion of less than 1 mm. Depth of invasion is closely related to the risk of nodal disease, and should be measured from the most superficial dermal papilla adjacent to the tumour.

Overall, about 30% of vulval cancers will have inguinofemoral nodal disease and about one-fifth of those with positive inguinofemoral nodes will have positive pelvic nodes (i.e. about 5% overall). It has been known for many years that pelvic nodes are rarely, if ever, involved if the inguinal nodes are negative. The low frequency of pelvic node involvement and the doubts surrounding the ability of surgery to control disease at this site have led most to conclude that the routine application of pelvic node dissection in vulval cancer should be discontinued.

The following clinical factors can predict for the presence of lymph node disease, although clinical examination of the nodes themselves is unreliable:

- lesion size;
- whether or not the nodes are clinically suspicious; and

Table 60.8 Relationship of depth of invasion to risk of nodal disease.

Invasion depth (mm)	Per cent node positive
<1	0
1.1–2	7.7
2.1–3	8.3
3.1–5	26.7
>5	34.2

Source: Hacker *et al.* [28].

- disease that involves both the labia minora and labia majora has a 50% chance of nodal involvement, whereas when only one of these structures is involved the risk is approximately 20% – Stehman and Look [57] have also suggested that clitoral or perineal siting of the tumour carried an increased risk of nodal disease.

Other risk factors depend on histopathological assessment of the primary lesion. Not surprisingly, these are similar to the general prognostic factors for outcome, and include:

- tumour grade;
- capillary lymphatic space involvement;
- degree of invasion (tumour thickness); and
- perineural invasion.

Management of the lymph nodes

Types of lymph node dissection

The primary lymphatic drainage of the vulva and distal vagina is to the inguinal (superficial femoral) and the nodes lying along the femoral vein. Efferent vessels from the superficial inguinal nodes drain to the deep inguinal or femoral nodes. The most cephalad femoral lymph node is the node of Cloquet. This is not a constant anatomical finding and has been noted to be absent in 54% of cadavers. The femoral nodes also receive some direct afferents, particularly from the clitoris and anterior vulva, thus explaining the observation of involved femoral nodes with uninvolved inguinal nodes. One prospective study [58] has suggested that superficial lymphadenectomy alone may be associated with a higher risk of groin relapse, although the relatively low relapse rate in early disease renders any conclusion somewhat unreliable.

Laterality

Extensive crossover of lymphatic channels of the vulva may result in nodal involvement of the contralateral groins in addition to the ipsilateral groin nodes. Because of this, bilateral groin node dissection is usually required. However in small (<2 cm) lateral tumours, only an ipsilateral groin node dissection need initially be performed. A lateralized lesion, agreed by the European Organization for Research and Treatment of Cancer (EORTC) Vulva Group consensus, is defined as one in which wide excision, at least 1 cm beyond the visible tumour edge, would not impinge upon a midline structure. If the ipsilateral nodes are subsequently shown to be positive for cancer, the contralateral nodes should also be excised or irradiated, as the nodes are more likely to be positive in this scenario.

Andrews *et al.* [59] noted that this was also the case for T2 lesions despite a relatively high ipsilateral positivity rate of 34%. However, exceptions have been reported. For larger lateralized lesions the picture is more confused and, until further data become available, bilateral node dissection (or selective sentinel node biopsies) would be advisable.

En bloc and separate groin incisions

The need for en bloc removal of the lymph nodes has received much attention, largely because it has been felt that this type of procedure accounts for a significant proportion of the morbidity (Fig. 60.5) and that the technique employing separate groin incisions (Fig. 60.6) results in a better cosmetic outcome. The triple incision technique was first described in 1965, although it only became popular in the 1980s. Those who have reported

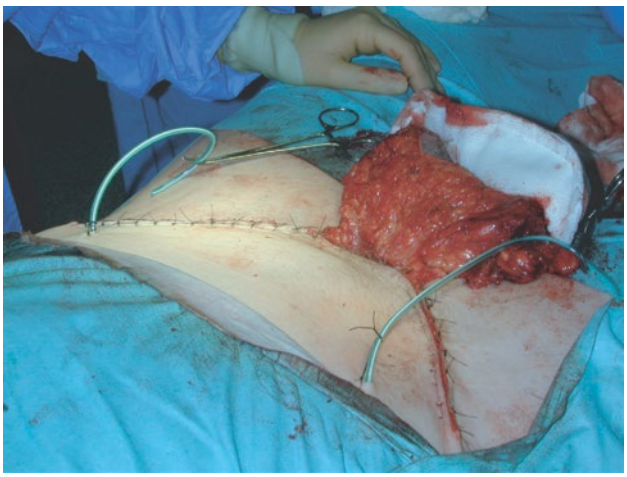

Fig. 60.5 En bloc dissection of the inguinofemoral lymph nodes. (*See also colour plate 60.5*)

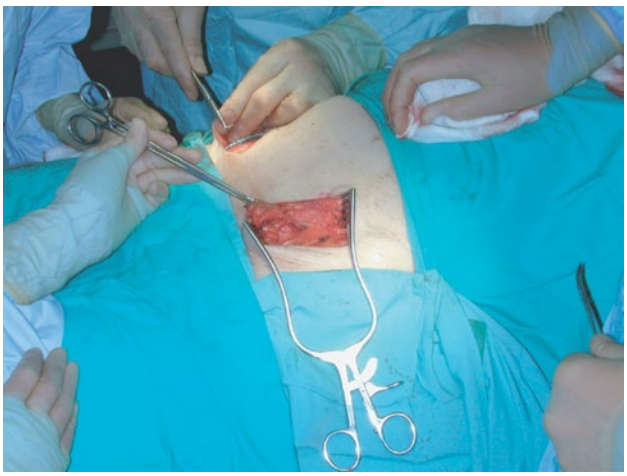

Fig. 60.6 Separate groin incisions. (*See also colour plate 60.6*)

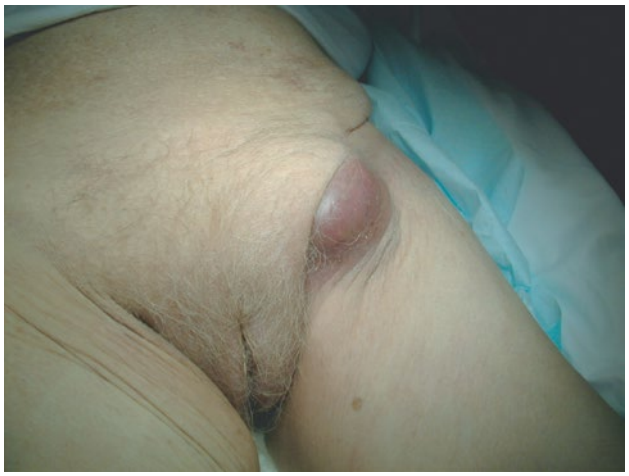

Fig. 60.7 Clinically suspicious left groin nodes. (*See also colour plate 60.7*)

on its use have not shown any disadvantages in terms of survival or local relapse for early-stage carcinomas, and there have been quite marked improvements in the morbidity.

The anxiety relating to the triple incision is the possibility of relapse in the bridge of tissue left between the vulvectomy or local excision and the groin nodes. This tissue will contain lymphatic channels, but whether lymphatic metastasis is an intermittent or embolic event or a continuous or permeation event remains uncertain. Certainly if the lymphatic channels contain malignant cells at the time of resection, then recurrence would seem to be a real possibility.

Current consensus would suggest that en bloc dissection of the nodes is probably best retained for large vulvar lesions and in situations where there is gross involvement of the groin nodes (Fig. 60.7). It would seem more logical to address the increased morbidity of the procedure with more attempts at reconstruction rather than undertreating with less than adequate primary surgery.

Management of involved lymph nodes

Resection of the groin lymph nodes provides prognostic information and might also confer some survival benefit. There are varying degrees of positivity, from microscopic deposits in one of many nodes to gross extracapsular spread in the entire group of nodes. As with the overall stage, this spectrum is also associated with a spectrum of outcomes (Table 60.9) and requires different approaches to management. The most important variable influencing survival is extracapsular spread from the lymph nodes; for patients who have only one node involved, the most important prognostic factor is the greatest dimension of the metastasis within the node (Table 60.10).

Table 60.9 Survival in relation to nodal status and size of vulval lesion.

Nodal status	Primary size	Survival (%)
Negative ($N = 385$)	≤2 cm	97.9
	2–3 cm	90.5
	>3 cm	75–80
	All	90.9
Positive ($N = 203$)	All	57.2
1 or 2 positive nodes	–	75
3 or 4	–	36
5 or 6	–	24
7 or more	–	0

Source: Homesley *et al.* [61].

Table 60.10 Management in relation to lymph node status.

Groin nodes negative	No further treatment
Groin nodes positive after surgery	–
One node only involved*	Observation only
Two or more nodes involved	Inguinal and pelvic radiation
Clinically positive before surgery	Resection followed by radiation
	Radiation followed by resection
	Radiation only

*In the situation where there is only one node involved but the node is either completely replaced by tumour or there is extracapsular spread, the author feels that adjuvant radiotherapy is justifiable.

These observations explain and underpin the 2009 revisions in FIGO staging.

In the past, pelvic lymphadenectomy was considered to be appropriate if the inguinofemoral nodes were involved. This practice has become increasingly uncommon, as it has been well demonstrated in Gynecologic Oncology Group protocol 37 [60] that in this situation pelvic radiation confers a better outcome than pelvic node dissection. Interestingly, the survival difference appeared to reflect better control of disease in the groin than pelvic or distant disease.

A final observation with regard to the lymph nodes is that all the available data are based on what is considered to be standard pathological evaluation of the groin nodes (standard sections stained with haematoxylin and eosin). In other tumour systems it has been possible to define a group of patients with micrometastases by using complete serial sectioning and immunohistochemical staining. These nodes positive for micrometastases would

have been negative on standard assessment. There are no studies available as yet indicating what, if any, clinical significance of such findings might be in vulval cancer.

Complications of surgical treatment

The complications of vulval and groin surgery are listed in Table 60.11. Any major cancer procedure carries immediate morbidity risks such as haemorrhage, thromboembolism and infection, and vulvar procedures are no exception to this. Prophylactic antiembolic strategies are of value and should be used in all cases. Reducing the length of hospitalization and early mobilization indirectly enhances such prophylaxis and may result from modifications of the radical approach.

Radical en bloc dissection (radical vulvectomy and bilateral node dissection) results in lymphoedema in between 8 and 69% of cases. Wound breakdown is very common, occurring in 27–85% of cases, and can become secondarily infected, resulting in cellulitis. The average hospital stay for this radical procedure varies from 17 to 33 days. The triple incision technique has yielded significant improvements in operative blood loss and length of stay, although high breakdown rates continue to be reported (22–52%) [62,63]. The occurrence of lymphocyst (Fig. 60.7) and lymphoedema does not seem to be significantly less than that with the radical en bloc technique. Unilateral groin dissection does appear to lower the incidence of morbidity, but there is no significant difference in morbidity when superficial is compared with deep groin node dissection. Van der Zee *et al.* [64] have reported significant reductions in wound breakdown, cellulitis, length of hospital stay and lymphoedema when sentinel node sampling is compared with inguinofemoral lymphadenectomy.

Less radical approaches to the vulva have certainly improved cosmesis and subsequent function. Other surgical modifications [65] to reduce morbidity include sparing the saphenous vein at the time of surgery to reduce wound and lower limb complications, although the data on outcome in terms of lymphoedema are inconclusive [66,67]. It has also been suggested that the tissues most lateral in the groin need not be resected. Sartorius transposition to cover the femoral vessels in thin and emaciated patients also helps to reduce wound morbidity [67]. Wound healing is also improved by avoiding undermining of the skin edges, performing tension-free closures, using wound drainage and administering prophylactic antibiotics. Increasingly, surgeons have employed grafting techniques either at the time of initial surgery or as a second-stage procedure. The grafts successfully employed have been the gracilis and rectus muscle myocutaneous flaps and rotational full-thickness skin flaps taken from the inner thigh or buttock (Fig. 60.8). The use of these flaps to fill considerable defects and a more conservative approach to excision have resulted in less scarring and more functional vulvas. As yet it has not been possible to demonstrate that this translates into improved psychological well-being, although the psychological trauma of radical excision without reconstruction is well documented [68].

Table 60.11 Complications of surgery.

Groin dissection
Wound breakdown/cellulitis
Lymphocyst
Lymphoedema
Vulval resection
Wound breakdown/cellulitis
Rectocele
Urinary problems
Psychological

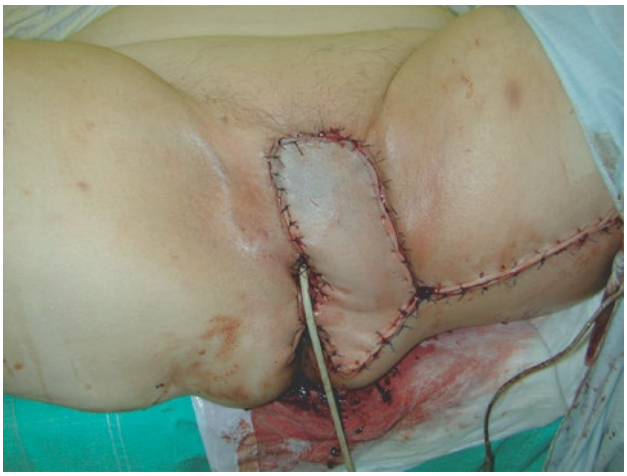

Fig. 60.8 Rotation skin flap to fill a large defect. (*See also colour plate 60.8*)

Management of complications

For lymphoedema, compression hosiery is prescribed along with rest and exercise, avoidance of trauma (skin care), simple gravity drainage and manual lymphatic drainage. For lymphocyst, a conservative approach is adopted and drainage under antibiotic cover is recommended only for symptomatic cases, but they tend to re-form.

Wound healing can be promoted with manuka honey dressing [69]. Recently, there have been anecdotal reports of using tissue sealant to promote healing in groin wounds that have broken down [70].

Radiotherapy and chemotherapy

The role of radiotherapy and chemotherapy in the treatment of vulvar cancer is less defined than that for surgery. However, there are data quite clearly indicating that squamous vulvar cancers are sensitive to both radiotherapy and chemotherapy.

Basal cell cancers are well recognized as being radiosensitive, and radiotherapy may be the treatment of choice if surgery is likely to result in either functional or cosmetic impairment. Melanomas have not been shown to respond and verrucous cancers have been reported as becoming much more aggressive as a result of radiotherapy.

Adjuvant radiotherapy

The factors influencing the need for adjuvant radiotherapy are (i) surgical margins and (ii) groin node positivity. There is insufficient evidence to recommend adjuvant local therapy routinely in patients with suboptimal surgical margins (<8 mm). Adjuvant treatment for positive margins is associated with improved survival when compared with observation alone [71]. A more recent multicentre retrospective study of 257 patients concluded that in patients with close or positive margins the addition of adjuvant radiotherapy improved overall survival from 29% to over 60% [72]. As with most retrospective studies, selection bias is a cause for concern.

Adjuvant radiotherapy should be considered when two or more lymph nodes are involved with microscopic metastatic disease or there is complete replacement and/or extracapsular spread in any node [58,73,74]. Treatment should be to the groins and the pelvic nodes, although there is no evidence to show whether treatment should be directed at both sides or to the involved side only. The increasing use of the sentinel node technique may require a re-evaluation of this strategy.

A large multicentre retrospective cohort study from Germany evaluated 1618 patients of whom 1249 had surgical groin staging and known lymph node status. Node-positive patients receiving adjuvant radiation ($N = 189$) fared better than 61 patients who did not receive adjuvant radiotherapy (progression-free survival 39.6% vs. 25.9%). This difference is significant and the authors concluded that the addition of chemotherapy would be likely to improve outcome further given the incremental improvements seen with other squamous cancer [75]. A subsequent study appears to lend weight to this assumption where, in a large retrospective cohort of patients eligible for adjuvant treatment, the addition of chemotherapy resulted in a 38% reduction in the risk of death [76].

Primary treatment

Radiotherapy with or without concurrent or sequential chemotherapy is being used more frequently in the management of advanced vulval cancer. Radiotherapy may, in certain circumstances, be the sole treatment, but more usually it is used preoperatively with a view to allowing for sphincter-preserving surgery.

Encouraging results were reported by Beriwal *et al.* [77] who were able to demonstrate a complete pathological response in 16 of 33 patients receiving preoperative chemoradiation. All but one remained disease-free at 26 months. In the remaining 17 patients, who had only a partial response, eight developed recurrence locally within 8 months.

Radiotherapy may also be of use in place of surgery for histologically proven involved groin lymph nodes. Whether such irradiated nodes require removal after treatment remains unknown.

Radiotherapy and chemotherapy schedules

Radical treatment usually requires that a prophylactic dose (45–50 Gy) is delivered to the primary and nodal sites and the tumour is then boosted by a second phase of treatment using electrons, conformal radiotherapy or brachytherapy to a total dose of 65 Gy. The total prescribed dose is determined by the clinical context.

A Cochrane review suggests that there is no evidence that prophylactic groin irradiation should be used in preference to surgery [78]. With regard to the use of concurrent chemotherapy and radiation therapy, there are no robust prospective data. Several retrospective studies have suggested that there may be some improvement in local control with regimens employing cisplatin and 5-fluorouracil, mitomycin C and 5-fluorouracil, and 5-fluorouracil alone.

When there is no obvious macroscopic disease and the sole intention is adjuvant treatment, the total dose is 45–50 Gy with no concurrent chemotherapy.

Complications of radiotherapy

The reason for the limited application of radiotherapy in this disease lies in the poor record of tolerance and high levels of complications reported in the older series. This almost certainly relates to the type of treatments and techniques available in these series. More modern equipment and a greater understanding of its potential and applications have resulted in a marked improvement in tolerance and morbidity [79].

Most women will note erythema and some moist desquamation as a result of radiotherapy. With appropriate care and attention to local hygiene, such problems rarely

result in premature discontinuation of treatment. Radiation-induced cystitis requires bladder irrigation and treatment of any infection. Proctitis is managed with prednisolone (Predfoam), Normacol and loperamide.

More severe side effects include necrosis of bone (symphysis and femoral heads) and fistula formation. Careful planning of field sizes, dose and fractionation minimize such risks.

Recurrent disease

Between 15 and 30% of cases will develop recurrence. The most common site is the residual vulva (70%), with the groin nodes accounting for almost 20% and the remainder of relapses occurring in the pelvis or as distant metastases. In a large prospective cohort of well-characterized unifocal cancers in the Groins V2 study, local recurrence was 27.2% at 5 years and 39.5% at 10 years after primary treatment [80].

Most recurrences occur 2 years after primary treatment, and close surveillance every 3 months in the first 2 years is usually practised. This is reduced to 6-monthly surveillance for a further 2–3 years and annually thereafter. Additionally, patients are encouraged to self-inspect and report any symptoms of pain, bleeding or discharge. It should be stated that this schedule for follow-up is empirical and not evidence based.

Survival is poor following regional relapse, hence the efforts to prevent this at the outset. Skin bridge recurrence has been reported to be more likely to occur in patients with positive lymph nodes [81].

In vulval cancer, disease can recur several years following presumed adequate treatment of the primary cancer. Furthermore, some features of the original disease seem to be associated with this late type of recurrence, to such an extent that other terms employed include 're-occurrence' or 'second field tumours'. Rouzier *et al.* [82] were the first to document this late recurrence potential with tumours associated with lichen sclerosus in the adjacent epithelium. In a large retrospective cohort [54] we have also documented this phenomenon. The Birmingham cohort comprised 201 patients extensively classified in terms of pathology, HPV status and treatment modality. Furthermore, the minimum follow-up was 5 years. It appeared from an in-depth analysis that both local recurrence and re-occurrence were significantly more likely in women who had evidence of lichen sclerosus when compared with usual-type VIN. Lymph node positivity was also a significant predictor for local relapse. As long as the primary tumour was completely excised, the excision margin was not a predictor of relapse. This hypothesis-generating cohort study proposes that local relapse in completely excised tumours occurs as a result of persisting bio-instability of the adjacent epithelium (second field tumour) or as a direct result of tumour emboli in the associated skin lymphatics. Further work is in progress to develop a clearer understanding of the bio-instability of adjacent epithelium and with it the potential for prophylaxis to reduce local recurrence risk.

Treatment

The management of relapsed disease will depend on the site and extent of the recurrence [83]. Wide excision of local recurrences can result in a 5-year survival rate of 56% if the inguinal nodes are negative [84]. If excision would risk sphincter function, radiotherapy should be considered as the first choice. If radiotherapy has already been given to maximum dose, then excision should be considered.

Groin recurrence has a much poorer prognosis and is difficult to manage. In patients who have not been treated previously with groin irradiation, radiotherapy (with or without additional surgery) would be the preferred option. The options are much more limited in those who have already been irradiated and palliation, which may include surgery, should be considered. There is no standard chemotherapy or other systemic treatment effective in patients with metastatic disease.

Summary box 60.3

- The current consensus is that radical excision of the primary lesion(s) should aim to achieve disease-free margins of at least 8 mm after fixation.
- All lesions with invasion greater than 1 mm should be considered for either ipsilateral or bilateral lymph node dissection.
- Adjuvant radiotherapy or re-excision should be considered if the excision margins are suboptimal.
- One lymph node replaced or breached by a tumour or two with microscopic deposits should prompt adjuvant radiotherapy.
- Advanced tumours or tumours where excision may cause functional compromise should have treatment individualized (surgery, radiotherapy and chemotherapy) to maximize cure and minimize functional compromise.
- Local recurrence may be managed by either re-excision or radiotherapy, whichever would be associated with the least functional compromise.
- Groin recurrences are difficult to treat and the outcome is poor.

Vaginal cancer

Background

Vaginal cancer is rare and accounts for only 1–2% of all gynaecological malignancies. They arise as primary squamous cancers or are the result of extension from the cervix or vulva. Most authors report a wide age range (18–95 years), with the peak incidence in the sixth decade of life and a mean age of approximately 60–65 years. There would appear to be no relationship with race or parity.

A systematic review of the treatment of vaginal cancer revealed only 26 publications [85].

Aetiology

The cause of vaginal cancer is unknown, although several predisposing and associated factors have been noted:

- previous lower genital tract intraepithelial neoplasia and neoplasia (mainly CIN and/or cervical carcinoma);
- HPV infection (oncogenic subtypes); and
- previous gynaecological malignancy.

Several authors report that approximately one in four or as high as one in three patients have had a previous gynaecological malignancy. Large case–control studies have not been able to confirm pelvic radiotherapy, previous hysterectomy, long-term use of a vaginal pessary and chronic uterovaginal prolapse as causative factors.

Presentation

The symptoms will depend on the stage of tumour at presentation. The most common presenting features are:

- vaginal bleeding, which accounts for more than 50% of presentations;
- vaginal discharge;
- urinary symptoms;
- abdominal mass or pain; and
- asymptomatic (approximately 10% of tumours will be asymptomatic at the time of diagnosis).

Vaginal tumours may be overlooked during vaginal examination, particularly when a bivalve speculum is used. Careful inspection of the vaginal walls while withdrawing the speculum is necessary to avoid this, otherwise the blades of the speculum may obscure a tumour on the anterior or posterior vaginal wall.

Pathology

Between 80 and 90% of tumours in the larger series are squamous. Other carcinomas include adenocarcinomas, adenosquamous carcinomas and clear cell adenocarcinomas. Other rare primary vaginal cancers are discussed separately.

Site and size

Tumours can occur at any site in the vagina. The upper third of the vagina is the site most frequently involved, either alone or together with the middle third in approximately two-thirds of cases. Approximately one in six will be found to involve the entire length of the vagina. There is no predilection for any particular wall of the vagina. Figure 60.9 demonstrates a well-localized lesion in the lower vagina that does not originate from the vulva.

As with site, the size of tumour shows great variation at presentation, ranging from small ulcers less than a centimetre in diameter to large pelvic masses, although the majority of tumours are a maximum of 2–4 cm in diameter.

Staging and assessment

Any tumour classified as a primary vaginal carcinoma should not involve the uterine cervix. There should be no clinical evidence that the tumour represents metastatic or recurrent disease. Staging should be carried out according to the FIGO classification. This classification is summarized in Table 60.12.

The staging process itself can present problems since it may be difficult to differentiate one stage from another. This applies particularly to stage I and II disease, which may be hard to separate clinically; similarly, it is difficult to separate stage IIa and IIb on purely clinical grounds. Differences also exist in interpretations of the significance of positive inguinal nodes and their effect on staging. The current staging does not indicate in which group such patients should be placed, and some authors would

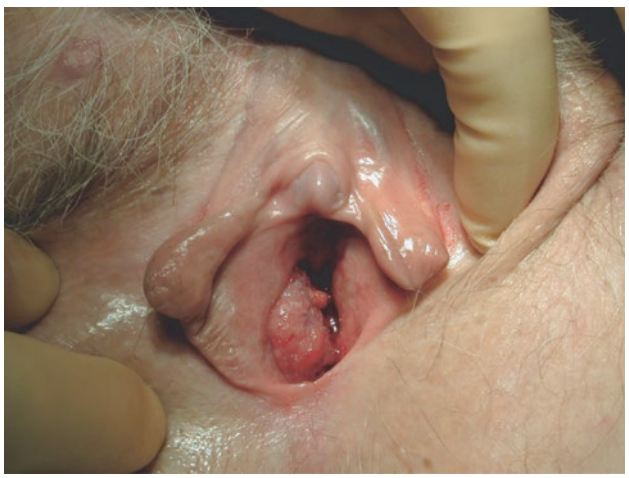

Fig. 60.9 Vaginal cancer. (*See also colour plate 60.9*)

Table 60.12 FIGO clinical staging of primary vaginal carcinoma.

Stage	Definition
0	Vaginal intraepithelial neoplasia III (carcinoma *in situ*)
I	Invasive carcinoma limited to vaginal wall
IIa	Carcinoma involves subvaginal tissue but does not extend to parametrium
IIb	Carcinoma involves parametrium but does not extend to pelvic side wall
III	Carcinoma extends to pelvic side wall
IVa	Involvement of mucosa of bladder or rectum (bullous oedema does not qualify for stage IV) or direct extension beyond true pelvis
IVb	Spread to distant organs

assign these patients to stage III with others preferring IVa or IVb.

The majority of series report that stage II disease is most commonly found at presentation (approximately 50% of all cases). Stages I and II combined consistently constitute 70–80% of cases.

Assessment

The assessment is best performed under general anaesthesia.

- The site and limits of the tumour can be accurately determined and a full-thickness biopsy taken for histological analysis.
- Combined rectal and vaginal examination is helpful to determine whether there is any extension of the tumour beyond the vagina and the extent of any spread.
- Cystoscopy and sigmoidoscopy are required to exclude or confirm the involvement of bladder or rectum.
- Chest X-rays or intravenous urograms can be used for the assessment.
- More complex radiological investigations such as rectal ultrasound scanning or MRI may be helpful in selected instances to define the dimensions and extension of the tumour.

Treatment

The majority of cases of vaginal carcinoma are treated using pelvic radiotherapy, although surgical excision is an appropriate form of management in selected cases. Experimental chemotherapeutic regimens are being developed both alone and in conjunction with radiotherapy for advanced cases or recurrent disease.

Radiotherapy

The proximity of the bladder and rectum means that, except in early cases, salvage of normal bladder and rectal function can only be achieved using radiotherapeutic techniques. Radiotherapy is certainly effective in treating vaginal cancer and survival rates have improved throughout the century as techniques have developed and improved. Techniques utilized have included:

- external beam radiotherapy (teletherapy);
- brachytherapy (e.g. interstitial implants, intravaginal cylinders or vaginal ovoids); and
- a combination of the two.

There is little place for using external beam therapy alone and the majority of tumours should be treated in combination with brachytherapy, with small early-stage tumours being suitable for treatment by brachytherapy alone. The optimal dose remains unclear but the mid-tumour dose should be at least 75 Gy. Above this dose any survival benefit must be weighed against the increased toxicity of therapy, and doses of 98 Gy or more have been shown to cause a higher incidence of severe side effects. Complication rates reported for radiotherapy vary according to dosage and techniques used and to the different grading systems used by different authors. Most report complications as occurring in 10–20% of patients. Life-threatening complications have been reported to occur in 6% of those undergoing radiotherapy for gynaecological malignancies, and vaginal carcinoma is no exception.

Acute complications include:

- proctitis;
- radiation cystitis; and
- vulvar excoriation or ulceration and even vaginal necrosis.

Significant long-term complications reported include:

- vesicovaginal or rectovaginal fistulae;
- rectal stricture; and
- vaginal stenosis.

In younger women, vaginal stenosis may be a long-term complication of great significance.

Surgery

There are relatively few reports of the use of surgery in vaginal cancer. Given what little information does exist, there are three general situations where surgery might be considered as first-line management.

1) Patients presenting with a stage I tumour in the upper third of the vagina, particularly on the posterior wall where resection may be technically straightforward. These patients can be treated with radical hysterectomy (if uterus *in situ*), pelvic lymphadenectomy and vaginectomy.

2) Patients with small mobile stage I tumours low down in the vagina, which if amenable to excision can be treated by vulvectomy with inguinal lymphadenectomy.
3) Bulky lesions that are unlikely to be cured by primary radiotherapy may be considered for exenteration in a few carefully selected cases.

It is undoubtedly possible in many instances to remove a vaginal carcinoma by surgical means, and there is little evidence to suggest that survival is improved following any of the treatment modalities. The choice of treatment will depend on the potential toxicity of the proposed treatment in relation to an individual patient and an individual tumour. Surgery is problematic in this respect because, to achieve adequate margins around the tumour, important structures (e.g. bladder or rectum) may be compromised.

The addition of lymphadenectomy would appear important as Stock *et al.* [86] reported that 10 of 29 patients (34%) undergoing pelvic node dissection and all three of their patients subjected to inguinal lymphadenectomy had positive nodes. High rates of metastasis to inguinal nodes from tumours of the lower third of the vagina have been noted. Early reports suggested that morbidity after surgical treatment of vaginal cancer was both frequent and serious.

However, the majority of complications were seen in patients undergoing surgical management of post-irradiation recurrence or following exenterative surgery for advanced disease. Serious complications include urinary problems (stress and/or urge incontinence) and fistulae. Lastly, any procedure requiring removal of the entire vagina will render the patient apareunic, although lesser degrees of vaginal excision usually allow subsequent sexual function.

Chemotherapy

There is little published work regarding the use of chemotherapy in vaginal cancer. Reports that exist concern combined chemoradiation as first-line treatment of advanced disease and the palliative use of chemotherapy for recurrent disease. In squamous vaginal cancer the use of chemotherapy should still be regarded as experimental.

Survival

Overall 5-year survival rates are now in the region of 50%, with rates of 39–66% reported. Survival is much higher in early-stage disease. However, there is some inconsistency in the allocation of cases to stages I and II. Survival rates for stage I disease are consistently reported at between 70 and 80%.

Prognostic factors

Stage, size, site and histological grade and type have all been proposed as factors that may influence survival. Only tumour stage and site, however, are consistently reported as being directly related to survival.

Recurrence

Recurrence occurs locally or within the pelvis in most instances, with about 20% relapsing with distant metastasis. The majority of relapses occur soon after primary therapy. Stock *et al.* [86] found a median time to relapse of 0.7 years. The outlook after failure of primary therapy is poor and in the majority further treatment is unlikely to be successful. As with cervical carcinoma, those patients with purely pelvic recurrence are sometimes suitable for salvage surgery by exenteration.

Uncommon vaginal tumours

Sarcomas

Leiomyosarcomas are most frequently diagnosed, with other types reported including adenosarcoma and angiosarcoma. Primary therapy is surgical involving wide local excision of the tumour with free margins. Adjuvant radiotherapy has been advocated for high-grade tumours or in recurrent disease. Adjuvant chemotherapy has been utilized by some but has not been shown to confer a survival advantage in soft-tissue sarcomas of the extremities. The majority of women present with discomfort or bleeding.

Rhabdomyosarcoma (sarcoma botryoides)

Rhabdomyosarcoma accounts for less than 2% of vaginal sarcomas. It is the most common soft-tissue tumour in the genitourinary tract during childhood. About 90% of cases occur in children under 3 years of age and almost two out of three occur in the first 2 years of life, although rare cases are reported in older women. Presentation is classically with a vaginal mass composed of soft 'grape-like' vesicles, but others may present with vaginal bleeding, discharge, a single small polyp or, occasionally, a black haemorrhagic mass.

Treatment involves conservative surgery (aimed at preserving function of the female pelvic organs) but depends largely on combination chemotherapy using vincristine, actinomycin-D and cyclophosphamide. Adjuvant surgery or radiotherapy may be added depending on response to chemotherapy. Survival has been greatly improved by the advent of combination chemotherapy and over 90% of individuals have been reported to survive following treatment.

Clear cell adenocarcinoma

As suggested by its name, it displays characteristic histological features that include the presence of solid sheets of clear cells, or of tubules and cysts lined by hobnail cells. The median age at diagnosis is 19 years (range 7–42 years) and approximately 61% of patients have documented exposure to diethylstilbestrol (DES) or to a chemically related non-steroidal oestrogen *in utero*. Although the risk of developing a clear cell adenocarcinoma following exposure to such drugs *in utero* was thought to be considerable, it is now appreciated that the risks are in fact very low (0.014–0.14%). Highest risks are for exposure that occurs early in pregnancy, the risk after exposure in the first 12 weeks' gestation being threefold that at 13 weeks. The majority occurs in the upper third of the anterior vaginal wall. Treatment is either by radical surgery or radiotherapy dependent on stage, in a fashion akin to the management of cervical carcinoma.

Although the peak incidence of DES-associated clear cell carcinoma in the USA was in 1975, a recent report suggests that there may also be an association with the development of non-clear cell adenocarcinomas occurring in older DES-exposed women [87].

Melanoma

Primary malignant melanoma of the vagina is an aggressive and rare gynaecological malignancy. Fewer than 200 cases have been reported worldwide to date but it is known that this disease has the worst prognosis of all gynaecological malignancies. Malignant melanoma of the vagina is 100-fold less common than melanoma of non-genital skin. The behaviour of this tumour also differs from that of melanomas found in other sites in that it is more aggressive than cutaneous melanomas (including vulvar melanoma) and that there is no difference in incidence between different races or skin types. The median age at presentation is around 66 years and the incidence increases with advancing age. The commonest presenting complaint is vaginal bleeding, but presentation may also be with a pelvic mass, vaginal discharge or dyspareunia. The optimal mode of treatment remains unclear, but whatever method is used the outlook is bleak. Prognostic factors that have been proposed include age, stage, tumour diameter, depth of invasion and mitotic rate. As with squamous vaginal carcinoma, the choice of treatment lies between surgery, radiotherapy or a combined approach. A number of recent articles support the use of radical surgery as a primary approach [88]. Radical surgery refers to either anterior or complete exenteration and it is suggested that although a 5-year survival is not necessarily increased by such measures, the median and disease-free survival may be prolonged.

Endodermal sinus tumour

Endodermal sinus tumours, which more commonly arise in the ovary or testis of infants, are also recognized in the vaginas of very young girls. Approximately 50 cases have been reported, with no patients aged over 3 years. Presentation will usually follow an episode of vaginal bleeding or discharge in a young girl who at examination is found to have a friable polypoid exophytic tumour.

Immunohistochemistry will reveal positive staining for α-fetoprotein, and in some cases serum α-fetoproteinlevels are elevated.

The behaviour of the tumour is locally aggressive but metastasis will also occur via haematogenous or lymphatic spread. Most tumours arise on the posterior vaginal wall and, if untreated, patients are known to die within 2–4 months of diagnosis.

The emphasis for treatment has moved towards limited excisional surgery combined with preoperative or postoperative chemotherapy. Multiagent chemotherapy is employed and is the same as that used for the successful treatment of ovarian endodermal sinus tumour.

Summary box 60.4

- Vaginal cancer is rare and most are squamous cancers.
- Superficial disease in the upper third may be managed similarly to cervical cancer.
- Superficial disease in the lower third may be managed as for vulval cancer.
- Deeply invasive disease and any disease whose excision would result in functional compromise should first be treated with radiotherapy with or without chemotherapy.
- Stage and tumour site are the most important prognostic variables.

Conclusions

The rarity of vaginal cancer means that many questions regarding its management remain unanswered. Many cases are amenable to treatment by more than one method, with comparable results in terms of survival. Choice of treatment may therefore often be made in relation to the potential toxicities of different treatments and should be tailored to each individual patient.

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61

Premalignant and Malignant Disease of the Cervix

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Premalignant disease of the cervix

Cervical cancer is largely preventable through treatment of screen-detected cervical lesions. It has a long natural history with a prolonged precancerous phase that is easily detectable and treatable. Exfoliative cytology has been the mainstay for screening of cervical pre-invasive disease (cervical intraepithelial neoplasia or CIN). Assessment of women with abnormal cervical cytology and the selection of those requiring treatment relied mainly on colposcopic impressions of the cervical transformation zone and the histological appraisal of directed punch biopsies. Local treatment for cervical pre-invasive disease is highly successful. The recognition that persistent infection with oncogenic human papillomavirus (HPV) causes cervical cancer has led to the development of HPV DNA test, other molecular biomarkers and prophylactic vaccines against HPV.

Epidemiology

Cervical cancer remains the most common female malignancy in virtually all developing countries and the seventh most common in women worldwide. Globally in 2012, an estimated 528 000 women developed cervical cancer and almost 266 000 died from this disease. Of all cervical cancers, 83% occur in the less developed world due to the absence of screening [1] (Fig. 61.1).

The trends in the incidence of cervical cancer in different countries relate largely to the availability, quality and coverage of screening programmes, as well as exposure to HPV and other risk factors, which reflect sexual habits and cultural and socioeconomic influences. The comparatively low incidence of cervical cancer in affluent societies is largely related to the implementation of population–based screening programmes and their coverage. This has led to a dramatic decrease in the incidence and mortality from invasive disease, as cancers are prevented or detected at an early stage (Fig. 61.2).

In the UK, it is estimated that cervical screening saves approximately 5000 lives every year. Although the overall age-standardized incidence of cancer increased by 3% in women during the 10-year period from 1993 to 2002, the corresponding data for cervical cancer showed a decrease of approximately 30%. The incidence of cervical cancer has fallen in the UK by 44% since 1975, and mortality from 7.1 per 100 000 in 1988 to 2.4 per 100 000 in 2007. The benefits became more obvious since the reorganization of the service in 1988 and the increase in coverage (from 35% in 1988 to 85% in 1998).

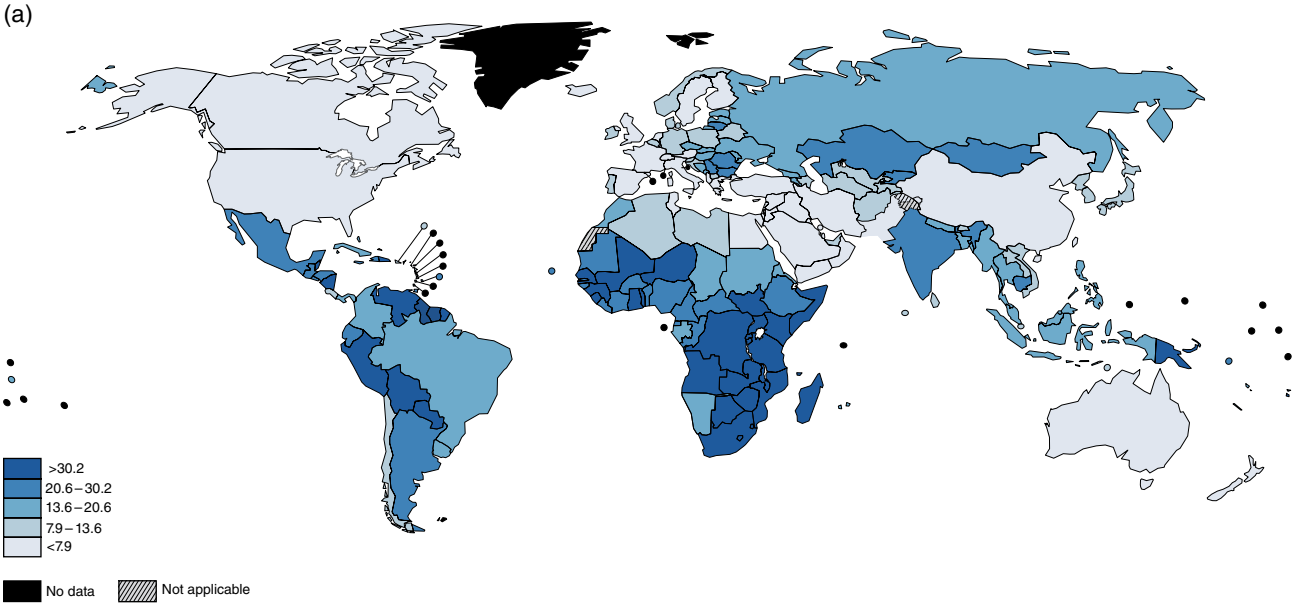
HPV infection, risk factors and natural history

Several risk factors for cervical cancer have been investigated over the years. There is now a strong and consistent body of evidence demonstrating that persistent infection by oncogenic high-risk HPV subtypes is responsible for instigating the neoplastic process and that this might be potentiated by other cofactors (Fig. 61.3). With more than 200 HPV subtypes recognized today, it is only a fraction of these that has been found to have carcinogenic potential. Of these, subtypes HPV-16 and HPV-18 are most commonly associated with invasive cancers and are thought to cause approximately 65–75% of cases, depending on the continent. The most frequent low-risk subtypes are HPV-6 and HPV-11, which also lead to the development of anogenital warts. The commonest types are classified according to their oncogenic potential as follows:

- low-risk subtypes HPV-6, HPV-11;
- high-risk subtypes HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-56.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

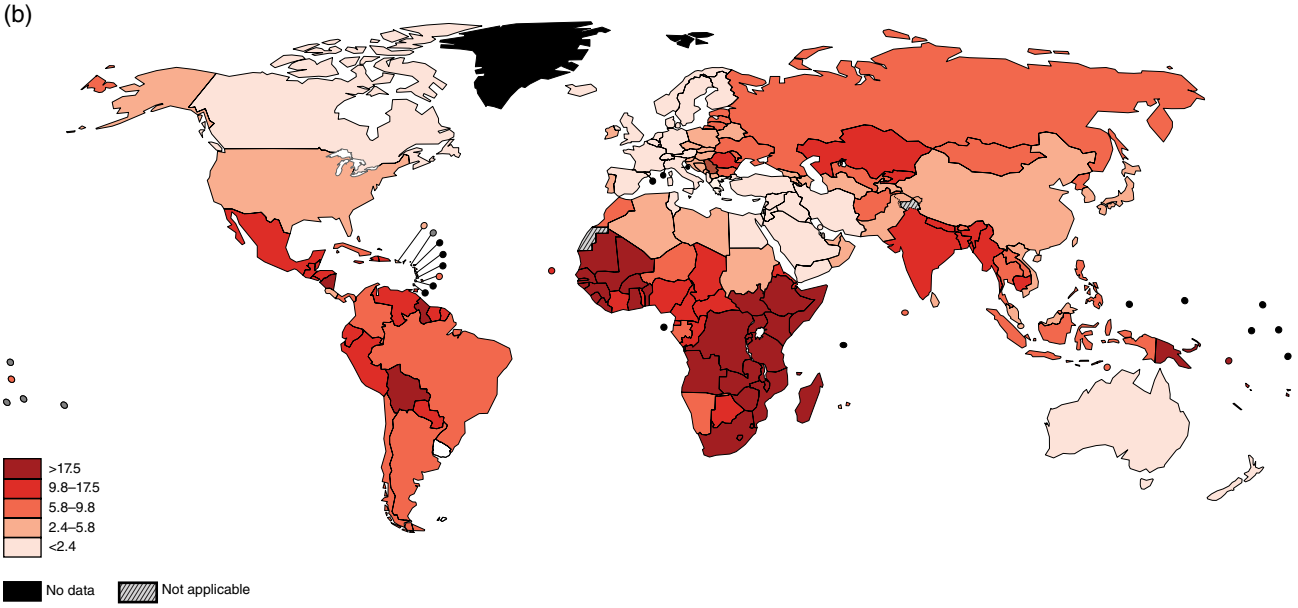
(a)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

(b)



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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

Fig. 61.1 Estimated cervical cancer: (a) age-standardized incidence per 100 000 women; (b) age-standardized mortality per 100 000 women. *Source:* Ferlay J, Soerjomataram I, Ervik M *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at http://globocan.iarc.fr, accessed 4 August 2016. (*See also colour plate 61.1*)

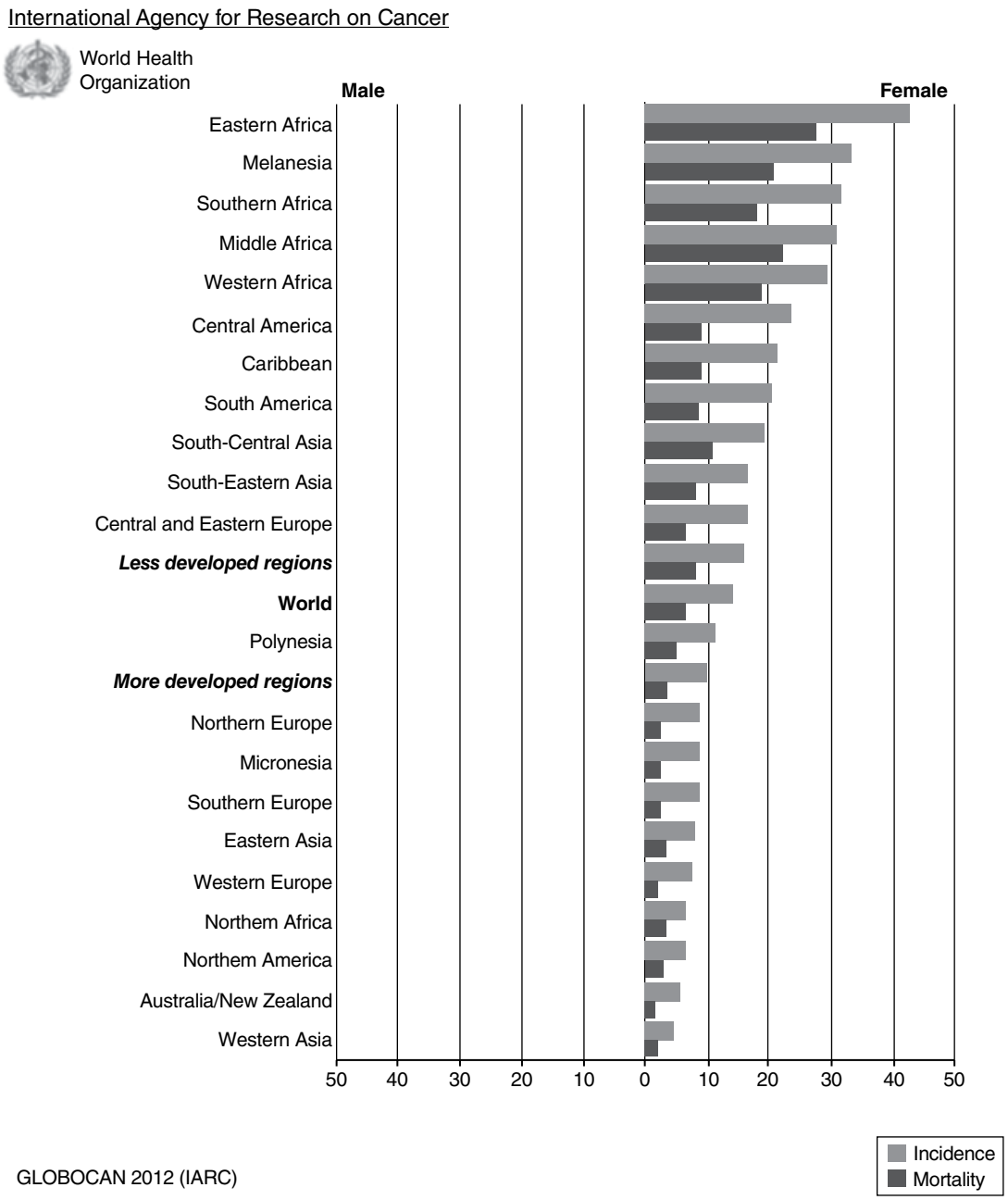

Fig. 61.2 Age-standardized incidence and mortality from cervical cancer worldwide per 100 000 women. *Source:* Ferlay J, Soerjomataram I, Ervik M *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at http://globocan.iarc.fr, accessed 4 August 2016.

The lifetime risk of acquiring any HPV infection probably exceeds 80%. With more sensitive testing available, studies show that HPV infection is more commonly the rule, not the exception. HPV types associated with the alpha species predominate in the anogenital area but other HPV types such as the beta and gamma HPV types, once thought to be predominantly cutaneous only, can also be commonly detected. Since the lifetime risk of developing invasive cervical cancer is much lower at 0.6%, cervical cancer should be regarded as a rare complication of a very common infection by HPV.

One of the early observations in most epidemiology studies was the high frequency of detection of the viral DNA. The more HPV types tested, not surprisingly, the higher the frequency of detection. In most studies, but not all, age influenced prevalence with young age being associated with higher rates, some as high as 45% in Western societies. This vulnerability is thought to be due

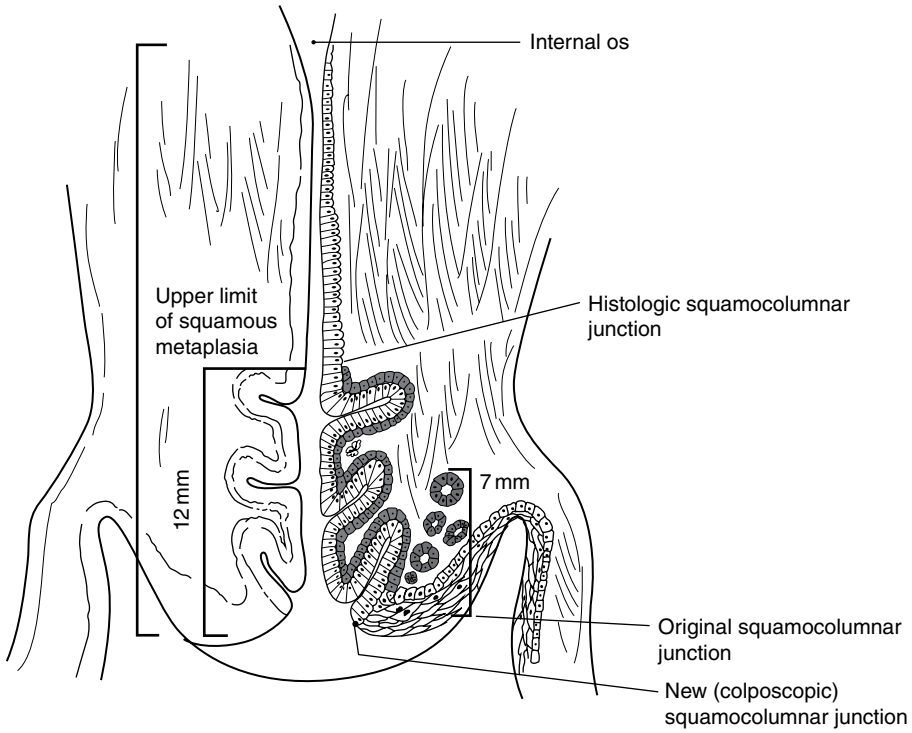

Fig. 61.3 The cervical epithelium and transformation zone.

to immature or naive immune responses as well as the biological vulnerability of the immature cervical epithelium seen in adolescents. The prevalence of HPV infection declines to about 5% in women above the age of 30.

Most HPV infections are transient. Approximately 60–80% clear spontaneously within 1–2 years, although the rest may result in CIN lesions within 2–4 years. The progression rate of CIN in women with high-risk HPV positivity is about 5% per year. In women over 30 years with high-risk HPV positivity and a normal cytology sample, the risk of developing CIN 3 is 116 times higher than in women with HPV but cytology negative. Even for women who develop CIN, the regression rates are high and depend, amongst other factors, on the grade of CIN and the woman's age. Above the age of 30 years, the regression rate is lower. Taken together, in the absence of intervention, roughly one-third of early precursor lesions disappear spontaneously, one-third persist and one-third progress to CIN 3 or invasive cancer.

HPV is a non-lytic infection, so that the inflammatory response to HPV is much more subtle than other mucosal infections, such as *Chlamydia trachomatis*. The initial immune response to acute HPV infections is most likely mediated by the local innate immune system, probably involving mechanisms such as activation of Toll-like receptors and natural killers cells. Persistent infections are cleared by the development of adaptive immune responses, which are dependent on antigen-presenting cells. HPV-16 is thought to downregulate both innate and adaptive immune responses. Final pathways to cancer result in interference with telomerase activity and viral integration, although a proportion of cancers are found to have episomal HPV DNA only. HPV E6 and E7 are known oncoproteins that control fundamental carcinogenic events including proliferation, senescence, and apoptosis. Cellular targets include p53, E6AP, CBP, p300, Bak, hTERT, MAGUK, cIAP, survivin, p107, pRB and p130.

Observational data show that the estimated time from infection to the development of invasive disease is approximately 15 years, although there may be swift progression in rare cases (Fig. 61.4). Cervical carcinogenesis normally has a lengthy precancerous phase that has been well defined through different grades of cervical preinvasive disease, although the continuum of the carcinogenic process has been questioned in some cases. Despite these major advances in our current understanding of the disease, the exact factors that determine infection and/or disease that will persist, progress or, conversely, spontaneously resolve are incompletely understood.

Several other risk factors of cervical disease have been described previously and have been correlated with heightened or reduced risk of cervical cancer in epidemiological studies. These include:

- low socioeconomic status;
- tobacco smoking (twofold);
- oral contraceptives (2.5-fold);
- early sexual debut;

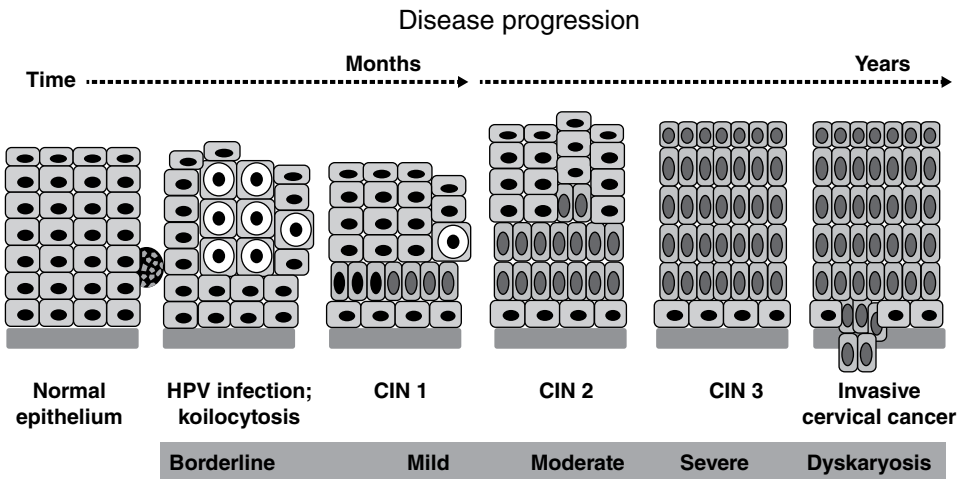

Fig. 61.4 Natural history of HPV infection and disease progression.

- multiple sexual partners (of woman or of the partner);
- other sexually transmitted infections (e.g. herpes simplex virus, *Chlamydia*) and bacterial vaginosis might influence HPV persistence and the probability of progression of HPV infection to dyskaryosis;
- immunocompromise, including HIV (fivefold).

The most consistent factors are tobacco smoking, oral contraceptive use and parity. All have biological plausibility. Nicotine and its carcinogenic metabolites can be detected in cervical mucus and smoking has been associated with a dampening of local immune markers. Both oestrogen and progesterone increase cell proliferation and hence vulnerability to DNA damage. Higher parity may be associated with high levels of hormone exposure and/or repeated trauma.

Most of the risk factors reporting a positive association are surrogates for sexual activity. They relate to increased risk for HPV infection and do not have a causal independent relation to cervical cancer. Others are potentially determinants of progression rather than prime aetiological agents.

Classification of cervical intraepithelial neoplasia

Squamous lesions

The Bethesda system for classification is widely used internationally. This was introduced in the USA in 1988 and was modified in 2001 [5]. This classifies abnormalities into:

- atypical squamous cells of undetermined significance, or ASCUS;
- atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (HSIL), or ASC-H;
- low-grade squamous intraepithelial lesion (LSIL), encompassing HPV and CIN 1;
- HSIL (encompassing CIN 2 and CIN 3) and squamous cell carcinoma.

The CIN classification introduced by Richart in 1967 for histological classification of cervical precancerous lesions has generally replaced the World Health Organization (WHO) classification and reflects the depth of epithelial involvement.

In the UK, cervical cytology was previously classified into mild, moderate and severe dyskaryosis, with borderline nuclear abnormalities used for changes that fall short of dyskaryosis. The previous terminology for cytology results used by the British Society of Clinical Cytology in 2001 was replaced by a new version introduced by the British Association for Cytopathology (BAC) and the NHS Cervical Screening Programme (NHSCSP) in 2013 (Table 61.1).

Table 61.1 Cervical cytology: classification of squamous lesions according to Bethesda and BAC/NHSCSP nomenclature.

Cytology		Histology
Bethesda 2001	*BAC/NHSCSP 2013*	
ASCUS, ASC-H	Borderline changes in squamous cells	HPV
LSIL	Low-grade dyskaryosis	CIN 1
HSIL	High-grade dyskaryosis (moderate)	CIN 2
HSIL	High-grade dyskaryosis (severe)	CIN 3
HSIL, SCC	High-grade dyskaryosis/?invasive SCC	SCC

ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude HSIL; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma.

Glandular lesions

Although the natural history and biology of glandular lesions is less clear, attempts have been made to mirror the range of cellular changes of the squamous into the glandular mucosa (cervical glandular intraepithelial neoplasia or cGIN). The Bethesda 2001 [5] system classifies glandular cytological abnormalities into four subcategories: atypical glandular cells (AGC); AGC, favour neoplastic; endocervical adenocarcinoma *in situ* (AIS); and adenocarcinoma. The BAC/NHSCSP 2013 classification system divides the glandular lesions into two groups, borderline changes and glandular neoplasia (Table 61.2).

Cervical cancer screening

Traditionally, cytology relied on the assessment of exfoliative smears on glass slides under the microscope, as first described by Papanicolaou in the 1940s. Liquid-based cytology has largely replaced conventional cytology in recent years. The technique has many advantages. It is semi-automated, creates a uniform spread of epithelial cells that are easier to read by cytotechnicians and cytopathologists, and reduces the rate of unsatisfactory samples. The fluid can also be used for reflex testing for HPV DNA and other biomarkers.

It is expected that cervical screening based on HPV DNA tests will replace cytology-based screening in the future, at least in women above the age of 30. Large randomized controlled trials and a meta-analysis of these documented the superiority of HPV-based screening when compared with cytology, with a 60–70% better protection against invasive disease. The optimal way of triaging women that test positive for high-risk HPV remains to be determined and some options include reflex cytology, HPV-16/HPV-18 genotype positivity or newer biomarkers. The use of HPV mRNA tests in primary screening has also been suggested but longitudinal data are required.

The age of screening initiation and the frequency of screening intervals vary across countries [2,4]. In the UK, for example, screening starts at the age of 25. Screening does not start earlier as the risk of invasive cancer at younger ages is small, while many lesions spontaneously regress without treatment in this age group [3]. Sentinel pilot sites are testing the introduction of HPV-based screening with reflex cytology for those that test positive for HPV. This may allow further extension of the screening interval to 5 years if women test negative (Table 61.3).

The current indications for referral for colposcopy in the UK are:

- one cervical sample showing borderline nuclear changes in squamous cells that are high-risk HPV positive;
- one cervical sample showing mild dyskaryosis changes in squamous cells that are high-risk HPV positive;
- one cervical sample showing mild dyskaryosis changes in squamous cells with unreliable, inadequate or no results for HPV test;
- three cervical samples showing borderline nuclear changes in squamous cells with unreliable, inadequate or no results for HPV test;
- one cervical sample showing borderline nuclear changes in endocervical cells;
- one cervical sample showing moderate or severe dyskaryosis;
- one cervical sample showing possible invasion;
- one cervical sample showing glandular neoplasia;
- three consecutive inadequate cervical samples;
- any grade of dyskaryosis following treatment for CIN;

Table 61.2 Cervical cytology: classification of glandular lesions according to Bethesda and BAC/NHSCSP nomenclature.

Bethesda 2001	BAC/NHSCSP 2013
AGC NOS	Borderline changes in endocervical cells
Endocervical	? Glandular neoplasia
Endometrial	Endocervical type
Glandular	Non-cervical
AGC favour neoplastic	
Endocervical	
Glandular	
Endocervical AIS	
Adenocarcarcinoma	
Endocervical	
Endometrial	
Extrauterine	
NOS	

AGC NOS, atypical glandular cells, not otherwise specified; AIS, adenocarcinoma *in situ*.

Table 61.3 Screening intervals in the UK proposed by the National Institute for Health and Care Excellence.

Age (years)	Screening interval recommended
Under 25 s	No screening
25	First invitation
25–49	Three yearly
50–64	Five yearly
Over 65 s	No screening

- three abnormal cervical samples of any grade over a 10-year period;
- suspicious symptoms and abnormal cervix.

Colposcopy

Hinselman first introduced colposcopy early in the last century (1925). Colposcopy comprises low-power magnification and illumination of the lower genital tract after application of various stains: acetic acid (3–5%) and Lugol's iodine. Apart from refinements to the optical and illumination systems and the introduction of a green filter that can enhance the vascular appearance, there has been little technological advancement since. New technologies (such as DySiS and Zedscan) are being assessed and have potential to improve the accuracy and reproducibility of the colposcopic assessment.

The objectives of colposcopic assessment are to:

- assess the presence and severity of the abnormalities detected on cytology;
- guide colposcopically directed biopsies from the area with the most severe changes;
- exclude invasive disease;
- aid in outpatient management and treatment of CIN;
- assist follow-up after treatment.

Colposcopy is deemed satisfactory when the entire squamocolumnar junction is visualized and the upper limit of any lesion is seen. The size and topography of the lesion should be ascertained, especially if there is any extension of the lesion into the cervical canal or onto the vagina. Both of these clinical scenarios are important in relation to appropriate treatment. Colposcopic abnormalities maybe graded according to a variety of indices, such as the appearance of the aceto-white epithelium, iodine negativity and vascular patterns such as mosaic, punctation and atypical vessels. The area between the original and the new squamocolumnar junction after replacement of the columnar epithelium after puberty by metaplastic squamous epithelium is called the transformation zone and should be described as type I, II or III [6].

The colposcopic assessment is subjective and prone to intra-observer variability, particularly in the diagnosis of low-grade as opposed to high-grade lesions. The predictive accuracy improves with the increased severity of the anticipated lesion. Agreement between the colposcopic impression and histology is achieved in only 37% of cases, while agreement within one grade is 75%. Formal training and a period of apprenticeship leads to certified expertise in this technique.

Management and treatment

One in ten women in the UK have an abnormal result at screening. Of these, 2–3% will present with high-grade findings at cytology and the remaining 7% with cervical samples classified as ASCUS or LSIL or their British terminology equivalents of borderline and mild dyskaryosis [7].

The management of the minor cytological abnormalities that are common in young women has challenges. Although the majority represent clinically insignificant lesions, some can harbour high-grade disease. Their management consumes a disproportionate amount of health resources, although their significance remains debatable. An HPV DNA test has recently been introduced in many countries to assist the selection of women with these minor abnormalities that should be further investigated with colposcopy. Women who test negative for high-risk oncogenic HPV types return to routine recall. Further management of confirmed CIN 1 lesions varies and depends on the woman's age, the length of persistence of the disease and her fertility wishes. Young women who have not yet completed their families are usually managed conservatively with surveillance. Older women or women at high risk of non-compliance with persistent disease may undergo treatment.

Most women with histologically high-grade lesions (defined as CIN 2+) will undergo treatment and CIN 2 on a biopsy is often considered the clinical threshold to proceed to treatment. Exceptions may apply in selected cases of young women with small CIN 2 lesions. Increasingly, clinicians manage carefully selected cases with close surveillance, as the regression rate in young women with small lesions is high.

Local conservative cervical treatment for CIN aims to remove or ablate the entire transformation zone and lesion with a cone-shaped part of the cervix to a depth of more than 7 mm to ensure eradication of CIN that may involve the gland crypt. The majority of the techniques are easy to perform, of low cost and are usually performed under local anaesthesia in an outpatient setting. The peak age of CIN is similar to the mean age of having the first child in Western societies. It is therefore important that the proposed treatment will eradicate the preinvasive disease with the minimum disruption in cervical function.

The treatment methods are divided into excisional and ablative (Table 61.4). Both have high cure rates of over 90% and have similar treatment failure rates, with the exception of cryotherapy for high-grade disease. The choice of technique relies on patient characteristics, the colposcopic appearance, the depth, severity and size of the lesion, the type of transformation zone, the age and fertility wishes, the clinician's experience/preference and the equipment available.

The need to maximize clinical resources, achieve quicker and more effective management of patients, limit postoperative complications and preserve reproductive function has led to the popularity of local

Table 61.4 Excisional and ablative treatment techniques.

Excisional
Large-loop excision of the transformation zone (LLETZ), Europe; loop electrosurgical excisional procedure (LEEP), USA
Needle excision of the transformation zone (NETZ); straight wire excision of the transformation zone (SWETZ)
Laser conization
Cold knife conization
Hysterectomy
Ablative
Cryocautery
Radical electrodiathermy
Cold coagulation
Carbon dioxide laser ablation

excisional methods for cervical premalignancy. Most centres use large loop excision of the transformation zone (LLETZ), as this is quick, easy to learn, of low cost and well tolerated. Excisional techniques provide a histological sample that allows the precise grading of the lesion, assessment of the excision margins, and the ability to confirm with certainty the absence of microinvasive or glandular disease. This further allows clinicians to adopt a 'see and treat' approach in appropriate cases at the initial visit. In contrast, ablative techniques destroy the cervical epithelium and demand pretreatment biopsies at a separate initial visit with the risk of noncompliance. Furthermore, punch biopsies under-diagnose the severity of the lesion in 20% of cases compared with the histology of the large loop.

Excisional techniques

The use of excisional methods only is indicated in cases of repeat conization, unsatisfactory colposcopy, suspected invasion, glandular epithelium involvement, and when there is discrepancy between cytology, colposcopy and biopsy. The specimen should ideally be removed as a single sample. After treatment, women should avoid intercourse, insertion of menstrual tampons and use of swimming pools for 4–6 weeks.

- *LLETZ/LEEP* using low-voltage apparatus is now the most widely practised technique. It is performed under local anaesthesia. There are different available sizes of loops. There should be minimal artefactual damage to the specimen and the cervix, and roller ball can be used for haemostasis.
- *NETZ/SWETZ* is a recent modification that uses a straight wire rather than a loop. This technique allows shaping of the excision, which can be particularly useful in asymmetrical lesions.
- *Laser conization* follows the same principle as LLETZ and NETZ, but can be technically more demanding, takes longer to perform and requires equipment that is expensive to buy and maintain.
- *Cold knife conization* is used rarely but particularly in cases of suspected invasion and glandular disease. The lack of diathermy minimizes the thermal artefact and allows accurate assessment of the excision margins. However, there is a comparatively increased risk of haemorrhage and reproductive morbidity, and the procedure can only be done under general anaesthesia and requires hospitalization.
- *Hysterectomy* still retains a place in the management of CIN in women who have other gynaecological conditions such as fibroids, menorrhagia or prolapse. It may also be used in cases of glandular lesions where fertility does not need to be spared, especially in cases of treatment failure or incomplete excision. It is important to ensure complete excision of the cervix, the transformation zone and any vaginal lesion; the preferential route is vaginal hysterectomy or laparoscopically assisted vaginal hysterectomy preceded by colposcopic assessment.

Ablative techniques

Ablative treatment may be an option in selected cases when the transformation zone and the lesion are fully visible, the colposcopy satisfactory and there is no discrepancy between cytology, colposcopy and histology. These techniques are contraindicated in women with glandular lesions, suspicion of invasion or history of a previous cone and where pretreatment biopsies are required.

- *Cryotherapy* destroys tissue by freezing using probes of various shapes and sizes, and is probably best reserved for small low-grade lesions as the rates of clearance of CIN 3 are poor in comparison to other techniques. The duration of freeze is 2 min from the appearance of the ice ball. A freeze–thaw–freeze technique is advocated as this increases the cure rate. Despite these reservations, the technique is worthy of consideration, especially in low-resource settings as cryoprobes are cheap and widely available.
- *Electrodiathermy* requires general, regional or local anaesthesia. Under colposcopic control it is possible to destroy up to 1 cm depth using a combination of needle and ball electrodes. The apparatus required is cheap and easy to maintain but thermal necrosis may be considerably more than anticipated and more difficult to control.
- *Cold coagulation*: in this technique, heat at 100–120 °C is applied to tissue using a Teflon-coated thermosound for 30 seconds. The procedure is easy and does not usually require analgesia.
- *Laser ablation*: a micromanipulator attached to the colposcope is used to manipulate the laser and treatment

is conducted under direct vision. As the technique is precise, it gives good control over depth of destruction, good haemostasis and excellent healing, with minimal damage to the adjacent tissue. The technique is particularly useful in lesions that extend to and involve the vagina. The vaginal epithelium does not have gland crypts and, as a result, a depth of destruction of about 2–3 mm is usually sufficient. Despite these benefits, the cost of the equipment and maintenance is high and not readily available in most units.

Complications of treatment

The complications of CIN treatment are rare, and are divided into early and late complications.

Early

- Perioperative pain.
- Primary haemorrhage (<1%) that is usually easily controlled with the use of ball diathermy, nitrate sticks and Monsel's solution. Haemostatic sutures may be required in difficult cases.
- Secondary haemorrhage usually presents within 2 weeks from treatment and is usually related to infection. This generally settles with a course of broad-spectrum antibiotics.

Late

- Cervical stenosis and, consequently, inadequate colposcopy. This is more common in cases of cold knife conization, in deep or repeat excisions and especially in cases where haemostatic sutures were required. Difficulties in obtaining sufficient cytological samples and unsatisfactory colposcopy reduce accuracy of follow-up and fertility problems may also occur.
- Reproductive morbidity: although treatment does not appear to adversely affect fertility and ability to conceive, all techniques have been correlated with an increased risk of second-trimester miscarriage and preterm birth. The risk appears to increase with increasing cone depth and is higher for excisional compared with ablative techniques [8–10]. Clinicians should therefore balance the risk and benefits of treatment for different lesions and minimize the removal of healthy tissue.

Follow-up after treatment

After CIN treatment women remain at higher risk of recurrent/residual disease and invasive cervical cancer as compared with the general population. Several risk factors have been associated with high risk of recurrence and these include positive margins for disease, particularly in the endocervix, glandular disease, large lesions, age over 40 and grade of the disease. Although the risk for high-grade recurrence is substantially increased in women with involved as opposed to clear margins (18% vs. 3%), repeat conization is not recommended, with the exception of women over 50 who have positive endocervical margins for high-grade disease [11].

The majority of therapy failures (90%) are detected within 24 months from treatment. Traditionally, women with a history of treatment were followed up closely for 10–20 years after their treatment. More recently, HPV DNA test with or without cytology has been introduced in most countries as a 'test of cure' and allows early discharge of women who test negative back to routine recall and better detection of those at high risk of recurrence.

Cytology after treatment is less accurate and sampling should ensure good representation of endocervical cells, particularly when treatment was conducted for glandular disease. In the case of HPV positivity or cytological abnormality, a colposcopic assessment should be undertaken. Colposcopic assessment is technically more difficult in women who have undergone treatment. Foci of CIN and/or invasive disease may be buried under an apparently normal epithelium. The transformation zone may be difficult to visualize in its entirety due to scarring and because it often retracts deep in the endocervical canal.

Challenging clinical groups

Glandular disease

The incidence of glandular disease is increasing and the epidemiology of invasive adenocarcinoma is changing, with a higher incidence now recorded in women under 35. Of cervical tumours, 20–30% are now classified as adenocarcinoma or adenosquamous carcinoma. These lesions have a more aggressive course than their squamous counterparts and a poorer prognosis that may partly reflect frequent delays in diagnosis. HPV-18, in particular, has been associated with glandular lesions. The evidence on how to best manage these relatively uncommon lesions is rather limited.

Atypical glandular cytology may be suggestive of invasive cervical adenocarcinoma or adenocarcinoma *in situ*. Other conditions often seen on this cytology include CIN and endometrial pathology. If endometrial cells are seen on the cytology report in a postmenopausal woman not taking hormone replacement therapy, this may indicate endometrial disease and should be investigated appropriately. If borderline glandular changes (AGC) are present, colposcopic assessment with appropriate cervical biopsies and selective endometrial biopsy are indicated. Colposcopic findings are usually non-specific

(e.g. stark aceto-whiteness in fused villi) but colposcopy is always essential, as a high percentage of these women have concomitant CIN. Punch biopsy in the setting of atypical glandular cytology is unreliable, as the lesions are often small and may occur in the base of gland crypts. Excisional conization for diagnosis and treatment is recommended.

The majority (90%) of these lesions are located within 1 cm of the squamocolumnar junction and coexist with CIN, although they can be found potentially anywhere in the endocervical canal. Women with glandular lesions can be managed conservatively with local excision provided adequate close surveillance is possible. The excision margins should be free from disease; if involved, further excision is recommended. If the family is complete, the option of hysterectomy can be considered. Hysterectomy should be also considered if the disease recurs and if surveillance with cytology is compromised by cervical stenosis.

Cervical pre-invasive disease in pregnancy

Women who have an indication for colposcopy and are pregnant should undergo the procedure. The aim of this examination is to exclude invasion, while biopsy and/or treatment should be postponed until the postnatal period. Colposcopy should be performed by an experienced clinician as more pronounced aceto-white changes due to increased vascularity can often lead to over-diagnosis. If invasive disease is suspected, a suitably sized biopsy is required. This can be a cone, a wedge or LLETZ and is diagnostic rather than therapeutic. All these may be associated with a risk of haemorrhage and miscarriage and suitable facilities to deal with this situation should be available in a theatre setting. Punch biopsy is not a reliable method of excluding invasive disease.

HPV vaccines

The discovery that HPV is causally associated with cervical cancer led to the development of HPV vaccines. The introduction of prophylactic vaccination is the latest important landmark in the history of prevention of cervical cancer. To date, two vaccines have been developed and clinically evaluated, the quadrivalent vaccine (HPV 16/18/6/11, Gardasil) and the bivalent vaccine (HPV 16/18, Cervarix). Results from trials indicate that the vaccine is safe, well tolerated and highly efficacious in HPV-naive women. The optimal target age is the prepubertal woman before coitarche, while it will remain an individual decision for older women. The first country to introduce a national HPV immunization programme was Australia in both males and females in 2007. In the UK, this was initiated in September 2008 in females only. Data from Australia, Denmark and other countries that implemented the vaccination revealed an 80–90% reduction in the incidence of anogenital warts (for quadrivalent vaccine). More recently, vaccinated populations were found to have significant reduction in the incidence of HPV infection and high-grade pre-invasive disease. The nonavalent vaccine (Gardasil 9) that includes a further five high-risk subtypes in the vaccine cocktail (31, 33, 45, 56, 58) was launched in 2016. Several studies are exploring the use of therapeutic vaccines in women with existing high-grade disease.

Vaccination and screening are complementary strategies and synergy in a cost-effective manner will be required for the next few decades. Further research to assess screening strategies in vaccinated cohorts is needed. The introduction of vaccination is especially important in the developing countries, but affordability remains a major issue.

Summary box 61.1

- Persistence of oncogenic HPV infection appears to be the necessary but not sufficient cause of cervical cancer.
- For the local treatment of cervical precancerous lesions, a depth of at least 7 mm is recommended to ensure eradication of CIN from gland crypts.
- Women should be aware that CIN and its treatment increase the risk of reproductive morbidity in a subsequent pregnancy.
- The incidence of glandular lesions of the cervix is increasing. Their natural history is less understood. Treatment should be balanced against the woman's age and fertility wishes. Close follow-up is necessary; the cytology should include endocervical cells.
- HPV DNA test has been introduced as a 'test of cure' in the follow-up after treatment and as a triage tool for women with ASCUS or LSIL findings at screening in many countries.
- HPV DNA has better accuracy than cytology in primary screening and will replace cytology; the optimum way of triaging women who test positive for HPV in primary screening is still unclear.
- The introduction of prophylactic vaccination is the latest important landmark in the history of prevention of cervical cancer.

Malignant disease of the cervix

Cervical cancer remains the second commonest female malignancy worldwide. Three-quarters of affected women live in developing countries that experience the major burden of disease. The disease primarily affects

younger active women and therefore the total years of life lost is proportionately higher than that for most other cancers with a later onset.

Countries with established screening programmes face different challenges, including improving the outcome for women with advanced disease, preserving fertility in younger women who increasingly bear the greatest burden of disease, and incorporating advances in medical technology such as positron emission tomography (PET) and minimal access surgery. The realization that persistent infection with oncogenic high-risk HPV is causally associated with cervical cancer has undoubtedly been the most significant advance globally that led, more recently, to the development of prophylactic vaccines.

Epidemiology

Cervical cancer is the seventh most frequent cancer worldwide, with an estimated 528 000 new cases leading to 266 000 deaths in 2012. The mortality is substantially lower than the incidence; worldwide, the ratio of mortality to incidence is 55%. Cervical cancer still remains an important public health issue in Europe, with more than 66 000 new cases and 29 000 deaths annually. The majority of these cases are diagnosed in eastern European countries where there are no screening programmes. In the UK in 2006, there were 2873 registrations, and 941 deaths in 2007. The incidence rate for cervical cancer peaks between 30 and 40 years of age, declines in incidence in older age groups but peaks again in the over-80 age group [12,13].

Pathological subtypes

The majority of cervical cancers are squamous in origin, but adenocarcinomas appear to be increasingly common, accounting for approximately 10–20% of all primary cervical cancers. This increase partly reflects an increased awareness of the disease. Adenocarcinoma is more likely to be diagnosed in younger women and has a largely poorer prognosis in comparison with cervical squamous carcinoma, which partly reflects the delay in diagnosis. Cytology screening programmes were designed to detect squamous lesions and, as a result, the endocervical distribution of glandular abnormalities reduces their accuracy. Specific oncogenic HPV types, in particular HPV-18, have been related to adenocarcinoma. Primary screening with HPV DNA test has been shown to improve the detection of glandular intraepithelial neoplasia and allows significantly better prevention of adenocarcinomas than cytology-based screening.

The rare but aggressive small-cell neuroendocrine-type squamous carcinoma typically behaves like similar disease arising from the bronchus. Adenocarcinomas can be pure, but a significant proportion (40%) have mixed adenosquamous cells, the adenosquamous carcinoma. Adenocarcinomas include many more histological subtypes than squamous cancers. About 80% are made up of cells of the endocervical type with mucin production (Table 61.5).

Clinical presentation and diagnosis

The symptoms associated with cervical cancer are common and non-specific and usually manifest in late-stage disease. Early-stage disease may be asymptomatic and suspected on a cervical cytology sample or diagnosed following treatment for cervical pre-invasive disease, commonly in the form of LLETZ. The classical signs and symptoms are irregular vaginal bleeding, especially post-coital, and abnormal appearance of the cervix. Invasive cancer is rare in women with post-coital bleeding, but assessment is merited as it is much more common in this group than in the general population. These symptoms are also common in women with *C. trachomatis* infection. Discharge and pain are often associated with more advanced disease.

Diagnosis requires a biopsy for histopathological review by an experienced gynaecological pathologist. The biopsy needs to be large enough to demonstrate stromal invasion and often an appropriately sized loop diathermy (LLETZ) may be used. The optimal biopsy site is often the edge of the tumour, which allows assessment of the transition from invasive to non-invasive tissue. Central biopsies may reveal only premalignant or necrotic material, though often there may be no alternative. The tumours may bleed briskly after biopsy and occasionally require packing. In very early disease, a cone with loop diathermy (LLETZ), knife (cold knife conization) or diathermy needle (NETZ) can be diagnostic but also curative. Biopsies in a pregnant patient are

Table 61.5 Histological subtypes of cervical cancer and frequency.

Histological subtypes	Frequency (%)
Squamous cell carcinoma	80–85
Adenocarcinoma	10–15
Adenosquamous	5
Other rare types	5
Small cell	
Primary sarcomas	
Primary and secondary lymphomas	

important if invasion is suspected, but should be performed by an experienced clinician as significant bleeding may occur.

Staging procedures and patterns of spread

Having established the diagnosis, the next step is to stage the disease, as this determines the ongoing management and helps to assess prognosis and exchange of information among health professionals.

Cervical cancer is still staged clinically using the International Federation of Gynaecology and Obstetrics (FIGO) system (Table 61.6). Traditionally, this included procedures such as pathology review, examination under anaesthesia with combined rectovaginal examination, cystoscopy, proctoscopy, chest radiography and perhaps intravenous urography. In current practice in most Western countries, all women diagnosed with cervical cancer undergo MRI and CT, while complex/advanced cases are also often offered PET-CT to determine the extent of the disease. Although the imaging results cannot change the clinical FIGO staging, they are often used to plan management. MRI has high accuracy (90%) in describing the size, stage and extent of disease and permits detailed assessment of lymph nodes; it is obviously superior to CT and has commonly made examination under anaesthesia combined with cystoscopy redundant. PET-CT seems to enhance the accuracy in diagnosing involved lymph nodes and extracervical disease but more robust studies are required.

Several studies have described the use of sentinel node biopsy, which may be assessed by open or laparoscopic surgery. Some authors have reported 100% accuracy, but this technique is assessed only in the frame of research trials at present. In more advanced cancers, retroperitoneal or transperitoneal laparoscopic staging has been used to plan the field of radiation. Although several studies have reported survival benefit following debulking of large nodes prior to radiation, the only available randomized controlled trial showed surgical staging to be negatively correlated with outcome compared with non-interventional assessment. PET-CT seems to be an alternative, accurate, non-invasive assessment tool to surgical staging.

Table 61.6 FIGO staging for cervical cancer.

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
Stage Ia	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm
Stage Ia1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
Stage Ia2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
Stage Ib	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage Ia*
Stage Ib1	Clinically visible lesion ≤4.0 cm in greatest dimension
Stage Ib2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
Stage IIa	Without parametrial invasion
Stage IIa1	Clinically visible lesion ≤4 cm in greatest dimension
Stage IIa2	Clinically visible lesion >4 cm in greatest dimension
Stage IIb	With obvious parametrial invasion
Stage III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney†
Stage IIIa	Tumour involves lower third of the vagina, with no extension to the pelvic wall
Stage IIIb	Extension onto the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
Stage IVa	Spread of the growth to adjacent organs
Stage IVb	Spread to distant organs

* All macroscopically visible lesions, even with superficial invasion, are allotted to stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue (superficial or glandular). The depth of invasion should always be reported in millimetres, even in those cases with 'early (minimal) stromal invasion' (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
† On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Table 61.7 Incidence of nodal disease in cervical cancer according to stage.

Stage	Positive pelvic lymph nodes (%)	Positive para-aortic lymph nodes (%)
Ia1 (<1 mm)	0	0
Ia1 (1–3 mm)	0.6	0
Ia1 (LVSI positive)	4	0
Ia2 (3–5 mm)	4.8	<1
Ia2 (LVSI positive)	11	<1
Ib	16	2.2
IIa	25	11
IIb	31	19
III	45	30
IVa	55	40

LVSI, lymphovascular space invasion.

Cervical cancers proliferate in the following ways.

1) Direct spread into the cervical stroma, parametria and beyond, into the vagina, body of the uterus, bladder and rectum.
2) Lymphatic spread into parametrial, pelvic side wall and para-aortic nodes. The incidence of pelvic lymph node and para-aortic disease according to stage is illustrated in Table 61.7.
3) Blood-borne spread is unusual.

Management and treatment

The principles of management are:

- tertiary review of pathology;
- staging;
- establishing the aim of treatment (i.e. curative or palliative);
- consideration of patient factors, such as age, fertility wishes, obesity, surgical and medical history, health status, preference;
- treatment of local and possible metastatic disease;
- presenting the patient with suitable options.

Specialized multidisciplinary gynaecological oncology teams should assess all these factors and determine the optimum management for each woman tailored to her individual characteristics. Decisions on how best to treat early disease in young women, especially when fertility-sparing techniques are considered, require considerable experience.

In principle, treatment options vary for each stage. An excisional cone is sufficient for treatment of microinvasive disease (stage Ia1) provided the margins are clear. The management of stage Ia2 disease is more controversial. Surgery and radiation have similar survival rates for stage Ib–IIa disease, while the combination of both increases morbidity. A large randomized controlled trial reported that radiation therapy and radical hysterectomy were equally effective in terms of 5-year overall and disease-free survival rates. Surgery has obvious advantages: it permits conservation of ovarian function in premenopausal women, the preservation of fertility in selected cases, and also reduces the risk of chronic bladder, bowel and sexual dysfunction associated with radiotherapy. Surgery provides a histological sample and permits the assessment of risk factors, such as lymph node status, that influence prognosis. Complications in the hands of skilled surgeons are uncommon. Late-stage tumours (IIb–IV) should be treated with chemoradiation as this is related to improved survival but also higher short- and medium-term toxicity in comparison with radiotherapy alone. Fertility-sparing surgical techniques such as radical trachelectomy may be appropriate in selected cases.

A more detailed description of the treatment options is described in the following sections.

Stage Ia (Ia1 and Ia2)

In early cervical cancer, surgical excision alone can be curative. Correct staging and identification of early disease allows the selection of a group of women who are not at risk of lymph node disease and can be treated with less aggressive and, importantly, fertility-sparing therapy. There are two aspects to consider: adequate removal of local disease, and identification and treatment of distant disease.

In stage Ia1, the risk for lymph node involvement is virtually zero. Consequently, complete excision of the invasive and pre-invasive disease with clear margins is commonly sufficient. The options of treatment include excision with knife or diathermy/laser or simple hysterectomy depending on the woman's wishes and fertility aspirations. The knife cone is often advantageous in this setting, as the absence of thermal damage allows a more accurate assessment of the extent of invasion in comparison with a diathermy excision specimen. However, on many occasions, microinvasion is only diagnosed retrospectively as an incidental finding after loop excision for pre-invasive disease. Small adenocarcinomas can probably be treated in a similar manner. If disease is present at the margins, further excision or hysterectomy is recommended. If lymphovascular space invasion (LVSI) is present, the risk of nodal disease rises to 3.6%; although some clinicians advocate node dissection in this setting, the possible benefits must be balanced against morbidity and the risk of lymphoedema.

In stage Ia2, management of the disease is more controversial. The risk of pelvic lymph node involvement in

this stage rises to approximately 5%. A very conservative approach cannot be adopted; the pelvic lymph nodes must be surgically removed and assessed, while management of the primary tumour remains less clear. When fertility preservation is an issue, radical trachelectomy and pelvic node dissection by a vaginal, laparoscopic or abdominal approach may be considered. Laparoscopic pelvic lymphadenectomy followed by a deep cold-knife conization has also been proposed, but high-quality evidence is still lacking. If fertility is not an issue, radical hysterectomy, or possibly simple hysterectomy and pelvic lymphadenectomy, should be recommended.

Stage Ib–IIa

Patients with stage Ib–IIa disease have two options: primary surgery or chemoradiotherapy depending on the individual characteristics, comorbidities and preferences.

Surgical options

Radical hysterectomy and pelvic lymphadenectomy Radical hysterectomy and pelvic lymphadenectomy ensures complete excision of the tumour with adequate margins. There should be at least 5 mm clear margin from the tumour. The pelvic lymph node dissection should include obturator, internal, external and common iliac nodes. Para-aortic lymphadenectomy is not mandatory.

Complications, even in the hands of skilled surgeons, are significant and include haemorrhage and direct trauma to the bowel, bladder, ureter or obturator nerve. Chronic bowel and bladder problems that require medical or surgical interventions occur in up to 8–13% of women due to parasympathetic denervation secondary to surgical clamping at the lateral excision margins. Prolonged bladder dysfunction requiring long-term intermittent self-catheterization is reported in 2.6% of patients overall and can be very distressing. Lymphoedema as a late complication that usually develops in the first year after surgery occurs in up to 15% of patients and is permanent. Although it is most commonly relatively mild, symptoms can be quite severe and significantly affect quality of life in 3% of patients. Lymphocysts can also occur. Sexual function and psychological issues such as grieving over loss of fertility, altered body image and reduced vaginal size are not uncommon. The risk of fistula is about 1%.

Surgical approaches are now moving towards less aggressive, nerve-sparing techniques. The evidence reveals that more radical approaches offer no survival benefit and often lead to higher incidence of perioperative morbidity and chronic bladder and bowel dysfunction. The Piver–Rutledge classification for radical hysterectomy is widely used; newer classifications have also been proposed (Querleu–Morrow) [15] (Tables 61.8 and 61.9).

A large multicentre randomized controlled trial initiated in Canada (SHAPE) is expected to clarify whether simple as opposed to radical hysterectomy and pelvic lymph node dissection is as safe in the management of women with low-risk small-volume disease.

Table 61.8 Piver–Rutledge classification of hysterectomy for cervical cancer.

Type	Description
1	Extrafascial hysterectomy; removal of all cervical tissue
2	Modified radical hysterectomy; removal of medial 50% of the cardinal and uterosacral ligaments; uterine vessels are divided medial to the ureter
3	Equivalent to the classical Wertheim–Meigs operation; wide radical resection of the parametrium and paravaginal tissues; ureter dissected completely to bladder entry; uterosacral ligaments divided at origin; cardinals divided at pelvic side wall
4	Ureter divided from pubovesical ligament; superior vesical artery ligated and upper two-thirds of vagina excised
5	More radical procedure with possible bowel, bladder or ureteric dissection

Radical trachelectomy In other sites such as the breast and the vulva, the surgical treatment of cancer has become less radical and consists of wide local excision and regional lymphadenectomy/sentinel lymph node dissection without an adverse effect on cure rates. Gynaecological oncologists have attempted to apply the same principle for stage Ia2 and small-volume stage Ib cervical tumours by adopting more conservative fertility-sparing techniques [14]. Advanced maternal age and detection of early-stage disease as a result of screening increasingly enhance the value of these techniques.

Radical trachelectomy was first described by D'Argent in the mid-1980s and involves a radical excision of the cervix combined with either laparoscopic or open lymphadenectomy [17]. The commonest route of trachelectomy is the vaginal approach, though more recently some surgeons are favouring an abdominal or laparoscopic approach that facilitates a greater excision of the parametrium. The insertion of abdominal or vaginal suture at the level of the isthmus that can accommodate a 6-mm Hegar dilator is recommended in an attempt to prevent cervical incompetence. Intraoperative complications are rare. Postoperatively, about one-quarter of women suffer dysmenorrhoea or, less commonly, cervical stenosis, suture-related problems and dyspareunia.

Meta-analyses and case series based on the vaginal approach have demonstrated recurrence rates of around 4%, with mortality of 2.3%. Most recurrences have occurred in high-risk pathological types, with tumours over 2 cm in size and in patients with LVSI. Of those

Table 61.9 Querleu–Morrow classification of radical hysterectomy (2008).

Type A	Minimum resection of paracervix. This is an extrafascial hysterectomy. The paracervix is transected medial to the ureter but lateral to the cervix. The uterosacral and vesicouterine ligaments are not transected at a distance from the uterus. Vaginal resection is generally at a minimum, routinely less than 10 mm, without removal of the vaginal part of the paracervix (paracolpos)
Type B	Transection of the paracervix at the ureter. Partial resection of the uterosacral and vesicouterine ligaments, ureter is unroofed and rolled laterally, permitting transection of the paracervix at the level of the ureteral tunnel. At least 10 mm of the vagina from the cervix or tumour is resected
Type C	Transection of paracervix at junction with internal iliac vasculature system. Transection of the uterosacral ligament at the rectum and vesicouterine ligament at the bladder. The ureter is mobilized completely. Between 15 and 20 mm of vagina from the tumour or cervix and the corresponding paracolpos is resected routinely, depending on vaginal and paracervical extent
Type D	Laterally extended resection. Rare operations feature additional ultra-radical procedures. The most radical corresponds to the laterally extended endopelvic resection (LEER) procedure
Lymph node dissection	
Level 1	External and internal iliac
Level 2	Common iliac (including presacral)
Level 3	Aortic infra-mesenteric
Level 4	Aortic infra-renal

This classification can be applied to fertility-sparing surgery and can be adapted to open, vaginal, laparoscopic or robotic surgery.

attempting pregnancy, 70% delivered at term; the risk of premature delivery, late miscarriages and low birthweight is substantially increased.

Careful selection of patients is crucial as detailed assessment may optimize outcomes and minimize adverse events. These decisions necessitate involvement of a multidisciplinary specialized team with considerable experience.

Stage Ib2

Management of bulky Ib tumours (especially stage Ib2) is controversial as these tumours are characterized by high rates of positive nodes and close surgical margins. Most centres offer chemoradiotherapy as opposed to surgery but a few elect to operate; these centres have published equivalent survival data.

Prognostic factors

After surgery, histological examination of the specimen provides information on several prognostic factors that affect survival and these are discussed later. If the histology review suggests high risk of recurrence with positive pelvic nodes and 'close' resection margins (≤0.5 cm), women are commonly offered adjuvant chemoradiation. Many institutions use the GOG score, which assesses factors such as size of tumour, depth of invasion and LVSI and gives the combination score that facilitates clinician decision-making.

Stage IIb–IV

Surgery with curative intent is not possible in women with advanced stages of disease. The available treatment modalities that offer potential of cure are radical radiotherapy and chemoradiation. Stage IVb is treated palliatively, often with a combination of chemotherapy and targeted radiotherapy.

Radical radiotherapy

Radical radiotherapy aims to treat the primary tumour and metastatic pelvic lymph nodes. It is delivered by external-beam radiotherapy (teletherapy) that intends to treat any pelvic spread and by intracavitary treatment (brachytherapy) that targets the primary site. The challenge of optimal dose planning is to cure the primary disease and pelvic spread with the least possible morbidity to bowel, bladder and sexual function. The external-beam radiotherapy sessions to the pelvis are delivered daily, usually over 20–30 days, and are followed by brachytherapy, delivered locally to the cervix by high-dose radiotherapy technique. Extended radiotherapy involving the para-aortic nodes increases morbidity with no significant survival benefit. However, it may be appropriate in selected cases if para-aortic node involvement is indicated by PET scan and surgical staging.

Chemoradiation

There is now consensus that the use of concurrent cisplatin-based chemotherapy with radiotherapy is superior to radiation alone for the treatment of cervical cancer [16]. Five randomized phase III trials from the USA have shown an overall survival advantage with chemoradiation that decreased the risk of death by 30%. Allowing variations in exact schedule, dose of treatment and stage across different studies, they largely included women with FIGO stages Ib2–IVb cervical cancer treated with

primary radiotherapy and women with FIGO stages I–IIa disease found to have poor prognostic factors (metastatic disease in pelvic lymph nodes, parametrial disease or positive surgical margins) at the time of primary surgery. As expected, higher rates of short-term and medium-term morbidity have been reported, although long-term follow-up data that are awaited will help clarify the true morbidity of this treatment regimen.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is the use of chemotherapy before definitive surgical treatment or radiotherapy. It has not been shown to be beneficial before radiotherapy and current evidence does not support such an approach. It has also been suggested that preoperative chemotherapy could be used to shrink disease and allow resectability of the tumour prior to radical surgery in inoperable cases and that this approach may be superior to radical radiotherapy. One randomized controlled trial suggested benefits but this has not been confirmed and inevitably the toxicity for those women who will require adjuvant radiotherapy seems unacceptable. Centres have also reported the use of neoadjuvant chemotherapy in women with bulky tumours prior to fertility-sparing techniques with good results.

Cervical cancer in pregnancy

Cancer of the cervix affects 1 in 10 000 pregnancies and represents about 1 in 34 cases of cervical cancer. Two-thirds of women diagnosed in the first or second trimester have a stage 1b tumour. Diagnosis may be delayed, as the symptoms may be attributed to the pregnancy and colposcopic assessment of the pregnant cervix is not always easy; advice should be obtained from an experienced colposcopist. If invasion is suspected, an adequate biopsy in the form of loop, knife or wedge cone should be taken. The principles of management remain the same and treatment is similar stage for stage.

The disease can be safely staged at examination under anaesthesia, with a chest radiograph and by MRI. For stage Ia1 disease, despite a high rate of positive margins, a LLETZ or knife cone is usually sufficient. Traditionally, more advanced stages presenting before 20 weeks' gestation are treated immediately, those presenting after 28 weeks are treated after delivery, while those presenting between 20 and 28 weeks remain in a grey zone. For stage I disease, diagnosed after 20 weeks, delaying treatment until after delivery is often the most favourable option. Delivery around 32–34 weeks is justified after administration of steroids to promote fetal lung maturation. Caesarean radical hysterectomy is recommended after delivery of the fetus by classical incision. Chemoradiation will cause spontaneous miscarriage or fetal death.

The management of cervical malignancy in pregnancy remains a challenge to the patient, the family and the multidisciplinary team involved. Careful and sensitive counselling is essential. Decisions on continuing or terminating the pregnancy and the modality of treatment should be made on an individual basis.

Follow-up and management of recurrent disease

The evidence on the role of post-treatment surveillance in the detection of recurrent disease is inconsistent, although follow-up enables much more than just detection of recurrent disease. It permits assessment of the complications of treatment and the psychological, physical and psychosexual morbidity and provides reassurance. There is no role for cervical or vaginal vault cytology in the follow-up period except in women who had fertility-sparing procedures.

In cases of suspected recurrence, MRI provides the most sensitive imaging modality that allows careful assessment of disease distribution and is required before considering further treatment. In confirmed cases, PET-CT is commonly required for the assessment of distant metastases and improved patient selection before planning radical treatment for apparently localized disease. The evidence demonstrates that this improves survival in operable cases and eliminates morbidity related to unnecessary interventions in unsuitable patients. Before considering further treatment, histological diagnosis is required followed by full re-staging.

The principles of the management of recurrent disease are similar to those of the primary tumour. The exact treatment depends on the primary treatment, the site and stage of the recurrence, the presence of distant disease, its resectability, treatment-related morbidity and the effect on quality of life, and the patient's general health and wishes.

Women treated initially with surgery should be considered for radiotherapy. If the disease is apparently confined to the pelvis, radical chemoradiotherapy is curative in 40–50% of cases. For those who have already undergone radiotherapy, the only potentially curative option is pelvic exenteration in some cases, provided the recurrence is central with no distant recurrence. Careful selection of cases and appropriate counselling is essential. In the hands of skilled surgeons and appropriate preoperative assessment, this surgery can result in a 5-year survival of 50%. However, up to one-third of procedures are abandoned intraoperatively; PET-CT appears to help patient selection.

Palliation

In progressive advanced cervical disease, urinary tract symptoms, fistulae and distressing pain due to infiltration

of the lumbosacral nerve plexuses are some of the common presentations. Ureteric obstruction and impaired renal function usually herald the terminal stage. Faeces and urine diversion with nephrostomies and stenting are only justified in cases where there is curative intent. Chemotherapy with cisplatin is also palliative and should be restricted to primary late stage or recurrent cases that are not considered curable with other treatment options. It may increase life expectancy by a few months, but this must be balanced against quality of life. Pain control and psychological and emotional support are of paramount importance in the terminal phase.

Survival and prognostic factors

The 1- and 5-year overall survival in patients with cervical cancer according to FIGO stage is shown in Fig. 61.5. Several prognostic factors influence survival.

- Stage of disease.
- Size, volume and depth of invasion of the tumour.
- Grade of tumour.
- Histological type: small cell tumours have clearly been shown to be associated with a worse prognosis.
- Lymphatic spread is probably the most important factor: the presence of positive nodes significantly reduces overall survival and LVSI is an additional prognostic factor.
- Parametrial invasion.
- Vascular invasion.
- Status of resection margins in cases where surgery was performed.

Psychological impact

Because cervical cancer usually affects young women, psychological morbidity is substantial and emotional support is essential, considering the significant effects of loss of fertility and early menopause. Treatment has a huge impact on the women's psychological and sexual well-being, with up to 50% of women suffering dyspareunia due to vaginal stenosis after chemoradiation. These issues often need to be addressed by clinicians and in some cases referral to a counsellor might be necessary [18].

The future

The single greatest advance in the prevention of cervical cancer during the last decade has been the development of the prophylactic vaccine against two oncogenic HPV subtypes, HPV-16 and HPV-18. It is estimated that this could reduce the incidence of cervical cancer by 70% in a high coverage population.

The use of MRI has improved the accuracy of the staging of cervical cancer. New imaging techniques such as PET-CT appear to improve the assessment of metastatic disease; this seems to be of value in the selection of the radiation field, particularly with regard to para-aortic node inclusion. PET appears also to be helpful in recurrent cases as the detection of disseminated disease influences management.

More conservative surgical approaches that can reduce morbidity might prove to be equally efficient. Research on the optimal management of early-stage, small-volume, low-risk cervical invasive disease is under investigation in a large randomized controlled trial. If this reveals no difference in outcomes, simple hysterectomy may replace the radical excision of the parametrium in selected low-risk cases. The use of conization or simple as opposed to radical trachelectomy is also under investigation in women who wish to preserve their reproductive potential. The use of neoadjuvant chemotherapy prior to fertility-sparing techniques has also been reported but further evidence is required on safety. Efforts to improve outcome for women with advanced disease, use of sentinel nodes and incorporation of medical technology advances such as PET-CT are some of the challenges of the future.

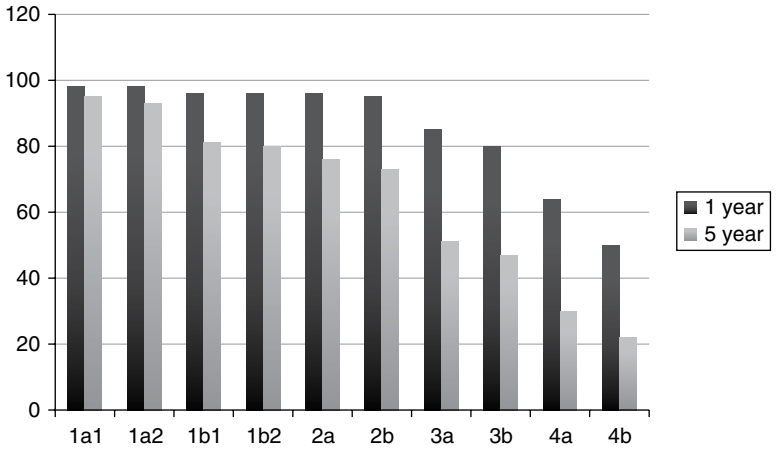

Fig. 61.5 Carcinoma of the cervix: overall survival by FIGO stage.

Summary box 61.2

- Cervical cancer is the second commonest malignancy worldwide; 75% of the cases are diagnosed in countries of the developing world that reflects the absence of screening.
- Adenocarcinomas appear to be increasingly common, accounting for approximately 20–30% of all primary cervical cancers, and have a poorer prognosis.
- Microinvasive disease can be treated by excisional cone alone.
- Surgery and chemoradiation for stage Ib–IIa disease have similar survival rates. Surgery has many advantages. Careful staging is important and allows selection of the most appropriate treatment modality as the combination substantially increases morbidity without survival benefit.
- Advances in imaging with MRI and PET-CT have improved management.
- Preservation of fertility is an option with fertility-sparing surgical techniques. Careful patient selection is required.
- The combination of chemotherapy and radiation significantly improves survival in comparison with radiotherapy but also has short- and medium-term toxicity.
- Management in pregnancy remains a challenge and decisions should be individualized.
- The disease and its treatment can have a huge physical and psychological impact on women.

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62

Endometrial Cancer

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In the UK there were over 9000 cases of endometrial cancer in 2015, which means that it is now the commonest gynaecological malignancy (Fig. 62.1). Some plausible explanations include the overall increased life expectancy, obesity and also the reduction in death rates from other related malignancies, in particular breast cancer. Combined with this is the 50% reduction in the rates of hysterectomy since the early 1990s [1]. Whilst the disease affects mainly postmenopausal women, approximately 20% of cases occur in premenopausal women. The staging of endometrial cancer (using the FIGO classification) has become well embedded in practice since its introduction in 2009 [2]. Recent and ongoing randomized clinical trials continue to try to identify the optimum therapeutic approaches to care, which though primarily surgery still require an evidence base as emphasized by the international variations in care [3]. There has also been progress in understanding the genetics of endometrial cancer, and in recent years an acceptance that some tumour types, in particular serous histologies, should be considered – in surgical management terms at least – somewhat similar to serous ovarian cancers. This chapter provides some updates on the management of this disease.

Aetiology

The recognized risk factors for endometrial cancer are shown in Table 62.1. Besides these, there are other environmental factors that influence the disease, as suggested by the variation in the disease in different countries (Fig. 62.2). The main risk is excessive exposure of the endometrium to oestrogen, which has a direct association with both obesity and diabetes. Other factors such as older age and hypertension are inter-related with the factors above. Age remains the main risk factor, with the highest incidence recorded in women over the age of 50 years.

Genetics

Only one condition has been specifically identified as having a hereditary relationship with the development of endometrial carcinoma. Known as hereditary non-polyposis colon carcinoma or Lynch type II syndrome, this is an autosomal dominant condition; the main associated primary malignancy is colonic carcinoma, normally developing in women under 40 years of age. The Amsterdam criteria are used to define those families who conform to the definition of this condition, with the final diagnosis genetically determined and including a variety of mutations, of which *MSH2* and *MLH1* are the commonest [4].

In such families the lifetime risk of developing endometrial carcinoma is about 40%, and also relevant is the fact that the lifetime risk of developing ovarian cancer is 12%, nearly 10 times the population risk. At present there are no strategies except prophylactic surgery to prevent these women developing endometrial cancer. Reports on a small series of women with this condition undergoing annual scans and endometrial sampling concluded that such an approach seemed to detect earlier cancers, suggesting that screening may be beneficial. However, the paucity of cases makes this very much an assumption, though an acceptable approach in managing those women desiring to retain reproductive function. A possible alternative is the potential of the Mirena® intrauterine system in preventing the disease in such women [5,6]. A clinical trial to evaluate this failed to recruit and was abandoned. Although this is intuitively a reasonable approach, women agreeing to this therapy need to be informed of the limited evidence. When the woman's family is completed, recommending a hysterectomy is a reasonable course of action, removing any need for ongoing unproven screening systems and likely alleviating the psychological aspects associated with the potential to develop this disease. The increased risk of ovarian cancer may also justify removal of the ovaries,

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Fig. 62.1 Rates of endometrial cancer in the UK. *Source:* Cancer Research UK.

Table 62.1 Risk factors for endometrial cancer.

High levels of oestrogen/endometrial hyperplasia
Obesity/hypertension/diabetes
Polycystic ovary syndrome [5]
Nulliparity (never having carried a pregnancy)
Tamoxifen use/breast cancer
Post-menopausal
Hereditary non-polyposis colorectal cancer

though each case must be managed in accordance with the woman's needs and wishes.

Nulliparity

Nulliparity is associated with a risk of endometrial cancer. However, this may only be one of many factors involved, with some relationship to the individual's hormonal profile during life. Nulliparous women have significantly increased episodes of endometrial shedding events during their menstrual lives in comparison with parous women. In ovarian cancer, there is a direct association between the lifetime number of ovulatory cycles and the risk of ovarian cancer (the higher the number of ovulatory cycles, the greater the risk), and this could be also applied to the risk of endometrial cancer.

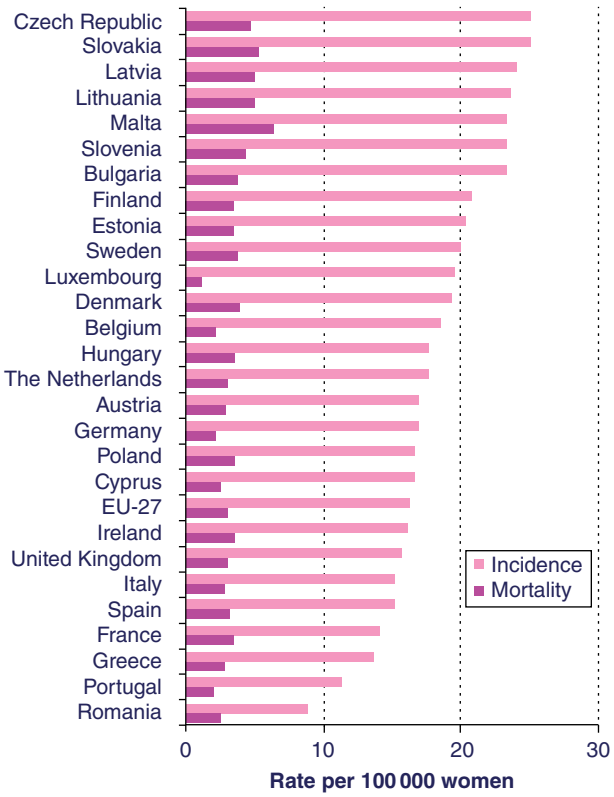

Fig. 62.2 Age-standardized (European) incidence and mortality rates, body of uterus cancer, EU-27, 2008 estimates.

The follicular phase of the cycle exhibits increasing proliferation (which increases the probability of abnormal cellular development) and strategies which reduce this may protect against abnormal mitosis. While this remains to be proven in endometrial cancer, it is a reasonable hypothesis. Of course, the use of the combined oral contraceptive, even with menstruation, affords some long-term protection (risk reduction of 50%) giving some support to the theory.

Obesity

Obesity is thought to be related to the development of about 30% of cancers in humans. In obese women, excess oestrogen is produced by the conversion of androgens in the fat, and thus the endometrial tissue has increased exposure to estrone. This is particularly pertinent considering the increased incidence of obesity in the Western world, and the concomitant increased rates of endometrial cancer.

Endometrial hyperplasia

Hyperplasia is defined as excessive proliferation of normal cells, and atypical hyperplasia is associated with a high risk of endometrial cancer. In a number of series, the risk of underlying malignancy has been shown to be higher than expected. A Gynecologic Oncology Group study in the USA of 348 women diagnosed with atypical hyperplasia on sampling were eventually found to have a frank malignancy in 46.8% of cases [7]. Similar data from the UK showed a risk of 45.9% [8]. Thus it may be preferable to consider these patients as having endometrial cancer and expedite surgery.

Clinical presentation

Postmenopausal bleeding is the commonest presentation in endometrial cancer, and up to 10% of these women will have a diagnosis confirmed. As such, their access to diagnostics must be deemed urgent. The final diagnosis is confirmed by histology. Based on the UK National Institute for Heath and Care Excellence (NICE) guidelines, all women with postmenopausal bleeding should have a transvaginal ultrasound and those with an endometrial thickness greater than 5 mm should undergo sampling of the endometrium. However, many use a cut-off of 4 mm, based on cost-efficacy and detection rates. Sampling can be undertaken in three ways: Pipelle, outpatient hysteroscopy or hysteroscopy and curettage under a general anaesthetic. All methods of sampling will miss some cancers but the rate of failure is not significantly different between outpatient sampling and hysteroscopy. Naturally, avoiding a general anaesthetic is preferable where possible and only patients in whom an endometrial sample cannot be obtained in outpatients should hysteroscopy under a general anaesthestic be considered, accepting the inevitable exceptions.

Abnormal bleeding in the premenopausal women, particularly intermenstrual bleeding in women over the age of 45, should prompt investigations including ultrasound and endometrial sampling. Whilst the overall incidence of malignancy in this group is small, nevertheless about 20–25% of all endometrial cancers occur in the premenopausal/perimenopausal age group.

Types of endometrial cancer

Endometrial cancer is categorized into type I and type II disease. The defining factors associated with these are shown in Table 62.2.

The main histological subtypes are shown in Table 62.3 and some of these may well be related to certain agents. In particular, the use of adjuvant tamoxifen in breast cancer has been proposed to be associated with some of the rarer tumours such as mixed Müllerian tumours, now called carcinosarcomas. There are no specific indicators regarding the other subtypes. Leiomyosarcomas are usually an unexpected finding following removal of a fibroid uterus. The mitotic activity of these tumours relates to their metastatic potential, with mitotic counts of less than 5 per high power field associated with a very good outcome, whereas a count above 10 per high power

Table 62.2 Endometrial cancer types.

Type I
Premenopausal and perimenopausal women
History of unopposed oestrogen exposure
Endometrial hyperplasia
Minimally invasive, low-grade endometrioid type
Good prognosis
Type II
Postmenopausal women
Not associated with increased exposure to oestrogen
High-grade tumours
Poorer prognosis

Table 62.3 Histological subtypes in endometrial cancer.

Endometrioid adenocarcinoma, 50–60%
Adenosquamous, 6–8%
Serous papillary, 18%
Sarcomas/leiomyosarcomas, 3–5%
Carcinosarcomas, 2–3%
Clear cell, 1–6%

field is associated with a worse prognosis. Other subtypes recognized as more aggressive include papillary serous and clear cell tumours, accounting for 10–15% of all tumour types. In most cases adjuvant therapies (after surgery) would be considered.

In some rare cases of sarcomas, preoperative diagnosis may be suspected when the endometrial sampling indicates this diagnosis histologically, or when a preoperative chest X-ray shows evidence of metastatic disease, normally called 'cannon-ball' metastases. The differentiation of the disease is also important, as the grade in association with other factors will influence the recommendation for adjuvant therapy.

Management

Preoperative investigations

The FIGO staging for endometrial cancer is shown in Table 62.4. This was redefined in 2009, with positive cytology, previously allocated to stage III disease, now abandoned as part of the staging process. As part of staging, there are agreed preoperative investigations which can be performed. A chest X-ray is recommended, although a CT scan may replace this. MRI/CT can be of value in some situations to ascertain if any extrauterine disease exists, which may influence the role of surgery. The value of MRI in defining the depth of tumour invasion has been examined with a view to deciding the need to excise lymph nodes but it has proved too inaccurate to be of clinical value.

Table 62.4 Carcinoma of the endometrium, FIGO staging 2010.

Stage	Description	5-year survival (%)
IA	Tumour confined to the uterus, no or less than half myometrial invasion	80–90 (I)
IB	Tumour confined to the uterus, greater than half myometrial invasion	
II	Cervical stromal invasion, but not beyond uterus	60–70 (II)
IIIA	Tumour invades serosa or adnexa	50–60 (III)
IIIB	Vaginal and/or parametrial involvement	
IIIC1	Pelvic node involvement	
IIIC2	Para-aortic involvement	
IVA	Tumour invasion bladder and/or bowel mucosa	10–20 (IV)
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes	

Besides these investigations, cystoscopy, sigmoidoscopy and an examination under anaesthetic are all part of the staging procedure. Notably, endometrial cancer can be staged both clinically and surgically, with surgical staging being most commonly employed.

Surgical interventions

Surgery remains the primary intervention for endometrial cancer. Whilst radiotherapy is an alternative, from retrospective case–control studies it would seem that surgery affords a better survival outcome. It is unlikely that there will ever be a randomized controlled trial comparing primary radiotherapy to surgery.

The removal of the uterus and (normally) the ovaries is the recommended basic surgical procedure. This may be performed by open laparotomy or by a laparoscopic approach. Studies have shown the advantages regarding short- and long-term recovery when the laparoscopic approach is taken, which may entail either a laparoscopic-assisted vaginal hysterectomy or a laparoscopic total hysterectomy [9,10]. Robotic surgery has also become part of the surgical approach, but the consensus is that where possible the minimally invasive approach is preferable. Obviously, it is recommended not to insert any instruments into the uterine cavity during such surgery. Also, clamping/ligating the fallopian tubes at commencement of surgery would seem a reasonable action to prevent any disease dissemination when moving or handling the uterus.

In some circumstances, the procedure could be performed vaginally, and indeed this is acceptable as long as the ovaries can be removed. However, a vagina-only approach will not permit access to the pelvic lymphatics, thus limiting this type of surgery to selected patients.

Lymphadenectomy in endometrial cancer

The risk of lymphatic spread in endometrial cancer is influenced by the tumour grade, type and depth of invasion into the uterine wall (Table 62.5). Knowledge of lymphatic disease forms part of the staging process and can influence adjuvant therapy. However, debate still

Table 62.5 Lymph node metastases in endometrial cancer.

Variable	Pelvic/para-aortic nodal disease (%)
<50% uterine invasion and grade1	0–3
<50% uterine invasion and grade2/3	2–6
>50% uterine invasion and grade 1	15–18
>50% uterine invasion and grade2/3	up to 30

surrounds the value of routine pelvic and para-aortic lymphadenectomy, and randomized trials are required to resolve this issue.

There has only been one prospective randomized trial reported on lymphadenectomy in endometrial cancer. This study, called ASTEC (A Surgical Trial in Endometrial Cancer), randomized over 1400 women with clinically early-stage disease [11]. The study included two parts: (i) patients randomized to pelvic lymhadenectomy or not, and (ii) patients randomized to adjuvant pelvic radiotherapy or not in high-risk cases. The use of brachytherapy (outome reported in Blake *et al.* [12]) was permitted and the decision made locally as to whether this was used. The patient cohort receiving radiotherapy were not necessarily those recruited to the surgical aspects of the study. The conclusions were interesting in that the use of lymphadenectomy did not alter survival rates, and indeed it was suggested that it may have a negative impact on outcome, for reasons yet to be explained. Also, the number of lymph nodes retrieved did not influence outcome. Although the study was confined to patients with disease localized to the uterus (based on clinical examination and imaging in some cases), it does indicate that lymphadenectomy should not be undertaken in this group of patients.

Lymphadenectomy and non-randomized studies

There are many non-randomized reports on the role of lymphadenectomy of pelvic and para-aortic nodes in endometrial cancer. All these studies naturally suffer from the fact that there are no randomized controlled trials. Some groups suggest that, in particular, para-aortic nodal excision has a therapeutic effect, based on the fact that those who undergo this therapy have longer survival and a notable reduction in relapse disease affecting the para-aortic region [13]. Also, such resection either permits the avoidance of adjuvant radiotherapy in some cases, or identifies those where the radiotherapy field can be extended to incorporate the para-aortic region. The main problem with these debates is the lack of appropriate high-level evidence that lymphadenectomy has a real therapeutic effect on survival and indeed that extension of the field of radiotherapy influences survival. Without doubt both these procedures increase morbidity. There is an urgent need to address this issue and ensure patients are been managed in a manner whereby the morbidity of the intervention can be justified by the improved patient outcome. It can be anticipated that such trials will be undertaken in the near future.

Debulking in advanced disease

When the disease has obvious macroscopic spread beyond the uterus or indeed the pelvis, then multimodal therapy will be required, be this surgery to alleviate symptoms followed by radiotherapy with or without chemotherapy. The combination of chemoradiotherapy increases morbidity, and in endometrial cancer this poses major challenges, as many patients have other comorbidities whereby such a combination may be deemed inappropriate. Debulking surgery, an approach taken in ovarian cancer for some decades, has been reported in some small series in endometrial cancer, with a suggestion that a smaller residual tumour load correlated with a better survival outcome. This is based primarily on retrospective data or small case–control studies and the evidence for this is very poor. There is no agreement that this should be considered accepted therapy for endometrial cancer at present. However, even in advanced disease, removal of the uterus may yield immediate alleviation of symptoms such as persistent vaginal bleeding, which could justify the intervention.

Fertility-sparing surgery

As women are increasingly delaying having children, the issue of fertility-sparing options has become more common, and this is relevant to many other malignancies. There are limited publications relating to such management and the number of cases is small, making firm conclusions difficult. Longer-term outcomes are equally lacking and therefore before embarking on this therapeutic option, it is imperative to provide the patient with advice based on current information and the 'unknown' risks, particularly as this is a deviation from the normal recommended intervention that could potentially exclude the patient from a recommended curative therapy.

In those cases reported, the disease was always well differentiated and on clinical and imaging evaluations confined to the uterus (i.e. FIGO stage 1). Women were then exposed to various progestagenic agents, with careful evaluation of response by curettage at 6 weeks, 3 months and 6 months from commencement of therapy [14]. Evidence of non-response resulted in immediate surgery and in those with response some pregnancies are reported. A hysterectomy was normally performed following a successful pregnancy.

Radiotherapy

Primary

Radiotherapy can be used either as a primary or adjuvant therapy. In primary therapy, this is normally where disease spread renders surgery impossible or inappropriate. It is not considered superior to surgical intervention, with an estimated reduction in 5-year survival of about 5% when compared with surgery in early-stage disease, though this is based on retrospective series.

Adjuvant

The use of radiotherapy in an adjuvant setting continues to be modified. Original studies indicated that the use of brachytherapy with external-beam pelvic radiotherapy may be beneficial in those with high-grade disease. This original study from the 1980s by Aalders *et al.* [15] randomized 540 patients with early-stage disease to brachytherapy versus brachytherapy and external-beam therapy after undergoing surgery. The relapse rates in the latter group was reduced, although overall 5-year survival was equivalent in both groups. Further analysis suggested that patients with grade 3 tumours infiltrating greater than 50% of the myometrium might benefit from the addition of pelvic radiotherapy.

Two recent trials, the PORTEC and ASTEC trials, have changed the role of adjuvant radiotherapy [12,16]. In the PORTEC study, 715 women with stage I disease were recruited and randomized to pelvic radiotherapy versus no treatment after undergoing a hysterectomy and bilateral salpingo-oophorectomy. The 5-year survival rates were 81 and 85%, respectively. The recurrence rates were lower in the radiotherapy groups (4% vs. 14%), but in those relapsing and then receiving radiotherapy the survival was the same. Analysis showed that radiotherapy was not necessary in women with stage I endometrial cancer who were below 60 years of age with grade 1 or 2 tumours and with more than 50% myometrial invasion.

The ASTEC study had two parts where patients were randomized, the second looking at external-beam therapy to the pelvis. All had undergone surgery, consisting of at least a total hysterectomy and bilateral salpingo-oophorectomy. The conclusions were that the routine use of external beam with brachytherapy reduced the incidence of recurrent disease, and increased the disease-free survival, but did not have any positive impact on overall survival. The authors also suggested that there may be a possible survival benefit in those with high-grade disease.

Chemotherapy

When distant metastatic disease is present, systemic treatments are required. For endometrial cancer, chemotherapeutic agents or hormonal therapies are used. Cisplatin and doxorubicin are the commonest cytotoxics used, with medroxyprogesterons the most used hormonal therapy [17–19]. Many trials reporting systemic therapies are small phase II studies, and the overall response rates range from 7 to 69% depending on the study. As previously stated, the comorbidities within this patient cohort often means that hormonal therapy is the best option due to its ease of administration and lack of adverse side effects.

Many smaller series have suggested that the combination of radiotherapy with chemotherapy may improve outcome, by reducing local pelvic recurrences and also extra-pelvic disease relapse. Such effects have been proven in chemoradiotherapy as used in cervical tumours. PORTEC 3 is an ongoing prospective randomized trial that compares standard radiotherapy with combination treatment, and the results should hopefully give guidance to the best option.

Relapsed endometrial cancer

The main issues with respect to deciding the best therapy for a patient with relapsed endometrial cancer are (i) prior exposure to non-surgical interventions, (ii) the site of disease relapse, whether localized or multiple, and (iii) the patient's physical condition. Thus investigations used are similar to those within the staging system, though where available positron emission tomography (PET) can be useful in selected situations.

The commonest site of relapse is the vaginal vault and if the disease is localized and the area radiotherapy-naive, radiation is the first course of intervention. If the disease is localized but has previously undergone radiotherapy, then surgical excision (partial vaginectomy) can be performed. If there are distant metastases, then systemic therapy is necessary and depending on the patient's physical condition either chemotherapy or hormonal therapies can be used. The response rates are variable but never very high, and the effect is poorer for disease relapsed within a field of radiotherapy.

Exenterative surgery [20], when bladder, vagina and rectum are excised, is only undertaken in very carefully selected patients, and may be occasionally justifiable as a palliative procedure. In the main, many patients have such comorbidities that such surgery is generally deemed unsuitable.

Conclusion

Endometrial cancer is a disease increasing in incidence though retains a relatively good prognosis. Primary intervention is mainly surgical, with selected patients having adjuvant therapies. Advances in surgical techniques continue to reduce surgically associated morbidity, though in a population with rising obesity, maintaining morbidity rates is challenging. In some early-stage disease lymphadenectomy is unnecessary, but in higher-risk populations trials are required to

define the role of lymphadenectomy, both pelvic and para-aortic. Randomized trials are redefining the role of adjuvant therapies; in particular the role of chemotherapy in high-risk patients is awaited. Prevention is inevitably the ultimate goal, and can be partially achieved through educational health policies in reducing the incidence of obesity. In the future, screening may detect premalignant or early-stage disease and thus also improve survival rates. However, the latter still requires further research to establish the optimum modalities to employ. Inevitable, the future will also include a greater understanding of the disease and improved individualized therapy, focused more on the actual disease biology rather than based purely on the disease stage and histological subtype.

Summary box 62.1

- Endometrial cancer is now the commonest gynaecological cancer due to many factors: obesity, reduced hysterectomy rates and longevity.
- Surgery remains the mainstay of therapeutic intervention.
- Clinical trials have revealed the limited value of pelvic lymphadenectomy in early-stage disease and the outcome of trials on lymphadenectomy in high-risk patients is awaited.
- Adjuvant radiotherapy is still used, although trial results regarding its benefit in combination with chemotherapy in high-risk patients are awaited.

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63

Surgical and Medical Management of Epithelial Ovarian Cancer

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Epithelial cancer of the ovary, fallopian tube or primary peritoneum, collectively described as 'ovarian cancer' or EOC throughout this chapter, is relatively uncommon. It represents 2% of total cancer cases in the UK (data from 2013) but is the most lethal of all gynaecological cancers. This is partly due to its insidious presentation but also because of its intrinsic histological and molecular heterogeneity [1]. EOC comprises at least five distinct histological subtypes (high-grade serous, endometrioid, clear cell, mucinous, seromucinous and low-grade serous), the most common and well studied being high-grade serous ovarian cancer (HGSOC). For the majority of patients after successful initial treatment with debulking surgery and chemotherapy, the disease will relapse and become increasingly resistant to chemotherapy with each episode of recurrence. Future treatment strategies, as well as improving response to front-line therapy, are focusing on ways to overcome chemotherapy resistance in the relapsed setting, with the judicious use of novel cytotoxic and/or targeted therapies. These options are realized with improvements in our understanding of the molecular behaviour of the disease. In this chapter, we summarize the current status quo of the surgical and medical management of ovarian cancer and present results from a number of key studies that have explored genetic, molecular and histological targeted strategies in the treatment of this disease.

Aetiology, epidemiology and genetics

EOC is diagnosed in approximately 7300 women every year in the UK and 239 000 women worldwide (www.wcrf.org). Although EOC is relatively uncommon, representing 2% of total cancer cases in the UK (data from 2013), it has a 46.2% age-standardized 5-year survival in the UK (www.cancerresearchuk.org) and the USA (www.seer.cancer.gov), indicating that more than half of patients diagnosed with the disease die within 5 years. It is generally a disease of older women, the incidence peaking at the age of 67 years [2,3]. There is geographic variation: it is more common in developed countries such as in northern Europe and in the USA, where rates exceed 9 per 100 000 women, than in developing countries such as parts of Africa and Asia [3]. As incessant ovulation is a contributing factor, the geographical variation is most likely due to differences in parity rates, with women in developed countries electing to have smaller families and therefore undergoing a higher number of ovulation events during their lifetime.

In large case–control studies, factors that interrupt ovulation like multiparity, breastfeeding, late menarche and early menopause reduce the risk of EOC [4]. The Collaborative Group on Epidemiological Studies of Ovarian Cancer conducted a re-analysis of 45 epidemiological studies and showed that 10 years of use of the oral contraceptive pill (OCP) gives a 33% reduction in risk of incidence of EOC before the age of 75. They estimate that the OCP has prevented 200 000 cases of EOC so far, and will prevent at least 30 000 cases per year in the future in developed countries [5]. Although the overall incidence of EOC has risen since the late 1970s, between 1997–1999 and 2011–2013 there has been an 8% decline in the European age-standardized incidence of the disease (www.cancerresearchuk.org). This most likely reflects the impact of the introduction of the OCP into UK family planning clinics from 1974 and its adoption by women who are now approaching their fifties and sixties. As use of the OCP has increased exponentially since then, the incidence of EOC is predicted to decline further. However, this decline may be reversed in future decades if intrauterine devices replace the OCP as the preferred method of contraception.

Factors linked to increased risk of the disease include late conception, smaller family size, obesity and use of

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

hormone replacement therapy (HRT), although the latter is still controversial, with data from a recent meta-analysis suggesting that women who use hormone therapy for 5 years from age 50 years have approximately one extra ovarian cancer case per 1000 women [6–8]. Less significant risk factors include increased height and weight (contributing to a 3% increase in the disease per decade [9]) and use of peritoneal talcum powder [10]. Interestingly, a recent analysis of epidemiological studies by histotype suggests that incessant ovulation risk factors are more predominantly linked to endometrioid and clear cell ovarian cancer [11] whilst the commonest and most lethal HGSOC has fewer associated risk factors.

Genetic factors dominate risk for 5–15% of EOCs, associated with three main inherited defects to DNA damage repair genes, *BRCA1* and *BRCA2* gene mutations (associated with site-specific ovarian cancer syndrome and breast–ovarian cancer syndrome) and mutation of mismatch repair (MMR) genes (associated with type 2 Lynch syndrome or hereditary non-polyposis colorectal cancer) [12]. The introduction of more widespread *BRCA* testing and the recent availability of commercial genomic testing kits (e.g. 23andMe) means that many women are presenting to clinicians with the knowledge they are at increased genetic risk of EOC.

It has been suggested that 50% of patients with sporadic HGSOC (i.e. who have not inherited a genetic mutation) have acquired the disease because of somatic alteration to either *BRCA* genes or other homologous recombination-associated genes such as *ATM*, *RAD51* and *FANC* [13,14]. This phenomenon is described as 'BRCAness' and is caused by a variety of mechanisms, such as somatic mutations, gene methylation or other epigenetic mechanisms, as well as downstream pathway alterations [15,16].

Summary box 63.1

- Risk of EOC (particularly endometrioid and clear cell histotypes) corresponds to number of lifetime ovulation events.
- Thus low parity, late parity, early menarche and late menopause are factors associated with increased cancer risk, whilst breastfeeding, multiparity and use of OCP are protective factors.
- Other minor risk factors include obesity, use of HRT, tall stature and use of peritoneal talcum powder.
- Between 5 and 15% of cases of EOC are caused by inherited genetic factors: *BRCA1* and *BRCA2* mutations and, less commonly, mismatch repair gene mutations.
- Tubal ligation is associated with reduced risk of endometrioid and clear cell ovarian cancer.
- Somatic aberrations to *BRCA* and other DNA repair genes have been identified in up to 50% of cases of HGSOC.

Subclassification of ovarian cancer

EOC is being increasingly recognized as consisting of a diverse group of tumours rather than a single tumour. Traditionally, it is classified by its histological features such as grade and type (e.g. high-grade serous, endometrioid, clear cell, seromucinous, low-grade serous, mucinous) and this is still the predominant information used to guide clinical care. In 2004, Shih and Kurman, pathologists from Johns Hopkins University, described a dualistic model in which EOC was further divided into two subtypes according to both its morphology and genetic features [17]. This has recently been updated by the authors [18] (Table 63.1).

Type I tumours comprise low-grade serous, endometrioid, clear cell, mucinous and transitional carcinomas. Apart from clear cell and mucinous cancers, these tumours behave in an indolent fashion, lack *TP53* mutations, are confined to the ovary at presentation and are relatively genetically stable. They are believed to originate from benign lesions such as endometriosis or a cystic ovarian neoplasm, sometimes via an intermediate step of borderline disease. In contrast, type II tumours comprise high-grade serous, undifferentiated, and malignant mixed mesodermal tumours (carcinosarcomas). These are highly aggressive and usually present at an advanced stage with a high frequency of *TP53* mutations.

The availability of genomic databases (e.g. The Cancer Genome Atlas, TCGA) has enabled further division of EOC into molecular subtypes (C1–6), four of which reclassify HGSOC into 'immunoreactive', 'differentiated', 'proliferative' and 'mesenchymal' subtypes [19]. Further analyses of these four subtypes have demonstrated association with survival outcome, the mesenchymal type having the poorest prognosis [20]. However, these subtypes are not, as yet, used to guide treatment decisions. As well as the high degree of genetic alterations, there is also a significant post-translational contribution to the ovarian cancer phenotype that is not captured in gene expression data.

Clinical presentation

EOC has often been described as a 'silent killer', with approximately 75% of patients being diagnosed at a late stage (stage III/IV). The current 5-year survival for EOC is 30–40%, but that of early-stage disease (e.g. stage I) is 84–94%, indicating a bias towards late diagnosis. This is mainly because the symptoms and signs of early-stage EOC are subtle or absent whereas those of advanced EOC include abdominal distension due to bowel gas or ascites, a pelvic mass, abnormal bowel sounds, difficulty in passing urine, palpable abdominal masses, lymphadenopathy, pleural effusion, an umbilical mass

Table 63.1 Subclassification of ovarian cancer.

Tumour type	**Type 1**						**Type 2**		
Histological classification	Endometrioid carcinoma	Clear cell carcinoma	Seromucinous carcinoma	Low-grade serous carcinoma	Mucinous carcinoma	Brenner tumours	High-grade serous carcinoma	Carcino-sarcoma	Undifferentiated carcinoma
Tissue of origin	Endometriosis	Endometriosis	Endometriosis	Fallopian tube	Germ cell/ transitional cell	Transitional cell	Fallopian tube	Fallopian tube	Fallopian tube
Features	Typically low grade, low proliferative activity, possible to identify early, slow and indolent growth						Typically high grade, high proliferative activity, good response to chemotherapy (but frequently recur), challenging to detect early, rapid and aggressive growth		
Common molecular pathway aberrations	MMR deficiency Wnt-catenin pathway activation, inactivating ARID1A, PI3K pathway activation, PTEN pathway inactivation			ERB2/KRAS/BRAF/MEK pathway activation		Unknown	Extensive genomic variations, HR DDR deficiency, P53 inactivation, CCNE1, NOTCH3 activation, Rb, NF1 inactivation	Unknown	Unknown

Source: modified from Kurman & Shih [18].

(Sister Joseph's nodule) and, rarely, intra-abdominal organomegaly. A number of ovarian cancer charities have championed increasing awareness of these symptoms amongst women and their primary care providers in the hope this will lead to earlier diagnosis, reduction in treatment-related morbidity and an increase in survival from the disease. The current guidance for primary care providers seeing women with symptoms suspicious of ovarian cancer recommends abdominopelvic examination, transvaginal ultrasound scan (TV-USS), serum CA125 test and, if any of these are abnormal, referral to the local gynaecology service.

Summary box 63.2

Symptoms associated with ovarian cancer

- Abdominal distension.
- Abnormal bowel sounds.
- Difficulty in passing urine.
- Dyspnoea from pleural effusion.
- Palpable lymphadenopathy.

CA125: ovarian cancer tumour marker

CA125 is a serum glycoprotein and the current gold-standard biomarker for EOC. Although it is an approved test both for the differential diagnosis of a pelvic mass and as a serial response marker in patients undergoing treatment for EOC, it has poor specificity for the disease. It is elevated in other benign and malignant ovarian and non-ovarian related conditions [21–23]. For this reason, as a stand-alone test, CA125 is neither adequate for diagnosis nor for screening (as described below). In addition, CA125 is elevated in only 80% of women with established EOC, and in only 50% of those with early-stage disease. In patients whose CA125 is elevated at diagnosis (i.e. raised above the normal range of 0–35 IU/L), serial CA125 measurement is a useful means of assessing response to chemotherapeutic treatment. The Gynecological Cancer Intergroup have developed criteria using change in CA125 as a validated measure of response to anticancer treatment. This is often used in combination with Response Evaluation Criteria In Solid Tumors (RECIST) criteria as a clinical outcome measure in EOC studies [24,25]. Levels of CA125 have been shown to have some prognostic significance [26], although other measures such as stage of disease at diagnosis are better predictors of survival outcome. Routine evaluation of CA125 (in those who express the marker) is performed in patients attending clinic for surveillance having completed treatment for front-line or relapsed EOC. An elevated CA125 is often the first warning of disease relapse, shown to precede emergence of symptoms by an average of 4.8 months [27]. Other markers have been evaluated for use in combination with CA125 to diagnose EOC, the most well-known being human epididymis 4 (HE4), a marker of proliferation in ovarian cancer cells. When used in combination with CA125 as a diagnostic, HE4 has been shown to marginally improve on the specificity of CA125 alone [28], particularly in discriminating endometriosis from malignancy. However, the lack of prospective evidence of superiority compared with existing methods of diagnosis (ultrasound, etc.) means HE4 is not approved for use as a diagnostic. However, in non-NHS settings, the HE4 test is being used in combination with CA125 calculated using the ROMA algorithm, to assist in the non-surgical evaluation of ovarian masses, even though recent evidence suggests that the combination is no better than CA125 alone [29,30]. Various studies have explored other combinations of markers but none have so far proved superior to CA125.

Summary box 63.3

CA125

- Serum CA125 is approved in the differential diagnosis of pelvic masses and as a means of monitoring response in patients receiving treatment for ovarian cancer.
- Levels of CA125 above 35 IU/L are considered abnormal.
- CA125 is relatively non-specific: it is elevated in benign conditions, but is normal in 20% of women with established ovarian cancer and in 50% of those with early-stage cancers.
- Other serum markers such as HE4 can be used to improve the diagnostic accuracy of CA125 alone.

EOC precursor lesions

Many epithelial cancers have defined precursor lesions that can be detected in coordinated screening programmes. Examples are serial Papanicolaou (Pap) smears used to detect pre-invasive cervical intraepithelial neoplasia (CIN) as precursors for cervical cancer; mammographic detection of ductal carcinoma *in situ* (DCIS) as a precursor of breast cancer; and endoscopic detection of dysplastic changes in the oesophageal epithelium (known as Barrett's oesophagus) that can precede oesophageal cancer. A similar screening programme for EOC is challenging as it has no clearly defined, or identifiable, precursor lesions. EOC was originally believed to arise from dysplastic squamous epithelial cells covering the ovary or inclusion cysts formed from invaginations of the ovarian

surface epithelium [31]. However, subsequent pathological and epidemiological studies have suggested there are distinct tissues of origin for each of the main EOC histotypes. For example, endometrioid and clear cell EOC are believed to be derived from endometriotic tissue that has migrated along the fallopian tube onto the ovary [32], consistent with the protective association between tubal ligation and reduced incidence of these (as well as serous) cancers [11]. Mucinous EOC is hypothesized to arise from Walthard nests, benign clusters of epithelial cells with morphological similarities to urothelial tissue present at tubal–mesothelial junctions [33]. The strongest precursor association has been between HGSOC cancers and fallopian tube premalignant lesions termed serous tubal intraepithelial carcinomas (STICs) located at the tubal–peritoneal junctions. This discovery came from pathological analyses of specimens collected at the time of prophylactic salpingo-oophorectomy in women with an inherited predisposition to EOC [34]. STIC lesions have also been identified in the fallopian tubes of 70% of patients with sporadic ovarian and serous peritoneal cancer, implying its association is not limited to *BRCA* carriers [35]. Whether STICs are precursors for all cases of HGSOC is still a matter of debate [36,37]. Of note, *TP53* mutations have been identified in STIC lesions and not in inclusion cysts, supporting STICs as bone-fide precursor lesions [38]. The finding of EOC precursor lesions not only facilitates preventative strategies but also provides potential screening opportunities.

Summary box 63.4

EOC precursor lesions by histotype

- High-grade EOC is believed to arise from fallopian tube STIC lesions.
- Endometrioid and clear cell EOC arise from retrograde transport of endometriotic tissue onto the ovary.
- Mucinous EOC is thought to arise from collections of urothelial-type cells called Walthard nests.

Screening and prophylactic oophorectomy

As around 75% of women with EOC present at an advanced stage, when cure rates are less than 30%, a case can clearly be made for screening women to try to identify the disease earlier and when cure is more likely. EOC screening is not currently part of routine clinical practice as it has yet to demonstrate a survival advantage in clinical trials. The two most influential studies were the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) study in the USA and the UK Collaborative Trial of Ovarian Cancer Screening study (UKCTOCS) that recruited 78 000 and 200 000 women, respectively.

In the PLCO study, which completed enrollment in 2001 and extended follow-up in 2016, around 78 000 women aged 55–74 were recruited across the USA and randomized to screening versus no screening. The 28 000 women in the screening arm underwent annual TV-USS for 4 years and annual CA125 measurement for 6 years but were also screened for colorectal and lung cancers [39]. Patients then received postal follow-up questionnaires for at least 13 years from randomization. Although more ovarian cancers were identified in the screening arm (212 vs. 176 in control group), these were not early-stage cancers and there was no improvement to short- or long-term mortality [40]. Positive predictive value (PPV, which gives a percentage of true positives over the sum of true plus false positives) was low at 3.7% in the CA125 group and 1% in the TV-USS group. This reflected the high number of false positives identified. As positive findings required surgical investigation, there was an associated risk of operative complications in these patients, with a 15% incidence of serious complications (such as infection, blood loss, bowel injury or cardiovascular event) incurred in those undergoing exploratory surgery in the false-positive group.

The UKCTOCS study recruited over 200 000 postmenopausal women aged 50–74 from centres within the UK [41]. Patients were randomized to no treatment (control arm), annual CA125 with subsequent TV-USS in the multimodal screening (MMS arm) or annual TV-USS alone (USS arm). A Bayesian CA125 risk score termed the Risk of Ovarian Cancer Algorithm (ROCA) was incorporated into the MMS arm in which each CA125 was compared with the patient's preceding values, and the likelihood that the CA125 profile reflected that of ovarian cancer, even if still within the reference range. The aim of this algorithm was to improve the PPV of CA125, particularly in the detection of early-stage disease. For patients with abnormal results, CA125 and/or TV-USS were repeated within 6 weeks or 3 months, which if again abnormal resulted in referral to a gynaecologic oncologist. Patients were screened for six consecutive years and followed up for 7 years from randomization. Although the primary end-point of this study was ovarian cancer mortality at 7 years, other measured outcomes were the psychosocial, physical and economic cost of ovarian cancer screening. Final data were published in 2015, 4 years after the last patient was recruited in 2011. Although the results indicated that those in the MMS arm had more early-stage ovarian/peritoneal cancers detected than those in the screening arm and a mortality reduction of 15% (compared with 11% in the USS group), there was no significant difference in survival. Interestingly, there was

evidence of a statistical trend towards improved survival outcomes at later time points. Although the follow-up period has therefore been extended to confirm late survival benefit, the UKCTOCS results have so far failed to provide unequivocal evidence that national ovarian cancer screening should be initiated.

Confining screening to patients with higher risk of EOC (such as those with a strong family history of the disease) would theoretically increase specificity. For women at known higher risk of a genetic cancer predisposition, the UK Familial Ovarian Cancer Screening Study (UKFOCSS) evaluated annual CA125 and TV-USS tests in women at high risk of EOC. The study recruited 3563 women aged over 35 with a strong family history of breast and/or ovarian cancer and completed recruitment in March 2010 [42]. The results showed that these tests were insufficiently sensitive to detect early-stage disease and so the second part of the study was opened in which CA125 was measured 4-monthly (instead of annually) with the ROCA algorithm applied. There were 4531 women recruited to part two that again failed to show sufficient sensitivity in identifying early-stage disease. These findings again highlighted the limited sensitivity of CA125 in detecting early-stage disease and reinforced the current approach of offering risk-reducing surgery (rather than serial CA125 measurement) to women with known ovarian cancer predisposing mutations.

Risk-reducing surgery

Prophylactic oophorectomy has been shown to reduce the incidence of subsequent ovarian and breast cancer by 96% and 53%, respectively, in women known to carry *BRCA1* or *BRCA2* germline mutations [43,44]. For many women in *BRCA* families this is considered the approach of choice. In general, where it is recommended, prophylactic bilateral salpingo-oophorectomy is performed on completion of childbearing or at the age of 40 years (whichever occurs first) and HRT is commenced thereafter until a point that corresponds to natural menopause at around 50 years. However, there are no clear guidelines in place and management of these patients varies widely. The suggestion that EOC arises from STIC lesions within the fallopian tube has raised the question of whether salpingo-oophorectomy (and all its associated postmenopausal effects on cardiovascular risk and bone health) is excessive and women should undergo a two-stage procedure, with an initial prophylactic salpingectomy later followed by oophorectomy once natural menopause has occurred. This needs to be investigated prospectively, but such a study would be challenging to conduct [45]. The 'tubal hypothesis' has resulted in more routine salpingectomies being conducted alongside hysterectomies. In addition, salpingectomy is increasingly being offered as an alternative to tubal ligation for contraception in view of its cancer-protecting effects.

Summary box 63.5

Three ovarian cancer screening studies

- PLCO study: no survival improvement using annual CA125 or TV-USS versus controls in women aged 55–74 years (sample size 28 000).
- UKCTOCS: no survival improvement using annual CA125 algorithm plus TV-USS or annual TV-USS alone versus controls in women aged 50–74 years (sample size 200 000), although extended survival analysis is ongoing.
- UKFOCSS: no survival improvement in 3500 high-risk women aged over 35 using annual TV-USS and CA125.

Staging of EOC

Most ovarian cancers have serous histology reminiscent of fallopian tube origin, often with characteristic psammoma bodies. Endometrioid adenocarcinomas and clear cell carcinomas are the next commonest histological type, and mucinous carcinomas are less common still. Ovarian carcinosarcomas are epithelial tumours with sarcomatous differentiation but these are rarely encountered. There is evidence that clear cell and mucinous ovarian cancers are far less responsive to chemotherapy than serous and endometrioid ovarian cancers.

An important feature of histological classification is the grade of the cancer, ranging from well differentiated (grade 1) to moderately differentiated (grade 2) to poorly differentiated (grade 3). Borderline tumours are not regarded as cancers and in general have an excellent prognosis.

Patterns of spread of ovarian cancer

The International Federation of Gynecology and Obstetrics (FIGO) classification for ovarian cancer is based on surgical staging and was updated in January 2014 [46]. The new versus old staging is shown in Table 63.2. The principal differences in the updated version are the subclassification of IC into IC1-3, removal of stage IIC, inclusion of lymph node status into stage IIIA and B (as well as C), reclassification of splenic metastasis to stage IV (rather than IIIC) and the subdivision of stage IV into IVA and IVB according to the site of distal disease.

Table 63.2 Previous versus updated FIGO staging for ovarian, fallopian and primary peritoneal cancer.

Previous FIGO		New FIGO		
Stage I: Tumour confined to ovaries				
IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings/ascites	IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings/ascites	
IB	Tumour involves both ovaries, otherwise like IB	IB	Tumour involves both ovaries, otherwise like IB	
IC	Tumour involves 1 or both ovaries with any of the following: capsule rupture, tumour on surface, positive washings/ascites	*IC Tumour limited to 1 or both ovaries*		
		IC1	Surgical spill	
		IC2	Capsule rupture before surgery or tumour on ovarian surface	
		IC3	Malignant cells in the ascites or peritoneal washings	
Stage II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer				
IIA	Extension and/or implant on uterus and/or fallopian tubes	IIA	Extension and/or implant on uterus and/or fallopian tubes	
IIB	Extension to other pelvic intraperitoneal tissues	IIB	Extension to other pelvic intraperitoneal tissues	
IIC	IIA or IIB with positive washings/ascites			
Stage III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes				
IIIA	Microscopic metastasis beyond the pelvis	*IIIA (positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)*		
		IIIA1	*Positive retroperitoneal lymph nodes only*	
			IIIA1(i)	Metastasis ≤10 mm
			IIIA1(ii)	Metastasis >10 mm
		IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extrapelvic peritoneal metastasis ≤2 cm in greatest diameter	IIIB	Macroscopic, extrapelvic peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
IIIC	Macroscopic, extrapelvic peritoneal metastasis >2 cm in greatest diameter and/or regional lymph node metastasis	IIIC	Macroscopic, extrapelvic peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
Stage IV: Distant metastasis excluding peritoneal metastasis				
IV	Distant metastasis excluding peritoneal metastasis. Includes hepatic parenchymal metastasis	*IVA*	*Pleural effusion with positive cytology*	
		IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes outside the abdominal cavity)	

Source: Prat *et al.* [46].

Like other malignant neoplasms, ovarian cancer can disseminate along locoregional, lymphatic and blood-borne routes. However, there are patterns of dissemination that are characteristic of the different histological subtypes of ovarian cancer. In HGSOC, the dominant pattern is that of transperitoneal locoregional dissemination often resulting in bulky intra-abdominal disease particularly involving the omentum as well as other peritoneal surfaces. This is often accompanied by malignant ascites and lymph node involvement is relatively common. With the exception of malignant unilateral or bilateral pleural effusion, and involvement of the umbilicus due to tumour spread along the remnant of the umbilical vein (Sister Joseph's nodule), it is unusual for HGSOC to present with visceral metastatic disease with metastases to the liver, pulmonary, cerebral or bone that are more commonly observed in other gynaecological malignancies. An exception to this situation is the *BRCA1*/*BRCA2* familial ovarian cancers that have a very high (73%) incidence of visceral metastatic disease [47].

Histopathological diagnosis of EOC

Histopathological type, tumour grade and FIGO stage are all determined by biopsies obtained using radiological or laparoscopic guidance or during formal staging laparotomy. Cytological diagnosis, such as from a sample of ascites, is considered inadequate for definitive diagnosis. Expression of markers such as p53 and oestrogen/progesterone receptor status can be useful information for the later management of the patient. Many centres are now routinely testing *BRCA* status in all patients with ovarian cancer, although National Institute for Health and Care Excellence (NICE) guidelines recommend testing for those with a greater than 10% risk (as defined using BRCAPRO, BOADICEA and/or the Manchester scoring system) of carrying a *BRCA* mutation [48]. This is a change from the 20% threshold previously defined by NICE guidance in 2006.

Prognostic factors

Unfortunately, the majority of patients with ovarian cancer will relapse and ultimately die from their disease. While the prognosis from earlier stage, low-grade EOC is good, with a cure rate of greater than 90%, across all stages (I–IV) the prognosis is poor, with 1-year survival of 71%, 5-year survival of 40% and 10-year survival of 33% (www.cancerresearchuk.org). The main factors that predict for survival remain FIGO stage of disease, tumour grade, surgical debulking status, histological subtype and sensitivity of disease to platinum-based chemotherapy. In ongoing research, whole genome molecular profiling analyses as well as individually characterized molecular target expression is being used to develop refined predictive and prognostic models.

Treatment of newly diagnosed ovarian cancer

The standard management of stage IC–IV EOC is to perform primary debulking surgery with the explicit aim of total macroscopic clearance and to enable complete surgical staging. This is followed by adjuvant carboplatin-containing chemotherapy for all patients other than those with FIGO stage IA and IB lower-grade tumours. In these early-stage patients, surgery is probably sufficient and chemotherapy is generally omitted, although the option of giving postoperative chemotherapy to these patients is the subject of ongoing debate [49]. In those with advanced disease with poor performance status or where primary debulking surgery is predicted to be too hazardous, chemotherapy is given alone (without surgery) or as neoadjuvant treatment, the latter with the intention of allowing delayed debulking surgery once disease bulk and overall health has been optimized.

Surgical management of newly diagnosed ovarian cancer

In recent decades, there have been significant advances in the surgical management of EOC, with the refinement of extensive upper abdominal cytoreductive techniques, incorporation of refined skills like bowel resection, en bloc extraperitoneal dissection and also highly specialized anaesthetic care for optimal perioperative management [46,50–55]. Many questions remain about the ideal timing of surgery, the value of surgery at relapse and how to optimize postoperative quality of life.

Imaging modalities and their value in the surgical decision-making processes

The decision-making process for the optimal management of patients with EOC is based on a combination of clinicopathological, biochemical and radiological factors together with patient preference but also the expertise, resources and overall institutional effort of the treating team. Conventional imaging like CT and MRI are important components of the preoperative and pre-chemotherapy investigations to define extent of disease and to identify or exclude potential second malignancies or incidental findings that would change the overall management, such as the discovery of incidental pulmonary emboli. Conventional imaging has not been shown to accurately predict operability in advanced ovarian cancer [56–59]. More advanced imaging modalities such as diffusion-weighted MRI are currently the focus of investigation in various clinical trials to ascertain whether they are superior to conventional imaging in their contribution to accurate preoperative decision-making [60].

There is currently no evidence-based prognostic and predictive value for the routine use of positron emission tomography (PET)-CT in ovarian cancer surgery, apart from situations with a specific question such as the evaluation of thoracic/mediastinal lymph node involvement in stage IV disease, especially in the context of relapsed disease, where intra-abdominal debulking surgery is considered [61].

Primary surgical staging and treatment

Surgery is the cornerstone of management of EOC as it provides accurate peritoneal and lymph node staging in early-stage disease and cytoreduction in advanced-stage disease. Non-fertility-sparing surgery consists of peritoneal washings or cytology, ideally taken prior to manipulation of the tumour, bilateral salpingo-oophorectomy,

hysterectomy, multiple peritoneal biopsies from the paracolic spaces and the two subdiaphragmatic spaces, supracolic omentectomy, and pelvic and bilateral paraaortic lymph node dissection (LND) up to the level of the renal vessels. Appendicectomy should be considered in case of mucinous histology [62,63] or if there is a radiological abnormality of the appendix. Depending on the histological grade and type, up to 30% of patients with apparently early-stage epithelial EOC will be upstaged after comprehensive surgical staging [64–66].

A single prospective randomized trial by Maggioni *et al.* [67] correlated the extent of LND with outcome. The study showed that, in early EOC, systematic LND versus just lymph node sampling reveals 13% more patients with occult lymph node disease and hence will have major implications on final stage determination as well as selection of adjuvant treatment. Positive nodes were detected in 22% of patients undergoing systematic lymphadenectomy compared with only 9% of patients who underwent lymph node sampling ($P = 0.007$). Although a trend for improved progression-free survival (PFS) and overall survival (OS) was observed for the lymphadenectomy group compared with control, the study lacked statistical power. Increasing evidence shows that the rate of positive lymph nodes in stage IA mucinous cancer is extremely low, and there is no value in performing systematic LND to avoid unnecessary morbidity [68,69].

A careful discussion is required for patients with early-stage cancer who opt for fertility-sparing surgery. Patients with stage IA and favourable histology (i.e. low-grade, mucinous, serous or endometrioid EOC) have been shown to have a lower risk of relapse after fertility-preserving surgery compared with patients with higher stages or grade of disease. In a large retrospective analysis, women with G3 disease or stage IC3 with clear cell histology had a higher risk of recurrence, but mainly due to the higher incidence of extra-ovarian spread observed in grade 3 tumours, rather than to a higher relapse rate in the preserved ovary [70]. Retrospective studies showed a risk of up to 11% of positive contralateral pelvic lymph nodes in women with unilateral disease despite negative ipsilateral nodes [71,72]. For these reasons, pelvic LND staging should be bilateral.

In advanced EOC, maximal-effort cytoreduction, aiming at total macroscopic tumour clearance, is associated with a significant increase in both OS and PFS in numerous prospective and retrospective trials [73–75]. It is not yet fully clarified whether this association is causal or whether resectable tumours are biologically more chemosensitive (than those that are unresectable) and therefore associated with a better prognosis [66]. Nevertheless, there are numerous data that patients treated within institutions with higher optimal debulking rates have significantly better survival. The first meta-analysis on this subject based on a total of 53 studies comprising 6885 patients was published by Bristow *et al.* [76] and covered the time period 1989–1998. They studied the influence of surgical tumour resection on OS, not of individual patients but of patient cohorts. Patient cohorts with a high rate of 'optimal' cytoreduction (defined at that time as <2 cm) of over 75% had a median OS of 36.8 months. In contrast, patient cohorts with a maximum tumour reduction rate of less than 25% had a median OS of only 23 months. Hence, every 10% reduction in tumour was associated with a 6.3% prolongation of median OS.

In order to achieve total macroscopic tumour clearance in peritoneally disseminated disease, maximal surgical effort is required, incorporating multi-visceral resection techniques such as extensive peritoneal stripping, full-thickness diaphragmatic resection, removal of bulky pelvic/para-aortic lymph nodes, splenectomy and bowel resection. Increasingly, more extra-abdominal cytoreductive techniques are nowadays applied especially in the thoracic and mediastinal cavity with resection of cardiophrenic/paracardiac lymph nodes, pleurectomy, and supraclavicular and axillary LND in order to achieve complete tumour clearance outside the abdominal cavity. Surgical expertise and training with continuous feedback of surgical outcome, morbidity and survival have been proven to be important tools in making extensive surgery safe for the patient without unnecessarily increasing morbidity [77]. For these reasons, national and international trends focus on the specialization of such procedures in centres with adequate infrastructure, resources and training.

Pelvic and para-aortic LND is part of the debulking procedure in the presence of bulky lymph nodes. The removal of bulky lymph nodes only versus a systematic LND has been shown to be associated with a decreased 5-year PFS of 21.6% compared with 31.2% in the full LND group without any significant difference in OS in a prospective randomized phase III trial [78]. However, the caveat was that, in this study, only approximately one-third of the patient cohort were optimally cytoreduced and hence would have obtained the potential survival benefit from a full lymphadenectomy. In three prospective randomized first-line studies [79,80] evaluating 1924 patients, lymphadenectomy was associated with superior survival in patients without gross residual disease. The median survival time for patients with and without lymphadenectomy was 103 and 84 months, respectively, and 5-year survival rates were 67.4% and 59.2%, respectively ($P = 0.0166$); in multivariate analysis a significant impact of lymphadenectomy on OS was seen (hazard ratio, HR 0.74, 95% CI 0.59–0.94; $P = 0.0123$). The value of systematic pelvic

and para-aortic lymphadenectomy in the absence of bulky lymph nodes was recently evaluated in the large randomized LION trial where 650 women with stage IIB–IV advanced EOC who had achieved complete macroscopic debulk but did not have bulky lymph nodes were randomized to pelvic and para-aortic lymphadenectomy versus no lymphadenectomy. The results revealed no progression-free or OS advantage to lymphadenectomy (HR 1.057, 95% CI 0.833–1.341; $P = 0.65$) [81].

There is an international ongoing debate as to the best timing of surgery in relation to first-line chemotherapy. Two prospective randomized trials [75,82] have demonstrated lower surgical morbidity and mortality but equal survival in the neoadjuvant approach. The weakness of both studies was that the complete resection rates were very low while surrogate markers of surgical effort, such as operation time, showed an overall suboptimal setting and effort. For these reasons it is difficult to adopt the findings of these trials on patients with good performance status who can be operated until tumour-free in specialized centres. Future trials are in development that will be conducted in centres with established surgical quality to answer the question of timing and will address additional issues, such as management of fragile patients, assessment of short- and long-term quality-of-life scores, and impact of ascites and pleural effusion on haemodynamic management, and would also have an additional translational component in an attempt to identify valid biomarkers that would predict operability and clinical outcome. A recent study by Rosen *et al.* [83] showed that the long-term survival for patients undergoing primary cytoreduction was far superior to those receiving neoadjuvant chemotherapy and delayed primary surgery (9% vs. 41%, $P < 0.0001$).

Integrated multidisciplinary care of ovarian cancer

EOC is optimally managed by centralized, integrated, multidisciplinary teams. This has been shown to improve outcomes [84]. In general, the team consists of a surgical oncologist, a medical/clinical oncologist, a radiologist, a pathologist and specialist nurses. The specialist nurse acts as a conduit between the patient and the multidisciplinary team. Palliative care specialist input may be required in all phases of the disease. Increasingly, multidisciplinary teams are developing integrated care pathways for patients with EOC that bring together hospital and community services within one framework. Most recently, survivorship programmes are beginning to become integrated into standard care, with randomized studies such as OvPsych2 assessing the benefit of supportive interventions on quality of life.

Advanced ovarian cancer

Carboplatin, paclitaxel and bevacizumab as front-line therapy

The current standard of care following surgery is a combination of carboplatin and paclitaxel, given for six cycles at 3-weekly intervals. The evidence for this is based on various seminal studies. The GOG111 and OV10 studies demonstrated that cisplatin with cyclophosphamide was inferior to cisplatin and paclitaxel [85,86]. The GOG132 study showed that there was no difference in survival for cisplatin given alone when compared with cisplatin given alongside paclitaxel [87], and in the ICON3 trial carboplatin plus paclitaxel was compared with the hitherto standard treatment options of carboplatin alone or CAP (cyclophosphamide, doxorubicin and cisplatin) [88]. Although ICON3 showed no difference between PFS and OS between the single-agent carboplatin and carboplatin–paclitaxel arms, a combination of paclitaxel and carboplatin has been widely adopted in patients who are fit, lacking in comorbidities (especially those exacerbated by the treatment or its supportive therapies) and able to cope with combination chemotherapy.

The GOG218 trial explored the role of the vascular endothelial growth factor (VEGF)-targeting antibody bevacizumab given alongside front-line chemotherapy and as subsequent monotherapy maintenance. It showed a 3.8-month improvement in PFS compared with chemotherapy alone (or chemotherapy with combined but not maintenance bevacizumab) but no difference in OS [89]. Similar results were obtained from the European study ICON7, although an OS benefit of almost 5 months (log-rank $P = 0 \cdot 03$) was demonstrated in those with 'high-risk' advanced disease receiving the bevacizumab arm, albeit at a lower dose (7.5 mg/kg) than was used in the GOG218 study (15 mg/kg) [90]. For this reason, bevacizumab (7.5 mg/kg every 3 weeks for a maximum of 18 weeks) was made available by the Cancer Drugs Fund for women with high-risk stage IIIC/IV ovarian cancer although it was not approved by NICE. The Japanese Gynecologic Oncology Group (JGOG) undertook a randomized study where, in addition to standard 3-weekly carboplatin (Area Under the Curve (AUC6)), intravenous paclitaxel was given either 3-weekly (175 mg/m^2) or as weekly dose-dense therapy (80 mg/m^2). In this trial, there was a significant 11-month improvement in PFS in the dose-dense arm with significant improvement in OS also [91]. A similar question was then addressed in the European ICON8 study, in which 1485 women with newly diagnosed advanced ovarian cancer were randomized to receive standard 3-weekly carboplatin and paclitaxel (Arm1), the 'Japanese' regimen of 3-weekly carboplatin with weekly paclitaxel (Arm 2) or weekly

AUC2 carboplatin with weekly paclitaxel (Arm 3). The final results of ICON8 are pending, but it is likely to reflect the findings of the GOG-0262 study [92] in which a lack of benefit of the dose-dense Japanese regimen over standard 3-weekly carboplatin was described in a smaller cohort of 692 patients. This raises the question of why the benefit of dose-dense paclitaxel was so much greater in the Japanese population compared with the (mostly) European and North American women enrolled in the GOG and ICON8 studies.

The ICON8B study questions whether bevacizumab is advantageous when given with the Japanese regimen compared with standard 3-weekly chemotherapy. In ICON8B, women with stage III/IV EOC are randomized to 3-weekly carboplatin and paclitaxel plus bevacizumab (Arm B1), the Japanese regimen without bevacizumab (Arm B2) or the Japanese regimen with bevacizumab (Arm B3). The GOG-0262 study answered a similar question by prospectively stratifying their EOC patients according to whether they wished to have bevacizumab and then randomly assigned them to receive it in addition to either 3-weekly carboplatin and paclitaxel, or the Japanese regimen. Interestingly, in those who did not receive bevacizumab, weekly paclitaxel was associated with a 3.9 month longer PFS compared with the 3-weekly regimen (14.2 vs. 10.3 months; HR 0.62, $P = 0.03$) [92]. However, among those who received bevacizumab, the weekly paclitaxel arm had similar PFS to the 3- weekly arm (14.9 and 14.7 months, respectively; HR 0.99, $P = 0.60$). The weekly arm was associated with worse quality of life, with a higher incidence of neuropathy and grade 3/4 anaemia albeit a lower rate of neutropenia. This implies that fractionated paclitaxel is as effective as bevacizumab, perhaps because it has anti-angiogenic effects when given more frequently. However, the study was not truly randomized as the study patients self-selected bevacizumab. The results also raise the question as to whether a 3-month improvement in PFS warrants the negative impact on quality of life.

Intraperitoneal chemotherapy

Ovarian cancer is principally a disease of locoregional peritoneal dissemination within the abdominal cavity. The idea of intraperitoneal therapy is not new, having been performed since the 1950s as a means of controlling ascites. By inserting a port through the skin and into the peritoneal cavity, chemotherapy can be delivered directly to the location of the disease and at a greater localized concentration. Over the last 20 years there have been many randomized trials comparing intraperitoneal with intravenous chemotherapy for the first-line treatment of patients with stage III ovarian cancer (reviewed in Elit *et al.* [93]). The common factor is that all have included platinum, and most have added a second drug. Meta-analyses of these trials showed a significant reduction in hazards of 0.88 with confidence intervals of 0.81–0.95 and an improvement in survival (in the three largest studies) of 8, 11 and 16 months for intraperitoneal over intravenous chemotherapy beyond an expected median survival of this optimally debulked group of 4 years.

The 2006 GOG 172 study [94] showed the largest difference ever in a randomized ovarian cancer trial, with median OS of 67 months compared with the intravenous control arm of 49 months, the improvement being 17.4 months with an HR of 0.71. This regimen utilized intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2 and intraperitoneal paclitaxel on day 8, of a 21-day cycle for six cycles. However, intraperitoneal chemotherapy was associated with enhanced toxicities, including neuropathy, gastrointestinal toxicity and myelotoxicity. Despite encouragement to adopt intraperitoneal chemotherapy as standard of care by the National Cancer Institute, clinicians were reluctant to integrate it into routine practice until further randomized trials had been performed because of concerns over the complications of intraperitoneal catheters and fear of excessive toxicity [95]. Updated survival data were subsequently published in 2015 and showed median survival of 61.8 months compared with 51.4 months in the intraperitoneal arm. Interestingly, subsequent molecular analysis of those patients deriving most benefit from intraperitoneal therapy showed it was those with low *BRCA1* expression. The PETROC/OV21 study looked at intraperitoneal platinum and paclitaxel chemotherapy following suboptimal interval debulking surgery in 275 women with stage IIb/III or IV (pleural effusion only) ovarian cancer [96]. The study modified its end-points due to accrual difficulties and concluded that, of three different regimens intraperitoneal carboplatin given with intravenous and then intraperitoneal paclitaxel was (i) superior to the equivalent regimen using intraperitoneal cisplatin and (ii) gave superior 9-month progressive disease rate of 23% compared with 42% in the control arm (intravenous carboplatin and paclitaxel) ($P = 0.03$). The intraperitoneal treatment was well tolerated with low complication rates. Importantly, this study demonstrated that carboplatin was a safe and well-tolerated alternative to cisplatin when administered intraperitoneally.

The issue of whether bevacizumab adds to chemotherapy in the context of intraperitoneal treatment was addressed in the multicentre phase III GOG-252 study, in which 1560 women with stage II or III ovarian cancer were randomized to intravenous carboplatin, paclitaxel and bevacizumab (Arm 1), intravenous paclitaxel and bevacizumab but intraperitoneal carboplatin (Arm 2), or intraperitoneal carboplatin and intravenous followed by intraperitoneal paclitaxel with intravenous bevacizumab

(Arm 3). Early results demonstrated no PFS advantage of intraperitoneal therapy over intravenous therapy in sharp contrast to the findings of GOG-172.

The issue of which treatment clinicians should select for their optimally debulked advanced-stage ovarian cancer patients is complicated. Centres are divided as to whether upfront debulking or neoadjuvant chemotherapy is preferred. Intraperitoneal chemotherapy is complicated by high morbidity and is costly to arrange, bevacizumab is not approved for routine use and weekly paclitaxel has shown little advantage compared with standard 3-weekly carboplatin and paclitaxel treatment.

The *BRCA*-positive patient

Perhaps the most significant revolution in EOC management over the last 5 years has been in the management of *BRCA*-mutated cancer patients.

As well as their well-documented increased risk of breast and ovarian cancer (and to a lesser extent pancreatic and prostate cancer), cancers that have developed in *BRCA* mutation carriers are highly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors. BRCA1 and/or BRCA2 proteins are required to repair DNA double-strand breakages in a process called homologous recombination (HR). HR uses an existing DNA sequence as a template to repair the opposite broken strand. In the cancer cell that lacks both copies of *BRCA1*/*BRCA2*, repair occurs using alternate means such as non-homologous end joining or single-strand annealing. As these methods are error-prone, cells that are deficient in BRCA1 or BRCA2 demonstrate chromosomal instability and are highly sensitive to drugs or irradiation that cause double-strand breaks [97]. PARP inhibitors repair single-strand DNA breaks via the break excision repair pathway. If these breaks are left unrepaired, they can result in double-strand breaks and are reliant on the HR pathway for their recovery. In those cells without HR (i.e. BRCA-deficient cells), the HR pathway is dysfunctional and the DNA damage cannot be overcome. This causes genomic instability and apoptotic cell death.

The discovery that inhibition of PARP causes targeted cell death in cells in which BRCA1 and BRCA2 are depleted [98], a mechanism described as 'synthetic lethality', has seen the emergence of a number of PARP inhibitors into clinical practice and as part of the routine management of women with *BRCA*-mutated ovarian cancer. The front-running PARP inhibitor is olaparib that, in 2014, was granted European Medicines Agency marketing authorization for use as maintenance monotherapy in *BRCA*-mutated ovarian cancer patients who have achieved complete or partial response following platinum-based chemotherapy. In January 2016, olaparib received approval by NICE as maintenance following at least three courses of platinum-containing treatment (usually this implies at least two courses of treatment for relapsed disease), echoing the FDA approval guidelines issued in 2014. This followed a number of clinical trials in heavily pretreated relapsed ovarian cancer patients with germline *BRCA* mutations in which responses were observed (34% objective response rate, 2% complete response) and demonstrated to last an average of 7.9 months [99]. In a phase II trial, 265 patients with platinum-sensitive recurrent EOC who had received two or more prior platinum-containing regimens and achieved a partial or complete response to their most recent platinum-containing treatment were randomized to maintenance olaparib versus placebo. A superior PFS was demonstrated in those taking olaparib as maintenance therapy compared with placebo and when subset analysis was conducted, patients with *BRCA* mutations demonstrated the greatest benefit (PFS 11.2 months vs. 4.3 months in placebo arm; HR 0.18, 95% CI 0.10–0.31; P <0.0001). Interestingly, patients without *BRCA* mutations also showed a survival advantage to olaparib compared with placebo (7.4 months vs. 5.5 months) but in neither groups was the PFS advantage converted to an OS benefit [100]. Other PARP inhibitors including rucaparib and niraparib have shown benefit beyond *BRCA*-mutated patients. In the case of rucaparib a 'loss of heterozygosity (LOH) score' identified patients with defective HR but with wild-type *BRCA*. In the ARIEL2 study, 204 patients with relapsed platinum-sensitive HGSOC were given maintenance rucaparib but stratified according to their *BRCA* status and LOH score. Those who were LOH 'high' had improved response to rucaparib compared with those who were LOH 'low', but this translated to a progression-free advantage of only a few weeks, considerably less than the 12.8-month PFS observed in the *BRCA* mutant cohort [101]. The PARP inhibitor niraparib has shown benefit as maintenance therapy in women with platinum-sensitive recurrent EOC, regardless of *BRCA* mutation status. In a phase 3 study [102], patients without genomic *BRCA* mutation receiving niraparib achieved a 15.5-month PFS advantage compared with those receiving placebo. However, whether this translates to an OS improvement is as yet unknown.

Recurrent ovarian cancer

Recurrent EOC is currently an incurable clinical situation, although survival improvement can still be achieved using appropriate chemotherapy and a multidisciplinary approach. Palliation and optimization of quality of life

are important considerations in this clinical scenario, including careful symptom management and the judicious use of chemotherapy, radiotherapy and surgery. Community palliative care and hospice provision are important components in this phase of the disease. Selecting treatments with minimal toxicities is also a major aim for patients in this clinical scenario.

Chemotherapy

Depending on the time interval between primary platinum-based treatment and relapse, recurrent EOC is arbitrarily divided into platinum refractory, resistant or potentially sensitive disease. Tumour that has relapsed more than 12 months following prior treatment is defined as platinum-sensitive, between 6 and 12 months as partially platinum sensitive, less than 6 months as platinum-resistant, and during or within 4 weeks of completing treatment as platinum-refractory [103]. Platinum-refractory EOC represents disease that is primarily non-responsive to chemotherapy, and implies that it is unlikely that these patients will respond to further standard chemotherapy agents. These patients often have aggressive disease and poor prognosis. They can be considered for phase I, and some phase II trials if sufficiently fit.

Platinum-sensitive recurrence

Platinum-sensitive recurrence has several definitions. A pragmatic definition is that of recurrence of EOC requiring treatment occurring more than 6 months after last chemotherapy. Blackledge *et al.* [104] showed that those relapsing more than 18 months after previous chemotherapy have up to a 94% chance of response to subsequent platinum-based therapy (as compared with 10% response rate in those relapsing within 6 months of last platinum therapy).

Eisenhauer *et al.* [105] looked at factors predicting response to subsequent chemotherapy in platinum-pretreated ovarian cancer using data from 13 randomized trials of six chemotherapy agents (not just platinum). They found that serous histology, tumour bulk (<5 cm) and number of disease sites (less than three) were significant factors, yet treatment-free interval was not a feature at first sight at odds with Blackledge's findings. These biological predictors were the main determinants of subsequent response, with the treatment-free interval correlating closely with tumour size.

A seminal randomized clinical trial, MRC ICON4, was conducted in patients relapsing more than 6 months after last chemotherapy. This trial asked if the addition of paclitaxel to carboplatin improved survival in platinum-resistant disease. This study was extremely important because the MRC ICON3 study had shown no improvement in survival for carboplatin and paclitaxel as front-line chemotherapy in advanced ovarian cancer. In the ICON4 trial, addition of paclitaxel significantly improved survival in platinum-sensitive recurrent ovarian cancer, with an HR of 0.82, an absolute survival advantage at 2 years of 7% and an improvement to median survival of 5 months; in other words, benefit of similar magnitude to the addition of platinum to front-line chemotherapy for ovarian cancer. There were no real differences in patient-perceived toxicity and, in general, where there are not reasons to avoid paclitaxel (e.g. previous severe neuropathy, concurrent medical comorbidity especially advanced diabetes) it can be recommended for patients relapsing more than 12 months from last chemotherapy [106].

Outside the trial setting, the current NICE-approved strategy is to offer combination chemotherapy to all patients with platinum-sensitive recurrent disease if it is not medically contraindicated. Patients with platinum-sensitive or partially platinum-sensitive disease are retreated with platinum alongside paclitaxel or pegylated liposomal doxorubicin hydrochloride (PLDH), the latter following the non-inferiority study CALYPSO which compared carboplatin plus PLDH to carboplatin and paclitaxel [107]. Patients who are allergic to platinum are offered single-agent PLDH, topotecan or weekly chemotherapy with paclitaxel. Other strategies include replacing platinum with an alternative cytotoxic such as the DNA minor groove binding inhibitor trabectedin, given with PLDH in the OVA 301 trial [108]. The OCEANS study reported a PFS (but not OS) benefit of adding bevacizumab to carboplatin and gemcitabine [109]. This was followed by the results from ICON6, in which a 3-month progresson-free benefit from the small molecule VEGFR inhibitor cediranib was observed when it was given alongside, and as maintenance following, chemotherapy for patients at their first platinum-sensitive relapse. A significant improvement in OS was also observed, but at the cost of toxicities including hypertension, fatigue, nausea and diarrhoea [110]. Interestingly, a phase 2 study of cediranib given with olaparib in women with platinum-sensitive recurrent (*BRCA* mutant as well as wild-type) EOC demonstrated a PFS advantage but this trial was not powered to address OS [111]. Although toxicity of the combination was higher than in those receiving olaparib alone, this study gave an indication that the spectrum of activity of a PARP inhibitor could be enhanced by combining with an anti-angiogenic agent. The recently reported benefit of niraparib maintenance (see above) in those with a good response to chemotherapy regardless of *BRCA* status has raised the question of whether this should be offered to all patients with platinum-sensitive EOC, but is not yet NICE-approved.

Platinum-resistant recurrence

There are various definitions of platinum-resistant recurrence; however, a pragmatic definition is one of recurrent disease requiring treatment within 6 months of completing last chemotherapy. These patients appear to benefit (or fail to benefit) equally from all conventionally dosed and scheduled chemotherapeutic agents. These monotherapies all have a 10–20% overall response rate. Agents that can be considered for this indication include PLDH, topotecan, oral etoposide and weekly paclitaxel. Of these, weekly paclitaxel shows the greatest impact in terms of response rate, evident from results of the phase 3 AURELIA study in which the investigators-choice arm demonstrated that weekly paclitaxel outperformed PLDH or topotecan monotherapy [112]. In addition, this study highlighted the benefit of the VEGF inhibitor bevacizumab in the platinum-resistant setting, yielding just over a 3-month PFS advantage compared with non-bevacizumab-containing treatments. However, this did not translate to OS benefit. Feasibility is also a concern when using bevacizumab in this context as patients have to be carefully selected to minimize their risk of bowel perforation. Platinum-resistant EOC remains an area of unmet need and is the subject of a number of novel approaches, including using immunotherapy (discussed below).

Surgical treatment at relapse

Despite the established value of cytoreduction in the primary setting, the value of tumour debulking surgery for recurrent EOC remains controversial and practice varies widely, nationally and internationally. While many supporters of surgical cytoreduction at relapse advocate that complete tumour resection may result in higher survival rates, opponents argue that the high associated complication rates and longer hospitalization times are inappropriate in patients with incurable EOC, especially without evidence of benefit to quality of life. Many authors have attempted to define a preoperative algorithm which would identify optimal candidates for secondary cytoreduction as based on well-defined selection criteria. The situation is even vaguer in the tertiary setting and beyond.

In platinum-resistant or refractory EOC, there is sufficient evidence that cytoreductive attempts do not result in a survival benefit and should not be performed unless for symptom palliation [113–115]. However, the situation is different in platinum-sensitive recurrent EOC. The DESKTOP I trial was a retrospective evaluation of 267 EOC patients and demonstrated that benefit from secondary surgery was derived only when total macroscopic clearance was achieved [116]. Complete tumour resection was associated with significantly longer survival compared with surgery leaving any postoperative residual disease (median 45.2 vs. 19.7 months; HR 3.71, 95% CI 2.27–6.05; P <0.0001). These findings challenge clinicians to accurately identify those patients in whom optimal debulking can be achieved. For this reason, based on a multivariate model, three clinical factors were identified as independently predicting resectability within the so-called 'AGO score': good performance status, complete resection at primary surgery (or early FIGO stage) and absence of gross ascites at relapse. The value of the AGO score lies it its simplicity. An exploratory analysis of the DESKTOP results to evaluate the role of peritoneal carcinomatosis present in recurrent EOC clearly showed that even though it was a negative predictor for complete resection in recurrent disease, it appeared to have no negative impact on survival if total macroscopic clearance could be achieved [117,118].

A subsequent confirmation and validation of the AGO score followed within the prospective multicentre DESKTOP II trial, in which the AGO score could be confirmed as a useful and reliable tool for predicting complete tumour resection in more than two-thirds of patients with platinum-sensitive relapsed EOC. Participating centres prospectively enrolled patients with platinum-sensitive EOC at first or second relapse. The AGO score was applied to all patients, but each centre was free to decide their therapeutic management. A total of 516 patients were screened within 19 months; of these, 261 patients (51%) were classified as score positive, and 129 patients with a positive score and first relapse underwent secondary tumour debulking. The rate of complete resection was 76%, thus confirming the validity of this score regarding positive prediction of complete resectability in more than two-thirds of patients [117]. Interestingly, a poor correlation was found when comparing the number and site of lesions by preoperative imaging with the number identified at surgery.

Perioperative morbidity and mortality appeared to be acceptable within the DESKTOP series, with a mortality as low as 0.8%, an 11% re-laparotomy rate mainly due to bowel leakage or fistula (7%) and a 2% deep vein thrombosis rate, while 52% of the patients required postoperative intensive care of a median 2 days (range 1–20 days). A subsequent multicentre randomized trial, DESKTOP III (AGO-Ovar OP.4), prospectively evaluate the impact of recurrent EOC surgery in platinum-sensitive patients with positive AGO score (tumour-free initial surgery, good performance status and ascites <500 mL). This demonstrated a PFS benefit in all patients undergoing surgery of around 4 months, but the benefit was only seen in those who had a complete macroscopic debulk. Secondary debulking surgery prolonged time to later relapse, although OS data are awaited [119]. The equivalent

American trial from the Gynecologic Oncology Group (GOG213) has commenced recruiting with the addition of randomization to systemic bevacizumab 15 mg/m^2 at maintenance. There are future plans to combine results from both trials to achieve a larger cohort and more robust survival data.

In one large systematic meta-analysis by Bristow *et al.* [113], 40 cohorts of 2019 patients with recurrent EOC were identified over a period of 24 years. After controlling for all other disease-related factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.0-month increase in median cohort survival time. Despite these encouraging retrospective data it is still not clear if the surgery itself is influencing survival or whether operability is just a surrogate marker of more 'favourable' tumour biology and therefore a better overall prognosis. The first two prospectively randomized surgical trials will definitively answer this question and may set new evidence-based standards.

The largest multicentre analysis on tertiary cytoreductive surgery (TCS) worldwide included 406 patients (median age 55 years, range 16–80) who underwent TCS between 1997 and 2011 in 12 centres across Europe, USA and Asia [120]. The majority of the patients had an advanced initial FIGO stage III/IV tumour (69%), peritoneal carcinomatosis (51.7%) and absence of ascites (72.2%), and 224 (54.1%) patients underwent complete tumour resection. The most frequent tumour dissemination site was the pelvis (73%). Median OS for patients without residual disease versus any tumour residual was 49 months (95% CI 42.5–56.4) compared with 12 months (95% CI 9.3–14.7; P <0.001). Most importantly, common clinicopathological characteristics such as tumour stage, age and histological subtype, which have been shown to be of significant predictive value at initial presentation of the disease, did not appear to be of any prognostic significance at the tertiary stage. A further clinically relevant finding was that a significant impact of third-line postoperative systemic chemotherapy on OS was identified, emphasizing the importance of combinative systemic and surgical therapy in the treatment of EOC, even in heavily pretreated patients. This may nevertheless constitute a selection bias since patients who are fit enough to tolerate chemotherapy following radical surgery may have more favourable survival rates than those for whom chemotherapy was contraindicated. Rates of major operative morbidity and 30-day mortality were 25.9% and 3.2%, respectively, and hence slightly higher than the equivalent data of secondary patients at the DESKTOP series. The most common complications were infection/sepsis (13%) and re-laparotomy (4.4%), but interestingly without any higher rates of thromboembolic events (2.5%).

Multivariate analysis identified platinum resistance, residual disease following secondary surgery and peritoneal carcinomatosis to be of negative predictive significance for complete tumour resection, whilst residual tumour at secondary and tertiary surgery, decreasing interval to second relapse, ascites, upper abdominal tumour involvement and non-platinum third line-chemotherapy were significantly associated with negative OS.

As in every surgical attempt in EOC, adequate patient selection is crucial to minimize morbidity and maximize benefit in a palliative patient cohort.

Management of bowel obstruction in the palliative setting

Patients with EOC often present with the clinical picture of impaired intestinal motility or even bowel obstruction in the advanced setting, attributed to diffuse tumour dissemination along the peritoneal layers [121]. In this context, targeted anti-angiogenic therapies are at risk of causing fistula formation or intestinal perforation [89,122]. Recurrent EOC complicated by such severe and acute events constitutes a therapeutic dilemma and surgery in these often heavily pretreated patients is highly challenging and associated with high morbidity and mortality. Surgical interventions include en bloc resection of the involved intestinal region with terminal proximal ileostomy or jejunostomy since, due to peritoneal carcinosis and inflammation, plane dissection with anastomotic and repair techniques are not feasible. This can result in short bowel syndrome requiring high institutional and physical resources and consideration of total parenteral nutrition.

In cases of acute intestinal complications such as perforation and peritonitis, therapeutic approaches are rather limited. Retrospective analyses have shown that patients operated in acute situations have significantly higher rates of anastomotic insufficiency compared with those operated electively [89,122]. In addition, rates of anastomotic insufficiency are higher at primary debulking surgery in patients with residual tumour compared to those without [122]. Benefits should be very carefully balanced with risks for each individual patient. Factors such as comorbidities, baseline quality of life, previous response to chemotherapy, treatment intervals and patient preference all need to be taken into account. Progress in endoscopic techniques, such as placement of intestinal stents and gastrostomies, have improved care of patients. However, in the case of multi-level bowel obstruction, a single stent or stoma formation is not helpful. Here, further options such as percutaneous endoscopic gastrostomy can used in highly selected cases.

Radiotherapy for relapsed disease

Radiotherapy is generally reserved for palliation of symptomatic disease, particularly symptomatic pelvic recurrence, cutaneous and intracerebral disease.

Future developments

It is likely that the future landscape of ovarian cancer treatment will be dominated by PARP inhibitors. *BRCA* testing is now being conducted in many clinical centres for HGSOC patients with or without a strong family history of the disease and patients with *BRCA* mutations will be managed with PARP-containing regimens throughout the course of their disease. It is questionable as to whether immunotherapy will also play an important role in the management of EOC. So far, checkpoint (such as PD1 or PDL1) inhibitors given alone or in combination with CTLA-4 inhibitors have transformed the management of many, hitherto lethal, cancers such as melanoma, renal cell cancer and non-small cell lung cancer. EOC has a low mutational burden, a factor that should predict lack of response to checkpoint inhibitors, but it has high levels of infiltrating regulatory T cells, believed to suppress immune activity. In a study by Hamanishi *et al.* [123] the anti-PD1 inhibitor nivolumab was given every 2 weeks to 20 patients with platinum-resistant EOC resulting in two complete responses and, across all participants, a disease control rate of 45%. In the phase IB KEYNOTE-028 study, 26 patients were given pembrolizumab and a disease control rate of 54.7% was observed. Larger randomized studies trialling immunotherapies in combination with chemotherapy, targeted therapies and other immune activators are currently underway for patients with platinum-sensitive and -resistant EOC. Enhanced understanding of the pathways underpinning chemotherapy resistance in EOC have led to a number of trials evaluating mTOR and AKT inhibitors in combination with chemotherapy in patients with platinum-resistant and -refractory disease, for example the OCTOPUS trial in which the mTOR inhibitor is given in combination with weekly paclitaxel. The greater availability and reducing costs of genomic assessment have opened the possibility of multi-armed studies in which patients are directed towards particular targeted therapies on the basis of their tumour mutational status.

Summary

The management of ovarian cancer is complex by virtue of its insidious presentation, heterogeneous histology and often rapid development of chemotherapy resistance mechanisms. Despite this, improvements have been made in 5-year survival over the last 20 years, reflecting advances in surgical technique and the use of more effective chemotherapeutic treatments, both initially and in recurrence. However, ovarian cancer still remains the most lethal of gynaecological cancers, warranting exploration into novel therapeutic strategies. These include personalization of treatment according to histology and genetic profile and the use of novel cytotoxics, targeted therapies and, perhaps also immunotherapy. Underpinning these and future developments is an ongoing commitment to unravelling the basic cellular biology of ovarian cancer. Only then can therapies be rationally designed or improved to make a significant impact on the outcome of this most deadly of cancers.

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Part 16

Sexual Health

64

Sexually Transmitted Infections

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Sexually transmitted infections (STIs) make a substantial and often under-appreciated contribution to gynaecological and obstetric morbidity, because their covert nature and transmission efficiency ensure widespread distribution throughout the entire sexually active population. Pelvic infection (Chapter 45), tubal factor infertility (Chapter 51), ectopic pregnancy (Chapter 43), genital ulceration, vulvo-vaginal discharge (Chapter 58), genital malignancy (Chapters 60 and 61), premature labour (Chapter 28) and neonatal infection (Chapter 19) have been widely researched and described in relation to STIs. Yet the role of infections, particularly chlamydia, in such common gynaecological problems as abnormal uterine and heavy menstrual bleeding due to endometritis, and right iliac fossa pain in teenage girls due to salpingo-appendicitis, is controversial and requires further elucidation.

Given the above, a sexual contact history – so often neglected in the past – is as important a part of routine gynaecological work-up as the menstrual or contraceptive history. Risk assessment cannot reliably predict the likelihood of infection nor its location in vagina, cervix, rectum or oropharynx, as no STI causes easily recognizable signs or symptoms in more than one-quarter of women, while most are obvious in less than one-tenth, and the partner's (or partners') contact history and infection status is usually unknown.

A thorough account of STI in women requires an entire textbook [1–3], so this chapter focuses principally on those aspects of bacterial and cutaneous viral STI which have the greatest relevance to daily gynaecology practice, excluding blood-borne viruses, while emphasizing the anatomical, hormonal and immunological factors which render women more vulnerable to infection by, and present differently with, the same conditions in men.

Epidemiology

Women are typically more vulnerable than heterosexual men to acquisition of STI as, in any sexual transaction, infections are more likely to spread to the biologically receptive partner. The rate of spread (R_0) of any infectious disease depends on a combination of transmission efficiency (β), rate of change of contact or partner (c) and duration of infectiousness (D), expressed in its simplest form as $R_0 = \beta cD$ [4].

Transmission efficiency of STIs to women depends on the infecting organism load and a combination of the amount and force of frottage or penetrative friction trauma and receptor tissue vulnerability, the latter being exacerbated by poor oestrogenization during use of progestogen-only contraception [5], breastfeeding or menopause, and the former by performance-enhancing drug use and non-consensual activity. Vulnerability, particularly to HIV, is greater in the rectum than in vagina or pharynx and can be diminished at all sites or substantially prevented by lubrication and condom use. Individual immune response and organism biology determines duration of infectiousness, which is typically short – a few weeks – for epidemic infections that are either briefly overtly symptomatic, such as urethral gonorrhoea in men or where there is transient high viraemia at seroconversion such as with HIV, or longer (months or years) for endemic STIs that remain covert in both sexes.

Thus well over 50% of women who have been sexually active with more than one partner will have acquired and/or transmitted endemic STIs such as herpes simplex virus (HSV), human papillomavirus (HPV) or *Chlamydia trachomatis* without ever displaying any signs or symptoms of infection, nor sustaining any significant harm. The latter two conditions will, in most cases, have been cleared spontaneously within 1 or 2 years (in many cases,

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

sooner) by the woman's normal immunological response [6,7]. Individual genetics and frequency of exposure, allied to hormonal and immunological status, typically define the minority of women who will develop symptoms and suffer adverse sequelae.

Most analysis of epidemiological trends reflects incidence of infections diagnosed and is dependent on appropriate provision of services, contraceptive choice, clinic attendance patterns, reporting systems and advances in diagnostic technology. The UK's system of free, confidential sexual health clinics has provided consistent methodology in clinical diagnosis and collection of statistics [8]. Reported cases of gonorrhoea in women over the past 70 years (Fig. 64.1) offers an important historical perspective of how subsequent generations have experienced different rates of infection. Plotted against teenage fertility it acts as a barometer of sexual mores and partner change rates, which is directly relevant to past and future provision of gynaecological care throughout women's life stages.

The immediate post-war 'baby boom' and its associated peak of infections was followed by a rapid fall in gonorrhoea (and syphilis) with the introduction of penicillin. The late 1950s to 1960s rise was due to sexual liberalization, demographic change and the introduction of the combined oral contraceptive pill (COC). Women who were teenagers in the mid-1970s – who are now recently menopausal – experienced the highest ever recorded rates of infection, coinciding with the greatest number of COC prescriptions issued and resulting in the lowest conception rates thereto. The effect of the HIV/AIDS education campaigns of the mid to late 1980s produced a dramatic fall in all STIs which lasted throughout the 1990s, so that women born between 1970 and 1980 had the lowest recorded rates of STIs (and greatest paranoia about infection) of any generation before or since, but had higher teenage conception rates as they used condoms in preference to pills. Women born since 1990 have intermediate infection rates due to less meticulous condom use, but are the first generation to grow up with freely accessible internet pornography, triggering a rise in coercion, acceptance and practice of rectal sex [11], and mobile dating apps offering a more efficient means of finding and changing new partners quickly. Yet they also benefited from widespread use of long-acting reversible contraceptives, and consequently had much lower pregnancy rates [10].

Rates of STIs such as gonorrhoea and chlamydia are unsurprisingly highest in women in their late teenage

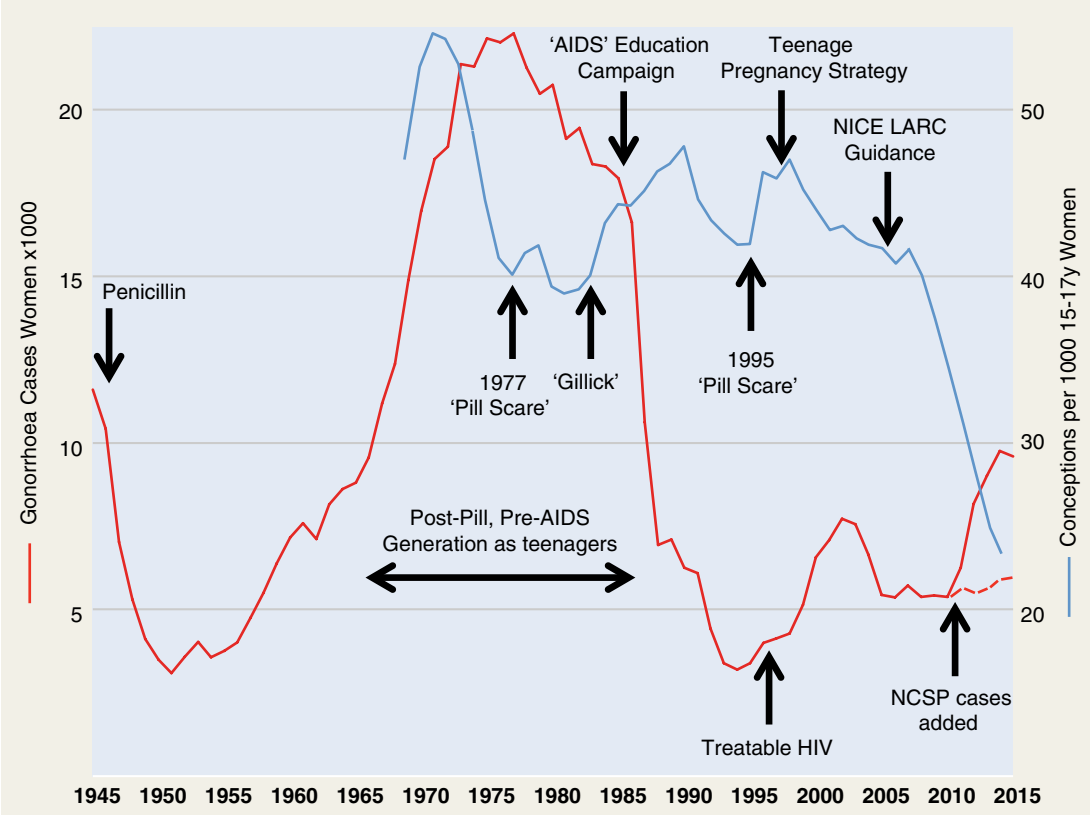

Fig. 64.1 England and Wales annual cases of gonorrhoea 1945–2015 (England only from 2010) and conception rates 1969–2014 [10]. Extrapolated from Public Health England [8] and Health Protection Agency [9] with corrections.

years and early twenties, peaking before those of young men, at the time when partner change rates are greatest and requiring repeated testing to aim for control of infections [12]. An individual's sexual behaviour and infection risk are substantially shaped by their demographic context and geographical setting [13]. Trends in STIs are broadly similar across northern European countries with similar sexual mixing patterns and the typical Western societal norm of serial monogamy with occasional infidelity. As the dating app-enabled 'half night stand' culture takes over, control of infections will become more challenging. Infection rates are already higher across entire populations where the religious cultural norm is a double-standard morality of male machismo and female virginity, as in southern Europe. STI rates are highest where poverty, drug use, economic necessity, ethnic tradition, or flight from conflict dictate that there will be large numbers of itinerant men having concurrent sexual partnerships [14] and wherever women's social, sexual and reproductive rights are least valued or respected [15].

Integrated approach to STIs in gynaecology

Any significant genital symptom, such as irritation, discharge, bleeding pattern alteration, pelvic pain or dyspareunia, should prompt enquiry and investigation as to whether the problem is due to change in hormonal milieu or a recently acquired infection, or a combination of both, given their equal contribution to these aspects of women's health (Fig. 64.2). The importance of this integrated approach [16] is particularly evident in women with recurrent pelvic pain, many of whom present to GPs and sexual health services and are presumed to have pelvic infection, when they actually have endometriosis [17,18]. These women receive antibiotics when they need hormones or surgery. The reverse occurs in women with abnormal uterine bleeding caused by chlamydial endometritis (see below): they present to gynaecologists or contraception clinics and get hormones or surgery when they need antibiotics.

Consideration of the complex interactions between a woman's hormonal status – whether due to cyclical variation, use of contraception, pregnancy, breastfeeding or life-stage changes – and their effects on systemic and local genital tract immunity is especially important for the management of recurrent genital infections (see below) and their associated symptoms. Any medical, or psychological, condition with a repeating and precisely timed cyclical fluctuation must have a hormonal cause or trigger, and might thus be amenable to hormonal treatment. Whilst biological plausibility for the latter is strong, the formal evidence base is weak due to lack of targeted research, which tends to focus purely on the infection while ignoring the contribution of luteal phase hormonally-induced immunosuppression.

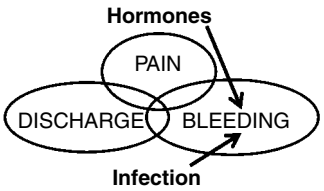

Fig. 64.2 Is it hormones or infection (endometriosis or endometritis) or both?

Sexual history-taking

This approach, and the reality of ubiquitous covert STI, requires that sexual history-taking should blend seamlessly into any routine gynaecology work-up by following on logically from menstruation details and contraceptive use. Special attention should be paid to onset of symptoms in relation to timing of hormonal or partner change. Questions do not need to be as detailed or intrusive as those typically taken in sexual health clinics [19] or following sexual assault. All that is initially required, after briefly stressing confidentiality and relevance of the questions to assisting diagnosis, is to enquire as to whether the woman is, or has been, sexually active, whether or not in a sexual relationship and, if so for how long, the interval since any previous sexual contact, be it recent or in the distant past, and whether she has had any post-coital bleeding or technical problems with sex.

By keeping questions brief, relevant and non-judgemental, sufficient useful detail should be gleaned without undue embarrassment. Clinicians should beware of making an automatic presumption of heterosexuality given the fourfold rise (to 8.7%) in experience of same-sex relationships among younger women in the most recent UK national survey [11]. Once rapport and trust in confidentiality have been established, this also represents an ideal opportunity to enquire routinely about sexual coercion or intimate partner violence [20]. Given the high prevalence and relevance of this problem, particularly during pregnancy [21], this should be considered an essential competence for any gynaecologist who supports women's human rights [22].

Relevant diagnostic tests should be taken and are discussed in Summary box 64.2. Treatment with appropriate antivirals, antifungals or antibiotics should ideally await the return of laboratory results and follow published national guidelines [23], which are regularly updated according to alterations in practice and resistance patterns, and are certain to have changed for some infections well before the next edition of this textbook (see Summary box 64.3). Immediate treatment may need to

be given, either presumptively depending on the urgency of the situation, or precisely if there is the luxury of access to accurate near-patient diagnostics [24].

Partner management

Unfortunately, immediate treatment gives less time for consideration of, and counselling about, the most neglected area of STI care in gynaecology, namely that of partner notification and treatment to prevent reinfection. Broaching the subject of sexual acquisition of infection and the need to treat the partner requires skill, discretion, privacy and accurate take-home information, and should not be rushed given the potential for misunderstanding and heightened risk of intimate partner violence [25]. Given these complexities, the minimum duty of care of a gynaecologist should be to advise abstention from intercourse until the partner or contact is treated and to seek immediate further assistance and support from health advisors and clinicians in the local sexual health clinic [26] or a nurse counsellor in their own department specially tasked with this remit. Local protocols should be established to facilitate this support, to handle confusion as results are frequently discordant and to assist the process of patient-delivered partner therapy, wherever this is part of the routine standard of care [27]. Summary box 64.1 contains some points of discussion to help reduce stigma and aid understanding.

Summary box 64.1

Discussion points on partner notification for STIs

- Any infection is likely to be asymptomatic in the partner or contact.
- There could be a long-standing pre-symptomatic phase in the woman.
- The infection could pre-date the start of the relationship.
- Given the above, an STI is not prima facie evidence of infidelity.
- Partners should be treated simultaneously to prevent reinfection, and should abstain from sexual intercourse during treatment.
- The diagnosis may not be proven and there may be other explanations for any symptoms, particularly for pelvic pain.
- Checking the partner or contact may improve the diagnosis and care of the woman.
- The partner's tests may not show infection as transmission concordance is not 100% and infections can clear spontaneously and at different rates in either partner.
- The partner should be checked and treated for their own future health.

Source: modified from Robinson & Greenhouse [26].

Diagnostic advances

Much of our understanding of STI in women has changed with the introduction of highly sensitive molecular diagnostic technology, starting with polymerase chain reaction (PCR) in the mid-1990s and other nucleic acid amplification tests (NAATs) by the mid-2000s, gradually replacing the traditional methods of microscopy and culture for gonorrhoea and *Trichomonas*, viral culture for herpes, enzyme immunoassay (EIA) for chlamydia and *in situ* hybridization for HPV [28]. For these organisms, the increase in sensitivity is of a magnitude between 50 and 100% greater than previously, amplifying the epidemiological fluctuations of the past century (see Fig 64.1) and suggesting that there was far more than the recorded fourfold greater number of gonorrhoea cases among women 40 years ago than nowadays. It also emphasizes the ubiquity of endemic infections, increasing the observed proportion of symptomless carriage to over 90% for most STIs in both men and women, and has prompted a thorough re-evaluation or clarification of research into disease associations such as those of chlamydia with premature labour (Chapter 28) and HPV with genital cancers (see Chapter 61).

The benefits of the ability to detect a positive signal from, in theory, a single organism or even a fragment thereof has revolutionized genital sampling. Previously, endocervical swabs with high organism copy numbers were essential for detecting chlamydia and gonorrhoea. Now self-taken vulvo-vaginal swabs are equal to, or even more sensitive than, those taken by the clinician from the cervix [29]. This substantially reduces the need for speculum examination except in cases of post-coital or other unexplained bleeding, intractable discharge, cytology sampling and colposcopy or intrauterine procedures. Where on-site vaginal microscopy is available, women with discharge can also take their own slides for Gram staining and/or wet mount, thus fewer women are having genital examinations in sexual health clinics [30]. Indeed, without access to immediate microscopy, it is difficult to understand how gynaecologists' management of vaginal discharge can be any better than the best-guess care of a competent GP or community contraception clinic [31]. A quick and simple low-tech solution is advocated by Donders *et al.* [32], using wet mount microscopy to diagnose bacterial vaginosis (BV), aerobic vaginitis, candidiasis and trichomoniasis for immediate treatment, although this lacks sensitivity for the latter two organisms.

Near-patient and multiplex testing

The latest developments have brought laboratory-quality analysis to the bedside or outpatient clinic with the

ability to produce reliable results in less than 2 hours. Near-patient testing for chlamydia and gonorrhoea has been shown to reduce unnecessary antibiotic treatment [33], with the added benefit of allowing partners to be notified quicker, thereby reducing onward transmission. This also has potential, as yet unresearched, to improve management of the acute abdomen, particularly in young women with right iliac fossa pain, by identifying or excluding STI before surgery is contemplated or antibiotics are started.

A further recent advance is the ability to test for several organisms simultaneously. As STIs frequently coexist, a vaginal swab sample routinely tested for some 8–12 organisms circumvents the *a priori* problem of knowing or guessing what to test for while apparently sacrificing very little in the way of sensitivity, and thus fewer unsuspected infections should be missed [34]. Unfortunately, some commercially available multiplex assays include organisms (e.g. *Mycoplasma hominis*, *Ureaplasma parvum*) which most would consider commensal or which have yet to be classified as genuinely pathogenic in women, resulting in unnecessary antibiotic treatment in some women seen privately or outside the UK.

The downside of test hypersensitivity is the potential for sample contamination from surfaces in clinics [35] and the problem of persistence of dead organisms for days or weeks after successful treatment, making timing of tests of cure problematical, particularly for chlamydia and gonorrhoea (see section on individual organisms).

Routine STI testing

Minimum routine STI screening in women consists of a vulvo-vaginal swab for a combined chlamydia and gonorrhoea NAAT, and bloods for syphilis and HIV [36] (see Summary box 64.2). Clinicians are accustomed to antenatal screening for the latter two infections. This should now extend to routine gynaecological care, given the consequences of missing these treatable hidden conditions, and is essential in cases of genital ulceration or wart-like lesions, and in areas where HIV prevalence is greater than 1 in 500 of the population [37].

Summary box 64.2

Essential STI screening: genital samples and additional tests

Asymptomatic screen
- Blood tests for HIV and syphilis and vulvo-vaginal swab for chlamydia and gonorrhoea (and other sites if indicated).

Vaginal symptoms
- Basic screen *plus* high vaginal swab for microscopy/culture of *Candida* and BV, wet mount/culture or NAAT for *Trichomonas vaginalis*.

Genital ulceration
- Basic and vaginal tests *plus* herpes swab(s).

Abnormal bleeding/intrauterine device (IUD) infection
- Basic and vaginal tests *plus* deep endocervical swab culture for aerobes and anaerobes.

High-risk scenario: intravenous drug user, sex worker, swinger, woman from high prevalence area or contact/partner of same or of bisexual man
- Basic and vaginal tests *plus* blood tests for hepatitis B and C.

Source: BASHH guideline [36].

STI in pregnancy

STIs affect all aspects of pregnancy, from subfertility, implantation failure, ectopic pregnancy, early and mid-trimester miscarriage, premature delivery and stillbirth to fetal anomaly and neonatal infection. Yet the relatively low prevalence of epidemic STIs in developed countries means that the most severe complications are rarely encountered in obstetric practice, and the consequences of endemic STIs may pass unnoticed.

Lessons from Africa

The most substantial effect of STIs on obstetric outcome is found in developing countries, particularly sub-Saharan Africa, where untreated infection rates are highest and cofactors such as poverty, poor nutrition and other endemic infectious diseases such as malaria and tuberculosis exacerbate the problem. In this setting, even after controlling for other variables, the risk of preterm birth is doubled by gonorrhoea and *Trichomonas*, quadrupled by chlamydia, and increased sevenfold if BV is diagnosed before 16 weeks' gestation [38]. Syphilis, with an overall antenatal prevalence of between 4 and 15%, affects some 2 million African pregnancies annually, of which 1.6 million remain untreated, resulting in half a million infant deaths [39]. It is associated with one-quarter of preterm births and half of all stillbirths [38].

Recent advances in near-patient testing using simple rapid combined syphilis and HIV kits produced much higher rates of positive diagnoses, and dramatically improved the proportion of syphilis cases treated from 51.1 to 95.2% [40]. A measure of the value of treating STIs can be estimated from pragmatic trials in Rakai, Uganda of a one-off antibiotic regimen (cefixime 400 mg,

azithromycin 1 g with metronidazole 2 g) given at around 28 weeks' gestation. In the late 1990s, this combination therapy would have been simultaneously effective against gonorrhoea, chlamydia and trichomoniasis, and should have rendered syphilis non-infectious. Despite non-treatment of partners and the risk of reinfection, the relative risks of low birthweight and neonatal death were both significantly reduced, at 0.68 and 0.83 respectively [41].

Based on the above, any effort to improve screening and treatment of STIs in pregnancy in any geographical setting should be rewarded with reductions in preterm birth and neonatal death, and increases in mean gestational age and mean birthweight, although these may be difficult to measure or prove depending on absolute disease prevalence. The effects of STIs on pregnancies in developed countries is considered in the sections on individual diseases, and is further discussed in Chapter 13.

Chlamydia

'The effect of chlamydial infection in women of reproductive age is overwhelmingly underestimated' [42]. *Chlamydia trachomatis* is the most important STI affecting women's health because of its ubiquity and causal association with adverse reproductive sequelae. As some 5–10% of young women are found to be infected in screening campaigns [8,12] it is probable that at least one-third to half will have been exposed to chlamydia in a lifetime. It is an obligate intracellular bacterium with a unique quasi-viral 48-hour life cycle, transforming between its extracellular infectious state as an elementary body (EB) and the intracellular reticulate body (RB), which uses cellular material to reproduce. Tissue damage is caused partly by this process, but principally by inducing an exaggerated cell-mediated immune response in a minority of genetically predisposed individuals [43]. Some RBs can convert to persistent non-replicative forms that retain long-term viability and are thereby less susceptible to clearance with antibiotics, leading to so-called heterotypic resistance, where treatment may fail with high organism load [44]. Chlamydia is almost entirely transmitted by direct sexual contact because the organisms do not grow on or infect external skin. It can only multiply in specific types of tissues, including the columnar epithelium of the endocervix, urethra, rectum, endometrium, peritoneum, conjunctiva and pharynx, and ciliated epithelium of the fallopian tubes, nasopharyngeal sinuses and bronchi. Pharyngeal carriage of chlamydia in women genitally infected is around 12% with almost all asymptomatic [45], but oral sex is considered a relatively inefficient route of chlamydial transmission.

As with most other STIs in women, highest rates are found in the late teens and early twenties due to greatest rates of partner change, with a substantial decline from the peak at age 18–20 identified in sexual health clinic testing and by the UK national chlamydia screening programme [8,12]. Unsurprisingly, total recorded case numbers increased and overall positivity rates fell as the screening campaign rolled out to a wider proportion of the population. A better perspective on recent chlamydial epidemiology can be gleaned from Swedish data collected since the early 1980s and derived not from population screening but from widespread, low clinical threshold, diagnostic testing [46]. The sustained fall in incidence from 1986 – which was a major impetus for the UK screening initiative – occurred not because of the testing programme, but due to HIV education campaigns reducing partner change rates and increasing condom use. Since HIV became treatable in 1996, chlamydial infection rates have risen consistently.

There is increasing concern as to whether widespread screening and treatment has any realistic effect on disease prevalence, given the rate of population mixing [47]. Repeatedly exposing large numbers of individuals to antibiotics for an infection which harms only a minority contributes to the generation of resistant strains of other organisms, such as gonorrhoea and mycoplasma (see below).

Longevity of infection and spontaneous clearance

For many years it was presumed that chlamydial infection would remain present and identifiable in an infected individual until such time as they were given appropriate antibiotic treatment. It has now been shown that the majority of adolescent and adult women will eventually clear the infection from the lower genital tract via their own immune system with no apparent long-term ill effects but that a minority will retain active or quiescent chlamydial infection within their endometrium, ovarian surface and/or fallopian tubes regardless of whether the organisms are identifiable by swabs taken from the cervix [48].

The rate of spontaneous clearance in a cohort of initially infected and untreated adult women of mixed ages has been demonstrated as 50%, 80% and 95% clear after 1, 2 or 3 years respectively [49]. It has also been shown that the speed of clearance increases proportionally with increasing age so that women in their thirties are likely to have cleared the infection within a few weeks or months [50]. This explains why women in their late teens appear to have more chlamydia than those in their mid-twenties, despite the latter's increased cumulative exposure to infection. It also explains how couples are often found to

be discordant for infection, with a different speed of clearance between partners causing misunderstanding and possible recrimination [26,27].

Spectrum and sequelae of chlamydial infection

The clinical spectrum of chlamydial infection in women runs from the asymptomatic millions, who clear their infections spontaneously without suffering tubal damage [51], to the moribund few hospitalized with acute pelvic infection (see Chapter 45). Between these extremes are a range of conditions such as endometritis, menorrhagia, ectopic pregnancy and tubal factor infertility variously referred to as 'subclinical salpingitis' [52], 'atypical PID' [53] or 'subclinical PID' [54] in which the role of chlamydial infection is covert, usually unrecognized and therefore untreated.

Chlamydia and abnormal bleeding: unanswered questions

Chlamydia is one of several infections contributing to cervical friability and overt mucopurulent cervicitis [55] (Fig. 64.3), which can result in increased vaginal discharge and post-coital bleeding (PCB). Yet both the physical sign of cervicitis and the microscopic finding of leucocytes are non-specific, having a very low positive predictive value for chlamydia, but being a strong negative predictor for absence of endometritis [56]. Management of PCB in the UK is inconsistent [57], and requires definitive exclusion or treatment of chlamydia, gonorrhoea and, probably, *Mycoplasma genitalium* before any ablative surgical treatment is contemplated for benign conditions such as ectropion.

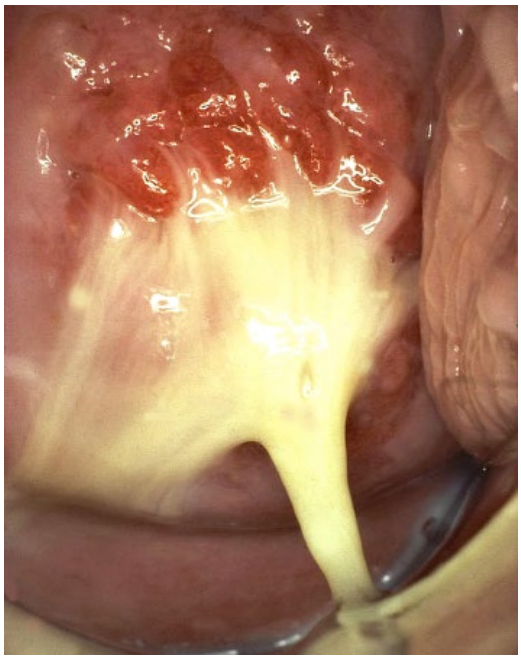

Fig. 64.3 Chlamydial mucopurulent cervicitis. Overt chlamydial mucopurulent discharge with endocervical gland oedema showing follicular cervicitis. A similar appearance is seen with gonorrhoea, but most chlamydia is covert showing little or no such obvious signs. *Source:* photograph by Peter Greenhouse FRCOG, 1992. (*See also colour plate 64.3*)

Any woman with upper genital tract infection (e.g. salpingitis, pelvic peritonitis, perihepatitis, periappendicitis) must, by definition, have a concomitant endometritis. Yet the extent to which chlamydial or other STI-related endometritis contributes to abnormal uterine bleeding (AUB) or heavy menstrual bleeding (HMB) is as yet unknown because of the paucity of specifically targeted research. Some 29% of women with recent-onset irregular intermenstrual bleeding (IMB) while taking COC pills were found to have chlamydia using a highly sensitive direct immunofluorescence test, compared with 11% who had vaginal discharge or new partners, and only 6% among new contraception clinic attenders [58]. Thus, second only to poor compliance with COC, chlamydia is the next commonest cause of IMB in young women.

Single-dose azithromycin (1 g) was shown to produce a 50% reduction in abnormal bleeding in a proof-of-concept study in predominantly African-American women attending a public sexual health clinic [59]. While histological evidence of plasma-cell endometritis reduced from 38% to 4% after treatment (P <0.001), this was not precisely linked to each case of successful resolution of bleeding.

Analysis of historical endometrial biopsies from women with unexplained AUB, who had been neither tested nor treated for chlamydia at the time of biopsy, found that some 58% had PCR evidence of chlamydia and that infection was strongly correlated (P <0.001) with the finding of macrophages, lymphocytes and plasma cells, leading the authors to make this section's opening quote on the unrecognized importance of chlamydial infection in women [42]. If this work were to be repeated prospectively and results confirmed, it would suggest that *C. trachomatis* infection could be sufficient to account for the majority of 'idiopathic' or unknown causes of AUB-E or AUB-I in the PALM-COEIN classification (see Chapter 48). Thus in the initial investigation of AUB and HMB, routine checking of pipelle or hysteroscopy samples for both plasma-cell endometritis and chlamydia, with appropriate pre-insertion treatment, might reduce the rate of persistently heavy or irregular bleeding patterns after levonorgestrel-releasing intrauterine system (LNG-IUS) insertion.

Chlamydia, periappendicitis and perihepatitis

According to Moritz in 1912, 'The causative relationships between adnexal disease and appendicitis still form

a dark area in gynaecology' [60]. The incidence of this commonest surgical emergency is significantly greater in women than in men only between the ages of 16 and 21, with a doubling in the excess rate of operation and trebling of 'negative' histology [61] coinciding with the sharp peak [8] in incidence of the commonest STI at ages 18–20. The coincident finding of chlamydia and serosal plasma cell periappendicitis [62] suggests that chlamydial 'salpingo-appendicitis' might explain this diagnostic dilemma and its ubiquity [63], necessitating chlamydia screening of all acute cases of right iliac fossa pain in young women regardless of where they present [64]. Accurate point-of-care STI tests could enhance acute management in emergency departments. If specific antibiotic regimens for chlamydial pelvic inflammatory disease (PID), such as one including high-dose ofloxacin (400 mg b.d. for 14 days), were used in future trials in this age group, this could improve the hitherto equivocal outcomes achieved [65] when comparing antibiotics with surgery, but this rationale has yet to be explored.

The association between STI and perihepatitis was first described in 1920 [66], and was originally thought to be caused by gonorrhoea. Curtis frequently found bridal veil and/or violin string adhesions between liver and diaphragm (Fig. 64.4) when performing pelvic clearance for end-stage gonococcal salpingitis [67]. The acute presentation of right hypochondrial pain, limiting deep inspiration, with positive Murphy's sign indistinguishable from that of acute cholecystitis, in association with gonococcal peritonitis was described by Fitz-Hugh [68]. Since the first isolation of chlamydia from the liver surface [69], very few cases of the Fitz-Hugh–Curtis syndrome have been described without evidence of chlamydial infection [70] or high anti-chlamydial antibody titres [71], because of the frequent coexistence of gonorrhoea with chlamydia. About 20% of PID cases have some degree of right upper quadrant pain that, in most cases, resolves rapidly with appropriate anti-chlamydial treatment, and requires adhesiolysis only in the rarest cases of persistent diaphragmatic restriction. Symptoms may present acutely without any apparent pelvic pain or other physical signs, but the association is strong enough such that any right hypochondrial pain in a young sexually active woman must be assumed to be chlamydial in origin until proven otherwise, because of the relative rarity of cholecystitis in this age group. Very rarely, women may present with pain over the left lobe of the liver or with perisplenitis.

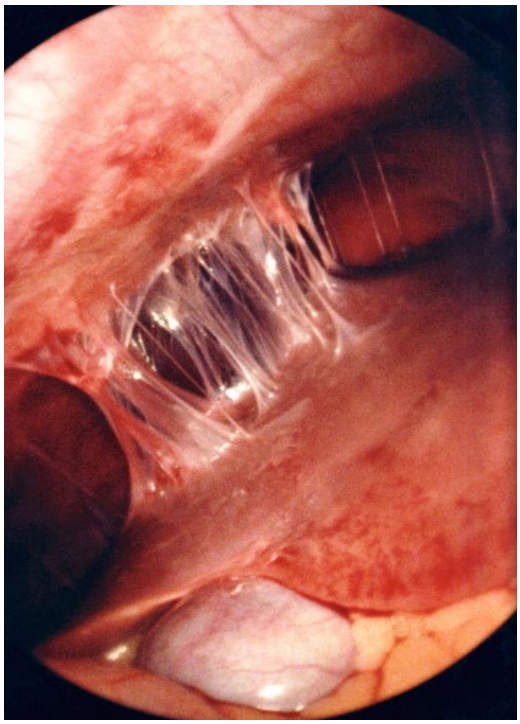

Fig. 64.4 Chlamydial perihepatitis/Fitz-Hugh–Curtis syndrome. Bridal veil and violin-string adhesions between liver and diaphragm due to chlamydial infection, causing right hypochondrial pain and restriction of respiration. Note normal gallbladder. *Source:* photography by Peter Greenhouse FRCOG, 1986. (*See also colour plate 64.4*)

Chlamydial PID and tubal factor infertility

There is a wide variety of opinion as to the proportion of women who will eventually develop tubal damage following chlamydial infection, and on the effectiveness of screening and treatment in disease prevention. Estimates range from the widely accepted 1–2% [72] to 17% in a recent thorough assessment which suggested that for every 1000 chlamydial infections in women aged 16–44 years, there would be approximately 171 episodes of PID, 73 of salpingitis, two ectopic pregnancies and five women with tubal factor infertility (TFI) by age 44 years [73]. Despite these predictions, prospective randomized studies of chlamydia screening to prevent pelvic infection report widely differing results, dependent on patient selection and data interpretation.

The Seattle PID prevention study found a relative risk of PID of 0.44 (95% CI 0.2–0.9) in screened and treated women of whom 7% had chlamydia compared with an unscreened population [74]. Yet the London Prevention of Pelvic Infection (POPI) trial found a small but non-significantly reduced number of cases in those screened and immediately treated, but the majority (79%) of incident PID cases occurred in women originally found to be uninfected [75].

As discussed in Chapter 45, the principal determinants of reproductive tract damage due to chlamydia are repeated exposure to and severity of infection [76], delayed treatment of symptomatic disease [77] and individual anti-chlamydial cell-mediated immune responses,

which are predetermined by single nucleotide polymorphisms [43] conferring enhanced susceptibility on a minority of women. These responses should theoretically become apparent at first and thus youngest exposure to infection. In contrast, some women are genetically protected against tubal damage. Those with the CCR5 Δ32 gene deletion, which also prevents infection by HIV, are four times less likely to have tubal pathology among subfertile women with anti-chlamydial IgG antibodies [78]. This raises the future prospect of being able to predict a woman's risk of infertility from genotype and chlamydial serology response [79], an approach which could be particularly useful in the investigation of 'unexplained' infertility [80].

The strongest link between TFI and chlamydial cell-mediated immune response is seen in a linear increase in anti-chlamydial antibody titre (CAT) with severity of tubal damage in subfertile women, when measured by the whole-cell inclusion immunoflourescence test [81]. As CAT is logarithmic, this fits a dose–response effect. Almost all of these women were negative on cervical NAAT screening and it is not yet known if women with high CAT would benefit from prolonged antibiotic therapy [80], though this could be an option in those with proven endometritis. Anti-chlamydial heat shock protein (HSP)-60 antibodies have been more widely studied, having highest titres in women with acute perihepatitis and salpingitis [71], and also being highly predictive of TFI when combined with markers of anti-chlamydial humoral immunity [82].

Failure of assisted reproduction techniques

Higher chlamydial HSP-60 titres are also associated with significantly greater risk of failure of assisted reproduction techniques (ART). Embryo implantation is more likely to fail [83], and early spontaneous miscarriages are more common [84]. As human HSP-60 has a similar structure to that of chlamydial HSP-60, the postulated immunopathological mechanism is either one of chronic covert endometritis preventing implantation, or a possible direct effect on early embryo development [84]. Increased expression of endometrial prostaglandin receptors has separately been proposed as a risk factor in chlamydia-infected women with recurrent miscarriage [85]. On a hopeful note, a significantly higher live-birth rate has been demonstrated in women whose chronic endometritis improved after a combination of antibiotic treatments, most of which included anti-chlamydials [86].

Chlamydia and ectopic pregnancy

Chlamydia probably contributes to the majority of ectopic pregnancies despite rarely being found on vaginal or endocervical swabbing at the time of presentation, and the range of estimated risk is a matter of dispute (see Chapter 43). Chlamydia causes suboptimal oocyte transport by partial deciliation and reduced ciliary beat frequency [87] in women who have not already suffered complete fimbrial enclosure. Over 85% of women with ectopic pregnancy have markedly raised CAT compared with women having live births [80,88]. In an ecological study, annual reduction in chlamydial incidence was directly related to a linear fall in ectopic pregnancy: among 20–24 year olds, extension of the plot line transected the zero point of the abscissa, suggesting that if there were no chlamydia in this age group, there would be little or no ectopic pregnancy [89]. The PCR finding of reverse-transcription chlamydial mRNA in fallopian tubes of women with ectopic pregnancy suggests that viable, metabolically active chlamydial infection remains present and contributing to tubal damage long after initial infection [90]. Taken together, these points suggest that young women with ectopic pregnancies may warrant extended anti-chlamydial treatment even if lower genital tract swabs are negative.

Chlamydia and arthritis

The first described example and strongest evidence of individual genetic response to chlamydia is that of HLA-B27 tissue type [91] conferring susceptibility to the triad of sexually acquired reactive arthritis (SARA), uveitis/conjunctivitis and urethritis (formerly known as Reiter's syndrome), which appears commoner in men than women [92]. SARA is an asymmetric multi-joint 'sterile' inflammation of synovium, fascia and tendons typically affecting hands, lower limbs and sacro-iliac joints, where chlamydia can be found in synovial membrane biopsy [93]. Joint involvement can occur in the absence of other features and isolated sacro-iliitis is probably frequently missed in women [94]. Treatment is by standard or extended anti-chlamydial regimens [94,95] in conjunction with anti-inflammatory drugs, and the condition is best managed jointly between sexual health clinicians and rheumatologists because of the high recurrence rate [94]. Azithromycin becomes highly concentrated in cartilage, but it is not yet proven if this regimen confers special benefit [95].

Chlamydia in pregnancy

Through the 1980s and 1990s, studies of chlamydia in pregnancy using relatively insensitive EIA testing consistently reported higher rates of spontaneous preterm labour and preterm birth (PTB) in chlamydia-infected women, but none reached statistical significance. No meta-analysis was performed, and it was assumed that chlamydial infection was not a major cause of PTB. Studies using early chlamydial DNA detection tests suggested a twofold to threefold increased risk of PTB if chlamydia was detected at 24 weeks [96].

In the treatment of women with BV in pregnancy (see Chapter 28), only systemic regimens containing recognized anti-chlamydial antibiotics (erythromycin, clindamycin) were successful in reducing PTB [97], explaining the failure of metronidazole-only regimens. Accidental treatment of chlamydial infection is probably the hitherto unexplained reason for the marked success of the only randomized antenatal trial of doxycycline (against presumed bacteriuria) yielding an odds ratio of 0.25 for PTB versus placebo [98]. Taking these facts together suggests that greater importance should be attached to antenatal screening for chlamydia [99], despite the problems of evaluating the relevance of treating an infection which can resolve spontaneously between antenatal visits in older women [49]. This is not recommended in the UK National Institute for Health and Care Excellence (NICE) guidelines [100], which merely suggest directing women under 25 years old to the National Chlamydia Screening Programme. This analysis failed to take account of the largest antenatal natural history study of untreated chlamydia, which showed adjusted odds ratios of 4.35 and 2.66 for PTB in infected women under 32 and under 35 weeks, with chlamydia accounting for 14.9% and 7.4% of premature deliveries at these gestations respectively [101].

Mother-to-child transmission of chlamydia occurs in up to 60–70% of infants born vaginally [102]. Vaginal and rectal infection in newborn girls is more likely to occur in breech deliveries, with a quoted 20% transmission efficiency [103]. Chlamydial ophthalmia neonatorum is much more common than that caused by gonorrhoea, but the incubation period is longer at around 1–2 weeks, with all infections presenting within 30 days [104]. Chlamydial pneumonitis can occur any time from 1 to 3 months after birth, with the majority presenting between 8 and 11 weeks [105].

Chlamydia treatment and prophylaxis

(see also Summary box 64.3)

Although recent UK guidelines [106] still recommend equal first-line treatment of uncomplicated chlamydia with doxycycline 100 mg b.d. for 7 days or azithromycin 1 g stat, there is increasing concern about the inadequacy of the latter regimen when assessed by test of cure (TOC) using NAAT [107,108]. Doxycycline is some 20% more effective than single-dose azithromycin for rectal infection [109], and as the rectum is a preferential site for chlamydial carriage even in women who have never had rectal sex [110], an alternative is needed. Azithromycin has a very long intracellular half-life, remaining above the MIC_{90} for chlamydia for 10 days, and is especially concentrated in uterus, fallopian tubes and bladder [111]. Yet its serum half-life is less than 24 hours, which explains its potential failure in high organism load infections [44], requiring an extended regimen prolonged over at least three and preferably five days [112]. Extended azithromycin using a total of 1.5 g minimum up to 3 g maximum (e.g. 1 g stat followed by 500 mg for 4 days) should almost certainly be used in preference to single-dose therapy when there is any suggestion of endometritis. This oral regimen was extrapolated from a successful PID monotherapy trial [113]. A further alternative for uncomplicated chlamydia is ofloxacin 200 mg b.d. (or 400 mg o.d.) for 7 days, but this must not be given to professional athletes because of the rare side effect of tendon rupture [106].

This new understanding of treatment inadequacy sheds light on, and may call into question, recommendations against antibiotic prophylaxis prior to uterine instrumentation to prevent PID, particularly before IUD insertion [114]. This analysis found no overall reduction in PID, yet a small but significant benefit with less women re-attending for pain or bleeding, in studies using a suboptimal azithromycin regimen (500 mg stat) or a homeopathic dose of doxycycline (200 mg stat). The current recommendation against routine prophylaxis [115] should be backed up by trials of an appropriately dosed anti-chlamydial regimen (i.e. extended azithromycin), particularly for young women requesting emergency IUD contraception. This is another example where near-patient high-quality diagnostics could lead to better-targeted antibiotic husbandry.

There are less therapeutic options for treatment of chlamydia in pregnancy or breastfeeding, as both doxycycline and ofloxacin are contraindicated, but are not apparently harmful in the interval between conception and first missed period. Azithromycin 1 g is recommended as first line [106] because of its safety [116] and superior tolerability to the alternative of erythromycin [117]. Amoxicillin 500 mg t.d.s. for 7 days is an alternative [118], but is not used outside pregnancy because of theoretical concerns of inducing latency. The importance of ensuring clearance of infection prior to delivery mandates a TOC, which must be performed no less than 4 weeks [119] to 6 weeks [106] after treatment has finished, because the persistence of dead chlamydial antigen can give a false-positive NAAT if taken sooner [107]. Assistance from sexual health colleagues is particularly useful in this scenario to handle sensitive relationship issues and ensure correct management of partners [106].

Further guideline-based regimens for upper genital tract chlamydia are considered in Chapter 45.

Gonorrhoea

Gonorrhoea is the second commonest bacterial STI, with less than one-tenth the prevalence of chlamydia in the UK [8], producing a similar range of gynaecological

morbidity. It is more often symptomatic because of its more direct mode of pathogenesis, but still remains unrecognized in some 70–80% of women. Gonorrhoea epidemiology, discussed in detail in Fig. 64.1, is more sensitive to changes in sexual behaviour than chlamydia. Even when cases were at their lowest in the UK in the early to mid-1990s, Black British or Black Caribbean compared with White ethnicity was associated with a 12-fold or eightfold greater risk of gonorrhoea or chlamydia respectively [120]. This was ascribed to much higher partner change rates and concurrency of relationships. This pattern is seen worldwide in other populations depending on these parameters and prevailing socioeconomic, cultural and other coercive factors.

Neisseria gonorrhoeae is a Gram-negative diplococcus which adheres via surface pili to columnar epithelial cells of moist mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva [121]. Transmission occurs by direct inoculation of warm secretions onto a surface with near neutral pH. Although it does not infect the vagina in adolescent and premenopausal adult women, gonorrhoea causes vulvovaginitis in prepubertal girls as the hypo-oestrogenic vaginal epithelium is thin with a neutral pH and is therefore easily inflamed, with most infections being symptomatic [122]. Gonococci produce a peptidoglycan-stimulating cytotoxic tumour necrosis factor (TNF)-α [123] and a lipopolysaccharide enzyme that facilitates direct spread of the organism particularly into glandular tissues, producing damage and potential abscess formation and contributing significantly to the more severe presentation of acute gonococcal salpingitis (see Chapter 45).

The principal lower genital tract symptoms, if present, arise from an endocervicitis manifesting as excess vaginal discharge – which can often remain unnoticed because of normal cyclical changes – and increased cervical friability which predisposes to PCB [124]. Gonorrhoea is nowadays much less likely to be missed as a cause of discharge and PCB because of the routine use of dual chlamydia/gonorrhoea NAAT, such as the Aptima Combo 2 [125]. Overt gonococcal urethritis is rarely seen in women compared with men, and urethral infection is now rarely tested for other than in hysterectomized women. When previously researched using culture it was commonly found in some 80% of women with endocervical infection [1], many of whom had only mild and largely ignored dysuria. Both rectal and pharyngeal gonorrhoea are asymptomatic in around 95% of men and women. The pharynx represents a major reservoir for oral sex transmission of gonorrhoea, and fellatio is the principal route of gonorrhoea spread in those who use condoms meticulously for other forms of sex [126]. Control of pharyngeal gonorrhoea is particularly important as most antibiotic resistance develops at this site [127].

Rarely, gonorrhoea infects paraurethral tissues including Skene's glands [3], and was classically recognized as the commonest cause of Bartholin's abscesses, although chlamydia also contributes to a lesser quantity of acute and chronic Bartholin's inflammation [128].

Disseminated gonococcal infection: arthritis and septicaemia

Disseminated gonococcal infection (DGI) may occur in up to 3% of cases [129]. It usually presents without obvious genital symptoms in women, commencing with a flitting polyarthralgia, tendon pain and pyrexia. Painful pustular lesions occur in hands and feet, with infectious micro-emboli lodging in the peripheral circulation. The main feature is one or two hot swollen joints (septic arthritis), most commonly the knee and wrist, with organisms identifiable from aspiration of synovial fluid [130]. DGI is more common in women than men and often presents during pregnancy, probably because the combination of lowered immunity, increased vascular permeability and hyperdynamic circulation may facilitate haematogenous spread. Rare complications of DGI are gonococcal meningitis and endocarditis [129]. Treatment requires higher and longer doses of the first-line agents [121].

Gonorrhoea in pregnancy

Gonorrhoea is too sporadic for trial research in a European setting regarding PTB, but much of this infection will remain unrecognized in pregnancy unless vaginal discharge is copious and dual chlamydia/gonorrhoea testing is used [131]. A new diagnosis in pregnancy raises acutely sensitive issues of partner treatment [132], mutual mistrust and support needed in case of intimate partner violence. As with chlamydia, correct treatment and TOC is essential [121] to reduce the risk of PTB and prevent ophthalmia neonatorum. This was first managed with silver nitrate prophylaxis by Credé over a century ago [133], but remained the principal cause of blindness, apart from syphilis, in the UK up to the 1920s. Symptoms of discharge and eyelid oedema typically develop within 2–5 days, but occasionally present up to 2 weeks after delivery [134], and must be treated immediately as corneal scarring can occur within 24 hours [135].

Treatment of gonorrhoea (see also Summary box 64.3)

Current UK [121] and European [136] guidelines recommend ceftriaxone as the only first-line antibiotic remaining to treat gonorrhoea effectively (including in pregnancy), with a current 99.2% cure rate [127].

Ceftriaxone 500 mg i.m. stat needs to be given with azithromycin 1 g [121] or 2 g [136] stat, regardless of chlamydia test results, to reduce the chance of resistance developing to the primary drug. After initial diagnosis by NAAT, a swab must be taken for culture before treatment is given. Gonorrhoea is best managed in conjunction with a sexual health service to provide this essential antibiotic sensitivity checking, partner notification and follow-up TOC. Timing of TOC must be delayed by 2 weeks to allow for clearance of residual gonococcal DNA [137]. In the case of allergy or other contraindication to ceftriaxone, choice of antibiotic is determined by the culture result on advice from the microbiologist based on local resistance patterns. Spectinomycin 2 g i.m. stat is one of the second-line recommendations, but this is ineffective against pharyngeal gonorrhoea [138].

The most pressing problem of gonorrhoea control is the likelihood that the infection will become untreatable within the next decade [139]. The organism can evade host immune responses by having a widely variable surface structure and rapidly evolves resistance mechanisms to each new antibiotic within a few years of its introduction. Antibiotic concentrations are higher in the genitals and pelvis than in the pharynx, where gonorrhoea mixes with commensal organisms, particularly *N. meningitidis*, from which it acquires resistance genetic information. Recommended antibiotic dosage regimens will increase as resistance 'drift' increases [140]. Complete resistance to ceftriaxone is currently rare, but first occurred in pharyngeal infection of a Japanese female sex worker [141]. The pharynx was the site of all resistant strains in the last European-wide report [142]. High-level azithromycin resistance in the UK was first reported among heterosexuals [143], probably occurring due to widespread use of the drug in the chlamydia screening programme, with cases of undiagnosed gonorrhoea being missed and suboptimally treated. The first dual failure of ceftriaxone and azithromycin was recently reported from the UK [144].

While awaiting newly developed antibiotics, future management of multidrug-resistant gonorrhoea will require reuse of combinations of older antibiotics, guided by culture results and newer molecular techniques [140], necessitating ever closer working between gynaecologists, sexual health clinicians and microbiologists to achieve therapeutic success.

Untreated or untreatable gonorrhoea

For obvious ethical reasons, no modern data are available on the long-term course or duration of untreated gonorrhoea in women but, in the worst-case scenario, the possibility of untreatable infection may prompt a return to heroic surgical intervention for chronic disease. Reading from pre-antibiotic era accounts of optimal choice of timing for pelvic clearance of 'burnt out' gonococcal salpingitis, it is probable that almost all infection will have spontaneously cleared within 2 years, in many cases much sooner [67,145].

Mycoplasma genitalium

Mycoplasma genitalium (MGen) belongs to a genus of the smallest known free-living organisms, having DNA and RNA but no cell wall. It is considered to be an emerging [146] and overlooked STI [147] as it has been shown to cause some 30% of non-gonococcal urethritis in men [148], yet a thorough review could not conclusively implicate *M. genitalium* as a cause of female urethritis [146]. An equivalent contribution to other lower or upper genital tract infection in women, over and above that of gonorrhoea and/or chlamydia, has been less widely researched because of its relatively recent discovery and the limitations of diagnostic expertise confined to a small number of centres.

Mycoplasma genitalium infects genital and respiratory mucosal surfaces, and other members of the genus (e.g. *M. hominis*, *Ureaplasma parvum*) have been found to be commensal in these sites. Although progesterone is a prerequisite for establishment of infection in laboratory animals, nothing is known of the interaction of hormones and *M. genitalium* in humans. *Mycoplasma genitalium* is associated with mucopurulent cervicitis, with one group showing a 3.3-fold greater risk [149]. Yet the difficulties of standardizing a definition of cervicitis hamper accurate comparisons between studies [146], and characterizing its role in vaginal discharge has remained elusive for similar methodological reasons.

Since the original report implicating raised *M. genitalium* antibody titres in acute PID [150], substantial work has been published linking the immune response to *M. genitalium* in women with TFI [151]. Despite this, another major study showed a lack of association of *M. genitalium* antibodies with PID and ectopic pregnancy [152]. *Mycoplasma genitalium* has been found in significantly greater proportions in women with endometritis, but its low overall prevalence in women with severe PID suggests a minor role only [153]. A recent meta-analysis suggests that the association is statistically significant [154], but might be only marginally clinically relevant due to the low pooled odds ratio (POR) of 2.14 (95% CI 1.31–3.49). This suggests that only a small minority of infected women are susceptible to significant damage while most are unaffected. These issues are also considered in Chapter 45.

Mycoplasma genitalium in pregnancy

In the antenatal setting, a large London study found a low (0.7%) prevalence of *M. genitalium*, suggesting it was

'unlikely to be an important risk factor in adverse pregnancy outcome in healthy women in the community' [155]. While an authoritative review found considerable evidence for the role of *M. hominis* in postpartum and post-abortal sepsis, there was difficulty differentiating the role of *M. genitalium* from that of BV in PTB [156]. The aforementioned meta-analysis [154] reached an alternative conclusion, suggesting a POR of 1.89 (95% CI 1.25–2.85) for *M. genitalium* in PTB, but this is considerably less than the OR of 4.35 (95% CI 1.3–15.2) for chlamydia in the Rotterdam study [101].

Treatment of *Mycoplasma genitalium*
(see also Summary box 64.3)

The greatest problem in management of *M. genitalium* is the inadequacy of treatment to clear infection, and the finding that some 40–50% of the 15% who fail treatment with azithromycin 1 g will have developed chromosomally mediated resistance at the 23S site, necessitating alternative treatment with moxifloxacin [157]. The European guidelines recommend extended azithromycin regimens for 3 or 5 day as first-line choice [157]. Yet as most people are never tested for *M. genitalium*, macrolide resistance is already endemic at around 40% in countries such as the UK and Norway because of widespread exposure to single-dose azithromycin, but not in Sweden where doxycycline is used in preference to treat chlamydia [158].

The latest PID treatment guidelines have introduced specific anti-mycoplasmal regimens for the first time (see Chapter 45), but routine screening for *M. genitalium* is not recommended by the CDC [159], and few UK sexual health centres currently offer testing. However, over the next decade, the true relevance of *M. genitalium* in obstetrics and gynaecology, and the implications of its increasing resistance to macrolides in populations with widespread exposure to single-dose azithromycin treatment of chlamydial infection, will become clearer as new diagnostic techniques are standardized and used routinely in sexual health clinic practice and in cross-disciplinary research.

Summary box 64.3

Antibiotic treatment for the main bacterial STIs (all doses oral unless stated)

Chlamydia trachomatis
- First choice — Doxycycline 100 mg b.d. for 7 days.
- Second line — Ofloxacin 200 mg b.d. or 400 mg o.d. for 7 days *or* erythromycin 500 mg b.d. *or* 250 mg q.d.s. for 7 days.
- Alternative — Extended azithromycin 1 g stat *then* 500 mg o.d. for 2 days *or* 250 mg o.d. for 4 days.
- Complicated — Ofloxacin 400 mg b.d. for 14 days *or* doxycycline 100 mg b.d. for 14 days *or* extended azithromycin 1 g stat *then* 500 mg o.d. for 4 days.

Neisseria gonorrhoeae
- First choice — Ceftriaxone 500 mg i.m. stat *and* azithromycin 1 g *or* 2 g stat.
- Alternative — Consult microbiologist and/or sexual health clinician.
- Complicated — Consult microbiologist and/or sexual health clinician.

Mycoplasma genitalium
- First choice — Josamycin 500 mg t.d.s. for 10 days *or* extended azithromycin 500 mg stat *then* 250 mg o.d. for 4 days.
- Second line — (if azithromycin resistant) Moxifloxacin 400 mg o.d. for 7–10 days.
- Third line — (after azithromycin and moxifloxacin failure) Pristinamycin 1 g q.d.s. for 10 days.
- Complicated — Moxifloxacin 400 mg o.d. for 14 days.

Trichomoniasis

Trichomonas vaginalis (TV) is a sexually transmitted flagellated protozoan which can cause sudden-onset vulvitis, vaginitis, cervicitis and copious yellow or green offensive vaginal discharge accompanied by pruritis, dysuria and introital dyspareunia, but which can also be harboured symptomlessly for many months or years in some women [160]. In men it can cause overt urethritis but typically remains asymptomatic and clears spontaneously within only a few weeks. Worldwide, it is the commonest non-viral STI, yet it is substantially underdiagnosed in both sexes due to lack of appropriate testing, and the insensitivity of traditional microscopy and culture [161], which can only identify some 50% and 75% of cases, respectively. Symptoms of mild trichomoniasis may be indistinguishable from those of simultaneous candidaisis and BV, and the classic haemorrhagic spots of 'strawberry cervix' (colpitis macularis) are only rarely seen in such cases [160].

Most UK and US studies have demonstrated a much higher prevalence of *T. vaginalis* carriage in women of Black Caribbean compared with Caucasian origin [162] and especially high rates in incarcerated women [163]. Ethnically targeted screening alone would have missed over 50% of cases in a large UK community study, which

also identified deprivation as a risk factor in white British women [161]. *Trichomonas vaginalis* was more prevalent than chlamydia or gonorrhoea at all ages except among teenagers, with highest prevalence found in women aged over 40 years, in a large study of residual Aptima Combo 2 screening samples [164]. A fivefold higher prevalence of *T. vaginalis* was found in postmenopausal compared with younger women [165] as the organism thrives better in the more alkaline environment of the hypo-oestrogenized vagina. In premenopausal women with *T. vaginalis*, vaginal pH is typically raised at around 6 or 7, with absent lactobacilli making it difficult to separate from BV or aerobic vaginitis [32] on Gram-stain microscopy alone. Specific testing for *T. vaginalis* – wet mount microscopy with culture, or, if available, NAAT [24,164] – is indicated when first-line presumptive treatment of either of these conditions has failed.

Trichomoniasis in pregnancy

There is conflicting evidence from African studies that treatment of *T. vaginalis* infection may have a detrimental outcome on pregnancy and that the infection not may be associated with preterm delivery and low birthweight in HIV-infected mothers [166]. Standard doses of metronidazole are safe to use at all stages of pregnancy but, likewise, treatment of *T. vaginalis* may not improve outcome in a Western setting [167]. *Trichomonas vaginalis* infection at delivery is significantly associated with maternal postpartum sepsis [168] requiring metronidazole treatment, which will render the breast milk sour and unpalatable.

Treatment options and metronidazole resistance

Metronidazole 400 or 500 mg b.d. for 5–7 days is the standard treatment for *T. vaginalis*, having a better than 90% immediate cure rate [160]. A 2-g stat dose is less effective. TOC is recommended at 1 or 2 weeks and it is often difficult to differentiate treatment failure from reinfection. Once the latter has been excluded by simultaneous partner treatment or confirmed abstinence, some 5% of *T. vaginalis* strains show varying degrees of imidazole resistance [169]. The majority are at low level, so higher doses of metronidazole with additional intravaginal treatment or switching to tinidazole is usually successful. In cases of continued treatment failure, there are many tried, but no proven, regimens. These include intravaginal dosage of paromomycin, furazolidone, acetarsol, nonoxynol-9 or povidone-iodine. Each has had limited success in small series or individual cases [160,163,169].

Recurrent vulvo-vaginal infections

Unlike *T. vaginalis*, which is almost entirely sexually transmitted, BV and candida do not require treatment of the male partner for resolution. Yet they are more common in sexually active women and after male partner change, are initiated and exacerbated by sexual activity, increased in the presence of other STIs, and can be considered as 'sexually shared infections' among lesbian women [170,171].

The substantial overlap of vulvo-vaginal symptoms of *T. vaginalis*, aerobic/atrophic vaginitis, BV and candidiasis/candidosis requires a consistent and thorough approach to diagnosis after first-line 'best-guess' treatment has failed in primary care. While management of uncomplicated, one-off episodes of infection is described elsewhere (Chapter 58), dealing successfully with recurrent vulvo-vaginal infections demands an understanding of the vaginal microbiome [172,173], its alteration by menstruation [174], contraception [175] and/or hypo-oestrogenism [176,177], and the role of cyclical hormonal fluctuation in premenstrual suppression of systemic [178] and cutaneous immunity [179], which creates a 'window of vulnerability' to infection in the luteal phase [180]. This may need the full armamentarium of Gram stain and wet-mount microscopy, using a consistent reference standard – the Amsel method, Nugent score or Hay–Ison criteria – with culture, sensitivity assays and molecular techniques to achieve an accurate diagnosis. Further management requires an assessment of systemic immunity, and a holistic therapeutic approach combining conventional oral or vaginal antimicrobials, probiotics, reduction or ablation of menstruation, and manipulation of hormonal milieu. Most formal research has concentrated on one or other therapeutic method in isolation, whereas tailored combinations of treatment may be required to achieve individual success, making robust evidence-gathering through trial randomization more difficult.

Recurrent bacterial vaginosis

As BV represents an imbalance of the vaginal ecosystem, treatment with antibiotics is a necessarily 'flawed approach' [181]. Principal among the many alterations of the vaginal microbiome in BV is the loss of H_2O_2-producing lactobacilli [181], a consequent rise in pH, and establishment of a wide range of mostly anaerobic organsims, including *Atopobium vaginae*, *Prevotella* spp., BV-associated bacteria and *Mobiluncus curtisii*, predominant among which is *Gardnerella vaginalis*, which is maintained in a vaginal wall biofilm that persists despite metronidazole treatment [182]. Menstruation itself alters the dynamic balance of the vaginal milieu, with BV-associated

organisms at maximal concentration and lactobacilli significantly reduced during menstruation, with a subsequent fourfold rise in lactobacilli concentration into the late luteal phase [183]. This explains the finding of transient, asymptomatic, spontaneously resolving BV in healthy clinician volunteers taking daily swabs [184]. More recently, molecular techniques tracking the concentrations of some 25 intravaginal organisms have graphically demonstrated this temporary upset and spontaneous recovery of the biome during and after menstruation [174]. This explains why menstruation is one of the principal triggers for BV, but this factor is rarely taken into account in conventional treatments. For many women with recurrent BV, repeated oral or intravaginal metronidazole [185] and/or clindamycin in various regimens and combinations are their clinicians' only therapeutic strategy, metaphorically – and literally – *ad nauseam* [186].

This has prompted alternative approaches to treatment that include intravaginal lactic acid and glycerol gel, which is claimed to be as effective as metronidazole in individual BV recurrences [187], and there has also been limited success with intravaginal instillation of lactobacilli such as *L. crispatus* [188]. As with repeated metronidazole or clindamycin, after cessation none of these regimens prevents recurrence. The practice of douching and intravaginal soap washing has long been associated with BV, but stopping these practices failed to reduce symptoms or recurrence rates [189]. Thus BV causes women to douche rather than vice versa. Newer intravaginal antiseptics have also failed to disrupt the *G. vaginalis* biofilm and have been unable to prevent BV recurrence [190]. Better long-term success has been achieved with a combination of extended antibiotics and intravaginal lactobacilli capsules, with a cure rate around 65% at 1 year. This study also found that relapse was very strongly associated with taking a new sexual partner [191].

Choice of contraceptive method affects BV recurrence rates, yet few clinicians actively employ hormonal strategies in this scenario. Women using copper IUDs have more BV because they have heavier and more irregular vaginal bleeding [192], and should therefore benefit from a switch to a LNG-IUS. Conversely, women taking COC pills have significantly less recurrent BV [175,193], because they have less bleeding. Reviewing Fig. 64.2, with bleeding leading to discharge, it seems logical to propose that, in women who have BV repeatedly triggered by menstruation, anything which reduces or prevents bleeding – treatment of chlamydial endometritis [42,59], followed by continuous COC, depot medroxyprogesterone acetate (DPMA) or LNG-IUS – should reduce BV recurrences. Anectodal success has been reported with this approach [194], which attempts to treat the cause rather than the symptom, but no formal trials have been undertaken.

The role of BV in PTB and PID is reviewed in Chapters 28 and 45 respectively.

Recurrent vulvo-vaginal candidiasis

Recurrent vulvo-vaginal candidiasis (RVVC) is defined as four or more episodes occurring in a year with substantial clinical improvement between episodes [195]. Similarly to recurrent BV, the mainstay of treatment of RVVC is repeated or extended courses of systemic and/or intravaginal therapy, aided by mycological culture typing and resistance profiling [195], although the latter reveals that over 90% of RVVC is due to *Candida albicans* and that resistance to fluconazole had been, until recently, relatively uncommon despite its ubiquitous use over the last two decades [196]. After exclusion of other causes of vulvo-vaginal itch such as *T. vaginalis*, and adjustment or treatment of causes of immunosuppression such as antibiotic and steroid therapy, diabetes and late-presentation, previously undiagnosed HIV, it is clear that the majority of women with RVVC are otherwise healthy, so genetic factors are relevant: Single nucleotide polymorphism (SNP) variation in Toll-like receptor (TLR)-2 confers a threefold increased risk for RVVC [197], and TLR response varies substantially across the menstrual cycle [198].

In most women with RVVC, episodes occur repeatedly during the luteal phase of the cycle, many on a specifically predictable day each month. The luteal phase represents an entirely different immunological milieu compared with the follicular phase, with T-helper 2 domination, T-helper 1 downregulation [178] and substantial changes in cytokines such as TNF-α [199], interleukin (IL)-6 and TLRs [198], so that women are premenstrually systemically immunosuppressed [178,180,199]. A measure of the magnitude of this effect is the fact that 25% of near-fatal asthma attacks occur on the first day of menstruation [200], and at least 15 different dermatological conditions – including oral and genital herpes, candidiasis, Behçet's syndrome, hidradenitis suppurativa, acne, urticaria, eczema, autoimmune dermatitis, angioedema, erythema multiforme and lupus – recur immediately premenstrually and spontaneously recover after menstruation [201–203]. As each of these conditions, including RVVC [195], improves and stabilizes after menopause, this raises the possibility that each could be amenable to successful treatment by hormonal suppression of the menstrual cycle. Some perimenopausal women have such severe cyclical RVVC that they are symptom-free only from day 7–14, then have gross inflammation and pruritis by day 15 or 16 until gradual remission starts on the day of menstruation.

A group of six such women, managed personally, had their symptoms completely and immediately relieved by gonadotrophin-releasing hormone (GnRH) analogue therapy, and two were permanently cured by oophorectomy. Although this is a radical approach to a desperate problem, it suggests that less drastic hormonal regimens addressing the underlying cause of the problem might be beneficial, and two uncontrolled studies have reported that long-term DPMA substantially reduced or prevented RVVC [204,205]. A further encouraging finding is a proven lower candidal relapse rate when adjunctive *Lactobacillus* therapy was used with a conventional extended fluconazole regimen [206], but this has yet to reach robust guideline evidence standards.

Cyclical predictability of RVVC has led to guideline suggestions of timed monthly [207] or weekly [195,208] maintenance fluconazole therapy. Recommendations for the less common azole-resistant *C. glabrata*, and the rare, intrinsically resistant *C. krusei* are also in the guidelines [209,210], but difficulties with the treatment regimens suggest that discussion with pharmacist, microbiologist and/or sexual health clinician would be useful. As oral agents are contraindicated in pregnancy, treatment is with topical and intravaginal therapy only for 7 days [211] and is discussed further in Chapter 13.

Summary box 64.4

Recommended regimens for severe and recurrent vulvo-vaginal candidiasis [207,209,210]

Severe vulval candidiasis

- First choice — Fluconazole 150 mg p.o. three doses at 72-hour intervals.

RVVC due to C. albicans

- First choice — 'Severe' regimen followed by maintenance fluconazole 150 mg at weekly or monthly intervals.

RVVC due to azole-resistant C. glabrata or C. krusei

- Possible choice — Boric acid 600 mg p.v. o.d. for 14 days.
- Alternative — Nystatin suppositories 100 000 units p.v. o.d. for 14 days.
- Alternative — Flucytosine 17% cream with or without Amphotericin B 3% cream p.v. o.d. for 14 days.

Vulvo-vaginal candidiasis in pregnancy

- First choice — Clotrimazole 500 mg p.v. stat *then* 100 mg pv o.d. for 6 days with clotrimazole 1% cream topical prn.

Genital herpes

The four principal areas of knowledge about genital herpes of most relevance to hospital-based gynaecologists are:

1) appreciation and recognition of the ubiquity and minor nature of most genital herpes;
2) emergency management of very severe primary genital or disseminated herpes;
3) management of first presentation and previously diagnosed genital herpes in pregnancy;
4) management of frequently recurrent genital herpes in perimenopausal women.

Genital herpes is caused by HSV types 1 and 2, which exhibit neurotropism and latency similar to other members of the alpha-herpesviridae group such as the ubiquitous varicella zoster virus. The majority of adults in the UK and similarly developed countries are infected with one or other type orally and/or genitally, with combined HSV infection rates around 85% in women and 75% in men by age 40 in Australia [212] and, among European blood donors, 78% of both sexes have HSV-1, with 20% of women and 9% of men having HSV-2 by age 30 [213].

Herpes episodes are described as primary (with no previous exposure at any site), first episode/post-primary (following previous covert exposure), or recurrent. Only some one-third of those infected with HSV-2 will develop symptoms at first genital exposure [214], in many cases because past oral HSV-1 infection – acquired in childhood from being kissed by parents and/or relatives, or in adolescence from pre-sexual petting – modifies and minimizes subsequent response to HSV-2 [214]. Most will be unaware of their infection or have had such minimal symptoms that the condition has passed entirely unnoticed or is presumed to have been a transient episode of 'cystitis' or 'thrush', and may indeed be misdiagnosed as RVVC. As the natural course of recurrent genital (or oral) herpes episodes is spontaneous healing within a few days of symptom onset, women use over-the-counter remedies that appear to work successfully and thus 'confirm' the incorrect self-diagnosis. This delays or prevents accurate diagnosis, until women can be taught to recognize the associated neurological prodrome, usually within the S2 dermatome, which heralds the true cause of their recurrent symptoms [215]. The relative proportions of those infected and (un)affected by genital herpes can be simply represented (Fig. 64.5), with the minimally and entirely symptomless groups (3 and 4, i.e. 7 of 10 cases) representing the main reservoir of infection. These individuals have usually been exposed to oral HSV-1 as children and genital HSV-2 as teenagers or young adults. Given that most herpes transmissions occur from asymptomatic shedding [214,215], they may

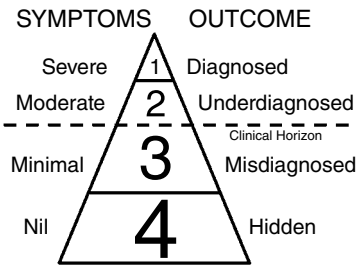

Fig. 64.5 Proportion of hidden genital herpes.

only discover their status when they take a new, previously unexposed, sexual partner who suffers a severe primary genital episode, and then wrongly blames them for knowingly spreading the infection.

Over the last three decades there has been a fall in the number of people exposed to HSV-1 in childhood, sufficient to alter the dynamic balance of those susceptible to true primary genital acquisition. At least 80% of first-episode genital herpes seen in young women is now due to HSV-1 [216], with a dramatic difference between the generations: 82% of primary anogenital herpes in the under twenties is HSV-1, compared to some 85% with HSV-2 in patients over age 50 [217]. This is relevant because genital HSV-1 is four times less likely to recur than HSV-2 [218], with less asymptomatic shedding [219], but is more likely to produce severe symptoms than HSV-2 [216] warranting hospitalization after primary genital acquisition.

Severe primary genital herpes

Most women with overtly symptomatic, true primary anogenital herpes present first with a flu-like illness, followed by genital itching similar to candidiasis and dysuria suggestive of urinary tract infection, before blistering, painful ulceration and tender inguinal lymphadenopathy become obvious. Symptoms typically commence 2–20 days after exposure, but the interval may be considerably longer if initial symptomless infection of sacral nerve ganglia is followed by delayed primary recrudescence [216]. A classic feature is sacral radiculopathy [220], mostly affecting the S2 dermatome and involving parasympathetic supply from S3 ± S4 which controls bladder and bowel function. Although the majority of women presenting to sexual health clinics can be managed as outpatients with oral aciclovir (400–800 mg t.d.s. for 5–10 days depending on severity) and topical lidocaine gel (which relieves pain within a few minutes), the 5% who experience acute retention of urine, constipation, loss of bulbocavernosus reflex and other signs of meningism [220] or cutaneous dissemination will comprise the majority admitted for gynaecological care.

As each hospital unit will see only sporadic cases with few individually published, local experience is limited and each presentation has differing individual features, with only two significant case series totalling 23 women reported in the literature [220,221]. The following account is gleaned from 40 years' clinical experience of some one or two cases per year since observing the larger initial series. Most women will be dehydrated and in severe pain, and will require rehydration, systemic and topical pain relief, attention to any systemic cause of immunosuppression, and intravenous aciclovir (10 mg/kg per 24 hours) [216] until symptoms improve or they can take oral treatment with either aciclovir 800 mg five times daily or valaciclovir 1 g b.d. Retention of urine may last from around 4 days to 3 weeks, and although in practice most women receive urethral catheters regardless of the severe pain inflicted on insertion, they would be far better served by suprapubic catheterization, as this is the only comfortable and convenient way of assessing recovery of urinary function. Subrapubic and lower abdominal pain may also be due to acute herpetic endometritis [222] or salpingitis [223], which are rarely described but probably more commonly missed. Fallopian tube lesions of acute herpetic salpingitis appear similar to cutaneous vulvo-vaginal blisters and ulcers at laparoscopy [223, and personal observation].

Severe vulval oedema and ulceration requires meticulous nursing care with saline bathing, wound separation and cool packs to prevent labial fusion, which may occur with symmetrically opposed lesions, particularly in adolescent women who may have delayed presenting for care [224]. Formal surgical separation is occasionally required [224], but has been anecdotally avoided by topical corticosteroid treatment [225] or awaiting spontaneous remission [226].

Very rarely, women may present to emergency departments with acute vulval pain – as if kicked by a horse – with a copious clear watery vaginal discharge but no external signs of ulceration, but with S2 neurology, inguinal lymphadenopathy and acute distress as above. Speculum examination (rarely performed in acute vulval herpes because of severe external pain) may reveal an acute necrotic cervicitis [227] (Fig. 64.6), and management is as above. For those women with more severe signs of meningism, frank meningitis [228] or severe cutaneous or intra-abdominal dissemination, which classically occurs in the immunocompromised, assistance from other specialists will be required and is outside the scope of this chapter.

Genital herpes in pregnancy

Management of genital herpes in pregnancy is discussed fully in the joint BASHH–RCOG guidelines [229] and in Chapter 13. One point which may be helpful in advising

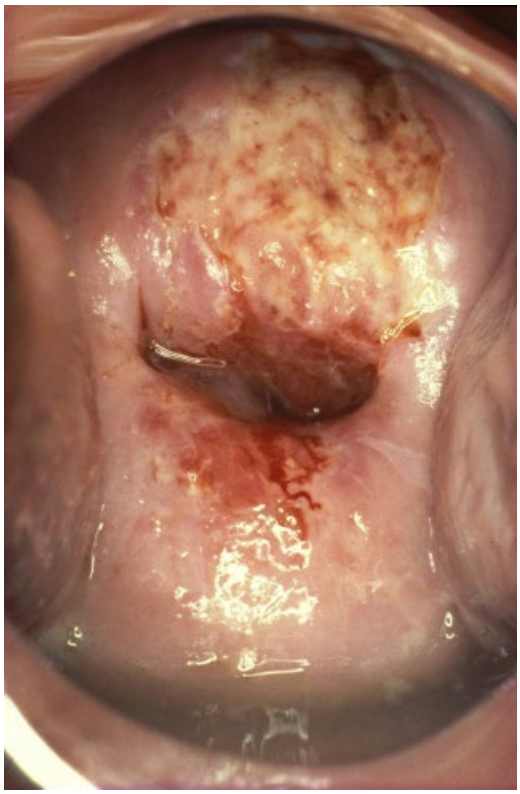

Fig. 64.6 Herpetic necrotic cervicitis. Extensive cervical ulceration caused by HSV-2, associated with copious clear watery vaginal discharge and severe vulval pain. *Source:* photograph by Peter Greenhouse FRCOG, 1996. (*See also colour plate 64.6*)

the mother and her partner is that only some 15% of pregnant women are seronegative at booking for both HSV-1 and HSV-2 [230], so most mid-trimester first appearance of herpes is post-primary infection, in all but the severest presentations. This represents the first visible appearance of infection covertly acquired in the distant past, caused by maternal immunosuppression, rather than infection which has been newly acquired. In the pre-aciclovir era, true primary herpes occurring in the second trimester was usually disseminated and often fatal for the infant and mother [231]. Nowadays, even primary disseminated infection in a doubly-immunocompromised pregnant diabetic woman (Fig. 64.7) should have a healthy outcome if managed as above.

Management of recurrent herpes in perimenopausal women

Most younger women with recurrent genital herpes will be managed in sexual health clinics using standard or individually tailored suppression or episodic treatment regimens [216]. Clinics have seen a doubling in attendance of the over 45s [232] and the rate of new herpes

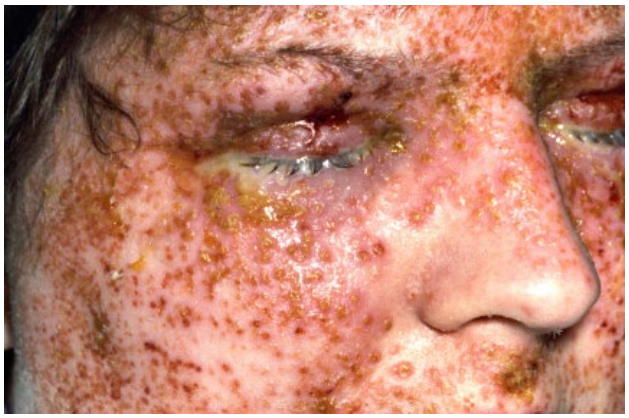

Fig. 64.7 Disseminated herpes in pregnancy. Second-trimester mucocutaneous and systemic dissemination of primary HSV-1 infection in a pregnant diabetic woman. Outcome after intravenous aciclovir: Complete recovery without scarring and healthy infant delivered near term. *Source:* photograph by Peter Greenhouse FRCOG, 1994. (*See also colour plate 64.7*)

diagnoses has increased faster in this than any other age group [8]. As clinic access in the UK is being restricted, gynaecologists can expect to see increasing numbers of older women with recurrent herpes requesting treatment.

The mainstay of treatment of herpes recurrences is aciclovir or valaciclovir given in a continuous regimen (see Summary box 64.5) for women with more than six recurrences per year, with long-term use of the former now extending over 35 years' experience since trials started in 1982 [233]. Less frequent recurrences can be minimized by a pre-prescribed short course, high-dose treatment, which is only effective if started immediately symptoms are recognized [216]. A combination of suppressive and episodic treatments can be offered to cover times of extra stress or holiday travel in those with less frequent episodes, provided the temporary suppression is started a few days beforehand. This allows the patient greater control and a degree of freedom from the stress of recurrence. Transmission in discordant couples can be reduced by long term suppression and condom use [234], but most seronegative partners will eventually acquire infection in the long term. Herpes antibody testing of prospective partners is an acceptable strategy, as most will be found to be unknowingly positive from previous covert infection, but the assays may occasionally give false-negative results [235].

Several women who acquired HSV-2 as teenagers or in their early twenties will have had frequent recurrences for a few years, then entered an asymptomatic phase for 5–10 years, before suffering monthly premenstrual recurrences as they become perimenopausal in their late thirties or early forties [236]. In many cases these episodes are as precisely cyclically timed as RVVC, due to

the same immunological changes [180,202]. Although there is little written in current scientific literature about catamenial herpes, it was first described over 130 years ago [237] and known as *bouton de règles*, being the commonest reason and timing for women to present with herpes. These recurrences can be successfully suppressed by giving aciclovir in the luteal phase only [236]. As many of these women appeared to have their herpes recurrences every month at the same time as their episodes of mood change in severe premenstrual syndrome (PMS), a proof-of-concept study aimed to treat the cause by using a recognized PMS treatment. Transdermal oestradiol, given during the luteal phase, or continuously in women with a levonorgestrel IUS *in situ* [238] successfully prevented almost all herpes recurrences in a series of 12 women observed over a 9-month follow-up [239].

Summary box 64.5

Recommended regimens for HSV infections (oral unless stated)

Primary genital episode

- First choice Aciclovir 400 mg t.d.s. *or* valaciclovir 500 mg b.d. for 5 days or until healed depending on severity.
- Second line Famciclovir 250 mg t.d.s. for 5 days as above.

Severe or disseminated primary episode (including pregnancy)

- First choice Aciclovir 5–10 mg/kg per 24 hours i.v. prn *then* aciclovir 800 mg five times daily until remission.

Recurrent genital episode

- First choice Aciclovir 800 mg t.d.s. for 2 days *or* valaciclovir 500 mg b.d. for 3 days.
- Second line Famciclovir 1 g b.d. for 1 day.

Suppression continuous dose

- First choice Aciclovir 400 mg b.d. *or* valaciclovir 500 mg o.d.
- Second line Famciclovir 500 mg b.d.

Suppression in pregnancy continuous dose

- First choice Aciclovir 400 mg t.d.s. from 36 weeks until delivery.

Genital warts

Around 90% of genital warts (condylomata acuminata) are caused by non-oncogenic HPV, principally types 6 and 11 [240]. Some 90% of the non-vaccinated sexually active population will have been exposed to at least one HPV type and infected by age 25, but less than 5% are ever visibly affected by overt warts. HPV infection is typically multifocal occurring over the entire anogenital area, but visible warts are seen most frequently in women at the fourchette, which is the principal area subject to friction trauma during intercourse. The lesions grow at and near the sites of healed microlacerations. Perianal warts often occur in the absence of any reported anal sex due to local inoculation by wiping. Diagnosis is by close visual inspection often aided by magnification, which can help differentiate the lesions from molluscum contagiosum or normal vulval papillae [240]. The rarest differential diagnosis is that of condylomata lata occurring in secondary syphilis, further illustrating the value of routine syphilis and HIV screening in all women with STI presentations. HPV typing and/or biopsy are rarely used in routine UK practice, but should be considered in lesions which are refractory to treatment or have a large or atypical appearance, such as the rare Buschke–Löwenstein tumour [241]. Oncogenic HPV and genital premalignancies are discussed in Chapters 60 and 61.

The incubation period for most visible warts ranges from about 3 weeks to 8 months [240], but some cases take considerably longer, appearing following sudden alteration in immune status, most commonly in pregnancy (see below). Most non-smoking immunocompetent individuals will spontaneously clear HPV within 1 year [242]. Although overt external genital warts rarely cause pain or bleeding from secondary infection, and can be considered a cosmetic nuisance, they cause substantial psychological distress by harming body image and sexual self-esteem, thus necessitating treatment at least of those lesions which are visible to the patient.

Effect of HPV vaccination

There is no evidence of cross-protection against benign HPV disease among the UK cohort of women who received the bivalent HPV vaccine (Cervarix) from 2008 to 2011 [240]. They were born between the late-1990s and mid-2000s. Slight reductions in reported cases of genital warts in UK teenagers from 2008 to 2012 [8] were due to much less genital examination being performed in asymptomatic women attending sexual health clinics [30]. This contrasts with the situation in Australia, where genital warts have been virtually eliminated since quadrivalent HPV vaccination (Gardasil) was introduced in women aged 12–26 years from 2007 [243]. This bodes well for women in the UK born from mid-2000 and vaccinated with Gardasil since 2012 but leaves a cohort of older unprotected women who may come to gynaecologists' attention.

Treatment options

Most genital warts are treated in sexual health clinics using a variety of topical modalities [240], which are chosen depending on the extent and character of the lesions. Multiple non-keratinized vulval warts are usually first treated with podophyllotoxin 0.15% cream or 0.5% solution; women with fewer or keratinized lesions are offered cryocautery with a cryoprobe or liquid nitrogen spray or, occasionally, trichloracetic acid. Second-line treatment of either may be with imiquimod 0.5% cream, the latter often being considered first choice in women with relative immunodeficiency. Diabetes, HIV, long-term steroid or other immunosuppressive therapy are three of the main contributors to the appearance, persistence, recurrence and/or unsuccessful treatment of genital warts and any high-risk HPV disease [242]. The principal avoidable cofactor is smoking, which causes Langerhans' cell depletion [244], thus preventing natural clearance of HPV [245]. Non-clearance and recurrence rates of genital warts after initial topical treatments are typically high, in the range 40–60%, thus it is important to exclude HIV and check diabetic control, and essential to advise smoking cessation [246], or at least immediate switching to vaping, as the first steps in managing any HPV-related disease.

The few women with extensive and persistent benign HPV disease who are referred to gynaecologists for formal wart excision or ablation are likely to have had many months of unsuccessful topical cream treatment and cryotherapy, and are nowadays most likely to be Cervarix-vaccinated teenagers with poorly controlled diabetes (Fig. 64.8). Assuming that all attempts to exclude or treat known causes of immunodeficiency have been made, consideration should be given to offering quadrivalent or nonavalent HPV vaccination if it has not already been used, although this approach is unlicensed. As only some one-third of individuals with overt genital warts have detectable circulating type-specific HPV antibody [247] there is a theoretical possibility that the very high antibody titres generated by vaccination might have therapeutic benefit. Several anecdotal successes have been reported, but other unseen factors may not have been excluded, and a randomized trial is currently in progress. Treatment options should be individualized, and include the very successful scissor-snip technique commonly used by colorectal surgeons for perianal warts, with further options of electrosurgical hyfrecation, local loop excision or laser ablation [248].

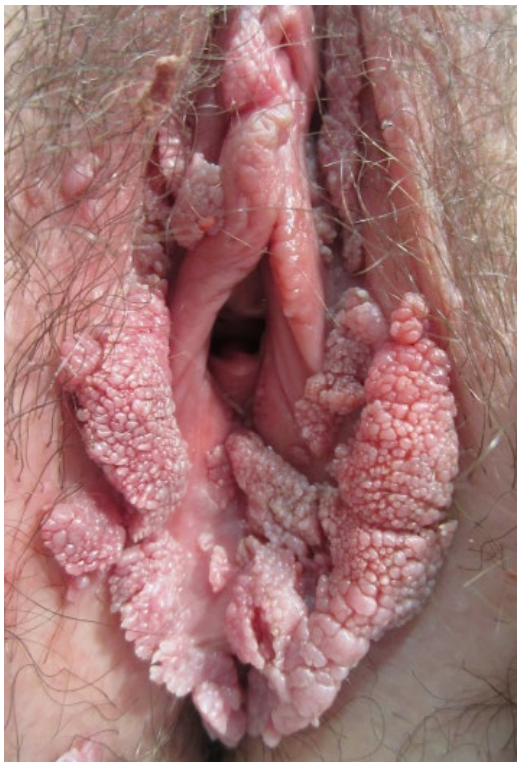

Fig. 64.8 Severe vulval warts. Florid warts after multiple failed treatments in a poorly controlled diabetic teenager who had received bivalent HPV vaccination 3 years previously. *Source:* photograph by Peter Greenhouse FRCOG, 2012. (*See also colour plate 64.8*)

Management of genital warts in pregnancy

Similar to herpes, many women experience their first ever episode of genital warts in the second trimester of pregnancy, which can be especially distressing for those in long-term relationships because of the automatic presumption of infidelity accompanying the diagnosis. They should be reassured that almost all such occurrences are due to previously hidden exposure to HPV in the distant past, rather than recent acquisition, and that the warts should heal spontaneously in the postpartum period because of the return of normal skin immunity. Imiquimod and podophyllotoxin are contraindicated in pregnancy [240,246]. Cryotherapy is the only commonly used treatment for cosmetic reasons, and many clinicians discourage its use as postpartum remission is the norm. Even from asymptomatic women, the risk of vertical HPV transmission varies widely from 4 to 87% [249], but almost all infant infection is covert and eventually cleared. It is exceptionally rare for vulval warts to be sufficiently large to obstruct labour but this may be an indication for caesarean section in extreme cases [250].

One study has suggested that children with juvenile recurrent respiratory papillomatosis, which is caused by HPV-6 and HPV-11, were more likely to have been delivered vaginally [251]. Its prevalence is only 1 in 100 000 [252] so the only practical prevention is via universal quadrivalent HPV vaccination.

Syphilis

Syphilis is caused by the bacterium *Treponema pallidum*, which produces a painless primary lesion within 9–90 days (average 3 weeks) of first exposure [253]. The primary chancre (see Chapter 58) presents so rarely with painless vulval ulceration that few specialists will ever have seen a case. Most acquisition is covert, with hidden vaginal, rectal or pharyngeal lesions healing spontaneously over 3–8 weeks before secondary dissemination of the infection from regional lymph nodes occurs some 6 weeks to 6 months (typically 3 months) after first exposure [254]. Only about 25% of syphilis cases have a clinically obvious secondary phase. Most remain hidden (i.e. latent) until discovered fortuitously often years later when an opportunity for screening arises. Latent syphilis is divided into early (<2 years) and late latent infection, roughly corresponding to the duration of infectivity through sexual contact. There are less than 300 cases of early infectious syphilis (primary, secondary and early latent) infection in women each year in the UK [8]. Most women present via routine antenatal screening or because of a secondary mucocutaneous skin rash, which also affects palms of hands and soles of feet, and can be easily overlooked. Among many other manifestations of secondary syphilis – including generalized lymphadenopathy, irregular alopecia, mucous patches, oro-genital ulcers, hepatitis, splenitis and rare meningitis or cranial nerve palsies – perineal and perianal lesions of condylomata lata closely resemble genital warts, and misdiagnosis is likely to occur if syphilis serology testing is omitted [254].

Thus genital wart-like lesions, or any genital ulceration, painless or otherwise, require syphilis serology. The local laboratory will offer the appropriate screening test (usually TPPA or a combined IgG/IgM assay) and then perform a full range of tests if screening is positive. The result requires discussion with and referral to a sexual health specialist [253]. However, it may be helpful to have a guide to the common patterns of serological results (Summary box 64.6), and to be aware that other rare forms of treponemal disease originating from the Caribbean, Africa and South America (yaws, bejel and pinta, respectively) produce serological results indistinguishable from those of *T. pallidum*. The panel of tests used in each laboratory differs, but the principal indicators of active syphilitic infection are the indirect antigen tests (VDRL, RPR) and the IgM assay, which becomes negative after some 18 months in untreated infection or shortly following treatment. The basic screening tests for antibody response (TPPA/TPHA and combined IgG/IgM) will remain positive after infection regardless of any treatment. A single isolated positive in any of the tests (particularly the VDRL or RPR) suggests a biological false positive, which may occur because of pregnancy, past intravenous drug use, tuberculosis, malaria, hepatitis, myeloma and connective tissue disorders such as systemic lupus erythematosus, among several other possibilities [253].

Summary box 64.6

Basic interpretation of syphilis serology results

VDRL, RPR	TPPA, TPHA	EIA-IgG/IgM, EIA-IgG	EIA-IgM	Likely diagnosis
Positive	Positive	Positive	Positive	Untreated primary, secondary or early latent syphilis
Positive	Positive	Positive	Negative	Untreated latent syphilis >18 months post acquisition *or* other treponemal infection (yaws, bejel, pinta)
Negative	Positive	Positive	Negative	Successfully treated syphilis
Positive	Negative	Negative	Negative	Biological false positive *or* very early syphilitic infection
Negative	Positive	Negative	Negative	Biological false positive
Negative	Negative	Negative	Positive	Biological false positive *or* very early syphilitic infection

Syphilis in pregnancy

Untreated syphilis is transmissible in pregnancy for up to 10 years [255] and has potentially devastating consequences for the fetus, with disease severity directly related to stage of maternal infection and showing a 'spontaneous gradual diminution of intensity' (Kassowitz's law) with time since primary acquisition [253,255]. Damage is greatest in mothers who have early syphilitic infection prior to or around conception [256]. Syphilis can be transmitted as early as 9–10 weeks, but most is thought to occur with and after syncytiotrophoblast invasion of the placental bed, between 12 and 16 weeks. The degree of placental inflammation strongly correlates with severity of infant disease [257], resulting in spontaneous miscarriage, polyhydramnios, intrauterine growth restriction, hydrops fetalis, stillbirth or early neonatal death, or severe central nervous system disease causing deafness and blindness. Lesser infection affects teeth, cartilage and bone, or causes cutaneous rashes.

The least severe infection is evidenced by positive syphilis serology in the infant only, with no physical signs. A full description of early and late congenital syphilis stigmata [258] and obstetric experience [259] has been gleaned from the extreme social deprivation and drug-related syphilis outbreak in the USA from the late 1980s to the mid-1990s.

Prevention of congenital syphilis

Early antenatal screening, with repeat screening in the third trimester for women in high-risk situations, provides a narrow window of opportunity to prevent severe congenital disease if treatment is commenced rapidly. Transmission is very rare if the rapid plasma reagin (RPR) titre is below 1 : 8 [260].

Active surveillance of congenital syphilis in the UK found that the incidence is below the World Health Organization threshold for elimination (<0.5 per 1000 live births), with only 17 cases in 5 years [261]. Since the 1996 peak of the syphilis epidemic in the former Soviet Union, congenital syphilis spread across eastern Europe to the rest of the continent. Thanks to exceptional efforts with enhanced antenatal screening, timely treatment and better control of heterosexually transmitted infection, there were only 69 cases of confirmed congenital syphilis across the entire region excluding former Soviet countries [262]. The highest incidence of cases was reported from Bulgaria, Portugal and Poland. Most recent cases have occurred in women who have defaulted much or all of their antenatal care, mostly through chaotic or coerced lifestyles, or by flight from conflict, many presenting only shortly prior to delivery.

Despite these advances, syphilis serology is positive in about 1000 pregnancies per year in UK practice, requiring a coordinated multidisciplinary team approach [261]. Of these, around 23% were false positives. Of the remaining true positives, 26% were newly diagnosed and 71% previously diagnosed, not all of whom had fully documented prior treatment. Thus some 40% required treatment according to the guideline recommendations (see below). The value of close communication between obstetric, midwifery, sexual health and neonatal teams, and the formulation of a birth plan for each case [253], was demonstrated in a UK scenario where cases were less likely to be missed as multidisciplinary care was instituted [263].

Treatment of syphilis

Uncomplicated early syphilis in non-pregnant women with or without HIV infection is currently treated with a single dose of intramuscular benzathine penicillin 2.4 mg [253]. The same regimen is first line in pregnancy up to the end of the second trimester. Two doses 1 week apart – maintaining serum levels effectively for 2 weeks – are required for adequate cure in the third trimester. In case of penicillin allergy in non-pregnant women, doxycycline 100 mg b.d. for 2 weeks is also effective. Patients should be warned about the Jarisch–Herxheimer reaction [264] which occurs in about 40% of treated cases, where an allergic reaction to toxins from dead treponemes generates an acute, transient flu-like illness that resolves within 24 hours. This can be mistaken for a penicillin allergy. Although this reaction has been reported to provoke premature labour [258], transient cardiotocographic changes were the only side effects of second- or third-trimester treatment [265], with no fetal loss following therapy.

Neither of the above regimens appears to have generated antibiotic resistance hitherto. However, no other regimens have been adequately evaluated and, as significant resistance developed rapidly to single-dose (2 g) oral azithromycin [266], treatment of penicillin-allergic women in pregnancy presents special problems, with the favoured approach being via penicillin desensitization [253,267], further emphasizing the need for a well-coordinated multidisciplinary team effort.

Conclusion

Thanks to population mobility, relationship instability, demographic change and modern digital communication technology, clinicians can no longer make a cosy automatic assumption that, regardless of age or social milieu, their patients' sexual activity is monogamous or heterosexual or volitional, an attitude which characterized paternalistic gynaecological care in the not-so-distant past. An open, non-judgemental, empathetic and inquisitive approach will identify more STIs, reduce misdiagnosis and, hopefully, answer some of the research challenges in women's sexual health posed by this chapter.

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Further reading

UK guidelines for management of all STIs and other sexual health issues are available at https://www.bashh.org/guidelines

Patient information leaflets for most of these conditions are available via the fpa at http://www.fpa.org.uk/resources/leaflet-and-booklet-downloads and via BASHH at https://www.bashh.org/pils

An interactive teaching summary of STIs in women is available at https://stratog.rcog.org.uk/

65

Contraception and Sterilization

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The average age of first intercourse in women is 16 years and average age of menopause is 51, so most women will need to use contraception for more than 30 years. Use of contraception in the UK is high. Despite this, unintended pregnancy is common, with abortion rates of between 11.6 and 16 per 1000 women of reproductive age in the UK in 2016 [1,2]. Around three-quarters of women presenting for abortion report having used a method of contraception around the time of conception, but the methods used are mostly of low effectiveness, or used inconsistently or incorrectly [3].

It is estimated that 30% of pregnancies ending in birth were unintended at conception [4]. Unintended pregnancies in the year following birth are also common. If a birth to conception interval is less than 12 months (short inter-pregnancy interval), then this increases the risk of preterm birth and neonatal death [5]. Obstetricians and gynaecologists should take key opportunities such as the antenatal period and routine gynaecological consultations to discuss effective contraception and provide methods where possible. The most effective methods comprise long-acting reversible contraception (LARC), including intrauterine contraception, implants and injectables. Greater uptake of LARC in the UK could prevent more unintended pregnancies, abortions and prevent short inter-pregnancy intervals for more women.

Effectiveness

The effectiveness of a method of contraception is expressed by the failure rates associated with its use. Effectiveness depends on efficacy of the method, compliance and continuation with the method. Perfect- and typical-use failure rates of methods (based on percentage of couples experiencing an unintended pregnancy during the first year of use) are shown in Table 65.1 [6]. Methods that make no demands on compliance after insertion have perfect-use and typical-use failure rates that are virtually the same. Compliance with oral contraception is not easy. In one study, almost 63% of users missed one or more pills in the first cycle, and 74% in the second cycle of use [7]. Typical-use failure rates are even higher with condoms, which rely on correct use with every act of intercourse. The progestogen-only injectable lasts 13 weeks but correct use demands the motivation and organizational skills required to receive a repeat dose. Intrauterine contraception (IUC) and implants are removed by a healthcare professional and are independent of user compliance for effectiveness.

Discontinuation rates are higher for methods which do not require removal by a provider. Data from the USA indicate that approximately 50% of women discontinue a pill or injectable within the first year of use, whereas approximately 80% of women continue the implant or IUC at 12 months [6]. Reasons for discontinuation are often associated with perceived risks and real or perceived side effects.

Pregnancy rates are still often described by the Pearl index, the number of unintended pregnancies divided by the number of woman-years of exposure to the risk of pregnancy while using the method. For long-acting methods of contraception such as IUC and implants, pregnancy rates with time (cumulative pregnancy rates) are often reported.

Medical eligibility for contraception

Most contraceptive users are young and healthy and can use all contraceptives safely. However, some medical conditions are associated with real or theoretical health risks with certain contraceptives. The World Health Organization (WHO) developed a system addressing medical eligibility criteria (MEC) for contraceptive use

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 65.1 Effectiveness of contraceptive methods: percentage of women experiencing an unintended pregnancy during the first year of use and percentage continuing use at the end of the first year (USA) [6].

Method	Typical use	Perfect use
No method	85	85
Calendar	9	
Sympto-thermal	2	
Diaphragm	16	6
Female condom	21	5
Male condom	15	2
Combined pill and progestogen-only pill	8	0.3
Combined hormonal patch	8	0.3
Combined hormonal ring	8	0.3
Injectable (DMPA)	3	0.3
IUD, copper T	0.8	0.6
IUS (Mirena)	0.1	0.1
Implant	0.05	0.05
Female sterilization	0.5	0.5
Male sterilization	0.15	0.10

(WHO MEC) [8]; this has been adapted by the Faculty of Sexual and Reproductive Healthcare (FSRH) for the UK setting (UK MEC) [9]. Using evidence-based systematic reviews, conditions are classified into one of four categories (Table 65.2). Category 1 includes conditions for which there is no restriction for use of the method, while category 4 includes conditions that represent an unacceptable health risk if the contraceptive method is used (absolutely contraindicated). Category 2 indicates that the method may generally be used. Provision of a method to a woman with a category 3 condition requires careful clinical judgement since use of that method is not recommended unless there is no acceptable alternative. The initiation and continuation of a method of contraception is sometimes distinguished and classified in the UKMEC. Initiation of a method may be appropriate in women with certain medical conditions, but if a medical condition develops while using a method, then this raises concern over continuation since use of the method may have contributed to development of the condition. It is important to note that the UKMEC categories relate to the safety of use of a method of contraception by a woman with a particular medical condition or personal characteristic. The efficacy of contraception may be affected by the condition or by a medication required for the condition but the UKMEC category does not reflect this.

Table 65.2 Definition of UK MEC categories.

UK MEC	Definition of category
1	A condition for which there is no restriction for use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
4	A condition which represents an unacceptable health risk if the contraceptive method is used

For each of the personal characteristics or medical conditions considered by the UK MEC, a category 1, 2, 3 or 4 is given.

Contraceptive choice

Many factors determine the method of contraception an individual chooses. These include age, fertility intentions, perceptions of effectiveness and of safety, familiarity and experience of others, ease of use and non-contraceptive benefits. Women should be given accurate information about all methods for which they are medically eligible. Studies show that women welcome information in an audiovisual formats (DVD, tablet, phone app) and that this may enhance uptake of the most effective methods [10,11].

Intrauterine contraception

Intrauterine methods of contraception include the copper-bearing intrauterine device (Cu-IUD) and the levonorgestrel-releasing intrauterine system (LNG-IUS). IUC is amongst the most effective LARC methods (see Table 65.1). In addition, the Cu-IUD can also be used for emergency contraception. Unfortunately, IUC is unpopular in many settings. More needs to be done to improve uptake, especially amongst young women at risk of unintended pregnancy [11].

- *Cu-IUD*: most Cu-IUDs available in the UK have a plastic frame with copper wire wound around the stem with or without copper sleeves on the arms [12]. Devices containing 380 mm^2 of copper have the lowest failure rates [13]. In the UK, the Cu-IUD that contains 380 mm^2 of copper is licensed for 10 years of use, while those containing 300 mm^2 of copper are licensed for 5 years.

- *LNG-IUS*: there are three types of LNG-IUS, a 52-mg, a 19.5 mg and a 13.5-mg device. The 52-mg LNG-IUS (Mirena® and Levosert®) is licensed for 5 years for contraceptive use (Levosert is anticipated to receive a licence for 5 years). The 19.5 mg LNG-IUS (kyleena) is licensed for 5 years. The 52-mg LNG-IUS releases 14 mcg of LNG per day. The 19.5 mg LNG-IUS releases 19 mcg of LNG per day. The 13.5-mg LNG-IUS (Jaydess®) is licensed for 3 years and releases 6 μg of LNG per day. The 19.5 and the 13.5-mg LNG-IUS has a slightly narrower inserter than the 52-mg device, and a slightly thinner and shorter frame. Both the 19.5 mg and 13.5-mg LNG-IUS also have a silver band at the proximal end, which is designed to facilitate visualization by ultrasound.

Although the manufacturers have recommended durations of use for IUC, there is evidence that efficacy extends beyond these limits. The FSRH advises that any Cu-IUD inserted at or after the age of 40 can be retained until contraception is no longer required, i.e. 1 year after menopause if last menstrual period (LMP) is in fifties, or 2 years after menopause if LMP is in forties [14]. The FSRH also advises that a 52-mg LNG-IUS inserted at 45 years can be retained for contraception for 7 years or if amenorrhoeic until the menopause. If the 52 mg LNG-IUS is being used as part of hormone replacement therapy (i.e. progestogenic opposition to exogenous estradiol), then it must be replaced after 5 years. All IUC should eventually be removed.

Efficacy

A large (>61 000 women) European prospective cohort observational study (European Active Surveillance Study, EURAS) of IUC reported that the 52-mg LNG-IUS had superior efficacy to Cu-IUD, although the failure rate was low with both [15]. For LNG-IUS, the Pearl index (pregnancies per 100 woman-years) was 0.06 (95% CI 0.04–0.09) in LNG-IUS users and 0.52 (95% CI 0.42–0.64) in the Cu-IUD cohort. High efficacy is also reported for the 19.5 mg LNG-IUS which has a pearl index of 0.29 (95% CI 0.16–0.5) and 13.5-mg LNG-IUS, with a Pearl index of 0.33 (95% CI 0.16–0.60).

Mechanism of action

Both the Cu- IUD and LNG-IUS work primarily by inhibiting fertilization due to the toxic effect of copper ions on ova and sperm, and LNG also has effects on sperm penetrability and transport. Both devices also prevent implantation; the Cu-IUD exerts a local inflammatory reaction in the endometrium and the LNG-IUS induces endometrial atrophy. LNG-IUS also causes thickening of the cervical mucus, which prevents sperm entering the uterus. Effects of the 52-mg and 13.5-mg LNG-IUS on endometrium and cervical mucus are similar.

Contraindications

There are very few women for whom IUC is contraindicated. Current pelvic tuberculosis, endometrial or cervical cancer, symptomatic sexually transmitted infection (STI) or pelvic inflammatory disease (PID) are the UK MEC 4 conditions [9]. Women at risk of STIs and women with well-controlled HIV on antiretrovirals can safely use IUC with safe sex and additional condom use promoted. Unexplained vaginal bleeding should be investigated before IUC insertion and a distorted uterine cavity (due for example to fibroids) may make insertion impossible. Although providers may be reluctant to offer IUC to nulliparous women or adolescents owing to myths that insertion will be difficult or carry higher risks, the best available evidence supports safety of use of IUC in these groups, and this is reflected in the UK MEC [9].

Risks

Perforation

Rates of perforation with IUC are low (2 per 1000 insertions). Increased risks include inexperience of the clinician, breastfeeding and being less than 36 weeks' post partum [14,16]. Sometimes the clinician will suspect perforation at the time of fitting IUC and if so the procedure should be abandoned. Alternatively, women may complain of lower pelvic pain, a change in bleeding pattern or give a history of painful insertion. Others have no symptoms and the diagnosis is made due to lost threads or pregnancy.

Absent threads in an IUC user should be investigated by ultrasound. A pregnancy test should be performed and emergency contraception provided (if unprotected intercourse) and alternative contraception provided in the interim. If ultrasound confirms absence of a device within the uterus, then an abdominal X-ray should be performed. If the IUC is visible on X-ray then this indicates it must be within the abdominal cavity. In most cases the IUC can be retrieved laparoscopically as an elective procedure.

Expulsion

It is reported that 1 in 20 IUC devices will be expelled, usually in the 3 months after insertion [14]. Similar expulsion rates are reported for the Cu-IUD and LNG-IUS. With increasing use of ultrasound, it is not uncommon for an ultrasound report to state that an IUC is 'low lying' within the uterus. Unfortunately, there is no good evidence to determine if non-fundally placed IUC provides effective contraceptive cover. The clinician should manage such cases on an individual basis along with the woman's preference, taking into consideration the risks of insertion of a new device.

Infection

The overall risk of PID following insertion of IUC is low (<1%) [14]. PID is more likely in the 3 weeks following insertion, and in women at risk of STIs. FSRH guidance recommends that STI screening before insertion is only necessary for those at risk of STIs. In the absence of STI results in women deemed at high risk of infection, then prophylactic antibiotics (to cover chlamydia) can be given if insertion is required, for example. Cu-IUD for emergency contraception.

A systematic review concluded that there were no differences in outcomes in IUC users with PID who had the IUC removed or left *in situ* [16]. If the IUC is removed, then oral emergency contraception should be provided (if required) and alternative ongoing contraception.

Actimomyces-like organisms (ALOs) are commonly identified through cervical screening programmes. ALOs have rarely been associated with severe pelvic infection in IUC users. If a woman with an IUC has ALOs and has no signs or symptoms of infection, then the device can be left *in situ* or safely removed and another inserted immediately. However, if the woman has symptoms of infection, then removal of the IUC is advised along with treatment with antibiotics (and testing for STIs) [14].

Ectopic pregnancy

The overall risk of ectopic pregnancy is much reduced in women using IUC compared with women using less effective methods or no contraception. The absolute risk of ectopic pregnancy is 0.01 per 100 woman-years (95% CI 0.00–0.003) for 52-mg LNG-IUS users, 0.07 per 100 woman-years (95% CI 0.02–1.78) for Cu-IUD users and 0.10 per 100 woman-years (95% CI 0.02–0.29) for 13.5-mg LNG-IUS users [14,17,18].

However, if a pregnancy does occur with IUC *in situ*, then the relative risk of an ectopic increases. In the EURAS study approximately 20% of pregnancies in IUC users were ectopic [14]. An ultrasound scan should be conducted in pregnant women with an IUC to exclude ectopic pregnancy. IUC should be removed before 12 weeks' gestation in view of the greater risk of miscarriage, preterm delivery and chorioamnionitis if left *in situ*.

Side effects

Menstrual disturbance

The endometrial effects of the Cu-IUD tend to cause increased menstrual bleeding and dysmenorrhoea. Conversely, women can be advised that a reduction in menstrual blood loss and an increase in amenorrhoea can be expected over the first year of use with the LNG-IUS. Amenorrhoea rates with the 19.5 mg LNG-IUS and the 13.5-mg LNG-IUS are less than with the 52-mg LNG-IUS (18.9%, 12.7% vs. 23.6% amenorrhoea at 3 years, respectively) [17]. Frequent and prolonged spotting is common with the LNG-IUS, particularly in the first months of use. Careful counselling about menstrual irregularities is vital to avoid premature discontinuation.

When abnormal bleeding patterns occur with IUC, gynaecological causes should be excluded. Pelvic examination, pregnancy testing and STI testing should be considered. In addition, ultrasound and/or endometrial biopsy (especially in women over the age of 45) should also be considered if abnormal bleeding is persistent or is associated with other features such as pain/dyspareunia [19]. Addition of a non-steroidal anti-inflammatory drug (NSAID) or antifibrinolytic (tranexamic acid) may reduce menstrual blood loss with the Cu-IUD. Alternatively, Cu-IUD users may consider switching to a LNG-IUS.

Mood, weight and libido

Hormonal side effects associated with the LNG-IUS are likely to decrease with time. A systematic review failed to demonstrate any differences in side-effect profile between the 52-mg LNG-IUS and Cu-IUD. Side-effect profile of the 13.5-mg LNG-IUS is similar to that of the 52-mg LNG-IUS [20]. Effects of hormonal contraception on libido are difficult to study because of the multiple factors that influence libido. Existing evidence fails to show that the LNG-IUS has negative effects on libido. Weight gain has been reported in users of both Cu-IUD and LNG-IUS, but this does not appear to differ between these methods [20].

Timing of insertion

IUC can be fitted at any point in the cycle provided it is reasonably certain the woman is not pregnant. A Cu-IUD will be effective immediately for contraception. No additional precautions are required if the LNG-IUS is fitted on day 1–7 of the cycle, and 7 days of additional contraceptive precautions (condoms/abstinence) are recommended if fitted later than this time [14].

Postpartum IUC insertion

Insertion of IUC can take place as soon as the placenta is delivered at caesarean section or following vaginal delivery (within 10 min of delivery of placenta or up to 48 hours later) (UK MEC 1). A Cochrane review concluded that insertion at this time is safe and effective with no increased risk of perforation or infection compared with insertion weeks later [21]. Post-placental insertion of IUC can be extremely convenient for women who, due to the constraints and pressures of having a new baby, may be less likely to attend for IUC at a later date. Expulsion

rates of IUC devices after vaginal delivery may be higher than at other times (reported from 4 to 38%) [22], but this may be outweighed by advantages of insertion at this time. For women choosing post-placental insertion of a Cu-IUD, the bleeding associated with insertion can be masked by lochia; women choosing the LNG-IUS can benefit immediately from reduced menstrual bleeding [23].

Post-insertion instructions

Women who have been fitted with IUC should be provided with clear verbal and written information on what signs and symptoms would indicate a possible complication, how to conduct a self-check of threads, which device they have *in situ* and when it needs replacing. Unless pregnancy is desired, removal should only be undertaken during menstruation or if one can be reasonably certain that there is no risk of pregnancy (no unprotected intercourse within 7 days).

Summary box 65.1

- The Cu-IUD is a very effective method of contraception; most devices last for 5–10 years and the method can be used by nulliparous women.
- If a Cu-IUD is inserted after age 40, it can be left in place until contraception is no longer required.
- The commonest side effect (and commonest reason for premature removal) of Cu-IUD is heavy bleeding.
- The risk of ectopic pregnancy is enormously reduced compared with women using no contraception.
- The risk of pelvic infection has been over-emphasized and by 3 weeks after insertion is not increased. Women with risk factors for STI should be screened before insertion but the Cu-IUD is not contraindicated.

Progestogen-only contraception

Progestogen-only contraception is available in a wide variety of delivery systems including IUS (see above), implants, injectable and oral. It has been less commonly used than combined hormonal contraception and so there are fewer data on the risks associated with long-term use. All methods of progestogen-only contraception have a number of mechanisms of action. The implant, injectable and desogestrel-containing pill inhibit ovulation. Older low-dose pill formulations inhibit ovulation only inconsistently. All affect cervical mucus, reducing sperm penetrability and transport. The LNG-IUS has little effect on ovarian activity but causes marked endometrial atrophy, thus compromising implantation if ovulation and fertilization occur. Failure rates for progestogen-only methods are shown in Table 65.1.

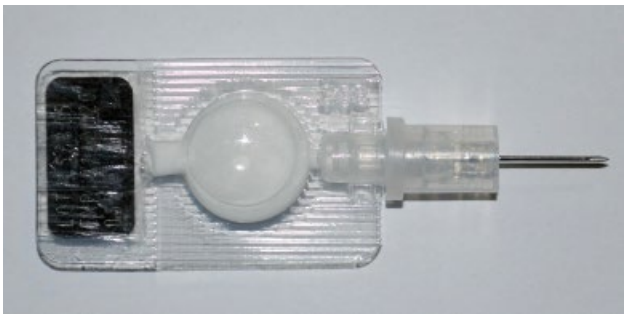

Fig. 65.1 Subcutaneous depot medroxyprogesterone acetate.

The methods

Subdermal implants

The only currently available implant in Europe (Nexplanon®) is a single rod containing 68 mg of 3-keto-desogestrel (a metabolite of desogestrel) providing contraception for 3 years. The initial release rate of 60–70 μg/day falls gradually to around 25–30 μg/day at the end of 3 years. The implant is inserted using local anaesthesia, subdermally on the inner aspect of the non-dominant arm, 8 cm above the elbow. The implant contains a small amount of barium sulfate which facilitates localization by X -ray to assist removal if not palpable. In the UK, FSRH certification of competence in insertion and removal techniques for the implant (and for IUC) is recommended [24]. Complications with insertion have been linked to subsequent difficult implant removals and rare cases of intravascular location of implants. Implants that are not palpable should be removed by someone experienced.

Up to 20% of implant users experience amenorrhoea. The remainder have regular bleeding, or irregular light unpredictable bleeding. Heavy bleeding is uncommon.

Injectable

Long-acting depot medroxyprogesterone acetate (DMPA) is available as a formulation that is given by deep intramuscular injection (150 mg) every 13 weeks (Depoprovera®) or as a micronized (104 mg) preparation that is administered subcutaneously (Sayana®) at the same interval. Both have the same efficacy and bleeding pattern, and the same effects on bone and on return to fertility after stopping [25]. The subcutaneous preparation is available in a simple delivery system consisting of a plastic reservoir filled with DMPA with an integral needle attached (Fig. 65.1) and is licensed for self-administration. Approximately 1 in 10 women may develop some lipoatrophy at the subcutaneous

injection site (dimpling or nodule of skin) and should be counselled about this.

The dose of progestogen in DMPA inhibits ovulation and by the end of 1 year of use over 50% of women will have amenorrhoea. Heavy prolonged bleeding may be a problem in around 2% of women [25].

Oral

The low dose of second-generation progestogen (levonorgestrel, norethisterone) does not consistently inhibit ovulation. A progestogen-only preparation (POP) containing the third-generation progestogen desogestrel inhibits ovulation in almost every cycle. Around 50% of women using a low-dose POP continue to ovulate and therefore menstruate regularly, while 10% experience complete suppression of follicular development and have amenorrhoea. The remainder have inconsistent ovulation and bleed irregularly. Almost 50% of women using the desogestrel POP experience amenorrhoea or infrequent bleeding periods, while the rest are likely to have irregular bleeding [26]. If a POP is taken late (>3 hours late for low-dose pill or >12 hours late for desogestrel pill), then the next pill should be taken, but additional contraceptive protection used for 48 hours (to build up contraceptive effect on cervical mucus) [26].

Indications and contraindications

Progestogen-only contraception is commonly prescribed for women in whom oestrogen is contraindicated. There are few contraindications to use of these methods. The UK MEC 4 conditions (unacceptable health risk if contraceptive is used) for use of progestogen-only methods include past breast cancer. A meta-analysis of data on use of DMPA on acquisition of HIV suggested a moderate increase in risk [27]. The biological basis proposed is a possible effect of DMPA on local immune function, or via vaginal atrophy. A WHO expert group review concluded that data were not sufficiently robust to determine if an association was causal as studies could not exclude important methodological confounders such as non-use of condoms amongst users of the injectable [28]. The use of DMPA by women at high risk of HIV is therefore a UKMEC 2 [9].

Side effects

Bleeding disturbances

The commonest side effect and cause for discontinuation of a POP is an unacceptable bleeding pattern. Inconsistent ovulation and fluctuating endogenous oestrogen production from irregular follicle growth lead to irregular bleeding. However, there is also evidence to suggest that POPs directly affect the vasculature of the endometrium, increasing the chance of bleeding. Bleeding patterns differ according to the dose of progestogen and the route of administration. It is important to ensure that women with unscheduled bleeding have no underlying gynaecological cause. In such circumstances, the FSRH guideline advises that in women using an injectable, implant or LNG-IUS may try concomitant use of the combined pill (in medically eligible women) as a short-term solution [19]. There is also limited evidence that mefenamic acid and tranexamic may reduce the duration of an episode of unscheduled bleeding in women using the injectable or implant [19].

Persistent follicles/follicular cysts

The effect of low-dose POPs on ovarian activity may result in functional ovarian cysts (persistent follicles). Usually asymptomatic, they can cause abdominal pain or dyspareunia. Most will disappear with menstruation and so treatment should be expectant management.

Other 'hormonal' side effects

Headache, nausea, bloating, breast tenderness, and weight and mood change are all common in women using and not using hormonal contraception. They often settle with time. A Cochrane review reported that injectable users had a mean weight gain of 3 kg after 2 years of use. Weight gain in adolescents who are new DMPA users is greater in those of greater baseline body mass index (BMI) [29]. Oily skin and acne can be a problem with the more androgenic progestogens such as levonorgestrel and norethisterone.

Delay in the resumption of fertility

Fertility returns rapidly after stopping low-dose progestogen-only contraception. However, it may take up to 1 year for fertility to return following cessation of DMPA which makes DMPA inappropriate for women wishing short-term contraception.

Serious side effects

Progestogen-only methods are much less widely used than the combined methods so data on long-term risks are sparse.

Cardiovascular disease

There is no evidence for an increase in the risk of myocardial infarction or stroke in association with progestogen-only contraception. Although a small number of case–control and retrospective studies suggested that DMPA may be associated with an increased risk of venous thromboembolism (VTE) compared with non-users, a causal association has not been demonstrated [30]. Use of DMPA amongst women with risk factors for VTE or a history of VTE is therefore a UK MEC 2.

Bone mineral density

Complete inhibition of ovulation by the injectable DMPA causes hypo-oestrogenism and amenorrhoea. Hypo-oestrogenism is associated with a reduction in bone mineral density (BMD). Current use of DMPA is associated with a loss of BMD compared with non-users. Prospective studies have reported statistically significant decreases in BMD over 2 years amongst DMPA users compared with non-users [31]. Limited evidence suggests that this bone loss is reversible on stopping. In spite of the effect on BMD, there is no significant association between DMPA use and risk of osteoporotic fracture after adjusting for baseline BMD. The FSRH advises that in women who wish to continue using DMPA, re-evaluation of the risks and benefits of treatment should be carried out every 2 years. In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.

Summary box 65.2

- Progestogen-only contraception is available in a wide range of delivery systems.
- The dose of progestogen determines the mode of action and side effects.
- Irregular vaginal bleeding is a common reason for discontinuation of low-dose progestogen-only contraception, which does not inhibit ovarian activity completely.
- Despite normal ovarian activity, the IUS is associated with amenorrhoea because of endometrial atrophy.
- DMPA inhibits ovarian activity completely and a high proportion of users have amenorrhoea.
- Progestogen-only contraception does not increase the risk of cardiovascular disease.
- DMPA is associated with decreased BMD.

Combined hormonal contraception

Combined hormonal methods contain both oestrogen and a progestogen and are available as oral, transdermal (patch) and vaginal preparations (vaginal ring). The mode of action (inhibition of ovulation), side effects and risks are similar. For efficacy see Table 65.1.

The methods

Oral

Most combined oral contraceptive (COC) pills in use in the UK contain ethinylestradiol in doses of 20–35 μg (so-called 'low-dose' pills). Recent developments have been COC pills containing 'natural oestrogens' such as estradiol valerate and 17β-estradiol, but these are not widely used as they have not been shown to confer any advantages over existing preparations and long-term safety data are not yet available. Risks and benefits must be assumed to be as for other COC and the same UK MEC categories apply.

Most COC pills are taken for 21 days followed by a 7-day pill-free interval when withdrawal bleeding usually occurs. COC pills are available as monophasic preparations, in which every pill in the packet contains the same dose of steroids. Phasic pills (e.g. triphasic, tetraphasic) have varied doses of steroids, but confer no advantage over monophasic pills.

Increasing numbers of women run packets of monophasic pills together, i.e. extended use. This is useful for reducing episodes of withdrawal bleeding, dysmenorhoea or headaches associated with the pill-free interval.

Transdermal

The contraceptive patch available in the UK (20 cm^2 in size) delivers 33.9 μg ethinylestradiol and 203 μg norelgestromin daily. Each patch lasts 7 days, three patches being used consecutively with a patch-free interval in week 4 when withdrawal bleeding occurs. Contraceptive protection lasts for up to 10 days, allowing for errors in changing the patch. Effectiveness is not significantly different from the COC (Table 65.1). Bleeding patterns and side effects are similar to those associated with the COC.

Vaginal

The combined contraceptive vaginal ring releases 15 μg ethinylestradiol and 120 μg etonorgestrel daily. It is made of soft ethylene-vinyl-acetate copolymer, has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. Designed to last for 3 weeks, a 7-day ring-free interval is associated with bleeding patterns that appear superior to those associated with the COC pill. In a comparison with a 30-μg ethinylestradiol COC pill, the incidence of irregular bleeding with the ring was significantly less (<5% vs. 39%). In all other respects, including efficacy, the ring is no different from COC, although there may be advantages in terms of demands on compliance.

Mode of action

The principal mode of action of combined hormonal contraception is inhibition of ovulation. Oestrogen inhibits pituitary follicle stimulating hormone (FSH), suppressing the development of ovarian follicles, while progestogen inhibits the luteinizing hormone (LH) surge. Most combined hormonal contraception is administered for 21 days followed by a 7-day hormone-free interval. The ovaries remain quiescent with seven hormone-free days, but if COC pills are missed so that

this interval is extended, then follicles can continue to develop and despite restarting contraception ovulation may occur. The FSRH advise that if two or more pills are missed, then the next pill should be taken and additional barrier methods used for 7 days. If the missed pills were after a pill-free interval, then emergency contraception is advised if unprotected sex occurred [32]. Manufacturers advise that additional barrier methods (or abstinence) for 7 days are required if a patch is applied 48 hours late or a ring is removed for more than 3 hours during the 21 days of treatment.

Additional properties of combined hormonal contraception include changes in characteristics of cervical mucus that interfere with sperm transport, a possible alteration in tubal motility, endometrial atrophy and impaired uterine receptivity.

Contraindications

The absolute (UK MEC category 4 conditions) contraindications to combined hormonal contraception (pill, patch and ring) are listed in Table 65.3.

Table 65.3 UK MEC category 4 conditions (unacceptable health risk) for use of the combined oral contraceptive pill [9].

Breastfeeding <6 weeks post partum
Not breastfeeding 0–3 weeks post partum with risk factors for venous thromboembolism (VTE)
Smoking ≥15 cigarettes/day and age ≥35 years
Multiple risk factors for cardiovascular disease
Hypertension: systolic ≥160 mmHg or diastolic ≥100 mmHg
Hypertension with vascular disease
Current or history of VTE
Major surgery with prolonged immobilization
Known thrombogenic mutations
Current or history of ischaemic heart disease
Current or history of stroke or transient ischaemic attack
Complicated valvular heart disease
Migraine with aura
Current breast cancer
Diabetes with vascular disease or nephropathy, retinopathy or neuropathy
Severe cirrhosis
Benign hepatocellular adenoma or malignant liver tumours
Positive antiphospholipid antibodies
Systemic lupus erythematosus with positive antiphospholipid antibodies
Cardiomyopathy with impaired cardiac function
Atrial fibrillation

Side effects

Contraceptive steroids are metabolized by the liver and affect the metabolism of carbohydrates, lipids, plasma proteins, amino acids, vitamins and clotting factors. Many of the reported side effects, particularly headache, weight gain and loss of libido, are also common among women not using hormonal contraception. A different dose of oestrogen or type of progestogen or a different delivery system may help. Side effects (real or perceived) often lead to discontinuation; weight gain is one of the commonest reasons for stopping.

Risks

The combined pill is extremely safe. Data from a large UK cohort study of over 46 000 women using the COC pill for up to 39 years showed that oral contraception was not associated with an increased risk of death [33]. Indeed, 'ever users' of the contraceptive pill (predominantly combined pill) had a 12% reduction in the overall risk of death for all conditions compared with 'never users' (RR 0.88, 95% CI 0.82–0.93).

Venous thrombosis

Venous thrombosis is rare in women of reproductive age. All combined hormonal contraception is associated with an increased risk of VTE compared with non-use. A number of studies have found differences in risk of VTE according to type of COC pill used. The biological mechanism is not fully understood but different progestogens appear to modify the thrombogenic effects of oestrogen to different extents. However, the absolute differences are very small. The European Medicines Agency (EMA) reviewed the risk of VTE associated with combined hormonal contraception and concluded that there was good evidence that the risk of VTE associated with different COC pills was influenced by type of progestogen, with levonorgestrel, norethisterone and norgestimate having the lowest risk (5–7 per 10 000 women) and those containing third-generation (desogestrel, gestodene) or fourth-generation (drospirenone) progestogens having the highest risk (9–12 per 10 000 women), compared with 2 per 10 000 women amongst non-users. However, the risk of VTE is low overall and is lower than the risk associated with pregnancy and the postpartum period (29 per 10 000 woman-years and 300–400 per 10 000 woman-years, respectively) [34].

Co-cyprindiol, a preparation containing ethinylestradiol in combination with the anti-androgen cyproterone acetate, is licensed for the treatment of severe acne and hirsutism. It should not be used routinely for other women, as evidence indicates that it is associated with an increased risk of VTE similar to that of COC pills containing desogestrel, gestodene or drospirenone.

The risk of VTE with combined hormonal contraception is greatest during the first year of use, possibly due to the unmasking of inherited thrombophilias such as factor V Leiden. Screening for known thrombophilias is not cost-effective. Although non-oral routes of administration avoid the first pass through the liver, thereby theoretically having less effect on clotting factors, the available evidence for the contraceptive patch and ring would indicate that the risk of VTE is no less than the COC pill and in the region of 6–12 per 10 000 woman-years.

Arterial thrombosis

The absolute risk of arterial thrombosis (myocardial infarction and ischaemic stroke) in women of reproductive age, even those with known risk factors, is extremely small (approximately 10 per 100 000 and 21 per 100 000, respectively). It is related to age, and the risk is strongly influenced by smoking. COC use has been associated with an increased risk of arterial thrombosis. A Cochrane review of 24 studies showed that women using the COC pill had a 1.6 relative risk of myocardial infarction and stroke (95% CI 1.3–1.9) compared with non-users [35]. The risks did not appear to vary according to the type of progestogen. However, increasing doses of oestrogen (>50 μg ethinylestradiol) were associated with increased risk.

Women who have migraine with aura have a higher risk of stroke than those without. In a systematic review of the limited publications, users of hormonal contraception with migraine had a twofold to fourfold risk of stroke compared with non-users [36]. Combined hormonal contraception is contraindicated in women who have migraine with aura at any age (UK MEC 4), but may be considered for women without aura. Many people describe their headaches as migraine, so it is important to make an accurate diagnosis of migraine and those complicated by aura. The UK MEC directs providers to useful websites and resources to diagnose types of migraine [9].

Malignant disease

Breast cancer

A meta-analysis of 54 studies involving over 53 000 women with breast cancer and 100 000 controls concluded that use of the COC pill was associated with a small increase in the risk of breast cancer. The increased risk persisted for 10 years after stopping the pill [37]. The relative risk for current users was 1.24; for those 1–4 years after stopping, 1.16; and for those 5–9 years after stopping, 1.07. After 10 years the relative risk was the same as that of non-users. It has been suggested that starting to use the pill may accelerate the appearance of breast cancer in susceptible women. Alternatively, women using combined hormonal contraception might have their tumours diagnosed earlier. A biological effect of combined hormonal contraception remains a possibility.

Cervical cancer

Data on the risk of cervical cancer among pill users are difficult to interpret since barrier methods confer some protection and any association identified in epidemiological studies may be the result of inadequate adjustment for sexual behaviour. A systematic review concluded that for women with persistent human papaillomavirus (HPV) infection, long-term use of the COC pill (>5 years) may increase the risk of cervical cancer. However, women should be advised that the risk can be significantly reduced through condom use, HPV vaccination (young people) and routine cervical screening.

Ovarian, endometrial and colon cancer

For ovarian cancer, epidemiological studies would suggest a 50% reduction in the risk of both epithelial and non-epithelial ovarian cancer after 5 years use of the COC pill [33]. This effect may be related to the reduction in the total number of ovulations, and therefore rupture of the ovarian capsule, experienced in a lifetime. This reduction in risk of ovarian cancer persists for 30 years after discontinuation of the COC pill. Protection is also evident for women with a family history of breast cancer. Epidemiological evidence also supports a reduction in endometrial cancer that is strongly related to the duration of COC use (20% risk reduction after 1 year, 50% after 4 years) and is sustained for 15 years after stopping the pill. There is also evidence that current or recent use of the COC pill may confer protection against colon cancer [33].

Practical prescribing

The FSRH recommends a pill containing 30 μg ethinylestradiol in combination with a second-generation progestogen for new users on the grounds that such pills are the safest and cheapest. COC pills containing other progestogens should generally be reserved for women intolerant of these and prepared to accept an increased risk of VTE.

Women should be carefully instructed how to use the pill, patch or ring and what to do when mistakes are made. Most women who stop the pill regain normal fertility after stopping. Secondary amenorrhoea is almost always the result of underlying conditions present before the method was started (such as polycystic ovarian syndrome) but regular withdrawal bleeds mask these conditions.

Drug interactions with hormonal contraception

Use of medications may increase or decrease serum levels of contraceptive hormones; likewise, hormonal contraception may alter levels of medications. This can potentially cause adverse effects. Prescribers should ask

women about all drug use and where necessary consult up-to-date and reputable internet drug interaction checkers.

Some of the commonest interactions with hormonal contraceptives are with medicines that induce liver cytochrome P450, which could reduce the efficacy of combined hormonal contraception and the progestogen-only pill and implant (e.g. some antiepileptic drugs, antifungals, antiretrovirals). These medicines are not thought to affect the efficacy of the injectable, Cu-IUD or LNG- IUS. If a woman using enzyme-inducing medication wishes to use a low-dose hormonal method, then use of condoms is also advised. Contraceptive effectiveness of the COC pill (and all other methods) is not affected by coadministration of most broad-spectrum antibiotics. While the antiepileptic lamotrigine is not an enzyme inducer, use of combined hormonal contraception increases the clearance of lamotrigine and reduces serum levels of this drug. Seizure frequency could therefore increase when initiating combined hormonal contraception and side effects may increase in the pill-free interval or when discontinuing this method of contraception.

Emergency contraception

Emergency contraception (EC) is defined as any drug or device used after intercourse to prevent pregnancy. The options for EC within the UK are the Cu-IUD or oral EC, either 30 mg of the progesterone receptor modulator ulipristal acetate (UPA) or 1.5 mg of the progestogen levonorgestrel. UPA is licensed for use up to 120 hours after unprotected sex, and LNG for up to 72 hours, although there is evidence that LNG may retain efficacy up to 96 hours.

In the UK, LNG has been available without prescription from a pharmacy since 2001; UPA has been available throughout most of Europe without a prescription since 2015. Whilst EC prevents pregnancy for individuals, there is no evidence that EC (or improved access) prevents unintended pregnancies or abortions at population level. Research has shown that women do not use EC for every act of unprotected sex. Additionally, many women have more sex in the same cycle after using EC, which increases the risk of pregnancy.

Efficacy

Effectiveness of EC is estimated by calculating the number of pregnancies that might have occurred in the absence of treatment but such estimates of efficacy are difficult to make [6]. Many women are unsure of the exact date of their LMP, many are of unproven fertility and many use it after an accident with a condom which may not in fact have resulted in the leakage of seminal fluid.

The Cu-IUD is the most effective EC, with pregnancy rates of around 1 in 1000. Copper ions are toxic to gametes and the Cu-IUD also induces endometrial effects that prevent implantation. It can be inserted for EC up to 5 days after the estimated day of ovulation (in a 28-day cycle this is interpreted as day 19, i.e. day 14 + 5 days = day 19). Although the Cu-IUD is widely used for EC, it may have limited acceptability to women because it requires an invasive procedure and the availability of a skilled provider. FSRH guidelines recommend that all eligible women should be offered a Cu-IUD for EC given its low failure rate.

The effectiveness of oral EC has been overestimated in the past. A meta-analysis of trials that compared both LNG and UPA for EC reported pregnancy rates of 2.6% and 1.8%, respectively. Since the expected pregnancy rate was calculated at 5.5%, this suggests that these methods might prevent half to two-thirds of pregnancies [38].

Mechanism of action

Both LNG and UPA work by delaying ovulation for at least 5 days (lifespan of sperm in the female reproductive tract). However, if taken in the immediate preovulatory period when the risk of conception is greatest (after the onset of the LH surge), LNG is ineffective but UPA remains able to delay ovulation. EC doses of LNG and UPA do not cause significant endometrial effects and are unable to prevent implantation *in vitro*.

Safety

Observational studies have shown no adverse effect of exposure to LNG on pregnancy outcome or subsequent infant development. Data on the effects of UPA on pregnancy are more limited. However, the available data on UPA have been consistent, with no increased risk of miscarriage, ectopic or congenital abnormality in babies compared with the general population [39].

Impact of obesity on EC

Secondary analyses of studies comparing LNG and UPA for EC suggested that obesity (BMI ≥30 kg/m^2) was associated with an increased risk of pregnancy and that failure of EC was greater amongst women with obesity treated with LNG than UPA. However, the EMA reviewed the data from published and unpublished clinical trials and concluded that the data were not sufficiently robust to conclude that obesity was associated with a decrease in efficacy of EC. The FSRH recommends that women with obesity can continue to use either UPA or LNG [39].

Starting effective contraception after EC

Given the higher risk of pregnancy if further sex occurs in the same cycle after EC, it is important that women start effective contraception as soon as possible. LNG does not interact with hormonal contraception. However, UPA is a progesterone receptor modulator and recent biomedical studies indicate that starting the POP desogestrel the day after UPA adversely affects the ability of UPA to delay ovulation, i.e. renders UPA less effective as EC. FSRH guidelines advise that after UPA for EC, women should wait at least 5 days before commencing hormonal contraception [39].

Summary box 65.3

- Ulipristal acetate is a progesterone receptor modulator that is available for emergency contraception.
- Ulipristal acetate has been shown in a meta-analysis to be more effective than levonorgestrel for emergency contraception.
- Ulipristal acetate can be given within 120 hours of unprotected intercourse.
- The most effective method of emergency contraception is a Cu-IUD.
- A Cu-IUD can be inserted up to 5 days after ovulation for emergency contraception.

Female sterilization

Female sterilization involves blocking both fallopian tubes at laparoscopy, hysteroscopy or, less commonly, laparotomy. Filshie clips are the method of choice for laparoscopic sterilization and result in immediate tubal occlusion. The Pomeroy technique, where a loop of tube is tied and excised, is the method of tubal occlusion during laparotomy. Postpartum sterilization using mechanical occlusion with Filshie clips is effective and quicker and easier to perform than partial salpingectomy. It is recommended that women wishing sterilization at caesarean section be carefully counselled, and that consent be obtained at least 2 weeks before the planned delivery [40].

Hysteroscopic sterilization has advantages of avoiding abdominal incisions and can be performed under local anaesthesia or simple analgesia in an outpatient setting. It is particularly suitable for women who present an anaesthetic or operative risk (e.g. high BMI, previous abdominal or pelvic surgery). The Essure® system uses micro-inserts that are expanding springs (2 mm diameter and 4 cm in length) made of titanium, stainless steel and nickel-containing Dacron fibres. A micro-insert is placed in the proximal section of the fallopian tube under hysteroscopy. These induce a local inflammatory response and, over the subsequent weeks, fibrosis of the intramural tubal lumen. An additional method of contraception should be used until fibrosis of the lumen has been achieved and imaging (radiography, ultrasound or hysterosalpingography) at 3 months has confirmed satisfactory placement of the inserts. In 2017, the manufacturers of ESSURE withdrew it from the European market for commercial reasons.

Efficacy

Follow-up data available for the Filshie clip suggests a failure rate of 2–5 per 1000 procedures after 10 years [40]. For sterilization by hysteroscopic micro-insert, pregnancy rates are approximately 2 in 1000. Sterilization failure may increase the risk of ectopic pregnancy, but there are no robust data on which to quantify this risk.

Risks of female sterilization

Regret rates are particularly high in women under 30 years of age (up to 30% in some studies), and so younger women should be encouraged to consider LARC. A number of failures are believed to be due to women unknowingly conceiving in the same cycle before the procedure is performed. Contraception (hormonal and IUC) should continue for at least 7 days after tubal occlusion. Risks of laparoscopic sterilization include failure and injuries to bowel, bladder and blood vessels. The risk of laparotomy as a consequence of a severe complication is 1.9 per 1000 procedures. Women considering sterilization should be advised that subsequent changes in menstrual bleeding patterns may be expected due to advancing age and stopping hormonal contraception. There is epidemiological evidence suggesting that bilateral salpingectomy may protect against developing high-grade serous ovarian cancer. It is postulated that this may be because some epithelial cancers may originate in tubal epithelium. Women should be carefully considered for removal of fallopian tubes, if their family is complete and they are undergoing pelvic surgery [41].

Although hysteroscopic sterilization can avoid the risks of a general anaesthetic, laparoscopy and abdominal scars, potential complications and adverse events include tubal perforation, infection, device migration, device expulsion and vasovagal and pelvic pain.

Vasectomy

Male sterilization is safer than female sterilization and is more commonly performed under local anaesthesia. The ability to check for efficacy (with semen analysis) is an advantage. Division of the vas deferens prevents the passage of sperm. A minimally invasive approach should be used to expose and isolate the vas deferens, as this results

in fewest complications [40]. The success of the procedure is verified by the absence of sperm on semen analysis (and contraception must be continued until this time). The time to azoospermia depends on the frequency of intercourse, but it is estimated that 20 ejaculations are required. In the UK seminal analysis is recommended at 12 and 16 weeks, although a routine second semen analysis is not required if the first confirms azoospermia.

Efficacy

Even after azoospermia has been confirmed, there is a failure rate of around 1 in 2000 procedures. In a small proportion of men, non-motile sperm will persist following vasectomy. In such cases, RCOG guidelines advise that consideration be given to stopping additional contraception when less than 100 000 non-motile sperm per millilitre are observed in a fresh semen sample after vasectomy.

Complications

Scrotal bruising occurs in almost everyone, and haematoma (1–2%) and wound infection (up to 5%) are common minor complications. The development of anti-sperm antibodies (thought to be in response to leakage of sperm) occurs in most men and appears to be harmless unless restoration of fertility is desired. Small inflammatory granulomas can form at the ends of the vas but can be effectively excised. Chronic post-vasectomy pain (testicular, scrotal, pelvic or lower abdominal) is a persistent pain of unknown cause. It has been reported in 1–14% of men after vasectomy. Concerns have been raised linking vasectomy with an increased risk of atherosclerosis, testicular cancer, prostatic cancer and other, mainly autoimmune, diseases. Several large studies have failed to substantiate these concerns and there seems to be no biological plausibility for such a link.

Assessment and counselling for sterilization

Couples sterilized at a young age, immediately after delivery or at the time of an induced abortion are more likely to experience regret. A change of partner is the commonest reason for requesting reversal. A history should be taken and scrotal or bimanual pelvic examination should be carried out either at initial consultation or before commencing the procedure.

Reversal of sterilization

Reversal of female sterilization (tubal re-anastomosis) involves laparotomy, does not always work (microsurgical techniques have around 70% success) and carries a significant risk of ectopic pregnancy (up to 5%). Reversal of sterilization with micro-inserts cannot be achieved via fallopian tube re-anastomosis, and therefore consideration should be given to *in vitro* fertilization. Reversal of vasectomy is associated with patency rates of almost 90% in some series. Pregnancy rates are much less (up to 60%), possibly due to the development of anti-sperm antibodies.

Barrier methods

Male and female condoms

The male latex condom is cheap, widely available over the counter and, with the exception of the occasional allergic reaction, is free from side effects. Polyurethane condoms offer an alternative for people with latex sensitivity. Condoms are effective in preventing STIs, including HIV. The female condom is a polyurethane sheath (single size) with flexible polyurethane ring and is placed inside the vagina. Failure rates are similar to those of the male condom (see Table 65.1).

Diaphragm and cervical cap

The diaphragm and cap are less popular than male condoms. In addition, they do not confer the same degree of protection against STIs since the vaginal mucosa is not covered. In order to select the correct size of diaphragm, a vaginal examination is conducted. Latex allergy, recurrent local vaginal infections and recurrent urinary tract infection are possible side effects. Caps fit snugly over the cervix but are seldom used.

Summary box 65.4

- All barrier methods have high failure rates when used typically.
- Male condoms reduce the risk of STIs including HIV.
- Spermicides should not be used alone and if used frequently and in large quantities may increase the risk of HIV transmission.

Fertility awareness methods

Fertility awareness methods (FAM) involve the avoidance of intercourse during the fertile period of the cycle [42]. For calendar or rhythm method, the woman calculates the fertile period according to the length of her normal menstrual cycle. The first day of the fertile period is calculated as the length of the shortest cycle minus 20 days, and the last day of the fertile period as the longest cycle minus 10 days. Therefore if cycle length varies from 25 to 30 days, the potential fertile period and days when intercourse should be avoided are days 5–20.

The mucus or Billings method relies on identifying changes in the quantity and quality of cervical and vaginal mucus. As circulating oestrogens increase with follicle growth, the mucus becomes clear and stretchy allowing the passage of sperm. With ovulation, and in the presence of progesterone, mucus becomes opaque, sticky and much less stretchy. Intercourse must stop when fertile-type mucus is identified and can start again when infertile-type mucus is recognized.

Progesterone secretion is associated with a rise in basal body temperature of about 0.5°C and so the basal body temperature method identifies the end of the fertile period. Other signs/symptoms, such as ovulation pain, position of cervix and dilatation of the cervical os, can be used to help define the fertile period. Personal fertility monitors use test strips to detect urinary metabolites of oestrogen, and LH (eg. Persona may be used by women to detect the fertile phase of the cycle); the monitor displays a green light for the non-fertile phase and a red light for the fertile phase. An increasing number of fertility apps for mobile phones, where the user inputs cycle length and/or symptoms such as basal body temperature, are being adapted for contraceptive purposes. FAM requires motivation, teaching and regular cycles. Whatever method is used, many couples find it difficult to abstain from intercourse during the fertile period. Failure rates are high (see Table 65.1).

Lactational amenorrhoea method

Breastfeeding delays the resumption of fertility after childbirth and the length of the delay is related to the frequency and duration of breastfeeding episodes. A woman who is fully or nearly fully breastfeeding and who remains amenorrhoeic has less than a 2% chance of pregnancy during the first 6 months after childbirth (lactational amenorrhoea method).

Non-contraceptive benefits of contraception

Hormonal methods of contraception in particular have many non-contraceptive benefits. When used for the management of a medical problem the risk–benefit ratio changes. The 52-mg LNG-IUS is highly effective for heavy menstrual bleeding and more cost-effective than other medical therapies and endometrial ablation. It reduces the pain of endometriosis and adenomyosis and protects against unopposed oestrogen. There is evidence that the 52-mg LNG-IUS prevents and causes regression of endometrial hyperplasia and protects the endometrium against the effects of tamoxifen (amongst women with breast cancer). The 13.5-mg LNG-IUS is not licensed for treatment of heavy menstrual bleeding, but does reduce menstrual bleeding and amenorrhoea rates improve with time.

There is good evidence that COC pills can help bleeding, acne and hirsutism, and symptoms of premenstrual syndrome. DMPA is effective in managing the symptoms of endometriosis and, given the high incidence of amenorrhoea, is also used for heavy menstrual bleeding. Hormonal contraception protects against certain gynaecological cancers, the most important being the significant reduction in ovarian and endometrial cancer with use of the COC pill. DMPA confers a high degree of protection against endometrial carcinoma and should theoretically also protect against ovarian cancer.

Conclusion

Obstetricians and gynaecologists often underestimate a woman's need for immediate effective contraception. Contraception can be started at any time if it is reasonably certain that a woman is not already pregnant. Immediately after pregnancy is a key time to provide contraception, since fertility and sexual intercourse resume quickly. Uptake of LARC at these times can prevent unintended pregnancies and short inter-pregnancy intervals that have negative consequences for maternal and child health. Hormonal methods of contraception can effectively manage a range of gynaecological conditions. It is essential therefore that obstetricians and gynaecologists can give high-quality information to women about the range of contraceptive methods and provide these for women.

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66

Sexual Dysfunction

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Sexual activity is associated with pleasurable and enjoyable experiences potentially throughout adult life in women as well as allowing for reproductive capacity in the childbearing years. Sexual function is recognized to be associated with both psychological and physical well-being. The first principle of clinical sexuality states that 'any sexual behaviour – normal and abnormal, masturbatory and partnered – rests upon biological elements, psychological elements, interpersonal elements, and cultural concepts of normality and morality' [1] and as such conveys sexuality's inherent rich complexity.

Society has changed considerably over recent decades and the impact of sexuality as an important contributor to quality of life has been emphasized by greater numbers of women approaching gynaecologists and other clinicians seeking help for sexual (and often relationship) problems. Alongside this is an expectation to be able to raise the matter with their healthcare professional without fear of rejection or embarrassment. There is anticipation that their clinician will be willing to discuss the issues when raised by the woman, or the physician, with confidence and without judgement. Provision of clinical services for the emerging specialty of sexual medicine remains limited within the UK and is best located where multidisciplinary teams can work providing sexual medicine, sexual therapy and gynaecology services together for women and their partners.

Summary box 66.1

- Sexual activities offer both reproductive and pleasurable recreational opportunities for women.
- Healthcare professionals should offer women the opportunity to discuss any areas of concern about their sexuality or relationship.
- Sexual medicine is a multidisciplinary field of medicine incorporating gynaecology, psychology and couples' psychotherapy.

Changing attitudes towards sex

This shift in attitudes has been highlighted by the findings from the consecutive UK National Surveys of Sexual Attitudes and Lifestyles (Natsal) conducted over the last three decades. In the most recent survey of individuals aged 16–74 years who lived in Britain (England, Scotland and Wales) that was completed between 2010 and 2012, data were available for 6777 women (and 4913 men) [2]. Some of the key findings for women were that low sexual function was associated with increased age and, after age adjustment, with depression and self-reported poor health status. Low sexual function was also associated with experiencing the end of a relationship, an inability to talk easily about sex with a partner and not being happy in the relationship. Associations were also noted with engaging in fewer than four sex acts in the preceding 4 weeks, having had same-sex partners and having 10 or more lifetime partners; 51.2% of women reported one or more problems in the past year, although self-reported distress about their sex lives was much less common. For women in a sexual relationship for the past year, 27.4% (and 23.4% of men) reported an imbalance in the level of interest in sex between partners, with 17.1% of women reporting that their partner had had sexual difficulties.

Trends were reviewed over the three decades that the surveys have taken place (Natsal 1, 1990–1991; Natsal 2, 1999–2001; Natsal 3, 2010–2012). Some of the findings were as follows. The percentage of women who thought that one-night stands were 'not wrong at all' increased from 5.4% in Natsal 1 to 12.2% in Natsal 2 and 13% in Natsal 3. The percentage of women thinking that female same-sex partnerships were 'not wrong at all' increased from 27.7% in Natsal 1 to 51.5% in Natsal 2 and 66.1% in Natsal 3. The authors conclude in their review that sexual lifestyles in Britain have changed substantially in the past 60 years, with changes in behaviour seemingly greater in women than men. The continuation of sexual

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

activity into later life, albeit reduced in range and frequency, emphasizes that attention to sexual health and well-being is required throughout the life course [3].

In another recent study involving middle-aged and older UK individuals (40–80 years), 56% of women reported having sexual intercourse in the last year and 18.8% of women engaged in sexual intercourse at least weekly. The most common problems reported were lack of sexual interest (34%) and lack of pleasure in sex (25%). Of some concern, 57.7% of women took no action when they had a sexual problem and only 16.7% of women reported talking to a medical doctor, with most women (82.3%) having sought no advice from a health professional. Talking to their partner was the most common action taken by women (32.5%) [4]. Only 4.2% of women had been asked by a doctor about possible sexual difficulties during a routine visit in the previous 3 years yet 29.2% of women thought that a doctor should routinely ask patients about their sexual function.

Despite this emerging evidence of patient need, it has been reported that women may present to a gynaecology or obstetric clinic without ever being asked, or disclosing any information, about their sexual lives. One study identified that over 98% of women reported one or more sexual concerns that often changed as women aged but that most of the women had not had the topic of sexual health ever raised by their physicians [5]. The clinic environment may not be conducive to routine enquiry but this should be addressed by changes to the patient clinic space to ensure patient confidentiality.

Summary box 66.2

- Sexual problems are common within the community but persistent problems for over 6 months are much more unusual.
- The commonest sexual problem is a lack of sexual interest, fantasy and desire.
- Women are more likely to discuss their problem with a friend or their partner than with a healthcare professional.

Sexual response: models of sexual function

Humans have three primary emotion–motivation circuits and these brain systems have evolved to direct and influence sexual behaviour. These are lust (sex drive, libido), driven by androgens; attraction (passionate romantic love), driven by dopamine; and attachment (bonding), driven by oxytocin [6,7]. Evolving evidence suggests that individual differences in human sexual behaviour may be in part due to allelic variants coding for differences in DRD4 dopamine receptor gene expression and protein concentrations in key brain areas [8]. A variant of the DRD4 dopamine receptor gene (a polymorphism found on chromosome 11 in humans) has been linked with uncommitted sexual behaviour and infidelity [9].

The aetiology of unhappiness within a relationship is multiple but failing to find a partner to love may arise when psychological intimacy is unable to be reached during courtship or is lost once in a stable relationship. When this arises, couples work may be appropriate should both partners be willing to attend to explore, amongst many issues, their ways of connecting, communicating and negotiating together. Other key areas may include dealing with issues of power and trust within a relationship.

The early models of sexual response were described as linear in nature, incorporating concepts of sexual drive (endocrine), sexual desire and libido (emotional and cognitive), excitation and plateau (vascular and emotional), orgasm (neurological, muscular and emotional) and resolution (Fig. 66.1). More recently, an intimacy-based model of a women's sexual response cycle was introduced by a team of experts (Fig. 66.2). This model reflects the key roles of emotional intimacy and sexual stimuli, unlike the earlier models which tended to neglect the importance of emotional intimacy as a motivator to find or be responsive to sexual stimuli. The basis of the more cyclical model is that the goal of sexual activity in women may not necessarily be physical satisfaction (by attaining orgasm), but rather emotional satisfaction (a feeling of intimacy and connection with a partner) [10]. However, there are additional models that may be important when considering sexual function and dysfunction and the interested reader is referred to a recent review [11].

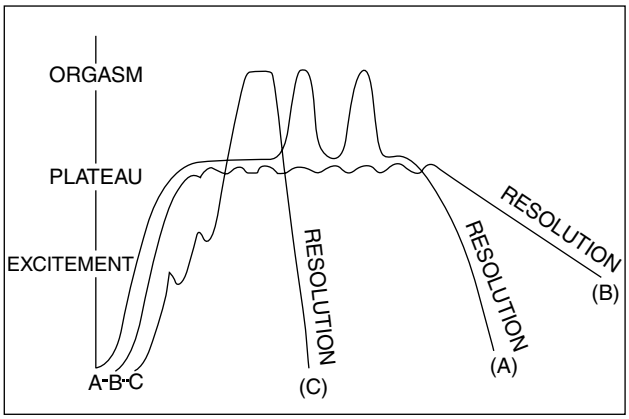

Fig. 66.1 Masters and Johnson's model of linear sexual response.

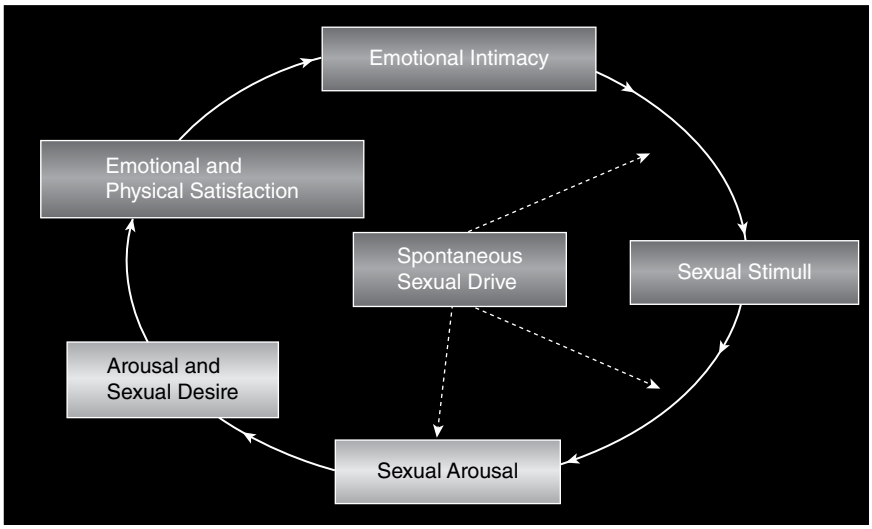

Fig. 66.2 Basson's model of cyclical sexual response. *Source:* Basson R, Althof S, Davis S *et al.* Summary of the recommendations on sexual dysfunctions in women. *J Sex Med* 2004;1:24–34. Reproduced with permission of John Wiley & Sons Inc.

Sexual response: anatomy and physiology

The anatomy and physiology of sexual function and dysfunction is not always overtly taught at medical school or in postgraduate courses, with several obstacles preventing sexual health from being adequately addressed in health professionals' curriculum. These include low priority given to the topic and a lack of standardized objectives and means for evaluating any current curriculum. Given the raised awareness that medical conditions can result in sexual dysfunction and the fact that sexual problems may be the presenting symptom for significant underlying disease, the argument for mandatory awareness and training in the field is increasing [12].

Vaginal lubrication comprises vaginal transudate, often with secretions from the Bartholin's glands and the paraurethral Skene's glands. The process of transudation depends on both intact innervation and normal oestrogen levels. The process of parasympathetic activation via the sacral nerves S2–S4 leads to an increase in vaginal blood flow. It has been shown that the process of vasomotion occurs with the random opening and closing of the capillaries of the vaginal wall (Fig. 66.3). The normal

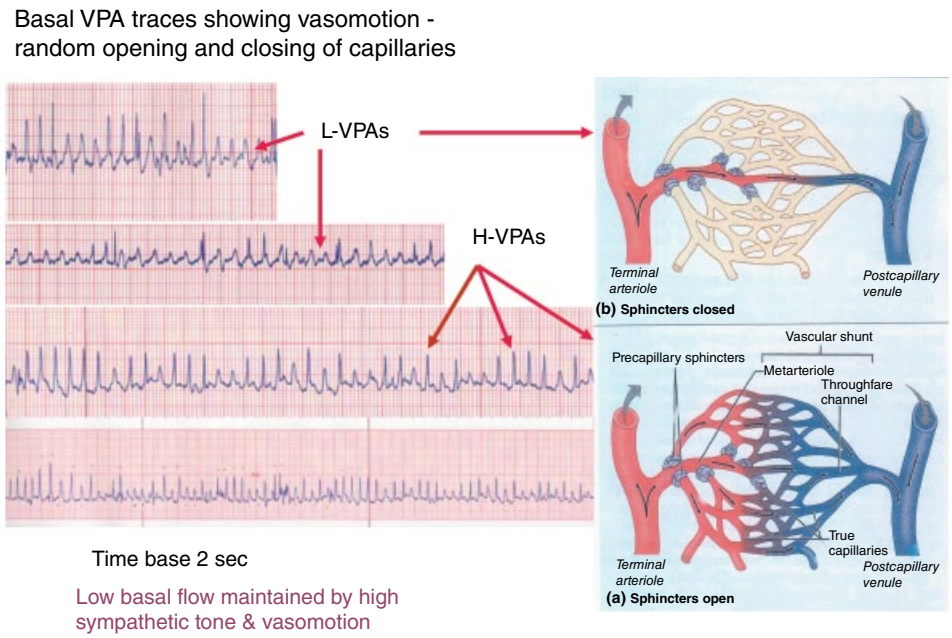

Fig. 66.3 Vaginal vasomotion.

low basal flow is maintained by both high sympathetic (T12–L2) inhibitory tone and vasomotion [13].

Concurrent with any increase in vaginal blood flow is an increase in the blood flow to the clitoris, an organ which is much hidden from routine inspection of the vulva. The perineal urethra is embedded in the anterior vaginal wall and is surrounded by erectile tissue in all directions, except posterior where it relates to the vaginal wall [14]. The erectile tissue brings about swelling and protuberance during sexual arousal. The clitoris appears to exist solely for the purpose of sexual pleasure. There has been much debate about the differences and importance (if any) between clitoral orgasm and vaginal orgasm and whether the presence of a G-spot exists to bring about sexual pleasure. In recent years a number of papers have been published with regard to the possible isolation of tissue identified to be the G-spot and the evidence and arguments are summarized in a recent commentary [15].

Sexual diversity

The gynaecologist should strive to offer a non-judgemental approach when exploring a woman's sexual identity regardless of any sexual dysfunction and this will be considered further in the following section. The principle issues involve sexual orientation, gender identity and the presence of any paraphilic patterns of sexual arousal.

Sexual orientation should be routinely enquired about with women in the clinical setting. It is difficult to be certain of the true prevalence of lesbianism but in one study, among women, 97.7% identified as heterosexual, 0.8% as lesbian or homosexual and 1.4% as bisexual. However, during this computer-assisted telephone interview, among women, 84.9% reported only opposite-sex attraction and experience. Thus, some same-sex attraction or experience was reported by 15.1% of women (compared with 91.4% of men). Of women, 8.2% reported sexual attraction and sexual experience that was inconsistent. Factors associated with this agreement or disagreement included age group, non-English-speaking background, education and socioeconomic status [16].

It is also important to distinguish and to ask about the gender that an individual may identify as. This may not always be as a binary female. The terminology and use of pronouns can be a difficult maze for the uninformed clinician and a review of the various terms has been published [17].

Trans people may transition with psychological and medical care that requires endocrinology and surgical intervention. For some trans men (i.e. woman to man), there may be a need for chest surgery and hysterectomy. If the individual has not yet decided to progress for phalloplasty, a gynaecologist may be approached, with medical recommendations and support for hysterectomy (and usually oophorectomy). Some women may present to gynaecologists having transitioned from a male gender role. These men and women should be offered the same clinical care as any women whilst recognizing there will be some differences in clinical needs during the post-perioperative care period and in the postoperative anatomy. Once transition has occurred, and where necessary, liaison with the surgeon involved in the gender confirmatory surgery may be indicated but it is not appropriate to access mental health services unless there are relevant clinical indications to do so. On some occasions, the gynaecologist may be the first person with whom a patient may raise the issue of a desire for gender transition (which if towards the male role would be as a trans man). An overview of guidelines for clinical care for trans people is available [18].

Sexual dysfunction

It is important to remember that there will be some women who do not openly share the details of their sexual life or sexual preference, even when asked about it. This can lead to some difficulties when a clinician first hears about a particular preference or practice, especially any that may be outside their own experience. An awareness of different sexual practices, particularly in the area of sexual preference as a normal part of the sexual repertoire for arousal and sexual pleasure, is considered next.

The paraphilias, or sexual preference disorders as listed in section F65 of the International Classification of Diseases (ICD-10), are a group of preferences that were considered outwith 'normal behaviour'. With the increasing acceptance of diversity over recent decades, many of the conditions historically described as 'sexual perversions' are no longer considered such and have been removed from the recent fifth revision of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and many will most likely be removed in the forthcoming revision of the WHO classification system (ICD-11). Although paraphilias have not disappeared completely from DSM-5, there is an attempt to clearly distinguish between the behaviour itself (e.g. receiving of pain for sexual pleasure: sexual masochism) and a disorder stemming from that behaviour (i.e. sexual masochism disorder) [19].

To differentiate between an atypical sexual preference and a mental disorder, DSM-5 requires that, for diagnosis, people with such interests exhibit the following: (i) 'feel personal distress about their interest, not merely distress resulting from society's disapproval'; or (ii) 'have a sexual desire or behaviour that involves another

person's psychological distress, injury, or death, or a desire for sexual behaviours involving unwilling persons or persons unable to give legal consent' [20]. To take the example of fetishism, a fetish is an object or body part that a person must focus on to become sexually aroused and in extreme cases to achieve sexual satisfaction. The reliance on some non-living object as a stimulus for arousal and sexual gratification may arise for a number of reasons. For many people there is experimentation with fetishistic behaviour, which is not a fetish by definition. Numerous sexual aids and 'toys' are easily available from high-street shops and mail order. Some fetishes require no inanimate objects but merely non-genital parts of the body. Preference for the feet or toes (such as sucking the toes of the partner and/or having their own toes or feet licked or rubbed) was the most prevalent fetish by a considerable margin in one recent large study [21].

Likewise, in a study to try to identify 'what exactly is an unusual sexual fantasy', the themes that were most reported by women included an exotic or unusual private place for sex (such as a deserted beach or forest) with a focus on her own submissive behaviour. Around one-sixth of women mentioned involvement of a stranger and around 8% mentioned either homosexual activities or group sex. The themes were very different from those mentioned by men, where voyeurism and fetishism were the highest reported. Clearly, this matter may lead to some difficulties for partners if they were to declare these openly or try to enforce these into the sexual repertoire, especially if they were not negotiated or discussed in advance [22].

Throughout this chapter, no attempt is made to discriminate against any of these sexual choices, and for brevity reference to a partner may be made whilst recognizing that many women may be without a partner at a certain time through preference or otherwise or may have multiple partners.

Psychosocial and psychosexual factors contributing to sexual well-being

The fourth International Consultation on Sexual Medicine (ICSM) convened in Madrid in 2015. The committee reviewing psychological and interpersonal dimensions of sexual function and dysfunction made a number of recommendations that are summarized here for women presenting with sexual problems. Exploration of the attachment style of the woman, her personality, her cognitive schemas, any infertility concerns, and sexual expectations should all be noted. Assessment of depression, anxiety, stress, substance use and post-traumatic stress (and their medical treatments) should be carried out as part of the initial evaluation. Clinicians should attempt to ascertain whether any anxiety or depression is a consequence or a cause of the sexual complaint, and treatment should be administered accordingly.

Assessment of physical and mental illnesses that commonly occur in later life should be included as part of the initial evaluation in middle-aged and older persons presenting with sexual complaints [23]. Further recommendations are to assess multiple aspects of sexual functioning, including, but not limited to, subjective aspects such as sexual self-esteem and sexual satisfaction, not just sexual dysfunction. A developmental approach to assessing the onset of sexual activity is recommended, including self-focused as well as partnered activity ranging from non-genital to genital expressions, the context around those experiences, as well as any associated beliefs and emotions associated with them. Crucially, there should be an attempt to explore their possible role in the individual's current sexual function and behaviour.

Clinicians should explore sensitively childhood experiences including sexual abuse and, if this occurred, its characteristics regarding frequency, duration and whether the perpetrator was known or not.

In addition, a number of life-stage stressors are evident for women, including infertility, postpartum experiences, ageing and menopause, and these can have a specific impact on psychosocial and psychosexual experiences. The prevalence of sexual dysfunction in women reporting infertility was higher than that in the fertile control group in one study using the FSFI questionnaire [24]. The recommendation to clinicians is that during all phases of infertility diagnosis, investigation and management the clinician, whenever possible, assess sexual function and satisfaction.

Approximately half (52%) of women resume sexual activity by 5–6 weeks post partum. However, it is less clear the extent of sexual dysfunction at 2–6 months post partum, with various studies suggesting this affects 22–86% of women (see Brotto *et al.* [23] for full review].

With regards to normal ageing, a survey of 3005 respondents in the USA (ages 57–85) found that the prevalence of sexual activity was 74.8%. Women were much less likely to report being sexually active than men. Half of the women (and half of the men) reported at least one bothersome sexual problem and were concerned about the impact of ageing changes on their sexuality. The most prevalent sexual problems among women were low desire (43%), difficulty with vaginal lubrication (39%), and inability to orgasm (34%) [25].

Stressors and adverse life events that may affect sexual function and satisfaction include sexual experience throughout life, attitudes toward sex, dysfunctional sexual partner, death of partner, sexual performance issues,

impaired self-image, physical or mental fatigue, disturbed family relationships, divorce, physical illnesses and disabilities, need for special care, changes in employment and financial status [23]. A drop in testosterone levels, and increase in cognitive and depression issues with older age may also impact on sexuality. Clinicians should be aware of the relationship between symptoms of ageing and psychological health (e.g. anxiety, irritability, insomnia, memory impairment and depressed mood) in older men, and request further investigation when needed.

Menopausal status has an independent effect on reported changes in sex life and difficulties with intercourse. The results from the Study of Women's Health Across the Nation (SWAN) [26] highlight the importance of including social, health and relationship factors in the context of menopause and sexual functioning. These factors and, in particular, feelings toward one's partner or starting a new relationship have also been identified by others as highly important [27–31]. Similar to a previous study [33], Avis *et al.* [26] found declines in all areas of sexual functioning according to menopause status. Controlling only for age, the Melbourne Women's Midlife Health Project also found greater declines in sexual functioning among 197 women who transitioned from premenopause to postmenopause compared with women who remained premenopausal. Previous sexual function and relationship factors were more important determinants of libido and sexual responsiveness than estradiol level [32,33].

Finally, there are limited data on the impact of sociocultural factors on female sexual function as well as on ethical principles to follow when clinical care falls outside traditional realms of medically indicated interventions. It is recommended that clinicians evaluate their patients and their partners in the context of culture and assess distressing sexual symptoms regardless of whether they are a recognized dysfunction. There are a number of practices with complex ethical issues (e.g. female genital cutting, female cosmetic genital surgery) that may need careful reflection and discussion with the woman and within professional peer supervision for the gynaecologist [34].

Summary box 66.3

- There are a number of aetiological factors that may predispose and perpetuate sexual problems for women.
- Psychological and psychiatric morbidities are commonly associated with all the sexual problems troublesome for women.
- Encouraging women to speak about their problems during consultations may be helpful and in many cases can facilitate further discussion between the couple.

Physical factors contributing to sexual well-being

A substantial number of factors can interrupt the normal process of sexual activity and can be considered as endocrine factors (typically androgens and oestrogens), neurological factors, vascular factors and iatrogenic factors. These will be considered within each section on the various sexual dysfunctions. There are also a number of common gynaecological conditions where interruption to usual sexual function can occur, such as cervical, ovarian and other gynaecological carcinoma, prolapse, incontinence, interstitial cystitis and procedures such as hysterectomy. Dermatological conditions such as lichen sclerosus and eczematous rash can cause a number of sexual problems. Indeed, any life event may bring about a change in mood and well-being that in turn interrupt the opportunity for usual sexual activity and opportunity for pleasure.

At the 2015 ICSM consensus meeting, the expert review of the contribution of hormones, other than oestrogens and androgens, to female sexual functioning and the evidence that specific endocrinopathies in women are associated with female sexual dysfunction (FSD) identified that treating hyperprolactinaemia might lessen FSD. Polycystic ovary syndrome, obesity and metabolic syndrome could be associated with FSD, but data are limited. However, there is a strong association between diabetes mellitus and FSD [35]. Not surprisingly, the overwhelming recommendation of the experts at ICSM is that a biopsychosocial model is used to understand how these factors predispose to sexual dysfunction and that the same model is applicable for effective management thereafter.

Overview of psychosocial and psychosexual interventions

Basic sexual counselling is an integral part of all medical consultations. The clinician should always try to give the patient the opportunity to talk about her own sexuality and to listen actively so that the woman feels accepted and understood and there may follow some emotional relief. During this stage assess the woman's and her partner's concepts and knowledge of sexuality, passion, intimacy, commitment and love. Include here collecting information and details of her sexual biography and usual sexual scripts. Take the opportunity to inform her about the reality of human sexuality and to put the variety of her personal experiences into perspective. Give information about the usual frequency of problems and about differences between female and male sexuality. Encourage communication about her sexual needs with

the doctor and the partner. With knowledge comes empowerment and self-confidence around sexuality.

Education is important to dispel any myths. Some common myths are that a healthy woman always has an orgasm, that sex must lead to orgasm and that masturbation is only for single women. Time can also be used to include suggestions about use of specific sexual positions, such as the female superior position. In certain circumstances suggestions about the use of erotica and the use of specific bibliotherapy may be helpful.

Talking therapies can be helpful if indicated and specialized psychosexual therapy may be offered but this will be dependent on individual training and experience and/or access to trained psychotherapists within the service. Typically, these therapies include body awareness education, cognitive behavioural therapy (CBT) with or without relaxation therapy, couple communication training, sensate focus and, less frequently, psychodynamic individual therapy. These are described in turn.

Body awareness training includes the use of exercises to try at home. These can be provided in both verbal and written format with the opportunity to answer any questions before or after the session. Typically, these include looking at the naked body from all sides in a large mirror (and to compare it with drawings or other photographs); looking at the genitalia using a small hand mirror and exploring the genitalia with the hand; exploring the genitalia for any sensitive areas and trying to identify areas of the body that are stimulating. For this latter exercise the clinician can provide additional guidance such as to try manual stimulation (where, how and how intensive), to increase intensity and duration, to think about using a vibrator and to try manual stimulation in the presence of the partner and then involving the partner. This is probably beyond the scope of a gynaecologist.

CBT involves focusing on individual thoughts, feelings and behaviour and encourages the woman to become aware of irrational beliefs and dysfunctional thoughts. The overall aim of this brief therapy over four to six sessions is to provide help in changing the ways of thinking.

Relaxation work includes making suggestions about how to manage stress, advice on how to relax the body musculature and to recognize the value of exercise in general well-being. Mindfulness therapy may be useful in certain situations for women who are able to use this intervention [36].

Couples relationship psychotherapy has been mentioned in a previous section. There is often a reluctance to involve a partner as the woman feels that the problem belongs only to her, or due to something she has done. Often, the partner may be reluctant to attend sessions, often citing a number of reasons why they cannot attend. A simple reframe of the problem as a shared problem rather than due to the physical pain experienced by the woman or the resultant depression and medication prescribed for the depression. Whilst all of these can be contributory to the sexual dysfunction, a biopsychosocial model prefers to offer a number of explanations for a problem and so offers a number of treatment options and interventions that may include some couples' therapy together.

On some occasions, there may be sexual problems within the partner. In heterosexual partnerships these may include erectile dysfunction or early or delayed ejaculation. Depending on the aetiology, these problems may need to be dealt with alongside any interventions for the woman or the couple.

Sex therapy typically involves sensate focus (Fig. 66.4): this may start as individual work such as a 'growth programme' with genital exploration and touching and moving onto work with a partner if both parties are in agreement. Typically, there is a 'ban on sexual touching and intercourse' during the early stages of the programme. The ability to receive and also to give pleasure will open the opportunity to learn (or relearn) knowledge about the partner and offer opportunities to experience psychological and physical intimacy and to be able to say to each other that they love each other. A carefully tailored programme is usually more helpful than just providing a sheet of instructions that are often read briefly and forgotten between sessions as the detail fails to appreciate the specific circumstances and needs of the women (and her partner).

Individual psychotherapy may consider a number of issues such as of trust, intimacy, closeness, power, control, attraction, boredom and lack of pleasure. When there is evidence of concurrent depression, body image issues, sequelae of sexual abuse, personality or relationship factors, then these matters are often better addressed first with the assurance that if the sexual problems remain, these will be attended to in due course. An experienced sexual and couples' psychotherapist may feel able to continue couples sex therapy work whilst the woman has separate work on these matters with another therapist or clinician as they may take some time to resolve whilst the woman is seeking resolution or improvement to her sexual life.

Summary box 66.4

- There are a number of therapeutic approaches that may be helpful for women with sexual difficulties and dysfunction.
- As there can be multiple sexual problems described during a consultation, careful history-taking can assist the physician in prioritizing interventions to the most likely primary factors.
- Permission giving, educational bibliographies and encouraging playfulness and changes to the sexual script are time-limited interventions that may be appropriate to offer to women (and their partners).

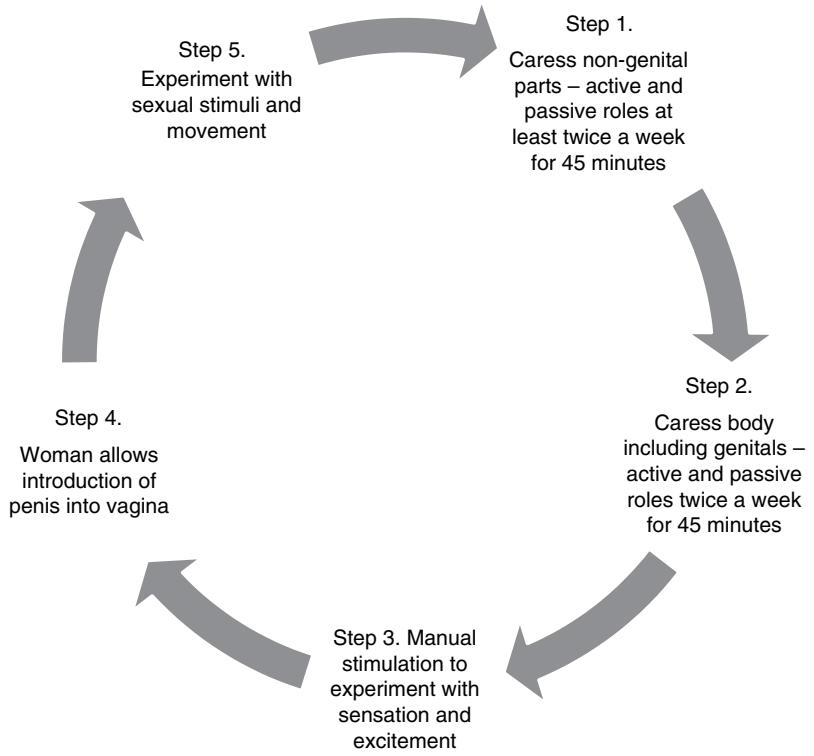

Fig. 66.4 Sensate focus management plan. *Source:* Claudine Domoney. Reproduced with permission of Claudine Domoney.

Table 66.1 Self-help resources.

British Society of Biopsychosocial Obstetrics and Gynaecology (BSBOG): www.bsbog.org
British Society for Sexual Medicine (BSSM): www.bssm.org.uk
College of Sexual and Relationship Therapists (COSRT): www.cosrt.org.uk
Institute of Psychosexual Medicine (IPM): www.ipm.org.uk
Relate – the relationship people: www.relate.org.uk
Sexual Advice Association (SAA): sexualadviceassociation.co.uk

There are a number of useful resources for women that can be accessed online and these are listed in Table 66.1.

Sexual desire disorder

A lack of sexual desire or 'sex drive' has also been termed a lack of libido. In this condition there is a lack of interest in or receptivity to sexual activity or an absence of sexual thoughts or fantasy.

The recent change to the DSM-5 classification system for sexual dysfunctions has combined desire disorder with arousal disorder to create the new diagnostic category of sexual interest arousal disorder for women (but not men). It is uncertain whether the revision to the ICD classification will follow the same direction, although there is considerable resistance to the proposal from many sexologists who consider the two processes to be separate albeit interdependent in many circumstances. The increased rejection of a linear model of sexual arousal was in part the basis for combining both disorders in DSM-5. Other changes of importance in defining a sexual disorder is that almost all DSM-5 sexual dysfunction diagnoses now require a minimum duration of 6 months as well as a frequency of 75–100%. Further, in order to make a diagnosis, the disorder must be deemed to have caused significant distress (the DSM-IV requirement of 'interpersonal difficulty' has been removed) [20].Women presenting with concerns about low sexual interest or desire and who are distressed about the situation will require a careful evaluation to identify the most likely aetiological factors. Medical factors include chronic medical conditions, cardiovascular disease, anaemia, obesity, diabetes mellitus, fatigue and chronic pain. Hormonal disorders include androgen insufficiency, Addison's disease, hypothyroidism and hyperprolactinaemia and it is also a consequence of the normal changes after pregnancy. The effects on sexual desire after bilateral oophorectomy (and surgical menopause) are well documented. Iatrogenic reasons can include

prescribed medications, such as the oral contraceptive and oral hormone replacement therapy (HRT) and tamoxifen (which all bind testosterone) and use of antidepressant or antipsychotic medication, benzodiazepines, thiazides, beta-blockers, cimetidine, steroids and lovastatin. Some psychiatric conditions may cause this problem, including anxiety, depression and substance misuse (including alcohol). Psychological experiences including environmental and life events (including work stressors), previous trauma or abuse can all influence sexual desire as can body image disorder and anorexia nervosa. As with all sexual problems, the desire problem may be secondary to other sexual problems such as dyspareunia or vaginismus. There may be problems with the way couples relate to each other, or their sexual repertoires (or 'sexual scripts') may have become mundane or boring. In some situations, there may be overt relationship problems.

Following a thorough assessment from history-taking, an effective way to exclude affective disorders is to administer the self-completed HAD questionnaire. A specific questionnaire that can be helpful in offering a measure of sexual function is the Female Sexual Function Index (FSFI). This questionnaire score can be used to assist in monitoring changes from clinical care interventions over a period of time.

Physical examination may be indicated by any comorbid conditions such as fatigue, irregular menses, pain, history of trauma or concurrent problems with sexual arousal.

To exclude endocrine disturbance, serum testosterone levels should be measured between day 8 and 20 of the monthly cycle, between 8 a.m. and 11 a.m. If these are low (<0.4 mmol/L), then the calculated free testosterone can be measured by rechecking the testosterone level and by also measuring sex hormone-binding globulin (SHBG) and albumin. The normal calculated free testosterone level is 0.4–0.8 ng/dL. It may also be prudent to measure follicle stimulating hormone (FSH), glucose and thyroid-stimulating hormone (TSH) and thyroid function as clinically indicated.

The clinical management of problems of sexual desire involves a number of options and the appropriateness of such will vary according to the findings from the assessment. Often the most reassuring factor is to normalize these experiences using data such as that available from the Natsal studies.

Herbal remedies are often enquired about by women but there has been no significant benefit identified in any recent reviews of the literature, with the exception of tribulus terrestris trialled in premenopausal married women reporting loss of libido, where a statistically significant increase in all variables, including desire, when compared with placebo (using the FSFI) was reported with only one patient out of 60 reporting any side effects [37].

If there is evidence of endocrine disturbance, tibolone or a trial of testosterone or dehydroepiandrosterone sulfate (DHEA-S) on an off-licence basis may be helpful for menopausal women. Tibolone (Livial) is often classed as a type of systemic HRT. It is a synthetic steroid with similar effects to the female hormones oestrogen and progesterone as well as testosterone. It can improve menopausal symptoms and a lack of sexual desire. Off-label prescription of bupropion is also worth trying in some cases, even in the absence of depressive symptoms.

The International Society for Sexual Medicine (ISSM) published suggested standard operating procedures for a number of sexual problems in 2013 and the reader who is interested in further details is signposted to these as well as to the reports from the ICSM 2015 [38,39]. Specific UK guidelines on the management of sexual problems in women and the role of androgens were published in 2010 [40].

The outcome of therapy is often asked about by patients before investing time and commitment to attend a number of sessions. In the review by Brotto *et al.* [23] for women with desire disorder, a meta-analysis yielded 20 controlled studies, most involving CBT approaches. Overall, a large effect size for the primary end-point of low desire and a moderate effect size on improving sexual satisfaction were reported. CBT approaches can also improve quality of sexual and marital life and sexual satisfaction. Inclusion of the male partner in CBT treatment for low desire yielded better outcomes. Two controlled studies evaluated mindfulness-based therapy compared with a wait-list control group and found that this approach led to significant improvements in sexual desire in women (strong effect size), but the research was limited by the absence of a treatment control group. Based on the meta-analysis showing strong effect sizes, it is recommended that clinicians use CBT in the treatment of women with low sexual desire and mindfulness-based therapy may be helpful. Whenever possible, use of couple- or group-based therapy over individual therapy can be helpful. Unfortunately, there is scant literature on the combination of therapies (psychological and/or biological) for women with any of the sexual dysfunctions.

Sexual arousal disorder

A lack of sexual arousal or not feeling 'turned on' is a lack of response to sexual stimulation, which can be experienced in the mind and/or the body. In the body this may include a lack of vaginal wetness (lubrication) and/or a lack of swelling, tingling or throbbing in the genital area.

Arousal may be categorized as (i) subjective sexual arousal disorder, where physical (genital) arousal can be evident but there is an absence of or markedly diminished

feelings of sexual arousal (sexual excitement and sexual pleasure) from any form of sexual stimulation; (ii) genital sexual arousal disorder; (iii) combined sexual arousal disorder or (iv) persistent genital arousal disorder (PGAD). In the rare condition of PGAD the woman may suffer from a persistent, unwanted and distressing increase in genital blood flow in non-sexual circumstances. It is characterized by involuntary genital and clitoral arousal that persists for an extended period of time and that does not go away following one or more orgasms. The genital arousal is unrelated to subjective feelings of sexual desire, feels intrusive and unwanted, and is usually highly distressing. Management is complex and the reader is referred to a recent review [41].

Aetiological factors for subjective and genital sexual arousal disorder can include medical factors such as chronic medical conditions, cardiovascular disease, diabetes mellitus, neurological disease and connective tissue disease. In postmenopausal women, the consequences of oestrogen deficiency on vaginal transudation is often marked. Iatrogenic factors include prescribed medications, especially antidepressant medications. Lactation may cause symptoms as a consequence of hyperprolactinaemia. Mental health conditions include depression, binge eating disorders and excessive dieting. Psychological issues include a history of previous abuse. Comorbid sexual problems, especially disorders of desire and pain disorders, decreased intimacy or couples' relationship problems, can also cause problems with sexual arousal.

The assessment by history-taking, questionnaires and physical examination are as listed for desire disorder. Useful blood investigations include testosterone, SHBG, free androgen index, FSH, estradiol and lipids. A measure of vaginal pH is easy to undertake during examination for measurement of acidity (normal ≤4.5). The role of specialist investigations is outside the scope of the general gynaecologist.

Treatment interventions will follow many of those listed for desire disorder. It is important to ensure adequate sexual stimulation and this can be emphasized during educational work or sensate focus therapy. Cognitive distraction is a significant contributor to sexual response problems in women and is observed more consistently for genital arousal than for subjective arousal.

Plentiful use of lubricants may be beneficial; KY Warming Liquid, Durex Warm, Durex Tingle, Zestra, Astroglide and Sylk may be useful. Clitoral vibrators may be helpful as can training about pelvic floor exercises (Kegel exercises). The clitoral therapy device Eros-CTD can be used to increase sexual arousal.

If estradiol is low, assessment for local (topical) or systemic oestrogen replacement may be helpful. If the woman wishes to try off-label medications, then after providing information and obtaining informed consent a trial of sildenafil, ephedrine, yohimbine or L-arginine may be helpful. Studies with pharmacological agents continue but are yet to progress to licenced clinical use.

A meta-analysis and a systematic review of outcome of psychotherapy for arousal disorder identified no controlled treatment outcome studies that focused on women with specifically sexual arousal complaints so no recommendations can be made [23].

The ISSM standard operating protocol is available [41].

Orgasmic disorder

When a woman has an orgasm the typical changes observed are increases in heart rate, breathing and blood pressure. The body musculature may tense, especially contraction of the genital and pelvic floor muscles, and a flush may appear on the body. There is then a period of deep relaxation. Some women may achieve multiple orgasms during a period of sexual stimulation. Problems reported with orgasm include absence of orgasm (anorgasmia), infrequent orgasms, delayed orgasm, reduction in the intensity of orgasmic sensations or painful orgasm.

Aetiological factors can include chronic medical conditions (renal or liver disease, etc.), cardiovascular disease, diabetes mellitus, neurological disease as well as the normal consequence of ageing. It is increased in endocrine situations such as post menopause and hypothyroidism. Orgasmic disorders can occur with pelvic floor weakness or damage. They commonly occur as iatrogenic consequences of medications, especially selective serotonin reuptake inhibitors (SSRIs), and are often associated with depression, high alcohol intake and use of illicit drugs. Further factors include previous abuse, age-related factors, social, cultural and religious factors, and comorbid sexual problems especially desire disorder and arousal and sexual pain disorders. Couples script or relationship problems are also associated with this disorder.

In addition to the blood tests noted for desire disorder, liver function tests and vitamin B_{12} and folate levels should be measured to exclude treatable causes of neuropathy.

Specific interventions include individual psychotherapy to consider resolution of unconscious fears about orgasm. CBT can promote changes and attitudes in sexually relevant thoughts. Couples' psychotherapy may focus on issues of trust and safety. Anxiety management may be helpful. Self-exploration work on desensitization of viewing and touching the genitals and guided masturbation exercises can be helpful. Use of vibrators including the 'rabbit', the vibrating condom ring and the Durex Play Wand can be helpful as can the Eros-CTD (alone or alongside sex therapy and sensate focus).

If the woman wishes to try medication, off-label use of bupropion (lower dose), yohimbine, sildenafil, buspirone, ephedrine, bethanecol, cyproheptadine, amantadine and oxytocin (10 IU sublingually) are all reported as valuable in selected cases within the literature or expert opinion. Topical oestrogen or testosterone may be helpful for age-related clitoral involution. The ISSM standard operating procedure guidelines are available [42].

Outcome of therapies has been reviewed by Brotto *et al.* [23]. Most treatment programmes for acquired female orgasm problems include a combination of sex education, sexual skills training, couples' therapy, directed masturbation and sensate focus. In a meta-analysis, there was a moderate effect size for the efficacy of psychological treatments on the primary end-point of anorgasmia and a moderate effect size for sexual satisfaction. In the only study evaluating the specific coital alignment technique, a significantly higher rate of orgasms during intercourse, simultaneous orgasms between partners, and satisfying orgasms was reported. Taken together, CBT is recommended for women with anorgasmia. Although the coital alignment technique is often used for women who wish to become orgasmic during vaginal penetration with intercourse, only one study evaluated the effectiveness of this method so the committee could only provide an expert opinion recommendation on this approach.

Genitopelvic pain/penetration disorder

This diagnosis replaces dyspareunia (pain felt during or after sex) and vaginismus in the previous classification system of DSM-IV. This set of problems often occurs concurrent with vulvodynia and other sexual pain syndromes. Regardless of the cause of the problem, if sex is painful then there is likely to be both physical, emotional and psychological distress.

Vaginismus is a reflexive contraction of the vaginal muscles that prevents vaginal penetration (including associated psychological associations such as trauma and abuse) and is often associated with other pelvic pain conditions. Vulvodynia is a chronic pain syndrome that affects the vulval area, may extend into the clitoris, may be burning in nature and occurs without an identifiable cause. Vulvar vestibulitis syndrome (VVS) is vulvodynia localized to the vulval region.

The aetiological factors can be considered in the following ways.

- Manipulation pain: labial pathology (infection, injury) or clitoral problems (irritation, lesions, hypersensitivity).
- Introital (often erroneously termed superficial) pain: hymenal irregularities, vulvovaginitis (e.g. candidal infection, *Trichomonas*, herpes simplex, atrophy, chemical irritation), Bartholin's cyst/infection, inadequate lubrication (including atrophic vaginitis and arousal disorders, e.g. diabetes mellitus, multiple sclerosis, spinal cord injury), traumatic factors (e.g. episiotomy scar, post radiotherapy), interstitial cystitis, urethritis, large penis size of partner.
- Mid-deep vaginal pain: may be due to a congenital shortened vagina, pelvic inflammatory disease, endometriosis, a fixed uterine retroversion, ovarian pathology, pelvic congestion, uterine contraction on orgasm (sometimes associated with low oestrogen levels), pelvic tumours, surgical adhesions, irritable bowel syndrome or constipation.

Physical examination is mandatory in women presenting with this problem, although this may have to be discussed but delayed from the assessment appointment so that the woman can prepare for the examination, which may be feared from the outset. A chaperone is essential in such circumstances [43].

Some specific interventions include education about anatomy of the vulva with mirror work. This may be helpful alongside use of biofeedback and control of pelvic musculature (including consideration of a referral to physiotherapy for specialist work). Individual therapy may include CBT that considers anticipation of pain, control of sexual encounters, managing any mood disturbance and exploring any history of abuse. Couples' therapy can also include communication training and explicit sharing of information about alternative ways of erotic stimulation and sexual activities that are consensual and enjoyable for both partners. Sensate focus can include self-massage of the vulva, sometimes alongside use of graduated vaginal trainers.

Specific medical interventions can include elimination of any micro-abrasions of the introitus using fluconazole or itraconazole; topical local anaesthetics (lidocaine) or oral agents (e.g. amitriptyline, carbamazepine, gabapentin or pregabalin) can also help manage the pain. The use of Botox for pain management is under review. Liaison with pain management services is often helpful and treatment will often involve regular psychotherapeutic work over many months.

Topical vaginal oestrogen therapy can be helpful for dystrophy, for example Vagifem® (vaginal tablet of estradiol, daily for 2 weeks then twice a week) for 3 months, Estring® (ring containing 2 mg estradiol, lasts for 90 days), Ovestin or Ortho-Gynest cream (estriol); these all require an annual pelvic review. Topical testosterone in oil/jelly (1–2%) can be helpful if there is vulval dystrophy. Topical steroids are useful for lichen sclerosus.

Lubricants such as Astroglide and Yes are helpful. In vaginismus, an oil-based and then a water-based lubricant can be used (unless a condom is used by the partner). Vaginal moisturizers include Replens, Senselle and Sylk.

The ISSM standard operating protocol is available [44].

Conclusions

Sexual problems are common in the general community and evidence suggests that they are more common in women attending gynaecology and obstetrics clinics. Clinicians should be mindful of this and be prepared to enquire about these issues using a sensitive manner and patient-based approach during routine consultations without judgement or embarrassment. Comprehensive history-taking can elicit contributions from physical, psychological and relationship perspectives to allow a biopsychosocial formulation and to propose a treatment plan. An awareness of the various interventions that may be helpful for the woman (and her partner) is valuable and the physician can assist in signposting women to the appropriate healthcare professional(s) if expertise or time does not allow direct support to the woman in the clinic where the issues have been raised and identified as requiring interventions from healthcare professionals.

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67

Rape and Sexual Assault and Female Genital Mutilation

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Sexual violence against girls and women is a significant public health problem across the world, with no country, community or culture immune to it. Whilst both males and females may be subjected to it, for the purposes of this chapter the focus is on female victims.

The Law

The laws around sexual offences differ from country to country. The Sexual Offences Act 2003 (England and Wales) applies to offences committed in England and Wales after 1 May 2004. Prior to that, the Sexual Offences Act 1956 would apply. The 2003 Act covers numerous different offences including the following.

Section 1 (statutory definition of rape)

1) A person (A) commits an offence if:
   a) he intentionally penetrates the vagina, anus or mouth of another person (B) with his penis,
   b) B does not consent to the penetration, and
   c) A does not reasonably believe that B consents.
2) Whether a belief is reasonable is to be determined having regard to all the circumstances, including any steps A has taken to ascertain whether B consents.

Section 5 (statutory definition of rape of a child under 13 years)

1) A person commits an offence if:
   a) he intentionally penetrates the vagina, anus or mouth of another person with his penis, and
   b) the other person is under 13 years.

Sexual activity with a child under 16 is an offence, including non-contact activities such as involving children in watching sexual activities or in looking at sexual online images or taking part in their production, or encouraging children to behave in sexually inappropriate ways.

Prevalence

A recent systematic review [1] reported that the global lifetime prevalence of intimate partner violence among ever-partnered women is 30.0% (95% CI 27.8–32.2) and the global lifetime prevalence of non-partner sexual violence is 72% (95% CI 5.3–9.1).

Reports from England and Wales [2] show that around 1 in 20 females (aged 16–59) reported being a victim of a most serious sexual offence since the age of 16. Extending this to include other sexual offences, such as sexual threats, unwanted touching or indecent exposure, increased the figure to one in five females reporting being a victim. The Crime Survey of England and Wales 2013 recorded that 2% of women and 0.5% of men had experienced some form of sexual assault (including attempts) in the previous year. The majority of victims do not report their abuse to the police.

Presentation

Given the high prevalence, it follows that any clinician having regular contact with patients will frequently encounter victims of sexual violence. Given the reluctance of most victims to disclose their abuse, the chances of the doctor discovering this important aspect in the medical history will be heavily dependent on an awareness of the scale of the problem, its potential sequelae, a natural curiosity and utilization of superior communication skills. The extent to which a patient may reveal details of abuse/violence will depend on issues particular

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

to them, the setting and the degree of confidence they have in the clinician to respond appropriately with the information. Creating an environment conducive to disclosure and a workforce that can then cope is key.

Presentations may be acute or historical. There may be a direct disclosure or the victim may present with issues secondary to the assault, such as unintended pregnancy, dyspareunia, anxiety and depression, without volunteering that they have been assaulted. The potential long-term health consequences are considerable as illustrated in Fig. 67.1.

Where a patient has either made a disclosure or the clinician has a high degree of suspicion that it has happened, a number of issues must be considered.

- What needs the patient may have (Table 67.1):
  - Medical
  - Forensic
  - Psychological
  - Social/practical
  - Safeguarding.
- What legal/statutory duties the clinician may have, such as:
  - Safeguarding referrals
  - Female genital mutilation reporting.
- What are the options for the patient and what are their ideas, concerns and expectations?
- What resources are available to assist (the patient and the clinician) and how might they be accessed?

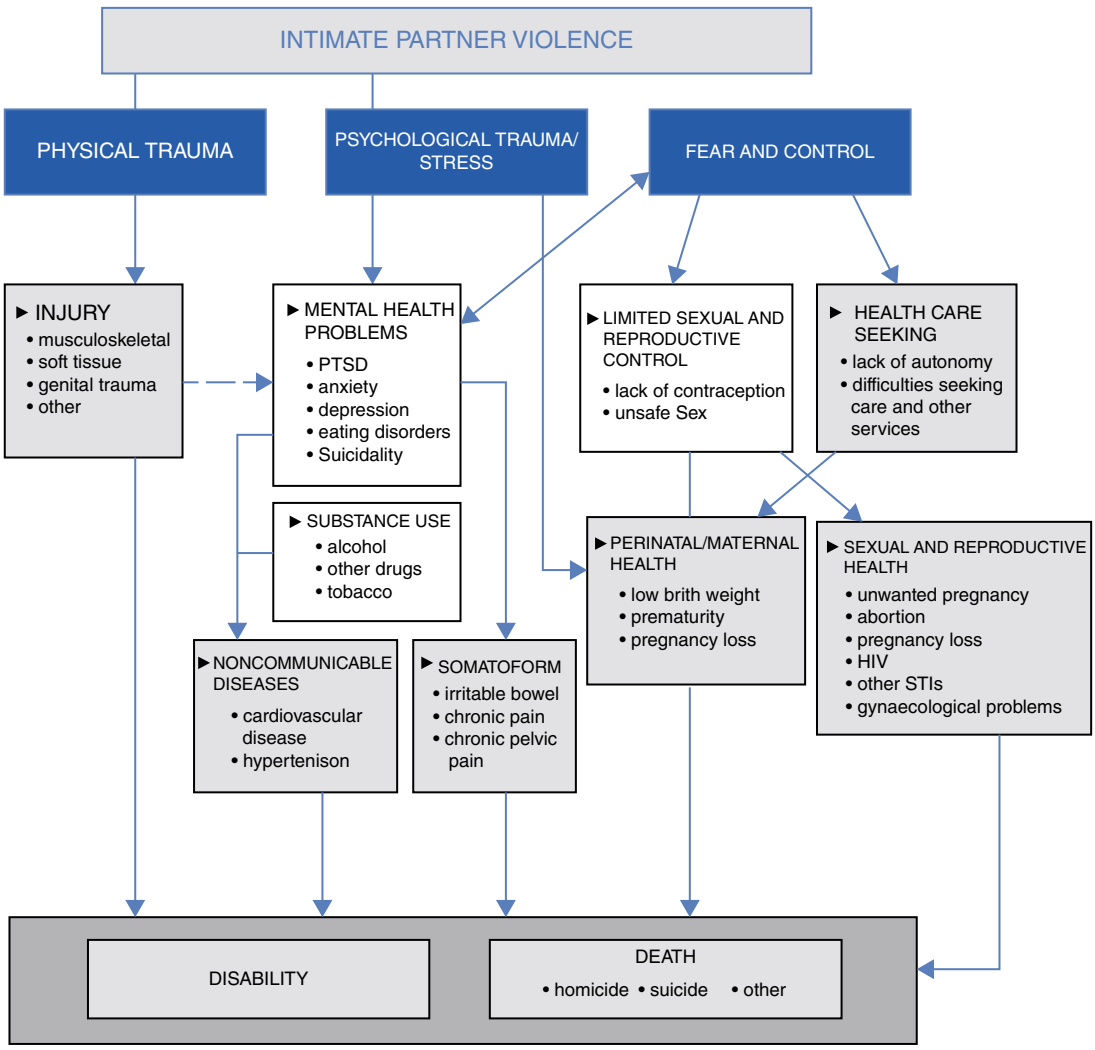

Fig. 67.1 Pathways and health effects of intimate partner violence. *Source:* World Health Organization. *Global and Regional Estimates of Violence Against Women: Prevalence and Health Effects of Intimate Partner Violence and Non-partner Sexual Violence*. Geneva: WHO, 2013. Reproduced with permission of the World Health Organization.

Table 67.1 Things to consider when someone discloses rape or sexual abuse.

Immediate safety
Are they safe now?
Are they at risk of domestic violence, honour-based violence?
Are they safe to go home?
Are there any third parties to consider, e.g. children, other dependants?
Are any safeguarding referrals required?
Are you safe?
Legal and ethical considerations
Do they have capacity to make decisions for themselves?
What are the limits to confidentiality?
Is there a statutory duty to report?
Are there any child protection or vulnerable adult concerns?
Are there public interest considerations?
What information sharing is warranted?
Medical needs
Injuries, assessment and treatment
Emergency contraception
HIV PEPSE
Hepatitis B PEPSE
Screening for sexually transmitted infections
Pregnancy testing
Forensic needs
Preservation of evidence
Documentation of injuries, including photography where necessary
Documentation of allegations
All to be done in a manner that makes evidence admissible to court
Psychological needs
Of the complainant (including risk of self-harm, suicide)
Of other witnesses
Of you

PEPSE, post-exposure prophylaxis following sexual exposure.

The clinician will need to have an understanding of the ethical issues involved in assessing a patient's capacity to make decisions, the possible limitations of confidentiality, and the potential competing duties to the patient, others possible at risk from the perpetrator and public interest. The clinician must be able to communicate all the above in a manner that allows the patient to feel empowered and start the process of regaining autonomy.

Many of these cases are complex and often made even more so by the high level of emotion that they can generate. Ideally, patients should be referred to a sexual assault referral centre (SARC) which will have the staff, including forensic physicians, with the knowledge, experience and skills to deal with these cases, providing a holistic response with ongoing support. That said, all clinicians need to be able to provide a safe initial response and have an understanding of the immediate and long-term medical issues as victims may present in a myriad of ways.

Summary box 67.1

- Sexual violence is common.
- Sexual violence may lead to multiple physical and mental health problems.
- Because of a reluctance on the part of victims to disclose abuse, clinicians need a high index of suspicion.

Management of a victim who presents acutely

Sexual violence is about control. During an assault a victim has no control over what happens to them. An important element of aiding recovery is to offer back control as soon as possible. This is best done by going at their pace, offering them information and outlining their options, and avoiding a paternalistic approach. Where possible the patient should be offered a choice of gender regarding healthcare workers. In all cases a chaperone should be used.

Capacity and consent

As with every patient encounter, the clinician has a duty to consider whether the patient has the capacity to make decisions. Whilst sexual violence can happen to anyone, there is a high preponderance of victims who are particularly vulnerable, by way of risk factors such as learning disabilities, mental health problems, and alcohol and substance misuse. Many may have a history of prior abuse, such as child abuse or domestic violence. For this reason extra care must be taken considering mental capacity.

The definition and assessment of, and responsibilities in relation to, capacity (also known as mental capacity) in England and Wales are laid out in the Mental Capacity Act 2005, which applies to all adults aged 16+. The Mental Capacity Act 2005 defines capacity as the ability to make a decision. It relates to the *process* of making a decision and not to the *outcome* of the decision. It is not limited to medical decisions, but can apply to any decision-making process (e.g. financial or social choices).

Capacity is task-specific: a person may be capable of deciding one issue but not another. Capacity is also time-specific: a person's capacity may alter with time. The Mental Capacity Act 2005 defines the lack of capacity as follows: if, at the time the decision needs to be made, patients are unable to make the decision because of an 'impairment of, or a disturbance in the functioning of, the mind or brain', they are deemed incapable. The term 'capacity' was previously used interchangeably with the

term 'competence'. Since the Mental Capacity Act 2005, 'capacity' is the preferred term.

The Mental Capacity Act 2005 lays out five statutory principles.

1) A person must be assumed to have capacity unless it is established that he lacks capacity.
2) A person is not to be treated as unable to make a decision unless all practicable steps to help him or her to do so have been taken without success. (This includes communicating in an appropriate way. In forensic practice the clinician may need to arrange for interpreters or signers to be present or use visual aids.)
3) A person is not to be treated as unable to make a decision merely because he makes an unwise decision.
4) An act done, or a decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his best interests.
5) Before the act is done, or the decision is made, regard must be had as to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person's rights and freedom of action.

Healthcare professionals are warned that a person cannot be judged to lack capacity simply because of age, appearance or behaviour.

Assessment of capacity

All adults are presumed to have capacity unless there is evidence to the contrary. In order to assess someone's capacity to make a valid treatment decision, two criteria have to be considered.

1) Do they have an impairment of mind or brain (temporary or permanent)?
2) Does the impairment mean that the person is unable to make the decision in question, at the time it needs to be made?

Where it is concluded that a patient does not have capacity to make the decisions in question, then an assessment of what is in their best interests should be made. Section 4 of the Mental Capacity Act 2005 contains a checklist of factors. The Code of Practice is available at https://www.gov.uk/government/publications/mental-capacity-act-code-of-practice

The Mental Capacity Act 2005 clarifies within the fourth statutory principle that any decision made, or any act performed on behalf of a person lacking the mental capacity to consent to the arrangements must be undertaken in that person's 'best interests'. Given the wide range of potential decisions covered by the Act, the term 'best interests' is not defined in the legislation. However, the Code of Practice provides, in Chapter 5, guidance on how to determine the best interests of a person who has been assessed to lack mental capacity to make the decision themselves. Using the best interests checklist as provided in Chapter 5 of the Code of Practice, the following factors need to be taken into account in determining the best interests of a person lacking capacity. In brief these comprise the following.

- Encourage participation.
- Identify all relevant circumstances.
- Find out the person's views.
- Avoid discrimination.
- Assess whether the person might regain capacity.
- If the decision concerns life-sustaining treatment:
  - Not to be motivated in any way by a desire to bring about the person's death. They should not make assumptions about the person's quality of life.
- Consult others.
- Avoid restricting the person's rights.

All the above should be taken into account, weighing up these factors to work out what is in the person's best interests.

Summary box 67.2

Sexual violence takes away power and control from the victim. Healthcare professionals can assist in addressing this by respecting the autonomy of the patient. Careful assessment of capacity and consent is vital.

History

The level of detail required in the history-taking will be dependent on the circumstances. For example, if the patient presents to a primary care clinician and there is a local SARC that the patient consents to be referred on to, then the history-taking can be limited to cover the immediate urgent needs (see Table 67.1). In broad terms, the history-taking should cover both the forensic and medical elements of the assessment (Table 67.2).

All clinicians should be mindful of the forensic aspects of the encounter and be aware that their notes are likely to form part of the evidence in any subsequent criminal justice process. Consequently, they should consider the following.

- Record keeping should be accurate, clear and contemporaneous.
- Consider what questions to ask and why. How might any information gained be relevant to the task at hand?
- Use open-ended rather than closed questions as much as possible and record responses verbatim.
- Go at the pace of the patient.
- Use language that the patient can understand.

Table 67.2 History-taking in sexual assault cases.

In broad terms questions will cover:	Examples of some of the reasons why they should be asked:
What has happened?	The nature of the assault will influence: • Assessment of need for emergency contraception • Prophylaxis in terms of blood-borne viruses such as HIV and hepatitis B • Where injuries may be found • Where forensic samples may be sought • Sites for screening for sexually transmitted infections • Subsequent criminal charges
When did it happen?	Again this will influence medical treatments such as emergency contraception, post-exposure prophylaxis, the need for forensic samples and the interpretation of subsequent results
Who was involved?	This will be of relevance to the criminal justice process. For example, where the abuser is alleged to be a child is likely to be approached differently from an adult suspect, especially where the adult is a person in a position of custody, care or control It will also influence the risk assessment of the need for HIV and hepatitis B post-exposure prophylaxis, for example a suspect who is known to be from an area with a high endemic level of HIV
Where did it happen?	This may assist in the criminal investigation. It may assist in the interpretation of injuries (or absence of injuries), for example a recent assault in a wooded area, or the importance of fibres detected on clothing
How did it happen?	This may include details such as threatened or actual violence and assist in injury interpretation (or absence of injury) Was this a drug-facilitated assault? Was there a particular modus operandi that may assist investigations?

- Explore the patient's ideas, concerns and expectations.
- Be non-judgemental in both attitude towards the patient and records made.
- Keep objective findings distinct from subjective opinion.
- There will be forensic as well as therapeutic aspects.

The history-taking will need to be modified depending on the circumstances of each case. For example, where child sexual exploitation is a possibility, the history should cover associated risk factors such as missing from home, school truancy, power imbalance in the relationship (see *Spotting the Signs: A national proforma for identifying risk of child sexual exploitation in sexual health settings* [3]).

Systems review

It is good practice to carry out a systems review as part of the history-taking. This should bring to light any problems that are a result of the sexual violence or that predate the sexual violence and may have a bearing either on examination findings or ongoing welfare of the patient.

Summary of key areas to be covered in the history

- Who gave the information and who else was present?
- History of alleged assault.
- History of actions since (such as washing, changing clothes).
- Medical history, past and present.
- Drugs and alcohol history.
- Past obstetric and gynaecological history.
- Bowel history.
- Social history.
- Discrepancies in account.
- Revisit the history if the examination findings indicate this would be helpful.
- Ongoing at-risk issues:
  - Children and adults.
  - Dependents of complainant.
  - Others at risk from alleged assailant.

Examination

As with the history-taking, the examination will have forensic as well as medical/therapeutic elements, and often there is an overlap (Table 67.3). Prior to commencing the examination, carry out the following.

- Explain to the patient what you wish to do, why you wish to do it and that you will explain any findings at the end.
- Recheck that you have consent to continue (remembering that consent is an ongoing process).
- Reassure the patient that they can halt the examination at any time.
- Ensure that a chaperone is present.

Table 67.3 Purpose of a forensic medical examination.

Therapeutic component	Forensic component
• Check for injuries or conditions that may need medical attention • Holistic assessment, particularly in child cases where other forms of abuse, apart from sexual, need to be considered • Identify medical conditions that may be mistaken for injuries • Consider and conduct risk assessment for possible medical needs: – Emergency contraception – Pregnancy testing – Post-exposure prophylaxis for blood-borne viruses, e.g. HIV and hepatitis B – Screening for sexually transmitted infection – Suicide/imminent self-harm risk	• Identify and document injuries, findings, etc. that may be of forensic significance • Identify findings, positive or negative, that may be of significance to aid the court in establishing the veracity or otherwise of any allegation • Gather forensic samples

- Ensure privacy with no unnecessary people present and no interruptions.
- Go at the pace of the patient; explain the process as you proceed using language they can understand.

The examination should be holistic, top to toe, starting with a general body examination before proceeding to an anogenital examination. Use a proforma as an aide memoire if possible. Document findings in the written notes as well as using body diagrams where necessary. Record negative as well as positive examination findings. If any aspect of the examination is not done, record this carefully as well as the reasons why. Objective findings should be clearly separated from subjective opinion.

Summary box 67.3

The history-taking and forensic examination should cover the medical, psychological and forensic elements of the assessment. It should be tailored to the circumstances of the case and done in a sensitive manner, taking into account the holistic needs of the individual.

Checklist for examination

Whilst the scope of the examination will depend on the circumstances of each case, it should be detailed and thorough (Table 67.4). The clinician's findings may be key witness in a subsequent legal process and accuracy and objectivity are therefore necessary.

Mental health examination

Every examination should include at least a brief assessment of the psychological state of the patient. The reasons for this include detection of conditions that might make the individual:

- more vulnerable to being a victim of sexual assault;
- more likely to have a history of sexual assault as a manifestation of a mental illness;
- demonstrate mental illness as a result of being a victim of sexual assault, e.g. post-traumatic stress disorder;
- at increased risk of imminent self-harm including suicide.

Table 67.5 outlines the key features of the mental health assessment. The clinician should consider the risk of imminent self-harm/suicide. Suicide risk assessment can be explored using a number of questions. Some, where answered in the affirmative, indicate a higher degree of risk (Table 67.6).

Summary box 67.4

- The examination needs to be thorough but done in a sensitive manner, with frequent checking that the patient is content to proceed.
- Sexual violence victims are at risk of self-harm and suicide and therefore all assessments should screen for this.

Anogenital examination

This is usually done after the general body examination. Again, recheck consent prior to proceeding. Go at the patient's pace and be as gentle as possible. Use of a colposcope for magnification and as a light source is often helpful. Images can be recorded as long as due regard is given to issues of consent, confidentiality and security of the images. This is not something to be undertaken

Table 67.4 Checklist for examination.

Examination component	Examples of possible features to note (this is not an exhaustive list)
1 Gait	Normal or not?
	Possible signs of intoxication, developmental problems or mechanical problems such as osteoarthritis
	Use of aids, such as wheelchair, walking stick
2 Sensory problems	Eyesight: wearing glasses
	Hearing aids
3 Clothing	Is it clean, appropriate for weather conditions?
	Any evidence of damage, e.g. torn
	Any evidence of trace material, e.g. body fluids, vegetation
4 Demeanour	Brief factual description of how patient seemed, e.g. weepy, quiet
	Take great care with choice of words. Keep descriptions objective rather than subjective
5 Signs of intoxication	For example: • Smell of breath, e.g. ketones • Blood-shot conjunctiva • Nystagmus • Slurred speech (Note: medical conditions such as hypoglycaemia or head injury may mimic or even coexist with intoxication)
6 Height	Use standardized approved equipment
	Record in metric with shoes off
7 Weight	Measure during examination rather than self-reporting by patient
	Minimal clothing to be worn
	Record in metric
8 Jewellery	Broad description rather than minute detail unless seems relevant, e.g. possible injuries associated
	Record if any jewellery absent, e.g. earring missing
	May possibly be a good source of forensic trace material, e.g. swabbing around a piercing where body fluids may have collected
9 Body markings, e.g. scars, tattoos, track marks	These may or may not be relevant to the alleged assault and it is unlikely that the doctor will know at the time of the examination. Either way they should be recorded in accordance with local policy on recording such information
10 Mental state	Document if alert, orientated in time, place and person
	If there seem to be any issues be prepared to examine and document in more detail
	See separate section on Psychological state examination
11 Hair	Is any hair missing, e.g. pulled out in the assault?
	Are there signs of infestation, e.g. with possible neglect?
	Look for debris, foreign hairs, fibres, etc.
	If hair samples are being taken at a later stage for toxicology (e.g. in suspected DFSA), document current colour, length, etc.
	If any hairs are found that may belong to possible assailant, document details of (and possibly sample) patient's hair
	See FFLM Forensic Guidelines for more details (www.fflm.ac.uk)
12 Scalp	Evidence of injuries including swelling or tenderness
13 Ears	Evidence of injuries including behind the ear
	Look for signs of perforated tympanic membrane where a history of direct blow to ear
14 Eyes	Injuries as a result of direct trauma or petechial haemorrhages from increased pressure, e.g. from strangulation
	Evidence of intoxication
	Evidence of alerted consciousness, head injury

(*Continued*)

Table 67.4 (Continued)

Examination component	Examples of possible features to note (this is not an exhaustive list)
15 Face	Evidence of injuries
	Body fluids, e.g. dry saliva from kissing, licking, biting
16 Mouth	Evidence of injuries
	Look especially for bruising on inner aspects of lips where pressure applied to outer aspect of lips has pressed them against the teeth
	Roof of mouth, especially if a history of forced oral sex
	Injuries to frenulae, especially in children
	Evidence of infection
17 Teeth	Absence of teeth due to trauma
	Dental health in cases of possible neglect
	Where bite marks present, may have to exclude possibility of them being self-inflicted
	Trace evidence (patient may have bitten alleged assailant and have trace material between teeth)
18 Neck	Injuries, in particular bite marks, love bites, bruising or swelling from strangulation
	Trace material
	Problems with swallowing
	May need to organize X-ray to exclude fracture to hyoid after strangulation
18 Nails	Length
	Presence of forensic trace material
	Missing nails (including false)
19 Upper limbs	Evidence of injuries
	Trace material
	Track marks from injecting drugs
	Scars
	Self-inflicted injuries (old or new)
	Right or left handedness
	Range of movement of joints
20 Axillae	Hair growth (as part of developmental assessment if appropriate)
	Injuries (especially bruising consistent with fingertip) if person carried/dragged
21 Breasts	Evidence of injuries
	Trace material, e.g. dry saliva from licking or kissing
	Piercings
	Tanner stage (if developmental assessment appropriate)
22 Anterior chest wall	Evidence of injuries
	Heart and chest auscultation if appropriate
23 Back	Evidence of injuries
24 Buttocks	Evidence of injuries
25 Legs	Evidence of injuries
	Restriction in range of movement of joints
26 Feet	Evidence of injuries
	Obvious trace material
27 Abdomen	Scars, masses, discomfort, etc.
	Extent of examination to be guided by the history

Table 67.4 (Continued)

Examination component	Examples of possible features to note (this is not an exhaustive list)
28 Genitalia	Position examined in
	Lighting and equipment used
	Tanner stage if applicable
	General features
	Discharge or bleeding present or not
	See Anogenital examination
29 Anal examination	Note examination position and lighting
	Injuries, tone, discharge, bleeding, etc.
	Perianal skin health
	See Anogenital examination
30 Neurological	Learning difficulties, associated communication difficulties
	Weakness, etc.
31 Musculoskeletal	Joint problems
	Mobility difficulties
32 Skin in general	Evidence of injuries
	Skin disease
	Trace evidence
	Scars, tattoos, etc.
	Colour
33 Where appropriate: (a) Cardiovascular and respiratory examination (b) Developmental examination	(a) Routine in young child examinations. In adolescents and adults, tends to be reserved where there is concern for immediate health (b) Routine for young children

DFSA, drug-facilitated sexual assault; FFLM, Faculty of Forensic and Legal Medicine.
Source: White [4].

Table 67.5 Mental state assessment.

Appearance and behaviour	General appearance	Grooming and hygiene
		Chronological and apparent age
		Physical deformities
		Height and weight
	Facial appearance	Expression
		Flatness of expression
		Dilated pupils, sweating, etc.
	Movements	Mania: may be restless, rapid and pressured movements
		Anxiety, may be tremulous and restless
		Depression: may be slow and ponderous and in extreme cases immobility and mutism (stupor)
	Social interaction	Over-familiar behaviour suggestive of mania
		Social withdrawal is associated with depression, dementia and schizophrenia
		Social disinhibition may be found in dementia and organic brain disease, e.g. frontal lobe disorder

(*Continued*)

Table 67.5 (Continued)

Speech	Volume	May be loud with mania, quiet with depression
	Spontaneity	May be delayed in depressive disorder or even absent (mutism)
		Manic patients may be uninterruptable
	Rate	Decreased in depression
		Increased in mania
	Amount	Decreased or absent (mutism) in depression
		Increased in mania
	Continuity	Loosening of associations (speech lacks logical connections, word salad)
		Flight of ideas with mania
Mood and affect	Mood is how a patient feels most days	Low or elated
	Affect is how they feel at a given moment	Labile, inappropriate
Thinking	Form	Preoccupations, including suicidal ideas. The patient can terminate these thoughts if desired
		Obsessive thoughts. These are intrusive. The patient may try to resist them. They may be distressing to the patient
		Delusions. A false belief which is both culturally unconventional and held on inadequate grounds. May be difficult to elicit as the patient either does not view them as unusual or is suspicious of the interviewer
	Content	Paranoid, persecutory or grandiose. Ideas of reference. Confabulation
		Depressive, relating to past, present or future
		Always check for suicidal content
	Flow	Flight of ideas, skipping from one topic to another in fragmented, often rapid fashion
		Perseveration: involuntary repetition of the answer to a previous question in response to a new question
		Loosening of associations
		Thought block: a sudden interruption of thought or speech
	Possession	Thought insertion, withdrawal and broadcasting are part of Schneider's first rank symptoms of schizophrenia. The patient believes that an outside agency is responsible for these events
Perception	Awareness of information from the sense organs	Illusions or distortions. These are perceptual errors or misinterpretations. Common in delirium
	Hallucinations	This is a false perception, i.e. without external stimulus. Common in schizophrenia
	Depersonalization and derealization	Subjective feelings of altered reality. May be associated with anxiety and depression
Cognition	Orientation	Orientation to time, place and person should be assessed. Patient should be asked: day, date, month and year; where he or she is; and if he or she knows who he or she is
	Concentration	Serial 7s: subtract 7 from 100 and keep subtracting 7, or spell 'world' backwards
	Memory	Short- and long-term memory should be assessed
	Intellectual ability	Ask about some recent events. Intelligence can be gauged by language. The patient can be asked to do some simple arithmetic tasks and literacy should be assessed
Judgement and insight	Insight	Assess if the patient is aware he or she has a problem, and his or her level of understanding of this
	Judgement	Assess the patient's capacity to behave appropriately. A hypothetical situation can be presented and the patient asked how he or she would behave

Table 67.6 Suicide risk assessment (high-risk indicators are in bold).

1) Do you have thoughts about harming yourself?
2) Are you thinking about suicide?
3) Do you have a specific plan to kill yourself?
4) **What methods have you considered?**
5) Do you have access to any of these methods?
6) **Do you have a date or place in mind?**
7) Have you ever self-harmed or attempted suicide in the past?
8) **Has anyone in your family died by suicide?**
9) Are you suffering from mental health problems?
10) **Have you suffered from mental health problems in the past?**
11) **Have you ever had contact with mental health services or seen your family doctor/general practitioner in relation to psychological or psychiatric problems?**
12) **Are you taking any medication for mental health problems?**
13) **Do you have a problem with drugs or alcohol?**
14) **Have you been drinking in the past few hours?**
15) **Are you experiencing particular difficulties in your life or struggling to deal with difficult past events (e.g. bereavement, divorce, running away from home)?**
16) **Do you have friends or family you can turn to for help?**
17) Do you feel that the future is hopeless and that things cannot improve?

lightly. Advice can be found in the document 'Guidance for best practice for the management of intimate images that may become evidence in court' [5].

Injuries

Whilst the majority of victims will have no injuries, any injuries must be documented accurately. The classification of injuries is as follows.

Bruise

- Due to blunt force.
- May not appear immediately.
- Under force of gravity may appear at a site distant to site of original trauma.
- Difficult to age.
- May also be called ecchymoses, contusion, haematoma.

Abrasion

- Superficial disruption of surface epithelium.
- May bleed.
- Do not extend or gravitate.
- Non-medical terms are graze or scratch.
- Document signs of healing, e.g. fresh bleeding, scab formation.

Laceration

- Full-thickness split of the skin caused by blunt trauma.
- Irregular edges and irregular division of tissue planes.
- Tissue bridges including blood vessels and nerves may be visible.
- May have abraded bruised margin.
- May contain debris.
- Often bleed.

Incision

- Due to sharp objects breaching the epithelium.
- Sometimes known as cuts.
- Edges tend to be straight with no associated bruising or abrasion.
- Tissues are cut in same plane, with nerves and blood vessels cleanly divided.
- May bleed profusely.

Burn

- Heat or chemical.
- Cigarette burns are a particular type of injury associated with abuse.

Documentation of an injury should include the following.

- Type of injury.
- Size.
- Shape.
- Depth, if possible (e.g. laceration).
- Edges, e.g. abrasion: is skin at one end?
- Laceration: is there debris or a foreign body contained in it?
- Colour: red, purple. Does it blanche with pressure? If a bruise, is there any yellow?
- Surface covering: dry or wet blood, scab, dirt.
- Swelling.
- Tenderness.

Anogenital injuries

From a medical perspective anogenital injuries tend to be minor, require little in the way of treatment and will heal rapidly, often within days. They must be considered when assessing the risk of blood-borne viruses and the need for prophylaxis. From a forensic perspective, an understanding of genital injury rates, type of injury, site and healing may assist the clinician to interpret the findings in the context of the allegations that have been made.

There are many myths and misunderstandings regarding anogenital injuries and rape and the clinician has a duty to dispel these.

Virginity testing and the myth of the intact hymen

Doctors may be asked to undertake 'virginity tests' on some girls and women. As the scientific evidence shows that it is not possible to determine with accuracy whether

or not there has been penile penetration of the vagina, *doctors should not attempt to do so*.

There are numerous issues with virginity tests.

- They have no scientific validity. A female may have been sexually active and still have an 'intact' hymen (one study of 36 pregnant adolescents showed that 34 of 36 had an 'intact' hymen [6]). Equally, a female may have some disruption to the hymen as a result of non-sexual trauma.
- They are demeaning, degrading and humiliating to the patient.
- They have significant negative social, physical and psychological impacts on the patient.
- They encourage inequality in terms of biased surveillance and control of female activity including sexuality whilst ignoring male activity.
- They treat the female body as the property and responsibility of her family and community.
- They do not address male behaviour.

Non-fatal strangulation

It is not uncommon for victims of domestic violence and sexual violence to have been subjected to strangulation. This may not necessarily be a prominent part of the history and the clinician should be proactive in seeking this information. Figure 67.2 shows the signs and symptoms of strangulation. Particularly in the context of domestic violence, it is a risk factor for subsequent homicide.

Forensic samples

There will be a number of elements to consider when deciding on the urgency of a medical examination (Table 67.7). Depending on the nature of the allegations and the time from assault to examination, forensic samples may be indicated. These would usually be taken by a forensic physician in examination conditions that minimize the risk of DNA contamination. The Faculty of Forensic and Legal Medicine has produced guidance on this which is updated every 6 months [7].

For any forensic samples to be admissible as evidence in a criminal investigation, there needs to be a clear *chain of evidence*. This is the documentation that follows any piece of evidence, from its initial retrieval up to its use in a court case. It should say what the evidence is, its source, the time and date it was taken, by whom and where and how it has been stored since.

Emergency contraception

For many female victims of rape a real concern may be the risk of pregnancy. Clinicians should undertake a risk assessment for this at the earliest opportunity and it may influence the decision regarding the timing of a medical examination given that, if required, there are time limits regarding efficacy. Guidance on emergency contraception can be found at the website of the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists (www.fsrh.org).

Post-exposure prophylaxis following sexual exposure

Sexually transmitted infections including HIV and hepatitis B will be a risk for some patients as a result of the sexual assault. An individual risk assessment which takes account of the nature of the assault and details of the alleged assailant needs to be done in a timely manner. This will inform the decision as to whether or not the patient would benefit from post-exposure prophylaxis.

$$\text{Risk of transmission} = \text{risk that source is positive} \times \text{risk of exposure}$$

Time is of the essence as commencing HIV post-exposure prophylaxis is not generally recommended more than 72 hours after the assault.

The British Association for Sexual Health and HIV (BASHH, www.bashh.org) produces useful guidelines on prophylaxis after sexual assault [8]. Advice from an HIV physician should be sought where there is any uncertainty or complicating factors, such as the patient is a child, pregnant or breastfeeding.

For hepatitis B, a risk assessment is also required. Here the time frame for commencing is a more generous 6 weeks. Usually an accelerated or a super-accelerated course is recommended. In cases where the assailant is known to be hepatitis B positive, then hepatitis B immunoglobulin may be offered.

Screening for infection post assault

As a general rule, the usual advice for screening time frames is as follows.

- Bacterial infections: 2 weeks.
- Blood-borne viruses: 3 months.

Safeguarding

As previously stated, the clinician should consider whether or not the case highlights any safeguarding issues, not only for the patient presenting, but also for their dependents or other vulnerable people, for example where the patient is from a care home and the alleged assailant is a care worker in the home. Local safeguarding

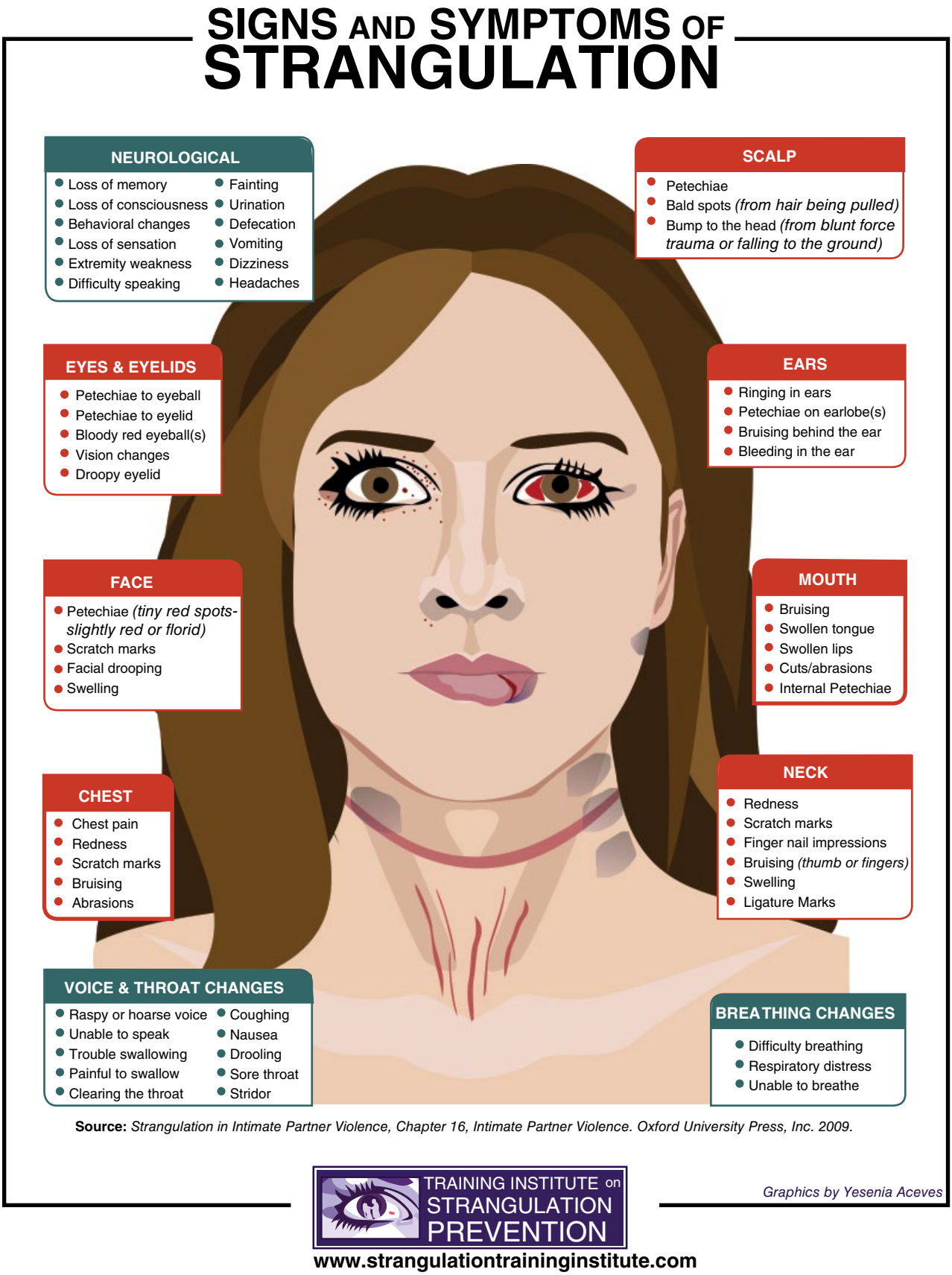

Fig. 67.2 Signs and symptoms of strangulation. *Source:* Alliance for HOPE International. Reproduced with permission of Alliance for HOPE International. (*See also colour plate 67.2*)

Table 67.7 Key time frames to consider.

Emergency contraception	Levonelle	A single oral dose of 1.5 mg as soon as possible after UPSI and within 72 hours
	Ulipristal	One tablet, orally, as soon as possible, but no later than 120 hours after UPSI
	Copper IUD (intrauterine device)	Up to 5 days after ovulation
PEPSE	HIV	Immediately, within 72 hours
	Hepatitis B	Up to 6 weeks
Forensic samples These should all be done immediately, check www.fflm.ac.uk for latest updates. Different time frames apply to some samples for prepubertal children. Times shown here are maximum rather than expected persistence	Mouth	2 days
	Female genitalia	7 days (12 hours if digital penetration)
	Male genitalia	3 days
	Anal swabs	3 days (12 hours if digital anal penetration)
	Urine for toxicology	3 days (14 days if drug-facilitated sexual assault suspected)
	Blood for toxicology	3 days
	Skin	7 days
Injuries	Most rape victims will have no or very few injuries. Some of the injuries that can be very significant forensically may be very minor in nature and heal rapidly, i.e. within days. Some examinations may be of benefit weeks, months even years post assault depending on the circumstances of the case	
Safety	Assessment of personal safety of victim and relevant third parties	Immediate

PEPSE, post-exposure prophylaxis following sexual exposure; UPSI, unprotected sexual intercourse.

policies should be followed and where there is any doubt the clinician should seek advice from safeguarding leads.

Domestic violence

Sexual abuse/violence is not unusual in the context of domestic abuse/violence. Domestic abuse should be considered in every case and be part of the routine inquiry during history-taking. Where there is a positive history, then a risk assessment should be undertaken. Resources including risk assessments are available in the document Safe Lives: Ending Domestic Abuse (http://www.safelives.org.uk/)

Honour-based crimes

Honour-based violence is a form of domestic abuse that is perpetrated in the name of so-called 'honour'. The honour code which it refers to is set at the discretion of a family or community. Those who do not abide by the 'rules' may be punished for bringing shame on the family. Infringements may include a girl or woman having a boyfriend; rejecting a forced marriage; pregnancy outside of marriage; inter-faith relationships; seeking divorce, inappropriate dress or make-up and even kissing in a public place.

Forced marriage is a component of honour-based crime. Women may present in a healthcare setting as a result. The clinician should be alert to the possibility that this is a problem and be able to deal with it sensitively and safely. More information and resources can be found at Honour Based Violence Awareness Network (http://hbv-awareness.com/). Advice regarding the law can be found at http://www.cps.gov.uk/legal/h_to_k/honour_based_violence_and_forced_marriage/#a02

Statements

The clinician may be asked to provide a statement for the courts. This is an opportunity to communicate information and the doctor should remember who the statement is intended for. In criminal cases this will ultimately be the jury. The key to writing a good statement includes:

- good contemporaneous records;
- clear simple language;
- logical approach.

The statement should include, for example:

- the qualifications and experience of the doctor;
- the circumstances in which the patient was seen;
- how the disclosure came about;
- what the details given were, who gave them, who else was present;

- the extent and findings of any examination;
- outline any care given.

It is important that the clinician writes any statement with objectivity and impartiality and within the limits of their competence.

Giving evidence in court

Most doctors find this daunting. The key to success is based on the following.

- Conducting a high-quality examination in the first place.
- Excellent contemporaneous medical notes, with a subsequent well-written report.
- Be prepared before attending court.
- Be professional and courteous.
- Communicate clearly in a manner your audience can understand.
- Stick to your area of expertise.
- Do not give opinions that are not evidence based or which are unjustifiable.
- Concede points where appropriate but do not be unduly subdued.
- Reflect and learn from each experience.

Long-term health consequences of sexual violence

Sexual violence can result in numerous health consequences with varying degrees of severity. These can be immediate, such as death or injury to more medium term and long-term problems. It can have physical, reproductive and psychological consequences.

Vicarious trauma

Most doctors will be used to dealing with distressed and distressing patients. That said, dealing with victims of sexual violence, hearing their accounts and the ramifications of the assaults can be harrowing. Doctors should be mindful of the effect this can have on them and other staff. Sometimes the effects may not be immediately obvious. Good self-awareness is essential. Clinicians have a duty to look after their mental health and should be encouraged to seek help sooner rather than later should they feel that a case has adversely impacted them.

Child sexual exploitation

Numerous myths and stereotypes regarding sexual violence exist for many reasons, some anthropological, some religious and cultural, but many through sheer ignorance. Common ones are shown in Table 67.8.

Female genital mutilation

The World Health Organization classification of female genital mutilation (FGM) is shown in Table 67.9.

FGM and the role of the healthcare professional

The clinician must be aware of the potential healthcare needs associated with FGM (see https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/525405/FGM_mandatory_reporting_map_A.pdf) as well as statutory/legal duties. Clinicians should be aware of it, appreciating what it may look like and also the possible short- and long-term health consequences, including infection, haemorrhage, vesicovaginal fistulae, and complications in pregnancy and labour.

The practice of FGM has long cultural roots. It is considered to be an abuse of human rights and a child protection issue [9] and is outlawed in many countries. In England, Wales and Northern Ireland, FGM is illegal under the Female Genital Mutilation Act 2003, and in Scotland it is illegal under the Prohibition of Female

Table 67.8 Common myths and stereotypes regarding sexual violence.

Most rapists are strangers	No. Most victims will know their abuser
Most abuse takes place outside the home	No. Most abuse takes place where the victim lives. This is especially true of child victims
Rape victims will have injuries	No. Most will not, and those injuries that do happen often heal quickly and fully leaving no scars
Rape victims will disclose the abuse at the earliest opportunity	No. Many never disclose at all. A significant number of those that do disclose will do so well after the attack and may only give partial details
Some rape victims must shoulder responsibility for the abuse	No. The rapist is responsible for his own actions
Men cannot be raped	No. Men and boys can be victims of sexual violence

Table 67.9 World Health Organization classification of FGM.

Type I	Involves excision of prepuce with or without excision of part or all of the clitoris
Type II	Excision of the prepuce and clitoris together with partial or total excision of labia minora
Type III	Excision of part or all of external genitalia and stitching or narrowing of the vaginal opening, also known as infibulations. This is the most extreme form and constitutes 15% of all cases
Type IV	Includes pricking, piercing or incision of the clitoris and/or labia; stretching of the clitoris and the labia; cauterization or burning of the clitoris and surrounding tissues, scraping of the vaginal orifice or cutting (Gishiri cuts) of the vagina and introduction of corrosive substances or herbs into the vagina

Genital Mutilation (Scotland) Act 2005. Under the 2003 Act, a person is guilty of an offence if they excise, infibulate or otherwise mutilate the whole or any part of a girl's or woman's labia majora, labia minora or clitoris, except for necessary operations performed by a registered medical practitioner or midwife (or a person undergoing training with a view to becoming a medical practitioner or midwife) on a woman who is in labour or has just given birth, for purposes connected with the labour or birth (these exceptions are set out in section 1(2) and (3) of the Act) [10,11]. The Serious Crime Act 2015 strengthened the legislative framework around tackling FGM by adding the following.

- An offence of failing to protect a girl from the risk of FGM.
- Extra-territorial jurisdiction over offences of FGM committed abroad by UK nationals and those habitually (as well as permanently) resident in the UK.
- Lifelong anonymity for victims of FGM.
- FGM Protection Orders which can be used to protect girls at risk.

In May 2016 the Department of Health updated 'Female Genital Mutilation. Risks and Safeguarding. Guidance for Professionals' [12]. This states that as FGM is a form of child abuse, professionals have a statutory obligation under national safeguarding protocols (e.g. Working Together to Safeguard Children [13]) to protect girls and women at risk of FGM. Since October 2015, registered professionals in health, social care and teaching also have a statutory duty (known as the Mandatory Reporting duty introduced through Section 5B of the 2003 Act) to report cases of FGM to the police non-emergency number 101 in cases where a girl under 18 either discloses that she has had FGM or the professional observes physical signs of FGM [14]. All cases should be dealt with under existing safeguarding frameworks, which for children under 18 who have undergone FGM would mean a referral to children's social care and the police. The guidance reminds the reader that once concerns have been raised about FGM, there should also be a consideration of potential risk to other girls in the family and practising community. Professionals should be alert to the fact that any one of the girl children amongst these groups could be identified as being at risk of FGM and may need to be safeguarded from harm.

Information sharing

In 2016 the government published multi-agency guidance on FGM [15] with an aim to provide front-line professionals with information on:

- identifying when a girl (including an unborn girl) or young woman may be at risk of FGM and responding appropriately to protect them;
- identifying when a girl or young woman has had FGM and responding appropriately to support them; and
- measures that can be implemented to prevent and ultimately end the practice of FGM.

To assist professionals regarding mandatory reporting, a two-page poster which includes FAQs and flowchart (see below) has been produced as a guide [16].

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Part 17

Miscellaneous Topics

68

Ethical Dilemmas in Obstetrics and Gynaecology

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Obstetrics and gynaecology is one of the most ethically and legally contentious areas of medicine. Not only can it involve the creation and destruction of new human lives, but also the doctor will sometimes be faced with two possible patients, the woman and the developing embryo/fetus. At the outset, it is worth noting that the only clinical practices to which healthcare professionals have the right to refuse to participate, if they have a conscientious objection, are abortion and fertility treatment (Abortion Act 1967, section 4; Human Fertilisation and Embryology Act 1990, section 38). These rights exist as a result of the recognition that there is profound disagreement over when morally significant life begins.

This chapter will provide a broad overview of three areas of practice in obstetrics and gynaecology: termination of pregnancy, the management of pregnancy and childbirth, and the provision of fertility treatment. As well as raising complex ethical and legal issues, there is also something distinctive about the provision of abortion and fertility services in the UK. The majority of abortions in the UK are provided in the independent sector, under NHS contract [1]. Very few abortions are carried out in NHS hospitals. Most fertility treatment in the UK is provided in the private sector [2]. In contrast, the private or independent management of pregnancy and childbirth is unusual, and almost all babies born in the UK are born in NHS hospitals.

Abortion

The morality of abortion

There will never be consensus over whether abortion is morally permissible. One view, associated particularly with Roman Catholicism, is that personhood begins at conception [3]. If the fetus is a person, abortion is murder. If the fetus is a person, it makes no difference to the wrongness of killing it that it was conceived as a result of rape. Nor does its age make a difference, so on this view, termination at six weeks is morally equivalent to termination at 36 weeks. If an abortion is necessary in order to save the woman's life, then, if the fetus has an equivalent right to life, it is not self-evident that its life must be sacrificed in order to save hers.

The law is clear, however, that legal personhood is acquired only once a child has an existence independent of its mother, that is once it has been born. Of course, some might argue that birth is simply a matter of geography, and that a newborn baby is not an intrinsically different entity from a fetus immediately prior to birth [4]. But in legal terms, geography is central. While a fetus is inside the woman's body, it cannot be considered a separate legal person.

A second approach to the morality of abortion instead emphasizes the physical invasiveness of pregnancy, and the degree of self-sacrifice involved in compelling a woman to carry an unwanted pregnancy to term, and go through childbirth against her wishes. One of the most famous philosophical 'thought experiments' used to illustrate this view is Judith Jarvis Thomson's 1971 article [5], in which she invites readers to imagine that they wake up attached to a famous, unconscious violinist, who needs to be plugged into their circulatory system for the next nine months. Thomson then asks: 'Is it morally incumbent on you to accede to this situation? No doubt it would be very nice of you if you did, a great kindness. But do you *have* to accede to it?' Although this sounds extraordinarily far-fetched, Thomson's point is to jolt readers into contemplating what it might be like to be compelled to use your body to support another human life for nine months.

A third 'middle ground' position on the morality of abortion would permit abortion subject to restrictions, such as time limits. According to this view, a fetus may not have legal personhood, but it is also 'not nothing' [6].

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

As legal philosopher Ronald Dworkin [7] has explained, this view on the morality of abortion is by far the most common: most people share a belief in the sanctity of human life, but at the same time they do not believe that the fetus has the same moral status as a person, otherwise it would be impossible to justify abortion where the woman is pregnant as a result of rape. Most people also believe that the respect accorded to the fetus increases as it matures towards birth. This is often described as the 'gradualist approach': many people believe that abortion should be available as of right in the first months of pregnancy, while not believing that it should be available as of right until birth.

Abortion and the law

To the surprise of many students, abortion is still a criminal offence in the UK. A Victorian statute, passed more than five decades before women had the right to vote, continues to apply today to the termination of pregnancy. Statutory defences have existed in England, Scotland and Wales for 50 years, but under sections 58 and 59 of the Offences Against the Person Act 1861, the maximum sentence for a woman who intentionally and unlawfully procures her own miscarriage continues to be life imprisonment, and anyone who assists her could be imprisoned for up to five years.

Before abortion was partially decriminalized in 1967, a test case in 1939 established that it could be lawful to carry out a termination of pregnancy if carrying the pregnancy to term might leave the woman 'a mental wreck'. In R v Bourne [8], a distinguished obstetric surgeon, Aleck Bourne, was prosecuted for carrying out an abortion on a 14-year-old girl, who was pregnant following a violent rape. His defence was that the operation was not unlawful, because, in his opinion, the continuance of the pregnancy posed an extremely serious risk to the girl's mental health. In his direction to the jury, Macnaghten J was clear that an abortion might be carried out lawfully not only where the pregnant woman was in imminent danger of death (as had always been the case), but also where the effect of carrying the pregnancy to term might be to 'make the woman a physical or mental wreck'.

Following Aleck Bourne's acquittal, safe 'legal' abortions were available in the UK to women who could afford them, and who could find doctors who were prepared to run the risk of imprisonment. Much more commonly, women with unwanted pregnancies relied on the services of illegal abortionists It is thought that there were probably around 100 000 illegal abortions each year before the Abortion Act came into force, and mortality rates were high. Abortion had become a public health issue and by the mid-1960s there was broad public support for bringing it within the safety of medical control.

The Abortion Act 1967 provides that an abortion will be lawful in England, Scotland and Wales (the Act does not apply in Northern Ireland), and no offence will have been committed if the criteria laid out in the Act are met. These are that two doctors must be 'of the opinion, formed in good faith', that the woman's circumstances satisfy one of the four statutory 'grounds' for abortion; that the abortion is carried out by a registered medical practitioner in an approved place; and that it is notified within seven days to the relevant Chief Medical Officer.

If a termination of pregnancy does not satisfy these criteria, a criminal offence will have been committed. In 2012, Sarah Catt bought abortion pills from an internet site which she took in order to terminate her own pregnancy, shortly before she was due to give birth. She was convicted under section 58 of the Offences Against the Person Act and initially sentenced to eight years in prison [9], reduced, on appeal, to three and a half years [10].

The most commonly invoked ground for abortion, often referred to as the 'social ground', is set out in section 1(1)(a) of the Abortion Act 1967. It requires two registered medical practitioners to be 'of the opinion, formed in good faith':

> that the pregnancy has not exceeded its twenty fourth week and that the continuation the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family.

In 2016, 97% of all abortions were authorized on the grounds that the pregnancy posed a risk to the pregnant woman's own health, and 99.8% of these were authorized solely because of the risk to her mental health [1].

This ground is very easily satisfied, and not only because the mental well-being of a woman who does not want to be pregnant will generally be promoted by allowing her to end her pregnancy. Through what is sometimes called the 'statistical argument', it could be argued that, because pregnancy and childbirth will almost always pose a greater risk to a woman's physical health than termination, this ground is satisfied in virtually every pregnancy.

The other three grounds for abortion are that two doctors are 'of the opinion, formed in good faith' that: under section(1)(1)(b) the termination is necessary to prevent grave permanent injury to the pregnant woman; under section (1)(1)(c) continuing the pregnancy involves a risk to her life; or under section (1)(1)(d) 'there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped'. None of these three grounds is subject to a time limit. In practice, however, terminations after 24

weeks are rare (fewer than 0.1%), and most are carried out because of the late detection of a grave fetal abnormality, such as anencephaly.

While the legalization of abortion is sometimes assumed to be part of the pattern of liberal law reforms that took place during the 1960s, it is important to remember that the 1967 Act does not, in any circumstances, give a pregnant woman the right to terminate her unwanted pregnancy. Even if a woman's pregnancy resulted from an act of rape or incest, she does not have the legal right to terminate it (of course, in practice doctors will invariably find that the first statutory ground is satisfied in such cases).

Instead the statute gives doctors considerable discretion over the legality of abortion. Notice, for example, that the statute does not specify that the section 1(1) grounds have to actually be satisfied. An abortion's legality depends solely upon whether two doctors have formed the opinion, in good faith, that that woman's circumstances satisfy one of the statutory grounds. So, for example, the legality of the 1% of abortions carried out under s.1(1)(d) depends upon two doctors agreeing, in good faith, that a particular handicap is 'serious', and that the risk of it materializing is 'substantial'. In deciding whether a fetus's abnormality is sufficiently serious, the Royal College of Obstetricians and Gynaecologists has recommended that doctors take into account the probability that effective treatment will be available; the probable degree of self-awareness and ability to communicate with others; the suffering that would be experienced; and the extent to which the person might be dependent upon others. There is, however, no definitive list of conditions which justify abortion, rather the test is simply whether two doctors have formed the opinion, in good faith, that there is a substantial risk that the child would be seriously handicapped.

The question of what might count as a serious handicap was raised by Joanna Jepson in 2003, following her discovery that an abortion had been carried out on a fetus with a cleft palate after 24 weeks [11]. Following her complaint, West Mercia police launched an investigation, but they decided not to prosecute the doctors who had signed the form. Ms Jepson sought and was granted leave to apply for judicial review of this decision, on the grounds that the case raised an issue of public importance, but Jackson J admitted that she would face substantial evidential and legal hurdles at the full hearing. Before this could take place, West Mercia police conceded that their initial investigation may not have been sufficiently thorough, and the case was reopened under a different team of officers. The case was then referred to the Crown Prosecution Service, which decided against prosecution because, as the Chief Crown Prosecutor for West Mercia explained [12]:

> both doctors concluded that there was a substantial risk of abnormalities that would amount to the child being seriously handicapped. The evidence shows that these two doctors did form this opinion and formed it in good faith.

An outdated statute?

There are three ways in which the Abortion Act 1967 is a poor fit with modern medical practice. First, to be lawful, an abortion must be carried out by a registered medical practitioner. This restriction made sense in 1967 when all abortions were surgical, but 62% of abortions are now medical and simply involve taking pills [1]. There is no clinical need for the pill to be provided by a doctor, and indeed nurse-led abortion services are both clinically and cost-effective. In practice, the courts have interpreted this provision in a way that facilitates nurses' involvement in medical abortions, provided that the nurse continues to be supervised by a doctor. In *Royal College of Nursing v Department of Health and Social Security* [13], the House of Lords decided that nurses could actively participate in the termination of pregnancy, provided that a registered medical practitioner is supervising the procedure.

Second, except in an emergency, 'any treatment for the termination of pregnancy' must be carried out in an NHS hospital, or in a place approved for the purposes of the Act by the Secretary of State (section 1(3)). Around two-thirds (68%) of NHS-funded terminations take place in independent clinics run by charities including Marie Stopes and the British Pregnancy Advisory Service (BPAS). Pregnancies of 24 weeks or more can only be terminated in NHS hospitals.

Once again, this restriction may be incompatible with best practice in the provision of early medical abortions. If taking mifepristone and misoprostol is 'treatment for the termination of pregnancy', then both pills must be taken in an NHS hospital or an approved place, despite the fact that it would be safe to take them in a GP's surgery, or even at home. It might be argued that it would be preferable for women to be able to take the second drug, misoprostol, at home, since this is what will usually trigger her miscarriage. Instead, in addition to the inconvenience of having to attend the clinic on two separate occasions, which may be particularly difficult for women with young children or those who live in remote rural areas, there is also a risk that the woman might miscarry while she is on her way home. There is considerable evidence that home medical abortion would be safe, and that most women would prefer it [14].

In 2012, BPAS sought, unsuccessfully, a declaration that it would be lawful to prescribe misoprostol when the woman attended the clinic to take the mifepristone, so

that she could take the misoprostol home with her, and subsequently take it at home. In *British Pregnancy Advisory Service (BPAS) v Secretary of State for Health* [15], Supperstone J held that the 'treatment', which had to take place in an approved place, was the taking of the drug, not its prescription. The irony of this is that a provision in the legislation which was intended to protect women's safety – by ensuring that surgical abortions only take place in properly equipped and staffed premises – in fact, in the case of early medical abortions, could make them *less* safe. By requiring the woman to take the second pill in a clinic, before allowing her to return home, there is a risk that she might miscarry in a public place.

Third, the provision of new birth control methods that might involve a woman taking a contraceptive pill only once her period is late, or once a month, is blocked by the Abortion Act 1967. Any method of birth control that works after implantation would involve 'procuring a miscarriage', and hence could avoid being a criminal offence only if all of the criteria in the Abortion Act are satisfied. Two doctors would have to agree that the woman's circumstances satisfy one of the statutory grounds for abortion; the woman would have to take the pill in an approved clinic or NHS hospital, while being supervised by a doctor. This would make post-implantation methods of birth control both inconvenient and expensive. As Sally Sheldon [16] explains:

> That archaic legislation, which has remained largely unconsidered for one and a half centuries, is drafted so as to block the development and use of safe, effective forms of fertility control that operate so soon after intercourse provides a compelling argument for a fundamental review of, at least, this aspect of its operation.

Sex-selective terminations

In 2012, undercover reporters from the *Daily Telegraph* filmed abortion providers allegedly agreeing to carry out terminations on the grounds of fetal sex. The reaction from the then Secretary of State for Health, Andrew Lansley, and the Chief Medical Officer, Sally Davies, was to declare that such abortions are unlawful. In 2014, the Department of Health issued *Guidance in Relation to Requirements of the Abortion Act* [17], in order 'to provide support for doctors by setting out how the law is interpreted by the Department of Health', according to which: 'Abortion on the grounds of gender alone is illegal. Gender is not itself a lawful ground under the Abortion Act'.

The assumption behind claims that abortion on the grounds of sex is illegal in the UK is that because 'fetal sex' does not appear as one of the grounds for abortion in section 1(1) of the Abortion Act 1967, abortion on the grounds of fetal sex must be unlawful. But this is to misunderstand how the Abortion Act works. It does not contain a list of legitimate reasons for abortion. As we have seen, rape does not appear as a ground for abortion in section 1(1), but this does not mean that abortion on the grounds of rape is unlawful. Instead, the Act gives two doctors considerable discretion to determine whether a woman's health would be better served by termination than by carrying the pregnancy to term.

In 2015, Fiona Bruce MP attempted to put the supposed illegality of sex-selective abortions beyond doubt through an amendment to the Serious Crime Bill. If passed, her amendment would have read: 'Nothing in section 1 of the Abortion Act 1967 is to be interpreted as allowing a pregnancy to be terminated on the grounds of the sex of the unborn child.' In the event, her amendment was defeated, not because there was support for sex-selective abortion in parliament, but because there were concerns that this provision might prevent women from terminating pregnancies where the fetus was suffering from a sex-linked disorder. Anxieties were also expressed about the use of the term 'unborn child' in legislation. Instead, an alternative amendment was passed which required research to be carried out into the incidence of sex-selective abortion in the UK. The Department of Health duly carried out this research and published its report [18] later in 2015. Its conclusion was that 'we have found no substantiated concerns of gender abortions occurring in England, Wales and Scotland'.

Termination of pregnancy in children and adults who lack capacity

Once children reach the age of 16, their consent to medical treatment is as valid as it would be if they were adults [19]. If a girl is under 16, but *Gillick*-competent – that is, she is mature enough to make the decision for herself – it is clear that she can give a valid consent to abortion, and that the termination can take place without her parents' consent or knowledge [20].

If a girl is not yet *Gillick*-competent, decisions about her medical treatment would normally be taken by her parents, subject to the possibility of being overridden by the courts if the parents' decision was not in her best interests. It is, however, hard to imagine circumstances in which it could be in the best interests of a girl who lacks capacity to terminate her pregnancy against her wishes, or, likewise, to force her to carry an unwanted pregnancy to term. Certainly this was the view of the President of the Family Division, Sir James Munby, in *Re X (A Child) (Capacity to Consent to Termination*) [21], a case involving a pregnant 13-year-old girl who was not yet *Gillick*-competent:

> I find it hard to conceive of any case where such a drastic form of order – such an immensely invasive procedure – could be appropriate in the case of a mother [*sic*] who does not want a termination, unless there was powerful evidence that allowing the pregnancy to continue would put the mother's life or long-term health at very grave risk. Conversely, it would be a very strong thing indeed, if the mother wants a termination, to require her to continue with an unwanted pregnancy.

So even if a girl lacks the capacity to make a decision about whether to have an abortion, her views will carry considerable weight.

For adults who lack capacity, the Mental Capacity Act 2005 applies, and the first question for the doctor will be whether a termination is in the patient's best interests. The Mental Capacity Act is clear that when judging what is a patient's best interests, the doctor should not just consider her clinical best interests, but also her 'past and present wishes and feelings' and 'the beliefs and values that would be likely to influence [her] decision if [she] had capacity' [22]. In *An NHS Trust* v *CS* [23], a pregnant woman who was in a violent relationship had told her sister that she did not want to 'keep the baby'. Following a further violent assault, as a result of which she now lacked capacity, Baker J decided that a termination would be in her best interests, and not only because this would promote her physical recovery: 'I consider that the clear and unambiguous views that she expressed prior to the injury are the crucial factors in this case'. Of course, deciding that a termination would be in the patient's best interests is not the end of the matter, and two doctors must additionally be of the opinion that the woman's circumstances fit within one of the statutory grounds for abortion, and the termination must be carried out by a registered medical practitioner, in an approved place.

Summary box 68.1

- Abortion is prima facie a criminal offence in the UK, but a defence exists in England, Scotland and Wales if a termination satisfies the criteria in the Abortion Act 1967.
- These are that two doctors must have formed the opinion, in good faith, that the woman's circumstances fit within the statutory grounds and that the abortion is terminated by a registered medical practitioner in an approved place.
- In practice, abortion is available 'on request' in the first months of pregnancy, and nurses are able to participate in the provision of abortion services, provided that they are under the supervision of a doctor.

The management of pregnancy and childbirth

In almost every wanted pregnancy in the developed world, the fetus makes its first 'public' appearance long before it is capable of independent life. Prenatal testing facilitates the accurate diagnosis of an expanding range of disorders, and an increasing range of conditions are treatable *in utero*. Given the ability to see, monitor, diagnose and treat the fetus, it is probably unsurprising that, even if it is established law that the fetus is not a person, there is no doubt that the fetus is now widely understood to be a patient.

Conferring 'patient' status upon a fetus presents no practical problems when the woman is a willing participant and, of course, most pregnant women will consent to any intervention in order to protect the life and health of their developing fetus. Nevertheless, fetal patienthood creates the potential for conflict if a pregnant woman wants to exercise her right to refuse unwanted treatment. Acting to save a fetus's life involves acting upon the body of the pregnant woman, and without the pregnant woman's consent, the practice of fetal medicine might amount to a battery or assault. Fetal surgery, for example, is possible only if the pregnant woman has given her consent to surgical intervention, consent that she entitled to withhold.

The right of an adult with capacity to refuse treatment that the doctor believes to be in her best interests is robustly protected by the law, and it exists even if the patient's refusal might lead to her death. If a pregnant woman has capacity, it is now clear that pregnancy does not interfere with her right to refuse unwanted medical treatment. In 1992, a judge had declared that it would be lawful to perform a caesarean section, without consent, on a woman who was refusing to consent on religious grounds [24]. That case is now of historical interest only, however. In two subsequent cases, the Court of Appeal has confirmed that pregnancy does not diminish the competent adult patient's right to refuse unwanted medical intervention.

In *Re MB (An Adult: Medical Treatment)* [25], MB lacked capacity as a result of her needle phobia, and an injection necessary to carry out a caesarean section was held to be lawful in her best interests. Nevertheless, in the course of her judgement in *Re MB*, Butler-Sloss LJ stated unequivocally that:

> a competent woman, who has the capacity to decide, may, for religious reasons, other reasons, for rational or irrational reasons or for no reason at all, choose not to have medical intervention, even though the consequence may be the death or serious handicap of the child she bears or her own death.

A year later, in *St George's NHS Trust v S* [26], the emergency caesarean section that had been performed upon S, following the granting by a judge in chambers of an *ex parte* order dispensing with her consent, was held to have been unlawful. The Court of Appeal defended the pregnant woman's right to refuse treatment that could save her fetus's life. As Judge LJ explained:

> She is entitled not to be forced to submit to an invasion of her body against her will, whether her own life or that of her unborn child depends on it. Her right is not reduced or diminished merely because her decision to exercise it may appear morally repugnant.

In practice, however, it may have been easier for the appellate court to strongly assert the primacy of the pregnant woman's autonomy, after the operation had been carried out successfully, than it was for the judge who had had to make a decision *ex parte*, when two lives were in immediate danger [27].

If the pregnant woman lacks capacity, the doctor is under a duty to treat her in her best interests, taking into account her past and present wishes and her beliefs and values. It is a fundamental principle of the Mental Capacity Act 2005 that capacity cannot be inferred just because someone makes a foolish or unwise decision [28], so the fact that a pregnant woman wants to take a decision that the doctor believes to be irrational does not justify a diagnosis of incapacity. In *The Mental Health Trust* v *DD* [29], one of several Court of Protection decisions (this one about an assessment of her capacity to decide upon future contraception) concerning DD, a pregnant woman with a complex obstetric history, learning difficulties and an autistic spectrum disorder, Cobb J explained that he had to 'review with particular care whether DD's decision making is simply "unwise" rather than evidence of her incapacity; if it were merely the former (i.e. unwise decision-making) [he] would have no right under the Mental Capacity Act 2005 to intervene'.

Summary box 68.2

- Pregnant women retain the right to refuse unwanted medical treatment throughout their pregnancies.
- If a pregnant woman lacks capacity, she can be treated in her best interests, under the Mental Capacity Act 2005.

Fertility treatment

The birth of Louise Brown, the first baby created by *in vitro* fertilization (IVF), in Oldham on 25 July 1978 undoubtedly represented one of the most important scientific breakthroughs of the twentieth century, for which Bob Edwards won the Nobel prize for medicine in 2010. As well as pioneering the development of IVF, the UK also has one of the world's most comprehensive and long-established systems for regulating fertility treatment and embryo research.

Four years after Louise Brown's birth, the government appointed Baroness Mary Warnock to chair a Committee of Enquiry into Human Fertilisation and Embryology [30]. The Warnock Report, published in 1984, formed the basis for the Human Fertilisation and Embryology Act 1990, which was substantially amended in 2008, but continues to apply today.

In 1990, babies born through IVF were called 'test tube babies' and there was considerable hostility to the provision of fertility treatment to anyone other than heterosexual couples. Times have changed, however, and it would now be unlawful for a fertility clinic to refuse to provide treatment to someone on the grounds of their sexual orientation or marital status. As well as changes in social attitudes, and in the law, there is now a great deal of high-quality longitudinal research into the well-being of families produced through different types of assisted conception. Perhaps unsurprisingly, given that these are all wanted children, the evidence is that children born as a result of assisted conception are doing at least as well, and sometimes better, on average, than children conceived naturally [31].

Regulating access to fertility treatment

Under the Human Fertilisation and Embryology Act 1990 [32], it is a criminal offence to create, store and use embryos, and store, procure, test, process or distribute gametes without a licence from the Human Fertilisation and Embryology Authority (HFEA). Centres licensed by the HFEA are inspected regularly. They must also provide the HFEA with detailed information about every treatment cycle carried out, in order that the HFEA can fulfil its duty to maintain a register of all treatments carried out in the UK and their outcomes [33].

Unlike some other countries, like France and Italy, which restrict access to fertility treatment to heterosexual couples, there are no eligibility requirements for assisted conception in the UK. Rather the only statutory restriction on access is that a woman must not be provided with treatment services 'unless account has been taken of the welfare of any child who may be born as a result of the treatment (including the need of that child for supportive parenting), and of any other child who may be affected by the birth' [34].

Although this 'welfare of the child' provision might sound uncontroversial, it has been subject to considerable criticism. For example, its logic might be questioned by invoking the 'non-identity problem': that is, it is hard

to see how a clinician could take into account a future child's welfare and decide, as a result, that it would be preferable not to bring that child into the world. There are very few would-be parents whose child's life would be likely to be so terrible that it would better for that child never to exist. The 'welfare of the child' provision has also been criticized for placing an unfair burden upon infertile people, who are no more likely to pose a risk to their children's welfare than fertile couples, who can reproduce without being vetted first [35].

In practice, this provision has been interpreted by the HFEA as a 'welfare of the child risk assessment'. The HFEA's Code of Practice instructs clinicians to consider whether there are any specific risk 'factors that are likely to cause a risk of significant harm or neglect to any child who may be born or to any existing child of the family' [36]. Examples given in the Code of Practice include previous convictions relating to harming children, previous child protection measures taken in relation to existing children, and a history of drug or alcohol abuse [37]. The Code of Practice also specifies that, in the absence of specific risk factors, all parents should be assumed to be supportive [38].

In their empirical study of how the 'welfare of the child' provision works in practice, Lee *et al.* [39] found that it was extremely rare for clinics to refuse to provide treatment on child welfare grounds. Nevertheless, the 'spectre' of the child abuser meant that clinic staff believed that it was important to be vigilant. Lee *et al.* also found an interesting distinction between would-be lesbian parents, who were often regarded as 'ideal' parents, in part, perhaps, because of their commitment to be open with their child about the circumstances of their conception, and single women, whose motivations for seeking treatment alone were more likely to be questioned.

A further practical restriction upon access to fertility treatment is that it is expensive and NHS provision is patchy at best. In 2014, NICE published a Quality Standard for Fertility Problems [40], according to which women under the age of 40 who meet the criteria for IVF should be offered three full cycles of IVF, or one full cycle if they are aged 40–42. Implementation of this quality standard is not mandatory, in the same way as NICE's technology appraisals of new medicines. In 2017 it was reported that only 12% of Clinical Commissioning Groups (CCGs) provide three full cycles of IVF to eligible women [41]; 23% offer two cycles; 61% fund one cycle only, and 3% fund no treatment at all. Access to NHS-funded fertility treatment is therefore subject to a post-code lottery. In addition, some CCGs impose further restrictions on access to treatment, such as a requirement that the woman's body mass index is below a certain threshold, or that neither would-be patient already has any children.

Consent

Unlike other more invasive medical procedures, consent to fertility treatment *must* be in writing [42]. Gametes and embryos can be used posthumously in the UK, but only where the gamete provider(s) explicitly consented to their posthumous use. In the late 1990s, there was considerable media interest in the case of Diane Blood, whose husband had had sperm samples extracted, at Mrs Blood's request, after he had lapsed into a coma. Although Mrs Blood claimed that they had discussed the posthumous use of his sperm, Mr Blood had not given written consent to the use of his sperm, and so it could not be used lawfully in treatment in the UK. Following her successful application for judicial review of the HFEA's initial refusal to permit her to export the sperm samples [43], in which the Court of Appeal was reassured that there should be 'no further cases where sperm is preserved without consent', Mrs Blood was allowed to export her late husband's sperm to Belgium where it could lawfully be used without his consent.

In 2008, the Court of Appeal's prediction that there would be no further cases in which sperm was stored without consent was proved wrong. L's husband, H, had died suddenly following routine surgery. Sperm was retrieved without H's consent after misinformation about the application of the Human Tissue Act 2004 to gametes was provided to an out-of-hours judge. When the legality of the sperm's storage and use subsequently came before Charles J [44], he concluded that the evidence that H would have wanted his sperm used posthumously by L was 'at least as compelling as that advanced by Mrs Blood'. The HFEA then permitted L to export her late husband's sperm to a clinic in the USA, where it could lawfully be used without his consent.

In 2015, the courts were first presented with a case involving the possible posthumous export of eggs, in the absence of specific written consent. AM had signed a form permitting the posthumous storage of her eggs. AM's parents believed that, before she died, AM had expressed the strong wish that one or more of her eggs should be fertilized and implanted in her mother, who would bring up the baby, along with AM's father. AM had not given specific written consent to the use of her eggs in her mother's treatment, and so they could not be used lawfully in the UK. The HFEA's Statutory Approvals Committee refused to permit the eggs' export to the USA, and AM's parents applied for judicial review of that decision. At first instance, their application for judicial review of that decision was dismissed, but the Court of Appeal allowed the parents' appeal on the grounds that there had been clear evidence that AM wanted her mother to be the surrogate mother of a child conceived using her eggs after her death [45].

A different consent issue arises if the gamete providers subsequently disagree about the use of their frozen embryos. In the UK the law is clear: the Human Fertilisation and Embryology Act 1990 allows for the variation or withdrawal of consent to the use or storage of an embryo [46]. In practice, this gives whichever partner does not want their embryos to be used in treatment a right of veto over their use. In 2007, this provision was challenged by Natallie Evans who, with her then partner Howard Johnston, had gone through one cycle of IVF, in which six embryos were created, before embarking on chemotherapy treatment for ovarian cancer. The couple subsequently split up and Mr Johnston withdrew his consent to their embryos' continued storage. Because the embryos represented her last chance to have a genetically related child, Ms Evans argued that giving her ex-partner the right to veto their storage and use was incompatible with her right to respect for her private and family life (under Article 8 of the European Convention on Human Rights). Having failed in the UK courts, Ms Evans appealed unsuccessfully to the European Court of Human Rights. While expressing considerable sympathy for her plight, the courts considered that the consent requirement in the 1990 Act served an important purpose, and that Ms Evans' right to respect for her private and family life did not take priority over her ex-partner's equivalent right to respect for his private and family life [47].

In 2008, the Act was amended to provide for a 12-month 'cooling off period' when one partner seeks to withdraw consent to their embryos' storage and use. The hope is that this will enable couples who disagree about their embryos' use or disposal to resolve their differences and come to an agreement. In practice, however, a similar case is unlikely to arise given the development of vitrification, a new and more successful technique for freezing eggs. A woman about to undergo chemotherapy treatment would now be likely to freeze her eggs, rather than embryos created with her partner's sperm. Regardless what happens to her relationship, her frozen eggs would continue to be available for her use in the future.

Gamete donation

Until 2005, most gamete donation in the UK was anonymous. Anonymity used to be thought to be in the interests of donors, recipients and children. It protected donors from unwanted contact with their genetic offspring, and it undoubtedly helped to persuade medical students to donate sperm safe in the knowledge that the children born as a result of their donations would not come back to haunt them in middle age. Anonymity was also believed to protect the privacy and security of the recipient family.

In recent years, these justifications for anonymity have been challenged, and it is now widely (though not universally) accepted that donor-conceived people's interest in information about their origins should take priority over other considerations. Regulations which came into force in 2005 prevented the use of anonymously donated gametes in treatment after 2006. Children born following this legal change have the right, once they reach the age of 18, to access identifying information about their donor. Although the abolition of anonymity has led to fewer students being willing to donate sperm, in practice, clinics have been able to recruit older donors, often with children of their own, or they have been able to import sperm from identifiable donors, most commonly from Denmark and the USA.

Of course, a child will only be able to apply to the HFEA for identifying information if she knows, or suspects, that she was conceived using donated gametes. Unless a child born to heterosexual parents is told about the circumstances of her conception, she will assume that she was conceived naturally, and will have no reason to make an application to receive identifying information about her donor. Her 'right' to information therefore exists only in theory. Of course, children born to lesbian couples or to single women will know from a relatively early age that a third party played a role in their conception, and their right to information will therefore be a real one.

Although there has undoubtedly been a trend towards openness, parents of children conceived using donated gametes do not always tell their children. All the evidence suggests that donor-conceived children who are told about the circumstances of their conception from an early age cope well, but that it is harder for children who find out later in life, or inadvertently. The HFEA's Code of Practice [48] makes it clear that patients should be strongly advised of the merits of being frank with their offspring from early childhood.

Since 2011, sperm donors have been entitled to a fixed sum of £35 per clinic visit to cover all their expenses, and egg donors to a fixed sum of £750 per cycle of donation, again to include all expenses. This sort of modest compensation is intended to be fair to donors, who undergo a series of medical tests and who have to make several visits to the clinic, and, in the case of egg donors, who also undergo an invasive surgical procedure, while not offering an incentive capable of 'overbearing their will'. A further justification for modest compensation emerged from Ravelingien *et al.*'s study [49] of Belgian recipients of sperm. They found that most recipients believed that donors should be compensated, provided that they did not receive 'too much'. Recipients were concerned that if donors received very large sums of money, clinics would attract the 'wrong kind of donor': 'lazy opportunists, people who are only interested in the money and don't

realize what is important in life'. Instead recipients wanted their sperm donors to be men with 'high moral standards', 'someone who is helpful and caring rather than egotistic and materialistic'.

Egg-sharing schemes involve women who need IVF treatment agreeing to donate half of the eggs retrieved during one cycle in return for free or much cheaper treatment. Given inadequate NHS funding, these schemes are attractive to women who struggle to afford private fertility treatment. Nevertheless, given that one cycle of IVF costs around £5000, it is clear that egg-sharing schemes involve substantial, albeit indirect, payment for egg donation, and some people [50] have argued that it does not make sense to pay egg-sharers several thousand pounds for their eggs, while limiting non-patient egg donors to £750.

Egg-sharing schemes carry no extra clinical risk, since the donor is undergoing egg retrieval for the purposes of her own treatment. Nevertheless, it has been suggested that it might be challenging for women whose own treatment fails to have shared their eggs for use in another woman's treatment. In practice, however, the assumption that women would find it difficult to come to terms with other women's successful treatment with their eggs is not supported by empirical evidence into the experience of egg-sharing [51], which instead suggests that egg sharers feel considerable empathy with the infertile women who received their eggs.

There is a limit on the number of children that may be produced from the gametes of one donor, which is expressed as 'up to ten families'. On the one hand, it could be argued that it would be sensible to set a higher limit, since this might be likely to increase the availability of sperm; on the other hand, it might be challenging for children to discover that they have an exceptionally large number of unknown half-siblings.

Unlicensed treatment

Thus far, this chapter has assumed that UK citizens receive fertility treatment services in licensed clinics, regulated by the HFEA. Two factors mean that this assumption is no longer warranted. First, it is increasingly easy for people to seek treatment overseas. They might do this for a variety of reasons [52], including cost (IVF is cheaper in the Czech Republic, for example), avoiding long waiting lists (there are more egg donors available in Spain), avoiding legal restrictions (in the UK this might mean travelling to the USA for sex selection), or a perception that treatment abroad will be better or more likely to succeed.

Treatment overseas can be safe and effective: the quality of care in Spain and the USA, for example, is often very high indeed. But there can also be risks. British women have returned from receiving IVF treatment in less well regulated countries pregnant with triplets and quads. In addition to the health risks for pregnant women and their children, higher-order multiple births impose significant additional costs on NHS neonatal care services, and because the children are more likely to suffer from disabilities, there will also be longer-term costs for the NHS and for social care services.

Secondly, the internet has produced a new phenomenon: online sperm donation. This can involve 'introduction websites', which operate in much the same way as dating websites, or donors advertising their services via Facebook. Online sperm donation will be subject to regulation only if it involves the 'procurement' of sperm, for which a licence from the HFEA is necessary. If would-be donors and would-be recipients simply get in touch with each other electronically and make their own arrangements, they are unlikely to fall foul of the prohibition on unlicensed procurement, and hence these arrangements are almost completely unregulated.

There are clearly risks associated with online sperm donation. There is no vetting of would-be donors, some of whom advertise themselves as offering 'NI [natural intercourse] only'. The sperm will not be tested for HIV and there will be no screening for common genetic disorders. There is no register of information for individuals conceived in this way, and no limit on how many families can be produced from one donor. Indeed, one Facebook sperm donor proudly advertises that he has created more than 800 children [53]. There are also legal risks. Unlike donors in licensed clinics, unless the woman is married or in a civil partnership and conception is achieved artificially, the informal sperm donor will be the child's legal father, and hence acquire the obligation to pay child support throughout the child's minority. It is thought that, in order to avoid child maintenance obligations, some online sperm donors use fake identities, meaning that they are not just anonymous but completely untraceable.

However, some women believe that there are advantages from seeking out online sperm donation, and not only because it will often be cheaper than treatment in a licensed clinic. It is clear from the profiles on these introduction websites that many would-be donors and recipients are interested in facilitating contact between the donor and his child during childhood. Jadva *et al.*'s [54] survey of members of an introduction website found that most were looking for ongoing relationships between the donor and the child. There is, however, scope for these arrangements to go quite badly wrong, and a few such cases have reached the UK courts. In one case [55], the mother was a lesbian woman who had sought an identifiable donor online, while the donor had unrealistic hopes for their future as a heterosexual family unit. In another case [56], in which the question for the court was whether the child's conception had been through artificial

insemination or sexual intercourse (the donor would be the child's legal father if conception had been through sex), the relationship between the mother and the donor had completely broken down and their dispute had cost them almost £300 000 in legal fees.

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) can be carried out lawfully under licence from the HFEA only where there is a significant risk that the child will have or develop a serious illness, disability or other condition [57]. Tissue typing in order to select a child who will be a good tissue match for an older sibling with a serious condition is also permissible. Although it is also possible to discover the embryo's sex through PGD, sex selection is lawful in the UK only for medical reasons: to avoid the transmission of serious conditions that affect only one sex, or which affect one sex significantly more than the other, such as haemophilia or Duchenne muscular dystrophy [58]. In 2014, the HFEA refused an application to carry out sex selection in order to avoid the inheritance of autism spectrum disorder (ASD) in a family with two 'severely affected' male children, on the grounds that PGD could not guarantee that a female child would be free from ASD [59].

Interesting ethical dilemmas arise for clinicians when a person seeks PGD for an adult-onset genetic condition which they know runs in their family, but for which they have not been tested. An obvious example is Huntington's disease. A minority of people who know that they are at risk of Huntington's have opted to be tested, with most people preferring not to know. It is, however, understandable that these people might nevertheless want to ensure that their children do not inherit the condition.

Of course, once the embryos are tested, it is likely that the clinicians will be able to tell whether the at-risk patient has the Huntington's mutation. In addition to the risk of inadvertent disclosure, it might also be difficult to preserve parental ignorance without resorting to unethical practices: if no embryos are suitable for transfer because all are affected, should the doctors fabricate an alternative reason why none are suitable (which would involve lying to the patients), or should they carry out a sham embryo transfer (which would be clinically inappropriate)? If the couple were to seek a second cycle of PGD, when the treating clinicians are sure that the at-risk patient is unaffected and that there is no risk that the child would inherit Huntington's disease, would it be unethical and perhaps even unlawful to carry out PGD? If the grandparent with Huntington's disease happens to still be alive, some of these difficulties can be resolved by instead carrying out exclusion testing, which involves excluding embryos that have inherited the relevant chromosome from the affected grandparent.

Since the 2008 amendments to the 1990 Act brought the regulation of PGD onto the face of the statute, a further use of PGD has been specifically prohibited, namely the positive selection of embryos affected by a particular condition, such as congenital deafness. No such cases had arisen under the previous legislation, but it had been anticipated that clinicians might be likely to invoke the requirement to take the future child's welfare into account in order to refuse to provide PGD to someone who wanted to screen in a genetic condition. The Act does not ban the transfer of affected embryos; rather it now provides that

> embryos that are known to have a gene, chromosome or mitochondrion abnormality involving a significant risk that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness, or any other serious medical condition, must not be preferred to those that are not known to have such an abnormality' [60].

In practice, it is not clear that any deaf parents have ever sought PGD in order to guarantee that their child will also be deaf. But the deaf community was offended by the symbolism of a statutory provision which mandates that unaffected embryos must be 'preferred' to embryos affected by congenital deafness.

Summary box 68.3

- The provision of fertility services in the UK is regulated by the Human Fertilisation and Embryology Act 1990, as amended in 2008, and by the Human Fertilisation and Embryology Authority.
- Access to fertility treatment is not subject to many restrictions, but account must first have been taken of the welfare of any child to be born. As a result of a lack of NHS funding, in practice the majority of treatment is provided in the private sector.
- Consent to the use of one's gametes or embryos in treatment must be in writing, and can be withdrawn before they are used in treatment.
- All gamete donors must be identifiable, though in practice if children are not told about the circumstances of their conception, they may not know to ask for information when they reach the age of 18.
- In recent years, it has become more common for people to travel overseas for fertility treatment, or to find gamete donors online.
- Pre-implantation genetic diagnosis is available only where there is a risk of serious illness or disability, or in order to ensure that a child is a good tissue match for an existing sibling.

Conclusion

The creation and termination of new human life raises extraordinarily profound ethical and legal issues for doctors. For patients too, unwanted pregnancy and infertility are among the most intimate, private and emotionally charged reasons for seeking medical intervention. In relation to assisted conception, there has been rapid scientific progress over the past 40 years, and IVF is now a common and routine way to start a family. New developments, such as mitochondrial replacement and gene editing, along with pre-implantation whole-genome testing are going to raise important new ethical and legal questions. Does the CRISPR-cas9 gene editing technique bring the possibility of prenatal genetic enhancement a step closer, for example?

More familiar technologies, like the internet, also have an impact upon the provision of abortion services and access to fertility treatment. It is relatively straightforward to purchase abortion pills online from an offshore pharmacy, and the internet also facilitates cross-border reproductive treatment and DIY sperm donation arrangements. If, as is increasingly common, patients' first port of call when facing a new health issue is Google rather than their family doctor, it is vitally important that accessible, high-quality and evidence-based information is readily available online so that people understand the risks of bypassing regulated treatment services.

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69

The Law and the Obstetrician and Gynaecologist

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In the last edition I noted that one plausible approach to the predicament of the law in managing society's expectations of the medical profession is to see it as a by-product of clinical success. The achievements of clinicians in providing safe remedies had naturally brought with it a process of adjustment, so that where the doctor used to be deferred to by the patient because he offered a possible but unreliable bridge over hazardous surgical waters, the declining threat of many diseases led to an uncomfortable revaluation of the clinician. Paradoxically, the improvement of the service has been associated with diminished confidence in the provider. Where safe and predictable clinical excellence can be produced, the fallible human agency delivering the service is routinely weighed in the balance and frequently found wanting. The eighteenth-century apothecary had a more comfortable relationship, precisely because the expectations of the remedy on both sides were so much lower. However, even in the last few years we have seen matters taken much further: the UK Supreme Court has followed the General Medical Council (GMC) in saying that the role of the doctor must embody far more of a teacher, a guide who must explain the advantages and disadvantages of the alternative remedies available, including those that are not recommended [1]. The changes implicit in this demand have been amplified beyond the anticipations of health service providers by the requirement that detailed records must be made by the clinician of every significant element in a consultation.

Summary box 69.1

Improvements in medicine have resulted in:

- impatience with doctors;
- acceptance of risk;
- intolerance of suboptimal outcomes.

The rise of autonomy

Because the service is expected to be safe and predictable, society also demands that it be delivered on the patient's own terms. Where the survival of the parturient mother and child is a hazardous matter, the clinician responsible for the delivery may insist on defining the terms, place and means by which the delivery is to be effected. The patient who refuses to take medical advice may be regarded as eccentric; whereas if it is safe and easy to deliver a child, then it readily comes to be viewed as a 'lifestyle choice' in which the pleasure to be derived from the occasion takes a higher priority than the reduction of an already modest risk. Although society is more risk-averse than ever before, it is also predisposed to doubt risks described by experts. The first generation to embrace evidence-based medicine and to limit the ability of clinicians to introduce new therapies that have not been subjected to a double-blind trial is oddly more willing now than in the past to embrace complementary medicine and to advocate the woman's right to home birth when neither has been subjected to any such evidence-based assessment of risk. The fact that the primary care deliverer is often a midwife who may be sceptical about the role of the doctor has proved to be a complicating factor in many Western societies, whilst the rarity of any sort of competent clinical support for many in sub-Saharan Africa is a continuing source of shame in our society.

When a 2010 meta-analysis based on over 550 000 deliveries reported that home deliveries involved a significant increase in the risk of infant mortality, *The Lancet* [2] suggested that 'women have the right to choose how and where to give birth, but they do not have the right to put their baby at risk' [3]. The meta-analysis found that the risk of mortality from home birth was increased from 0.09% to 0.2% and the question that *The*

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Lancet editorial ignored was whether the increased risk of about 0.11% was reasonable or not. Nor was it clear whether the 'right' *The Lancet* was debating was legal or ethical. In law, women do have the right, broadly speaking, to do whatever they like in this regard, as the unborn child has no legally enforceable rights against its mother, in England at least. In ethics, the distinction between the right of the parent to do as she wishes before the birth and the obligation to act in her child's best interests thereafter is certainly less clear, because the parent has the same obligation to act in her child's best interests whether the child has separate legally enforceable rights or not. Legally she may smoke and drink to an extent that will put her child at risk, whilst acting unethically in the views of many.

Advances of medical understanding and the extent to which they have been shared with the public have both undermined the liberal position. In 1859 the author of *On Liberty*, John Stuart Mill, could identify such behaviour as a 'self-regarding sin' and defend himself against attacks from a renowned judge, Sir James Fitzjames Stephen, and formidable moralists such as Mathew Arnold. Today such voices are marginalized if not silent. The ethicist certainly recognizes the parental right and duty to take various decisions on their children's behalf, including the acceptance of certain risks. Thus parents have the right, for example, to take their children on a sailing dinghy provided they do not stray too far from land, that it is not too stormy and there is a life jacket. It is a question of degree, but the acceptance of risk is permissible.

What may raise more troubling ethical questions is the associated demand for an increased share of scarce resources. We already face a shortage of midwives in the UK as we enter an era of rapidly increasing austerity in the National Health Service (NHS). How far is it ethical for a woman to exercise her autonomy at the expense of her sisters who can be handled by fewer midwives in hospital? How far are the advantages of home delivery that were acknowledged by *The Lancet* editorial – shorter recovery time and fewer lacerations, postpartum haemorrhages, retained placentae and infections – attributable to more intensive one-to-one or even two-to-one care by more senior midwives in an effort to make the home birth safer?

The shortage of resources has become a more strident voice in this as in all other medical debates. UK Health Ministers used to deny that there was any rationing of resources and such suggestions were seen as political attacks on the parsimony of the Treasury. Today it is the conventional view that the British public is not prepared to pay through the Treasury for the healthcare that it demands through the press, the courts, the regulators such as the Care Quality Commission: where most OECD countries spend over 9% of gross domestic product (GDP) on healthcare, Britain is spending under 8% and the aspiration to increase this figure that was accepted in the 7 years of plenty that followed the publication of the Wanless Report in 2001 seems a distant memory. There is a striking analogy here with maternal mortality in Africa where it is accepted that 80% of maternal mortality could be avoided with a different application of the resources available within those countries.

This development spreads beyond obstetrics and gynaecology. Most aspects of medicine have become safer and more predictable, and as a consequence the relative importance of different ethical obligations upon the doctor has changed. Thirty years ago, when medical ethics was first recognized as having practical implications for mainstream clinicians, it was accepted that there were four different ethical obligations that the doctor needed to balance. The primary obligation was to do good, and that obligation preoccupied the thoughts of the clinicians of the 1970s. They might say 'first of all do not harm', but in reality that usually meant take reasonable care and the aspiration to non-maleficence took second place since it appeared to be of less practical importance in most circumstances. Third was the obligation to act justly, since it was crucial in circumstances where doctors were more responsible for the management of the NHS and therefore the allocation of resources. The modern reader of a textbook such as Ian Donald's *Practical Obstetric Problems* (1976) will be surprised by the extent of the advice on how to manage the labour ward effectively. That obligation could cause the accoucheur to hesitate before leaving the labour ward as part of what was then called the Flying Squad. The idea that the patient's autonomy should be respected came fourth. It was seen as an important part of good manners, but beyond ensuring that the patient signed the right consent form before surgery, it was hardly a fundamental aspiration of the service rendered by the doctor. Women in the 1970s took themselves to a doctor for the treatment of an ailment rather than the exercise of their autonomy.

Today, respect for the patient's autonomy has grown like a cuckoo in the nest and threatens to drive all other considerations to the margins. A vivid illustration of this was seen in the case of *Chester* v *Afshar* involving spinal surgery which came to the House of Lords in 2004 [4]. The court found that Miss Chester was not told that there was a 1% risk of significant morbidity associated with spinal surgery. The defence accepted that every reasonable surgeon would have warned of this risk, which is in itself a striking change since the *Sidaway* v *Bethlem Royal Hospitals Governors* case [5] failed on precisely that issue in 1985. Miss Chester said that if she had been

told of the risk, she might well have undergone the surgery in any event and very likely in the hands of the same surgeon, but only after obtaining a second opinion. On a conventional analysis, this meant that Miss Chester could not prove that her surgeon had caused her any damage. However, the House of Lords felt that in these circumstances the plain meaning of the English language needed some trifling adjustment. It did so on a twofold basis.

First, that it was of vital importance that Miss Chester's autonomy be respected, and in circumstances where she was contemplating spinal surgery this demanded that she must be told the risks that she was letting herself in for, otherwise she would be stripped of her dignity as a human being when she disrobed on admission. Second, that if it was not held that the erring doctor became the insurer of the patient's damage, the duty would be emptied of its content. The law would not be upholding the duty. Thus, in order to enforce the duty the law should hold that in these circumstances the doctor has caused the patient damage. Some felt that there would have been more logic about it if the House of Lords had invented a new tort of Showing Disrespect, or *Dis* as modern slang would have it, and said that in these circumstances they would order the surgeon to compensate the patient for the complete tort of advising and treating with disrespect; that would have the advantage of forcing the surgeon to compensate the patient for the insult he had rendered, whether or not she was unlucky enough to get a complication which sounded in damages. A minor solatium of £500 would uphold the duty and reflect society's real evaluation of the insult. Since he had not really caused the complication, it seems illogical to pretend that the law is enforcing a duty to advise that is equally important whether the complication results or not.

Another oddity of the case was that Miss Chester was at no less risk if she opted for conservative therapy. The evidence was conflicting, but some experts thought that she was at greater risk of long-term disability if she did not undergo surgery. As she was in significant pain preoperatively, she would need to persuade the court that she would have undergone surgery or recovered spontaneously to recover full compensation when her quantum was assessed.

Summary box 69.2

Doctors must advise their patients so that they can

- exercise their autonomy;
- even if that demands a greater share of NHS resources than they need.

The problem is more acute for obstetricians and gynaecologists than it is for other specialties for a number of different reasons. In gynaecology, apart from cancer, most procedures are designed primarily to enhance the woman's comfort or reproductive choices. They are truly elective procedures, which the woman must be free to accept or reject on her own terms. In obstetrics, the reduction of maternal mortality and the marginalization of infant mortality have meant that the woman feels that she should be put in a more powerful position. In *Montgomery* v *Lanarkshire Health Board* the UK Supreme Court has spelled out the importance of advising on the alternatives, even when no surgical intervention is planned [1].

Summary box 69.3

It is not possible to record the sort of advisory session that the law demands in a conventional outpatient clinic.

Abortion

Doctors have been in the front line of the legal control of abortion since *R* v *Bourne* in 1938 [6]. There has been thrust upon them a dual role in which they are seen as the servants of the law as well as their patients. Until the Abortion Act 1967 was passed, the doctor who performed an abortion in most circumstances committed a professional offence as well as a crime and would be struck off on conviction. The day the Abortion Act came into force, the medical abortionist ceased to be a criminal and so prosecutions before the GMC ceased. This struck no-one as odd because the law had been changed by the Queen in Parliament and if abortions were going to be performed lawfully then the GMC had to permit them. The professional offence had been to break the law. Yet the change in GMC policy as a result of the change in the law served to emphasize the fact that the GMC did not impose any distinct medical ethic or code of behaviour as had been supposed since Hippocrates, it simply reflected the law. In this respect at least there was no separate stream of doctor-made laws controlling the profession and the Oath of Hippocrates might prohibit abortion but it proved to be subordinate to the general law of the land, perhaps a litmus test for much else that has happened in medicine over the 70 years since *R* v *Bourne*.

Yet the change in abortion law went far beyond that foreseen by Parliament. When Parliament decided that it should be lawful to perform an abortion when the doctor believed that continuation of the pregnancy would be more hazardous to the health of the mother or other

children in the family than the termination of the pregnancy, few realized that this in effect legalized abortion on demand since enough doctors honestly believed that such a continuation would always be more hazardous. In 50 years, no doctor has been prosecuted before the GMC for exploring the limits of this envelope.

The predicament of the obstetrician who is asked to treat a woman for an unwanted pregnancy was made more complicated in 1990. In essence, Members of Parliament (MPs) faced a widespread doubt about the wisdom of the existing law when the new Human Fertilisation and Embryology Act was being debated. A sizeable group of MPs wished to bring down the upper limit for abortion, which was then when the fetus would be capable of being born alive. Others took a more liberal view. The compromise agreed upon was that until the pregnancy has exceeded its twenty-fourth week, abortion should be available on the existing criteria, which effectively meant abortion on demand, even where the fetus may be larger than those in the adjacent neonatal intensive care unit. Since women do not become pregnant before they ovulate, which on average is not before the fourteenth day of the cycle, this means that a doctor who believes in good faith that the social ground is satisfied may lawfully terminate a pregnancy until 26 weeks from the last menstrual period. I stress that this is untested in court and the conventional view within medicine is that the limit has been set at 24 weeks; however, to sustain that view the court would have to say that the maturity of the pregnancy referred to the time since ovulation.

After that limit, apart from where it is necessary to save the mother's life or health, abortion is lawful only when the doctor believes there is a substantial risk that the child, if born, would suffer from a serious handicap. Neither 'substantial' nor 'serious' was defined by the Act. In essence, MPs, who could not agree amongst themselves, decided to leave matters to doctors and women. The doctor was given the power to decide in consultation with the patient when it would be appropriate to perform an abortion. A substantial risk is generally speaking regarded as something of substance, to be taken into account in the organization of one's affairs. Usually this means less than the balance of probabilities. If that were right, it would be lawful at any point prior to delivery to abort a fetus who, on the balance of probabilities, would be born healthy.

Parliament did not consider such questions as whether the child had to be abnormal at birth or destined to remain handicapped permanently. So we do not know if it is lawful to terminate in the case of Huntington's chorea, which does not usually afflict a person until the fourth decade of life, or the person born with a surgically remediable lesion.

The intervening years have not been kind to a compromise based upon deference to the judgement of an individual clinician. With the rise of personal autonomy and the decline of medical authority, there is little role for a doctor to decide what is best for a patient and there is much less of a role for a doctor to tell a patient what they must and must not do. If a medical service is available, the assumption is that the doctor must provide it if the patient demands it and it is clinically appropriate. Something of a crunch point was reached in 2004 when a curate of the Church of England recognized in the statistics issued by the Department of Health that a pregnancy had been terminated at 26 weeks where the indication given was a cleft palate. If the lesion was a part of a broader syndrome, that was not apparent in the information published by the Department of Health. The curate complained to the police, who sought guidance from the Royal College of Obstetricians and Gynaecologists (RCOG). The police decided not to investigate further and an application was made for judicial review of that decision. The police agreed to reconsider matters and did investigate with a view to prosecution. Eventually they decided that the evidence available did not enable them to conclude that a prosecution would have a better than 50% chance of persuading a jury that the doctors did not have the bona fide belief that the circumstances of the Act were satisfied.

However, the case triggered a debate around several issues. The first is whether the compromise decided by Parliament was far more liberal than can be defended in view of intervening medical developments. Where advances in ultrasound have made it possible to visualize the unborn child more clearly than ever before, the difficulty in defending a decision to terminate on grounds of cleft lip and palate is harder to justify. The autonomy that the law accords the pregnant woman is based on the recognition that the unborn child is part of her body: this is challenged by the ability to visualize the fetus and watch it moving on ultrasound films that the mother carries on her mobile phone and to interact with it by performing medical procedures for its benefit. Nor does it help that advances in neonatology have brought the age of viability down still further, so that the fetus who is being killed is more often capable of being born alive and of surviving than ever before, often more mature than babies being treated in the critical care unit.

This is something about which obstetricians may provide expert advice to the legislature but must remain essentially neutral. Thus, the RCOG has published the reports of working parties on the extent to which a fetus may experience pain [7] and provided guidance on the termination of pregnancy for fetal abnormality [8], but in

neither case is it articulating a moral view to its fellows and members in the fashion in which the Hippocratic Oath bound all doctors not to procure abortion until comparatively recently. However, the RCOG does express strong views about the problems facing the service. Abortion is now the commonest procedure paid for by the NHS, almost 200 000 cases a year, and yet most cases are outsourced to commercial organizations that provide little or no training. Complex procedures are confined to the NHS, but many places expect to face problems in delivering the service when the present generation of seniors retire.

There is a second underlying debate about the role of the clinician. Is the doctor expected to exercise a judgement about whether the procedure is in the patient's best interests? If so, on what basis? If the indication for the procedure is choice, how can or should the doctor second guess the patient? When Parliament said that it wanted the decision to be taken by doctors and patients together, did it mean that the patient should have complete freedom to decide if the doctor believed that the unborn child would suffer from any recognizable handicap? What is the extent to which it is proper to expect obstetricians to be put in the guise of judges at all in such circumstances? The assessment of the degree of handicap should be undertaken by those appropriately trained for the purpose. Often they will be members of another specialty; in some places such patients are referred to paediatric surgeons for advice, and the RCOG Working Party [8] in 2010 suggested referring to a paediatrician with experience of affected children. I wonder if we will not go further in the future: sometimes the assessment of long-term handicap might be enhanced by a multidisciplinary assessment involving specialists in neurological disability, physiotherapists, speech therapists or occupational therapists. The effect of a given physical lesion will vary greatly from case to case, depending on the personality of the victim and the resources available, as well as the severity of the lesion. The difficulty is that it is hard to see how such an assessment can be organized swiftly enough when the pregnancy is advancing.

The law here has to balance society's interest in protecting the autonomy of the pregnant woman and ensuring that she is not forced to carry to term a baby which she does not want. That right has to be balanced against the right of the unborn child; since Parliament has decreed that the unborn fetus has no right, this has to be expressed as society's interest in protecting the fetus. Few think it appropriate to provide women with an unqualified right to demand the destruction of a normal third-trimester fetus. The need to balance these issues calls for a political and judicial assessment. Although doctors were placed in the front line, it is increasingly hard to understand what role society allots to them or how it expects them to perform this task. In few other areas of medicine are doctors asked to legislate between conflicting interests in this fashion; and where they have been granted a broad margin of discretion hitherto, as in end-of-life decisions, that flexibility is being curtailed.

In these circumstances the individual clinician needs to be aware of the conflicting obligations which are imposed by the law and the demands of patients. My own advice now is that, so far as possible, obstetricians should ensure that they have written objective advice from appropriate specialists on which to base their decisions. In contentious cases I suspect that we will soon advise obstetricians to transfer the decision to the place where it should properly be made, Her Majesty's Judiciary. At least that way we will get some guidelines. It will be very unfortunate if the first time that any guidelines as to the law's assessment of the meaning of substantial risk of serious handicap comes to be decided is in the context of a criminal prosecution. Under the law, until 1990 the reluctance of the police to intervene meant that no-one attempted to find out what 'capable of being born alive' meant between its passage into law in 1929 [9] and the advent of a negligence action in respect of an obstetrician's failure to advise a woman of the failure of an alpha-fetoprotein test to detect abnormality. The Court ducked the question then and was forced to determine it in 1989 when a radiologist was sued in respect of his failure to recognize spina bifida [10]. Only then was it established that 'capable of being born alive' meant capable of maintaining life by means of ones' own breathing, even though 60 years had elapsed since the Act was passed.

In the meantime, obstetricians should be advised to cover themselves by seeking to buttress their decisions by obtaining the sort of written evidence that a court would demand. That evidence should explicitly answer the statutory questions: Is the risk substantial and would the handicap be serious? The RCOG has recently reiterated its advice of 1996, and until we have guidance from a court on the meaning of the word 'substantial' in this Act, it would be wise to err on the side of caution [8]. How a court would interpret the meaning of 'substantial' could well determine on the context in which the question was posed. We could get almost any answer, from 20% – on the basis that a substantial risk is one that sensible people would take into account in ordering their affairs – to beyond all reasonable doubt, on the basis that a mature fetus should not be killed unless you are sure it will be handicapped. The latter is perhaps an extreme and unlikely view, but the court could easily demand the balance of probabilities.

Summary box 69.4

The current emphasis on patient rights is inconsistent with the role of the doctor as a co-decision maker assumed by the abortion law under the 1990 Act.

Professional discipline

Another feature of the landscape of which clinicians need to be aware is the changing role of the GMC. After the profession suffered body blows in public esteem through a series of scandals in the 1990s, the GMC was reformed so as to make it much tougher on the under-performing doctor. The standard of proof was reduced from the criminal to the civil standard: it was emphasized that the civil standard does not simply mean the balance of probabilities but the panels tend to take a confident approach to issues of fact. The innovations were surrounded with honeyed words about reform and rehabilitation, but in practice those doctors who have been identified as under-performing through the GMC processes have rarely found their way back into mainstream practice again. The National Clinical Assessment Service also grapples with the problem of the under-performing doctor, but its success rate for getting doctors back into practice once they have been identified as under-performing has not been good. These processes usually lead to the end of the clinician's career. The Medical Practitioners Tribunal Service, which adjucates on prosecutions by the GMC, now has a minority of doctors on its panels and the people who are there sometimes have a critical view of the profession.

It was also agreed by the profession that it should embark on some formal system of revalidation. Continuing professional education was instigated in the 1990s in response to the minimal-access surgery furore, and as a result the RCOG was the first College to instigate a system of formal recorded continuing professional education in the UK. It was agreed that revalidation needed to be something more, involving not only evidence of learning and reflection but also evidence of continuing ability, but the more ambitious programmes of revalidation fell on the stony ground of the unaffordable.

Postgraduate training

Another issue that is concerning for the future of the profession arises from the developments in professional training over the last 15 years. The introduction of the Working Time Directive in the UK halved the number of hours per week that the junior hospital doctor works. The introduction of the Calman Reforms and the Specialist Registrar Grade reduced the number of years of experience in training grades that a newly appointed consultant can be expected to have achieved by a similar proportion. The result is that the newly minted consultant acquires a fraction of the clinical hours of experience of their predecessor 30 years ago.

In dealing with junior hospital doctors over the last 30 years, one feels that the profession has squandered a monastic tradition of devotion and apprenticeship. The *BMJ* reports, for example, that junior surgical trainees are unable to tie knots, a basic skill that used to be acquired by medical students [11]. As a result, trainees cannot be entrusted, even under supervision, with the simplest procedures that recent predecessors could manage alone. Seniors report occasions when assistants have walked out at 17.00 sharp, although the operation had reached a critical point. The sense is that doctors are there to do a job within the hours for which they are paid, rather than to undertake a commitment to patients throughout the clinical pathway.

The result is a decline in continuity of care and an attitude to handover that depends on written records rather than real communication to another doctor who will accept the same responsibility. Far more time is devoted to handover so that the proportion of junior time available for the management of the sick has fallen still further.

Worst of all, the exposure of the junior doctor in each hour of experience that is gained is markedly reduced. One understands the need to protect patients and to ensure that the service they receive is safe and consistent, but the effects have been extreme. A newly appointed senior registrar of the 1970s would be likely to have performed more surgical procedures alone and to have experienced significant complications more frequently than the newly appointed consultant of today. These events were good for neither patient nor doctor. The emphasis on using the hours of training for that very purpose is all to the good, in the sense that the juniors are well taught in a procedure-specific sense. But it is no way to acquire an understanding of the natural history of disease in humans, or the flexibility to recognize when things are going wrong.

At the moment, the position is still being mitigated by the presence of senior consultants who benefited from the old-fashioned model of training. We are pedalling backwards to protect this year's patients at the expense of the experience of next year's consultants; thus, the last three National Confidential Enquiry into Perioperative Outcome and Death case studies have advised that all acute admissions should be seen by a consultant within 12 hours.

Every year these consultants retire and are replaced by colleagues who simply do not have the same sort of training. To some extent the problems can be mitigated in elective surgery by increasing subspecialty and higher training in courses post appointment as consultant, but we are encountering a brave new world in more and more hospitals where there is no consultant who benefited from the old-fashioned sort of training. The idea that junior consultants are going to acquire the experience and training that they need in the course of their early consultant years overlooks the fact that they are not in a training grade and that increasingly there is no-one there to train them if they do have the modesty to ask for help and guidance.

For a time it looked as if the newly appointed young consultants would take on the attitudes of their seniors when appointed and accept the notion of 24-hour responsibility necessary to provide continuity of care for those they regarded as their patients. The NHS decided in 2003, apparently in ignorance of the fact that most consultants still maintained the same standards of dedication they had acquired as juniors and worked way beyond the hours for which they were paid, that it would pay consultants for the hours they worked. The result was a massive bill that that threatened to cripple many Trusts and there had to be some firm negotiation. This change represented a turning point: the older doctors continue to provide the service their patients need despite the nominal fact that they are not being paid for it, but their attitudes already appear old-fashioned and are being replaced by a new respect for an appropriate work–life balance. A new generation has emerged, shaped in a fashion devised by the managers of the service rather than their clinical seniors.

Summary box 69.5

The modern intolerance of risk makes demands that are challenging the training of the next generation of consultants.

The conflict between the lack of training and the hostile environment

The combination of this crisis in professional training and the less-forgiving professional environment in which doctors work means that the prospects for the individual doctor are ever gloomier. The basic premise of the reforms proposed by the Shipman Inquiry was that there is a plentiful supply of newly minted doctors available to replace those who are found not to have kept their professional skills up to date. This premise is profoundly mistaken and an unprincipled attempt to entice doctors to quit poorer countries – it cannot provide a sustainable solution. In defending doctors before the GMC, we already find an unforgiving atmosphere and an assumption that someone must have done something wrong whenever a patient has died. The notion of being just to the doctor who is the respondent to a complaint is low down on a set of priorities which are headed by making sure that the service is 'safe' and giving satisfaction to somebody simply because they have complained.

Outside the portals of the GMC the complaints system within hospitals has been reformed and made similarly more hostile to the profession. The advice that one gives to professionals in these circumstances is much the same as it has always been – spend time with patients, talk to them and listen to them; explain in detail what is proposed, recognizing that the purpose of the consultation is to put your knowledge at the patient's disposal so that she can make her decision about what she wants to do. This explicitly involves an acceptance of the proposition that sometimes patients will make decisions which the doctor thinks are surprising, if not profoundly misconceived. The patient has an unfettered right to refuse surgery for good reason, bad reason or no reason. The doctor must ensure that the risks of inaction are spelled out as clearly as the risks of the intervention in question. The doctor's role is to advise and to recognize that while their skills are for their patient, their notes are for themselves and their own protection. It is as important to make detailed records of what is said to and by the patient as it is to make records of the clinical history that is elicited and the signs that are found.

It must also be recognized that the patient's right to choose in effect must sometimes mean a right to demand therapy that the doctor thinks is contraindicated. This is an issue with which the profession and the NHS is only beginning to grapple. It found its first utterance in the National Institute for Health and Care Excellence (NICE) guidelines concerning caesarean section [12]. The patient who demands an unfair share of resources in the form of a caesarean section that the doctor thinks is not medically indicated is not in the same position as the woman who insists on home delivery against medical advice. Both are demanding a share of medical resources that seems to exceed the clinical indication in the eyes of the medical attendant, but the woman who demands an operation is demanding that her doctor does something that appears to be inappropriate. She should be offered referral to a colleague where practical, but doctors should never find themselves doing an operation that they believe is contrary to their patient's best interests.

In other areas, the service operates on the premise that patients will not demand surgery which is not in their interests. How far that premise is well founded is unclear. We do have some experience of professionals being sued

for unnecessary procedures in the context of dentistry. There is a long-established line of cases in which patients have demanded extravagant, conservative restoration of teeth whose roots are unsuitable. The smile may be attractive at first but the life expectancy of the bridge is short. The same thing happens even more often in cosmetic surgery. The courts almost invariably criticize the dentist or the cosmetic surgeon for having performed a procedure contrary to the patient's best interests as the professional saw them. The conventional advice to a professional is that when a patient demands a procedure which appears to be contrary to their best interests, the professional should decline to perform it and offer to refer to someone else. That conventional advice must still be good in 2018, but as professional autonomy advances the question must arise as to whether the patient's right to choose will sooner or later entitle them to demand surgery which the doctor thinks is contraindicated, with the same freedom as the waiter should accept an order for an unsuitable combination of dishes. If the autonomy of the patient is paramount and the playing field of knowledge of the implications of medical procedures becomes ever more level, it is difficult to understand how the status quo can be preserved indefinitely.

Cerebral palsy

All this is a long way from the core of the issues which were at the forefront of professional concern when this chapter's first predecessor was written in 1999. Then, the concern of the obstetrician with the law was as it had been since 1980 when the House of Lords gave judgement in *Jordan* v *Whitehouse* [13] that the doctors involved would be sued by children suffering from cerebral palsy who sought to blame their disability on the doctor. Although Mr Jordan's case resulted in a victory for the defence, the experience of the defence organizations was that the public remembered only that a claim had been brought in respect of a brain-damaged child, not that it was lost. Although the defence witness who gave evidence that the damage could not have been caused by the actions of which complaint was made, Professor Ronald Illingworth found his evidence rejected at trial. He subsequently wrote an influential article in the *BMJ* 'Why blame the obstetrician?' [14], which drew on work already being done by neonatologists in America, and over the succeeding 30 years we have become used to a much more measured assessment of causation in these cases.

About half of the money paid by the NHS Litigation Authority, which deals with claims against the NHS, is devoted to cases of birth injury. However the provisions for future payments are dominated by these cases and these are growing at double the amount paid by commissioners for obstetric services. It is also true that the number of children in the population suffering from cerebral palsy has remained roughly constant despite improvements in obstetrics and paediatrics that have transformed the rates of infant mortality and the prospects of survival of the child once delivered. This is probably due to the increased age of the parturient woman since the introduction of *in vitro* fertilization, and has been associated with increased rates of maternal obesity, diabetes and associated complications. The EPICure II study [15] has found that advances in neonatology have brought more survivors from the extremes of prematurity, but still many suffer from the associated disability. It is also true that social expectations for a perfect result have made it difficult for us to defend such cases, even where the extremity of prematurity makes it clear that survival at all is astonishing. The introduction of a programme of Early Notification, requiring the NHS Litigation Authority to investigate potential cases before the parents complain, is likely to result in substantial increase in the number of such claims.

The advent of NHS indemnity in 1990 has taken the financial burden of these sorts of cases off the shoulders of the medical profession. Claims handling was centralized in 2002, so that there is an additional level of insulation between the individual doctor and the damage. Risk management and clinical governance demand ever higher and more intolerant standards, but the massive financial impact of these claims is insulated from the services delivered in the individual Trust in that year. There was a period when a multimillion pound claim against the Trust would or could cause cashflow problems that sent the Chief Executive cap in hand to the regional office of the Department of Health. That at least has gone, but as NHS liabilities now increase by £8 billion a year it has been replaced by the NHS going cap in hand to HM Treasury.

Outside the NHS, private obstetrics is being driven to the wall in England by the problems inherent in asking indemnifiers to cover claims that are regularly pleaded at over £40 million in an individual case.

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70

Evidence-based Medicine in Obstetrics and Gynaecology

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Clinical care constantly challenges health professionals to ensure that techniques for diagnosis, prognosis and treatment are up to date and consistent with best practice. Given the exponential rise in the numbers of scientific publications, doctors increasingly face the double challenge of keeping up with the latest information and choosing the best tests or treatments based on sound evidence from appropriately conducted research.

One way of doing this successfully is to practice evidence-based medicine (EBM). EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients [1]. It involves integrating clinical experience and skill with the best available external clinical evidence and awareness of an individual patient's situation and preferences in making clinical decisions about their care.

In this chapter we explore all three components and show that EBM is not the preserve of non-clinical researchers but that it is feasible to incorporate EBM within everyday practice by busy clinicians who devote their scarce reading time to selective, efficient, patient-driven searching, appraisal and incorporation of the best available evidence. Clinical decisions should be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament and preferences, and thus whether it should be applied. Evidence-based guidelines, however, cannot compensate for poor clinical skills in eliciting a diagnosis or interpreting a test result or performing a procedure.

Practical evidence-based medicine

Any clinic consultation throws up a number of questions. For example, in a woman presenting with pelvic pain, what investigations are useful? If endometriosis is diagnosed, what is the best treatment which is consistent with the woman's circumstances and preferences? Similarly, if no cause can be found what is the most effective way of dealing with the symptom of pain? The key principles underpinning the practice of EBM in this and other similar situations are captured in the five As: Ask, Acquire, Appraise, Apply and Audit.

Ask: framing a structured question

The first step in the practice of EBM is to transform an overarching clinical question, for example what is the best way to manage a particular case, into a series of focused answerable questions in a manner which facilitates a systematic enquiry. A standard approach is to use five components – *p*opulation, *i*ntervention, *c*omparison, *o*utcome and *d*esign (PICOD) – to refine the question and enable a literature search to be carried out. Table 70.1 shows examples of how to frame similar questions. Although this approach may appear to be stilted, it merely disarticulates the steps of decision-making which most clinicians accomplish intuitively and rapidly in everyday practice.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

Table 70.1 Framing a structured question

Component	Question in Obstetrics	Question in Gynaecology
Population	Overweight or obese pregnant women	Women with heavy menstrual bleeding
Intervention	Antenatal intervention comprising exercise and/or diet	Endometrial ablation
Comparator	Usual antenatal care	Levonorgestrel Intrauterine System
Outcome	Large for gestational age baby (wt > 90th centile)	Improved quality of life
Design	Randomised trial	Randomised trial

Summary box 70.1

Steps of evidence-based clinical practice

- Ask: a PICOD (*p*opulation, *i*ntervention, *c*omparison, *o*utcome and *d*esign) based approach to refine a question.
- Acquire: a hierarchical approach to literature searches, starting with known repositories of clinical practice guidelines and evidence-based reviews before moving onto primary research data.
- Appraise: all search contents should be subjected to a rigorous process of evaluation in the local context.
- Apply: applying the results of critical appraisal involves interpreting the evidence in the local context and integrating it with clinical expertise and awareness of patients' values and expectations.
- Audit: true adherence to the principle of EBM requires regular evaluation of clinical performance.

Acquire: searching the literature

A structured detailed literature search can be cumbersome and time-consuming, something that systematic reviewers and information scientists are well aware of. For busy clinicians there are significant advantages to a hierarchical approach to literature searches, starting with known repositories of clinical practice guidelines and evidence-based reviews rather than primary research data (Fig. 70.1). However, it is important that the methods used by guidelines, systematic reviews and individual studies are robust and reflect the nature of the clinical questions. Guidelines and evidence summaries in obstetrics and gynaecology are regularly produced and updated by a number of organizations including professional bodies such as the Royal Colleges and professional societies as well as national organizations such as the National Institute of Health and Care Excellence (NICE) in the UK, and in some conditions by international bodies such as the World Health Organization (WHO).

If high-quality evidence-based guidelines are unavailable, the next step is to search for good-quality systematic reviews relevant to the questions at hand. If none is found, the next step is to seek primary research papers whose methodologies need to reflect the clinical question. For example, for effectiveness of interventions such as medical or surgical treatments or more complex interventions, the appropriate studies are randomized trials. Either cohort or case–control studies might be appropriate for investigating the aetiology of clinical conditions, while cohort studies are suitable for assessing prognosis. Test accuracy is often evaluated by cross-sectional studies in which new tests are compared against a gold standard.

Summary box 70.2

Sources of evidence relevant to clinical questions

- Guidelines: include evidence as well as its interpretation in a specific context.
- Systematic reviews: synthesis of available evidence.
- Randomized trials: best way of evaluating treatments.
- Observational studies: demonstrate association between causes and consequences.
- Diagnostic test accuracy studies: assess the ability of a test to correctly identify a condition.

A list of some relevant sources of guidelines and evidence-based summaries is shown in Table 70.2. The Cochrane Library and the Centre for Reviews and Dissemination (CRD) databases, including Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) Database), undertake high-quality evidence synthesis exercises in a number of topics including obstetrics and gynaecology. In addition, publications databases such as Medline and PubMed are also sources of many systematic reviews. PubMed contains a systematic review filter called PubMed clinical queries, while Medline has the indexing time 'reviews, systematic' as a 'publication type'. If no systematic reviews can be found, it is necessary to search for primary studies of relevance.

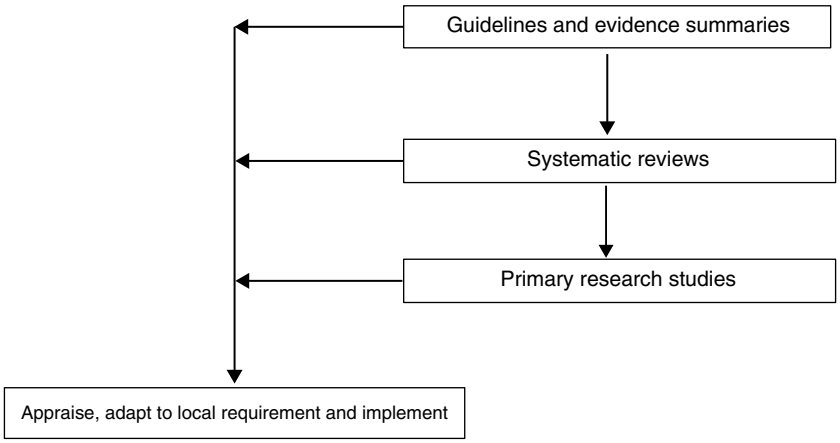

Figure 70.1 Searching the literature for evidence.

Table 70.2 Sources of some guidelines and evidence based summaries in obstetrics and gynaecology

Royal College of Obstetricians & Gynaecologists	https://www.rcog.org.uk/guidelines
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/guidance/published?
American College of Obstetricians and Gynaecologists	http://www.acog.org/Resources-And-Publications
International Federation of Gynaecology and Obstetrics	http://www.figo.org/publications-resources
NHS National Library for Health	https://www.nice.org.uk/about/what-we-do/evidence-services/journals-and-databases

Finding articles of relevance in order to answer a clinical question amongst over 1 million biomedical articles published each year is hugely challenging. It is necessary to choose appropriate keywords to search databases for publications. Strategies that increase the accuracy and efficiency of searches are available at the site established by the Centre for Evidence-Based Medicine (http://www.cebm.net/category/ebm-resources/). A systematic search needs training and practice and input from a librarian or information scientist. It requires careful choice of keywords, which need to be matched to medical subject heading terms and combined using Boolean operators such as 'and' or 'or'. Within PubMed, three tools which are particularly useful include PubMed Clinical Queries, PubMed Slider Interface for Medline and PubMed, and PubMed Related Article.

Appraise: critical evaluation of the literature

Because of methodological variations, recommendations from guidelines and the conclusions of systematic reviews and primary research papers cannot all be accepted with confidence. Many may be methodologically sound but not be directly relevant to the particular clinical question under consideration. Some may not be affordable, feasible or culturally acceptable. Thus it is important that all search contents are subjected to a rigorous process of evaluation in the local context.

Guidelines

Guidelines can vary in quality. Good clinical guidelines must be multidisciplinary, evidence-based and evidence-linked. The Grade Working Group [2] offers useful advice on how to link guidance to the strength of the evidence base and its relevance to the clinical question and its context. A good guideline needs to be scientifically valid, usable and reliable. Most importantly, it must lead to better patient outcomes [3]. The AGREE collaboration has developed an appraisal instrument for clinical guidelines, tested it across a number of countries and found it to be user-friendly and consistent and able to discriminate between guidelines of varying quality. Criteria for high-quality clinical guidelines include clear articulation of scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. It is available at www.agreecollaborartion.org.

Systematic reviews

A systematic review generates an overview of relevant studies using an explicit, methodical and reproducible way to locate, appraise and synthesize data. It may or

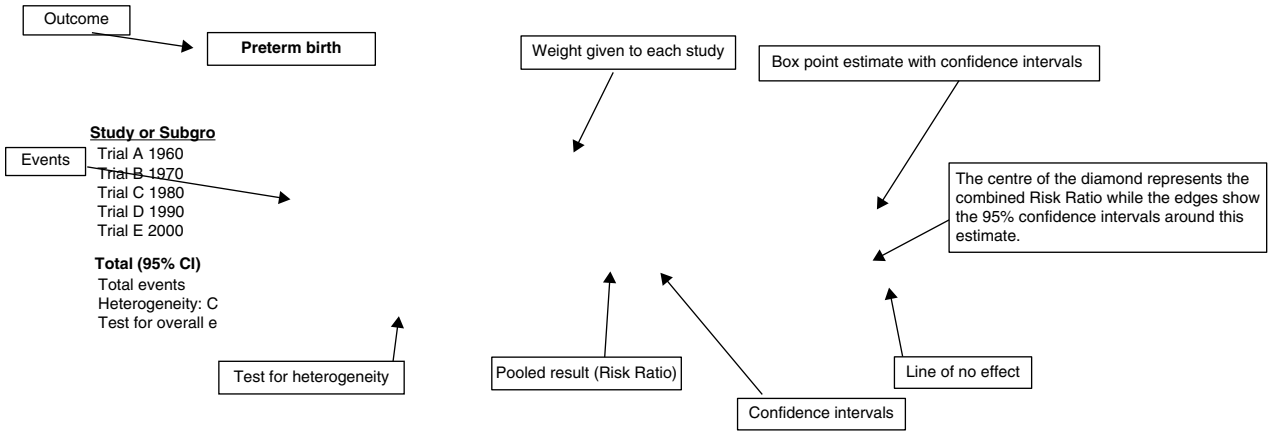

Figure 70.2 Forest plot of aggregated data from randomised trials.

may not include formal aggregation of quantitative data from individual studies or meta-analysis. Results of meta-analysis are often presented as Forest plots (Fig. 70.2). Good systematic reviews have a clear question, comprehensive and methodical search of the literature, explicit criteria for inclusion and exclusion of studies, assessment of study quality and meta-analysis where appropriate. As sources of high-quality evidence, well-conducted systematic reviews of randomized trials are preferable to individual randomized trials, as single studies may be unrepresentative of the total literature on a subject. Inconsistent results across studies can be explored and the ability to pool data allows greater precision around estimation of effects in interventions.

An initial appraisal of the quality of a systematic review should include an assessment of the credibility of the methods used and confidence in the effect estimates [4], i.e. the validity of the methods and effect size and precision of the results. The results of any research need to be relevant to the local context, be applicable to the patient group under consideration and address outcomes which are important for patients. The treatment must be affordable and provide benefits which outweigh any harms. Formal ways of evaluating the quality of systematic reviews are discussed below.

Randomized trials

A randomized trial should be able to transcend many of the risks of bias associated with observational studies. In large trials, random allocation to the treatment or comparison group should result in women in both arms being similar as regards known and unknown confounders. Differences in treatment outcomes between them can then be assumed to be genuinely due to the treatment itself rather than any other factor [5]. Non-randomized studies with control arms may offer some information about the effect of the treatment in question but they could exaggerate the potential benefits of treatment due to deliberate selection of women most likely to benefit from it. Because flaws in the design, conduct, analysis and reporting of randomized trials can distort the impact of treatment, a formal assessment of risk of bias is important in assessing trial quality. There are a number of sources of bias associated with the conduct and reporting of clinical trials.

Selection bias can occur if there are major differences between the randomized groups that could influence the outcome of the intervention being evaluated, and can be minimized by using robust methods for random sequence generation. Concealment of allocation up until the point of randomization is critical in order to avoid any chance of prior knowledge about which option (intervention or comparison) a participant would receive. Performance bias can be mitigated by masking participants and clinicians so that knowledge of the allocated intervention does not influence care or interpretation of outcomes. Masking of personnel can also minimize the risk of detection bias, where knowledge of the intervention received could affect interpretation and reporting of outcomes. Attrition bias reflects loss of patients to follow-up in a non-random fashion and could bias the final results; this can be avoided by ensuring that outcomes are reported in all patients, with clear reasons for any exclusions. Finally, reporting bias can occur if only certain outcomes were included in the final publication. The Cochrane risk of bias tool [6] addresses potential chances of selection, performance, detection, attrition and reporting bias as well as any other sources of bias in a systematic manner with clear criteria for reporting high, low or unknown risk of bias.

Diagnostic test accuracy studies

Tests used in clinical practice are usually evaluated by diagnostic accuracy studies in terms of sensitivity, specificity, predictive values and likelihood ratios. Conventionally, patients are classified into those who test either positive or

negative for a particular condition. A common way of evaluating tests is to determine the proportions of patients with normal and abnormal test results who are identified correctly. Sensitivity is the proportion of true positives and specificity refers to the proportion of true negatives that are correctly identified by the test. However, none of these parameters gives us an estimate of the probability that the test will give the correct diagnosis. This information is presented in terms of positive and negative predictive values. Positive predictive value represents the proportion of patients with positive test results who are correctly diagnosed while negative predictive value is the proportion of patients with negative test results who are accurately identified. The predictive value is strongly influenced by the prevalence of the condition under investigation. If the prevalence of the disease is very low, the positive predictive value will be poor even if both sensitivity and specificity are high. In population-based screening, as in cervical smear tests, it is inevitable that many women with positive test results will be false positives. We can compare the probability of getting a test-positive result if the patient truly had the condition of interest with the corresponding probability if he or she were healthy. The ratio of these probabilities is called the likelihood ratio, calculated as sensitivity/(1 – specificity). The likelihood ratio indicates the value of the test for increasing certainty about a positive diagnosis. In general, the higher the likelihood ratio of an abnormal test, the greater its usefulness. For example, likelihood ratio values of 10 or more suggest that the test could be extremely useful, while a value of 1 suggest that it is useless. For a negative test, a likelihood ratio of 0.1 or less suggests that it is useful, while a value of 1 indicates that it is not. In practice, the applicability of a test depends on a given context, prevalence of the condition being tested for, clinical and cost consequences of being test positive, and personal preferences of the patient.

Observational studies

While randomized clinical trials are the best way of assessing effectiveness of treatments, data from observational studies are useful sources of evidence in answering questions regarding cause, diagnosis and prognosis of clinical conditions. Most randomized trials are able to report on adverse effects which are relatively infrequent and/or take many years to present due to limitations of power and duration of follow-up. Large observational studies with long-term follow-up data can be helpful in terms of identifying long-term side effects as well as demonstrating whether the outcomes achieved in the context of a trial can be duplicated in an unselected population.

Where trials do not exist, are underway or are simply not feasible due to ethical or other considerations, the only source of data on the effectiveness of an intervention could be controlled non-randomized prospective studies (i.e. cohort studies). It must be remembered that these studies are prone to bias and their results could be overturned by the results of future randomized trials. For example, observational data on hormone replacement therapy suggested that it was protective against myocardial infarction, but randomized trials suggested an increase in risk [7].

Formal methods used for critical appraisal of systematic reviews and primary research studies

There are several sources of guidance for critical appraisal of research studies. The Centre for Evidence-Based Medicine offers training as well as practical tools for critical appraisal (http://www.cebm.net/critical-appraisal/). One of these is CATmaker (http://www.cebm.net/catmaker-ebm-calculators/), a computer-assisted critical appraisal tool that helps to create Critically Appraised Topics (CATs). The Critical Appraisal Skills Programme (CASP, http://www.casp-uk.net/#!casp-tools-checklists/c18f8) also offers a set of tools which assist clinicians in assessing the quality of research evidence. CASP favours a three-step approach, assessing first the validity of the results to decide whether the study was unbiased by evaluating its methodological quality. The second step is to consider whether the study's results are clinically important and the level of precision around the results. The final step is establishing how the data apply to a specific question and how likely it is that the intended population shares the same characteristics as those of the research subjects. Criteria for assessing the quality and relevance of systematic reviews, randomized trials and diagnostic studies are summarized in Table 70.3.

Applying the evidence

One of the major challenges is the global evaluation of the best available evidence not just in terms of precision but also validity and local relevance in order to estimate our level of confidence and inform the strength of any clinical recommendations arising from it. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has addressed this issue by categorizing the quality of evidence into four groups [8]. High quality indicates that further research is very unlikely to change our confidence in the estimate of effect. Evidence is deemed to be of moderate quality if further research is likely to have an important impact on confidence in the estimate of effect and could change it. Low quality implies that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality evidence suggests significant uncertainty around any estimate of effect [8]. Results of randomized controlled trials

Table 70.3 Criteria for critical appraisal Based on the Critical Appraisal Skills programme (CASP) checklists (http://www.casp-uk.net/#!casp-tools-checklists/c18f8)

	Systematic reviews	Randomised trials	Test accuracy studies
Validity	Clear research question	Clear research question	Clear research question
	Inclusion of papers with the appropriate design	Random allocation of patients to treatments	Appropriate reference standard (gold standard test)
	Relevant studies included	Masking of participants and clinicians	New diagnostic test and reference standard administered to all
	Quality assessment of the included studies	Similar baseline characteristics	Test results independent of results of reference standard
	Clear justification for aggregation of data	No difference in clinical care between intervention and comparison group apart from allocated treatment	Clear description of disease status of the tested population
		All participants accounted for	Detailed description of test
Precision	Effect size		
	Precision of effect size (confidence intervals)		
Relevance	Applicability of the results to the local population		
	Inclusion of all important outcomes		
	Balance of benefits versus potential harm and costs		

are initially regarded as high-quality evidence, but can be downgraded for several reasons: study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias. Study design and precision of results have been discussed earlier. Consistency refers to similarity in the direction of effect across studies, an explanation for outliers and plausible outcomes in subgroups. Directness signifies the extent to which people and outcomes in the literature are relevant to those of interest. This can be due to a number of factors, including lack of direct comparison, differences in the nature of individual treatments within a single generic group, publication of surrogate rather than definitive outcomes, and cultural differences in perceptions of harm and benefit.

Conversely, observational studies reporting on treatment outcomes are rated as 'low quality' but may be upgraded if the effect of an intervention is substantial, if there is a convincing dose–response relationship or if all plausible biases are likely to decrease (rather than inflate) the magnitude of any treatment effect.

Applying the results of critical appraisal involves interpreting the evidence in the local context and integrating it with clinical expertise and awareness of patients' values and expectations. In the first instance, a key question is whether the findings are applicable to the specific patient group. It requires consideration as to whether the treatment or test would be effective in the patient or clinic population concerned and asks the question: Are there reasons to believe that the results from the literature would not apply to them? Many treatments which are otherwise effective are associated with adverse effects, such as drug side effects or operative and postoperative complications. While a detailed analysis may not always be possible, it is important that all clinically relevant outcomes are assessed over a reasonable period of time, thus allowing a balanced appraisal of the harms, benefits and costs.

Patients may have a different set of values which may inform their priorities and preferences around healthcare. Appreciation of the patient's perspective and facilitating a balanced discussion that allows joint decision-making are essential components of this step. If true EBM is to be practised, the current conflict between the objective collection of data and its subjective interpretation has to be addressed. Ways of overcoming bias at this very last stage of implementation include decision analysis, involving explicit decision-making algorithms [9] and computer-based decision support systems. In many situations, particularly in benign gynaecological settings, there could be several options which patients could consider. Involvement in the decision-making process and confidence in the decision made could improve their perceived effectiveness of the intervention itself.

Evaluating performance

True adherence to the principle of EBM requires clinicians to evaluate their own performance. This can involve assessing progress at each step of the process in terms of whether the questions asked were answerable, if evidence was identified and appraised and integrated with clinical expertise and the patient's circumstances to generate a rational treatment plan. It also allows the

clinician to reflect on whether the risks and benefits of treatment were considered along with the patient's own preferences [1].

Conclusion

EBM allows clinicians to offer treatments which are effective. This is accomplished through improved skills in asking relevant questions, finding and appraising the best evidence before application of the results in routine practice. Increased popularity of EBM has been accompanied by a growth in web-based access to clinical guidelines and systematic reviews as well as tools for critical appraisal. There is now universal agreement that successful decision-making in clinical situations needs to integrate the highest quality of evidence with clinical expertise and the values, preferences and personal circumstances of each patient.

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Index

Note: page numbers in *italics* refer to figures; those in **bold** to tables.

Dewhurst's Textbook of Obstetrics & Gynaecology, Ninth Edition. Edited by D. Keith Edmonds, Christoph Lees and Tom Bourne.

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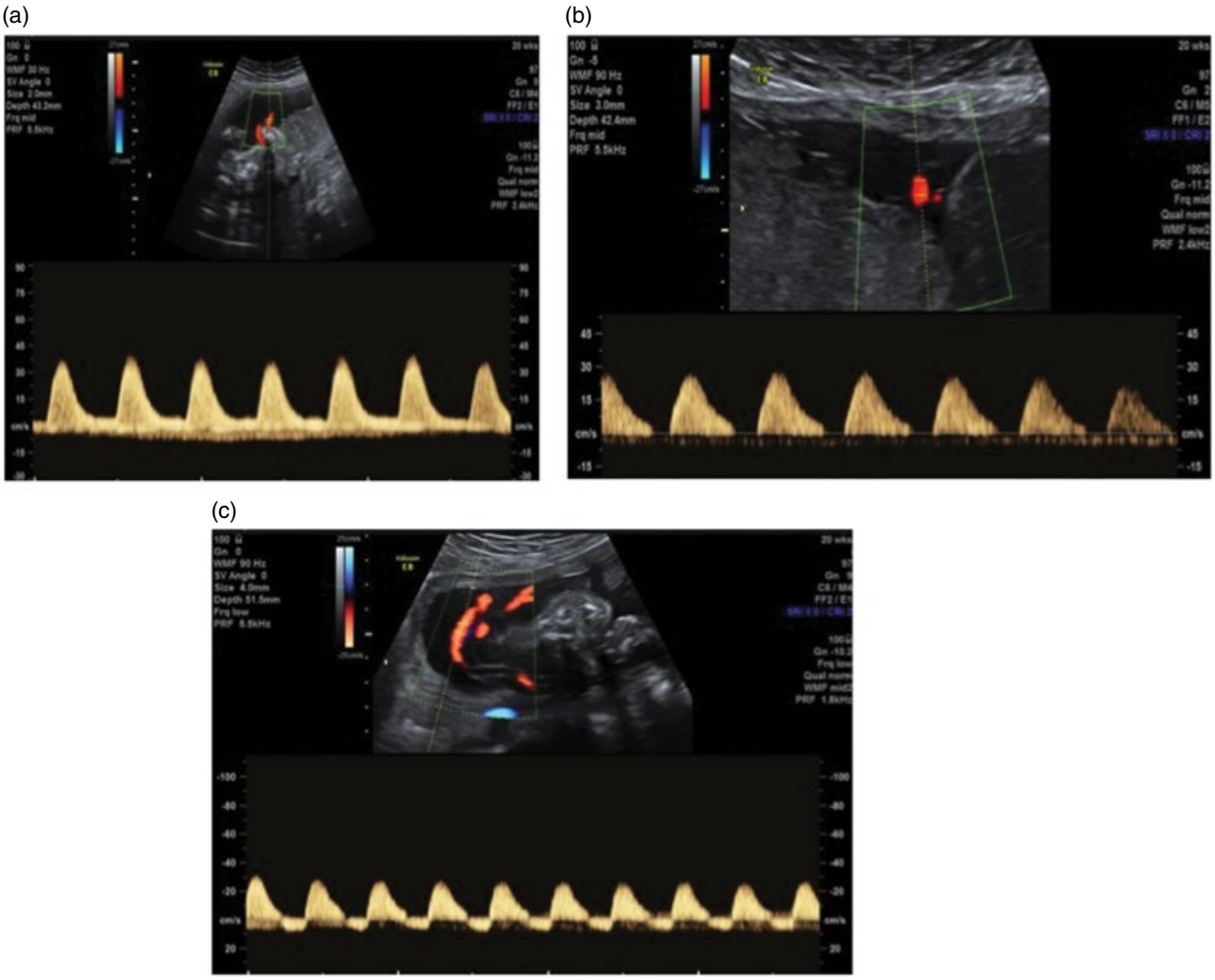

Plate 17.2 Umbilical artery Doppler waveforms: (a) normal; (b) absent end-diastolic flow; (c) reversed end-diastolic flow.

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(a) (b)

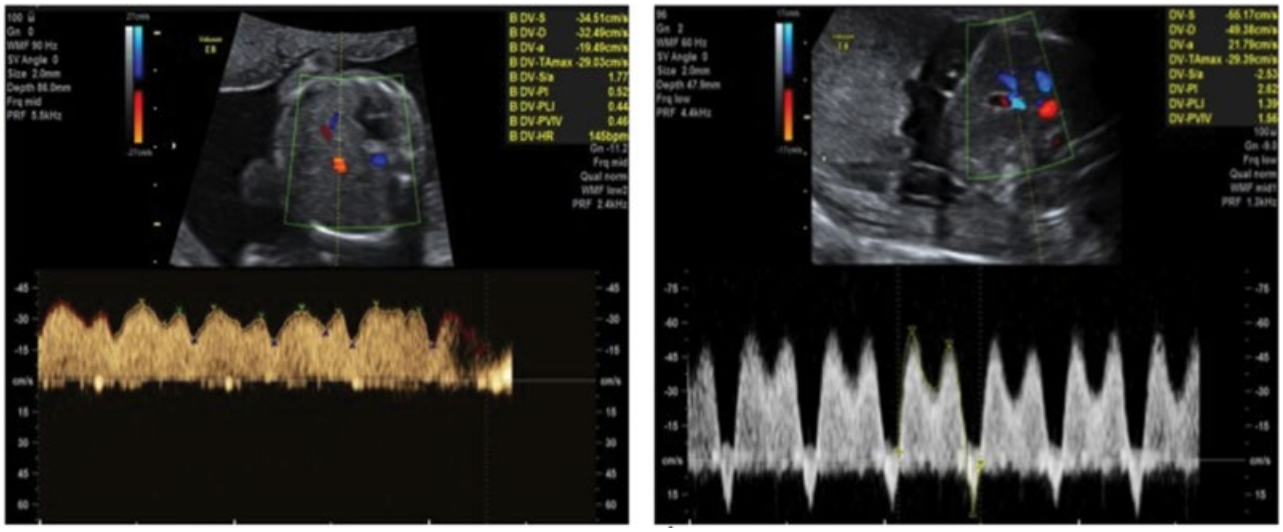


Plate 17.3 Ductus venosus waveforms: (a) normal; (b) reversed a-wave.

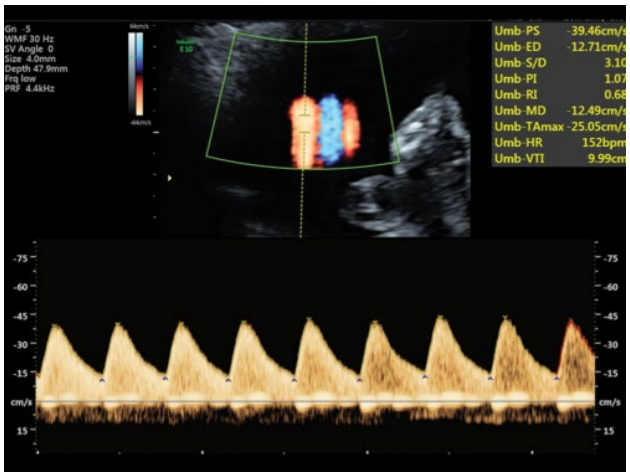


Plate 18.4 The umbilical artery is typically assessed in a free loop. The vein and arteries can be identified with colour Doppler and pulse wave is used to illustrate the waveform characteristics, which can be measured and compared with standardized charts. In this example there is forward flow in diastole, a normal finding in the third trimester of pregnancy.

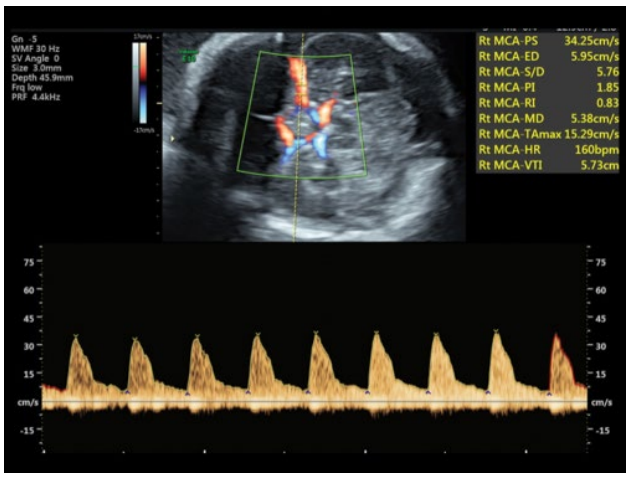


Plate 18.5 The middle cerebral artery waveform can also be assessed by first identifying the vessels running away from the circle of Willis, then using pulse wave to demonstrate the waveform (sampling approximately 5–10 mm away from midline structures). In this example there is low flow in diastole, a feature of normal perfusion.

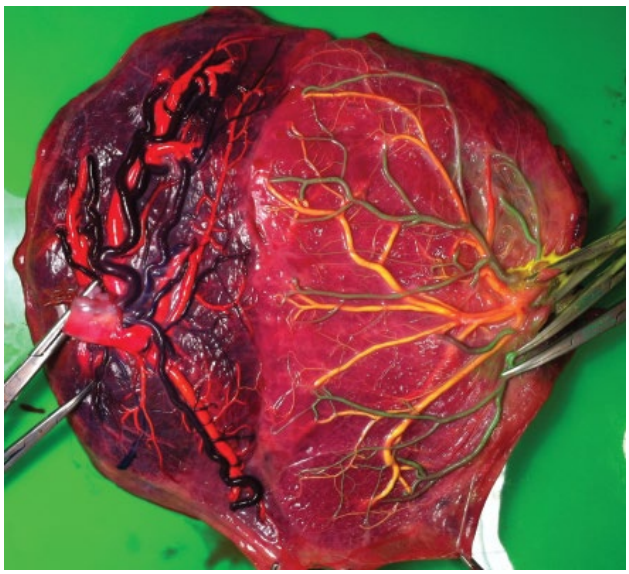


Plate 21.1 TAPS is believed to be due to the presence of miniscule arteriovenous anastomoses (<1 mm). *Source:* Dr E. Lopriore. Reproduced with permission of Dr E. Lopriore.

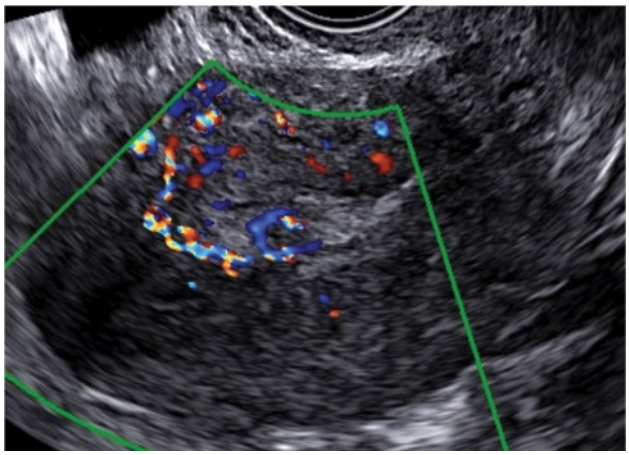
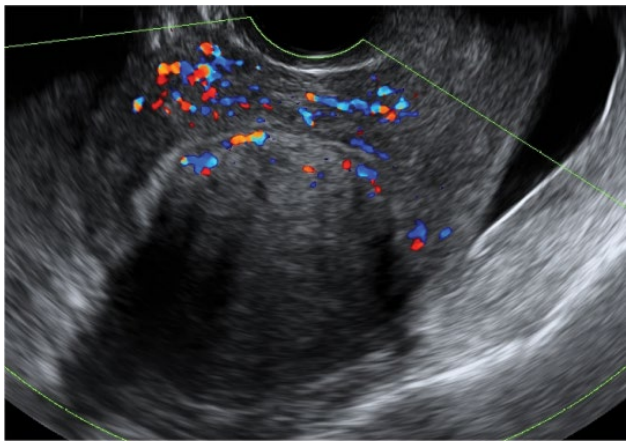


Plate 36.4 Endometrial polyp with 'pedicle artery' sign on colour Doppler imaging.



Plates 36.5 Uterine fibroid with typical features: a well-circumscribed round lesion, presence of acoustic schadowing and limited circumferential vascularization on colour Doppler imaging.

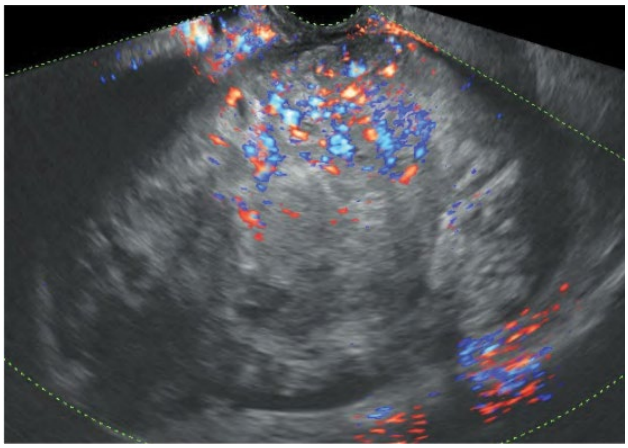


Plate 36.6 Uterine sarcoma: large oval-shaped lesion with heterogeneous echogenicity and prominent intralesional vascularization on colour Doppler.

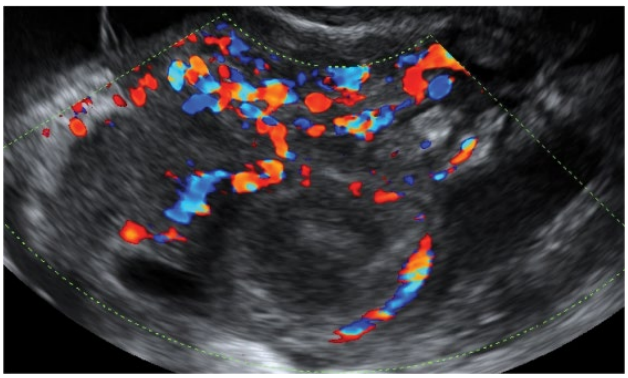


Plate 36.12 Tubo-ovarian abscess: loculated process with oedematous walls and prominent vascularization on colour Doppler. Normal ovarian stroma is no longer visible.

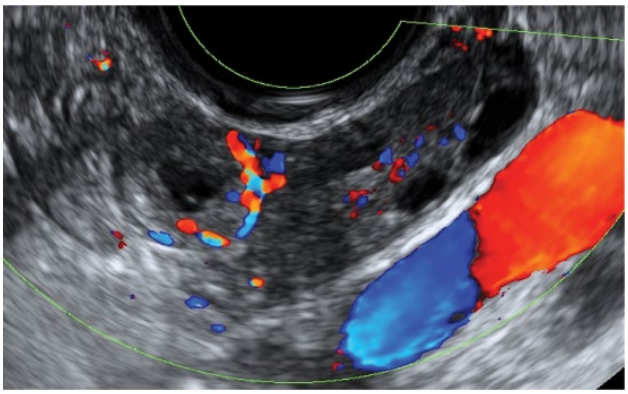


Plate 36.14 Tubal ectopic pregnancy with 'bagel' sign. Extrauterine gestational sac is visible in a transverse section through the fallopian tube, which could be mobilized from the normal ovary on pushing with the probe.

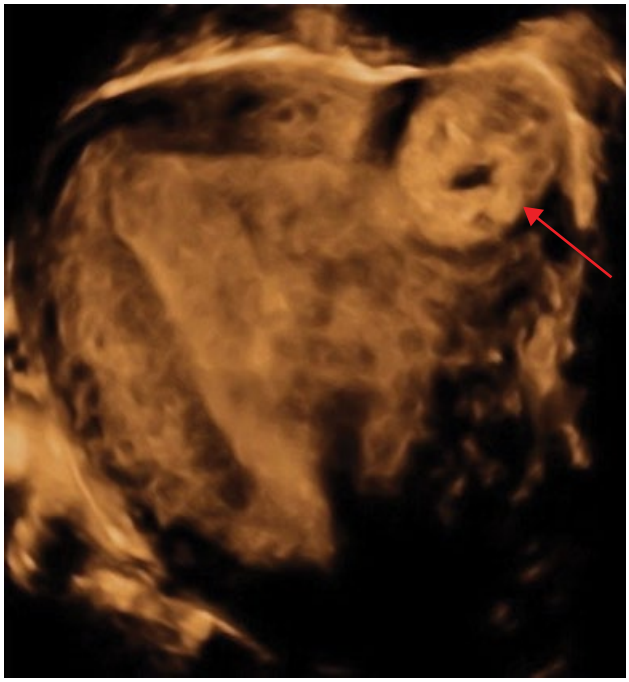


Plate 43.2 Coronal view of the uterus showing an interstitial ectopic pregnancy (arrow).

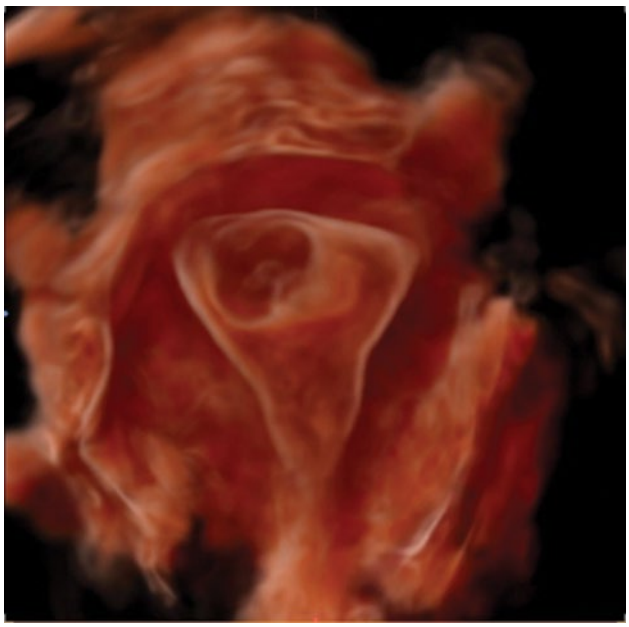


Plate 51.1 Rendered three-dimensional ultrasound scan showing a type 0 fibroid in the endometrial cavity.

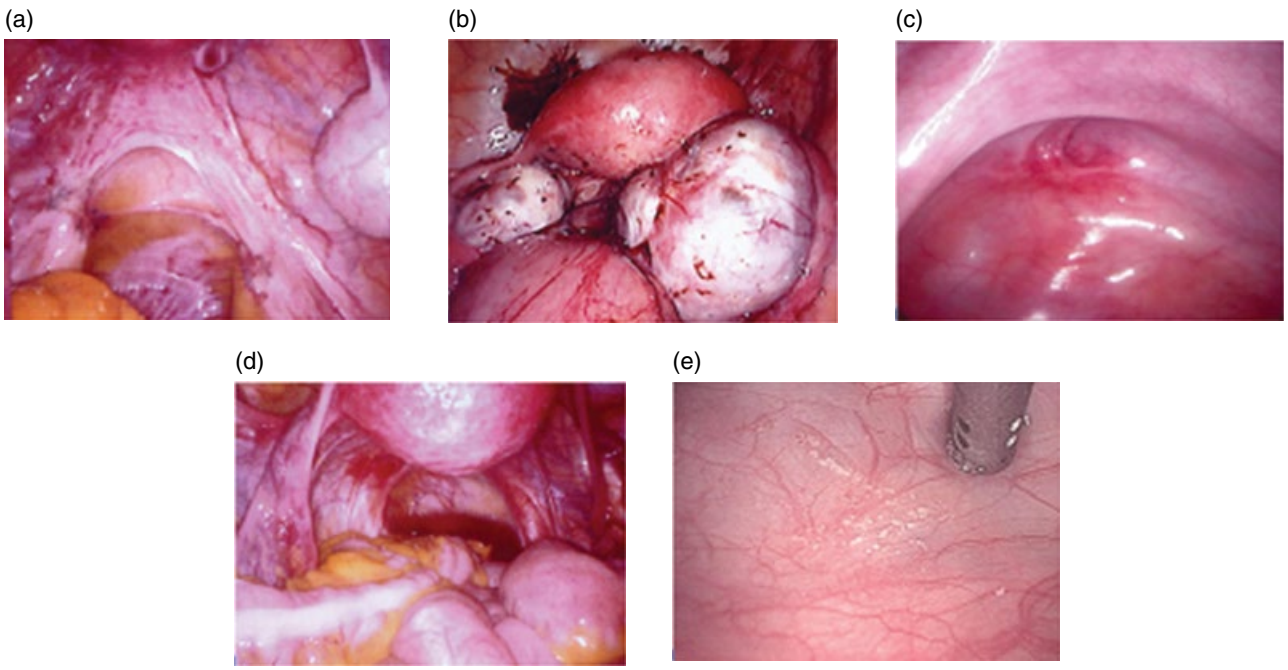


Plate 53.1 Laparoscopic appearances of different endometriosis phenotypes: (a) peritoneal (typical) endometriosis adjacent to deep endometriosis of the left uterosacral ligament; (b) endometrioma of the right ovary; (c) peritoneal pocket in the anterior pouch of Douglas; (d) uterine adenomyosis and flame endometriotic lesion of left broad ligament; (e) subtle endometriosis vesicular lesions of the peritoneum. Images (a), (b), (d) and (e) kindly contributed by Dr Michael East, Gynaecologist, Oxford Women's Health, Christchurch, New Zealand.

(b)

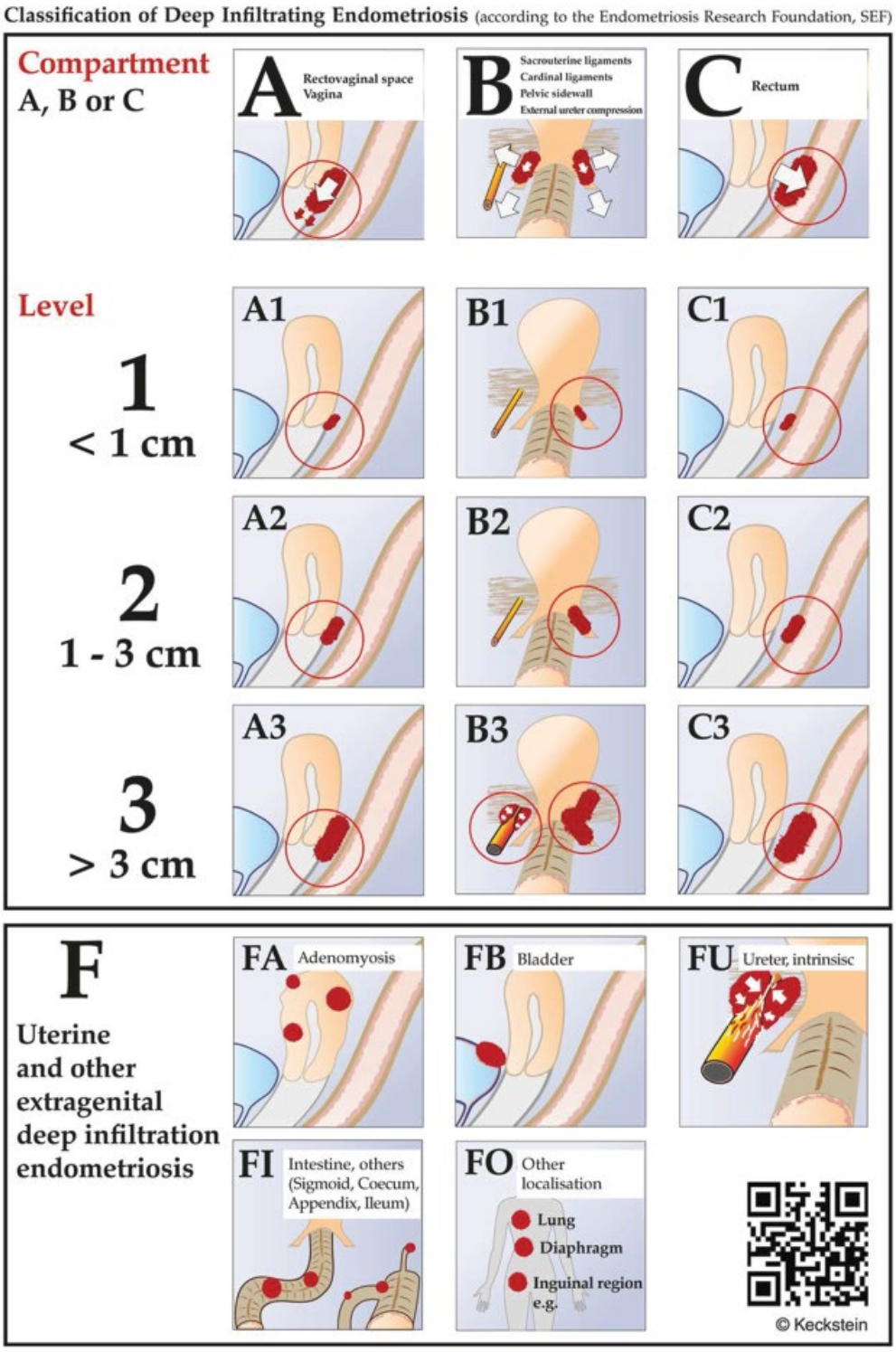


Plate 53.3(b) Classification systems for endometriosis: Enzian classification system for women with deep endometriosis.

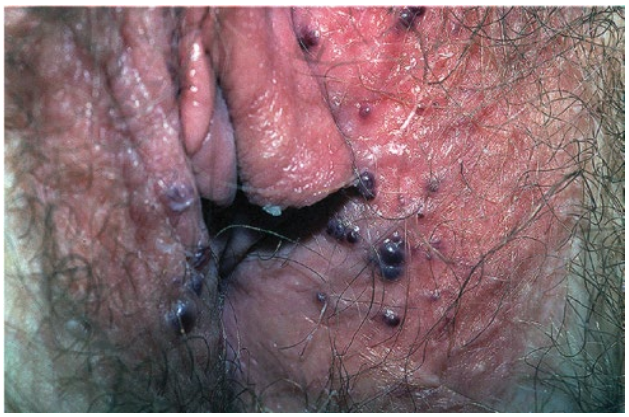


Plate 57.1 Angiokeratomas: dark-red papules seen on the labia majora.

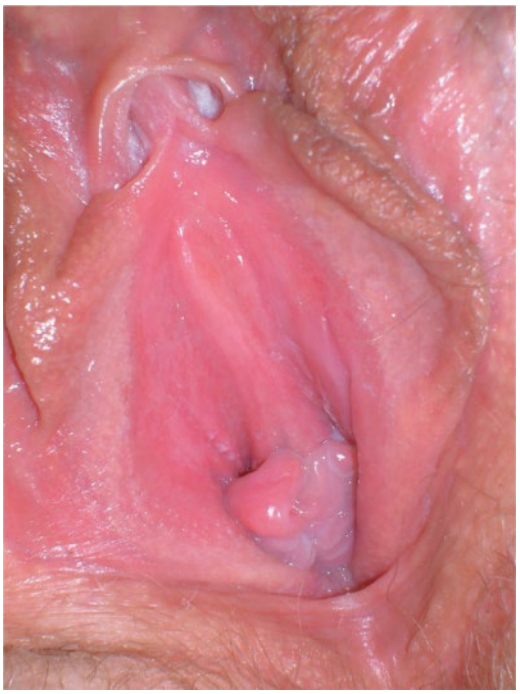


Plate 57.2 Hart's line demarcating the junction between the keratinized skin of the labia minora and the non-keratinized mucosa of the vestibule.

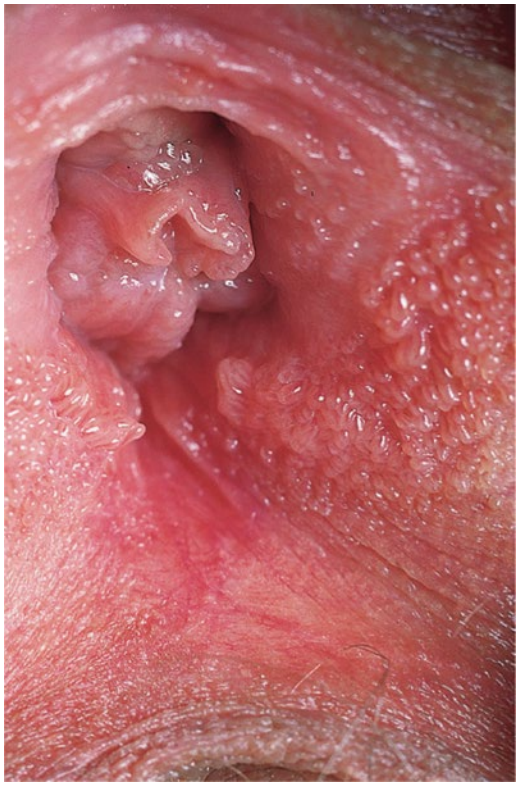


Plate 57.3 Vestibular papillae: filamentous projections of the vestibular epithelium.

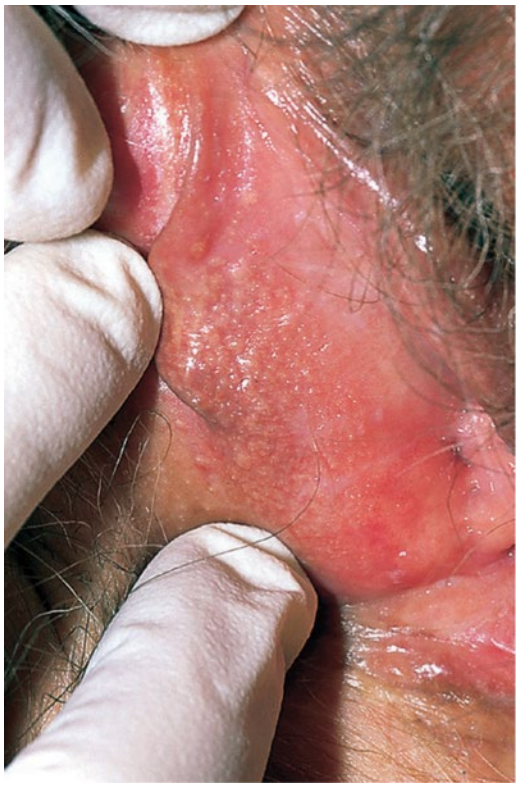


Plate 57.4 Fordyce spots: tiny yellow papules on the inner labium minus.

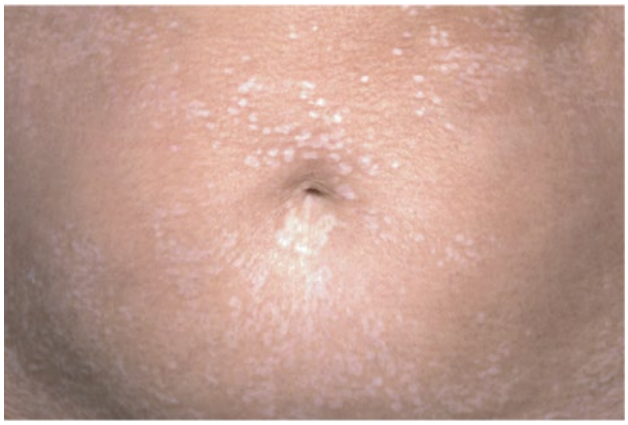


Plate 57.5 Extragenital lichen sclerosus: 'white spot disease'. Flat white lesions which can coalesce into plaques. Follicular plugging may be seen.)

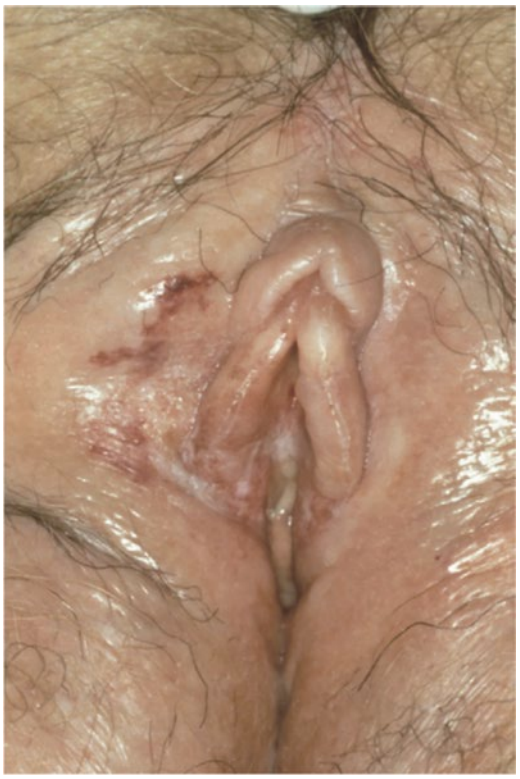


Plate 57.6 Vulval lichen sclerosus: early established disease showing rubbery oedema of labia minora and clitoral hood and stark whitening extending to perianal skin. Note currently healing fissure at 6 o'clock position.

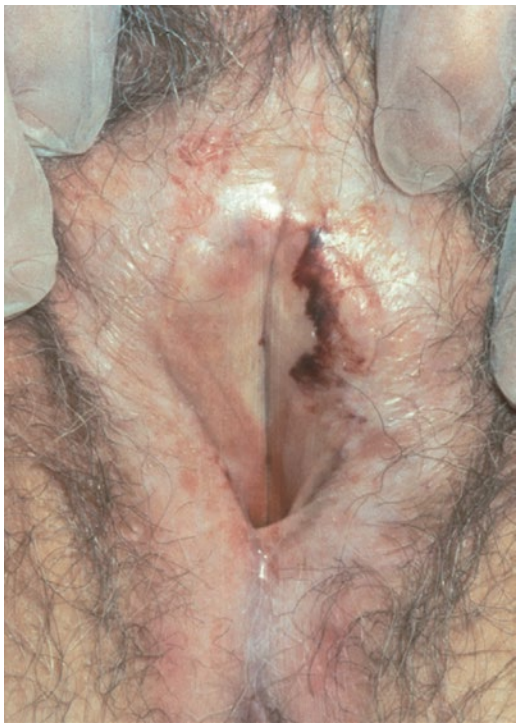


Plate 57.7 Advanced vulval lichen sclerosis: white sclerotic change, complete burying of the clitoris and total replacement of architecture with 'plastering' down and resorption of labia. Gross ecchymoses and narrowing of vaginal introitus.

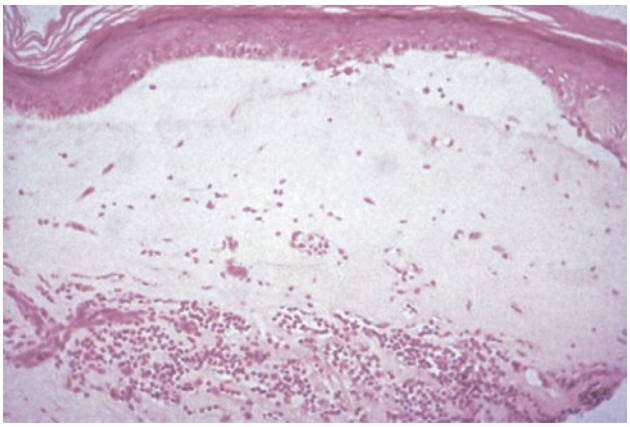


Plate 57.8 Histology of lichen sclerosus: an atrophic epidermis is seen over the homogenized band of collagen and, below this, a lymphocytic infiltrate. Haematoxylin and eosin × 40.

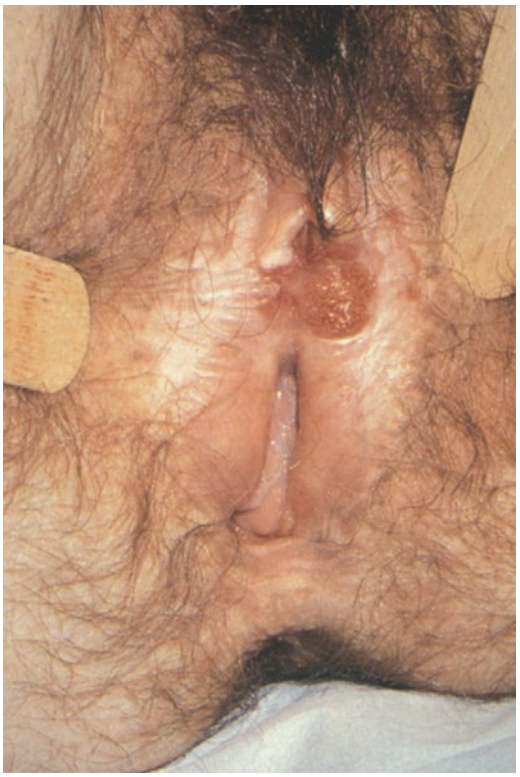


Plate 57.9 Lichen sclerosus complicated by squamous carcinoma. Note the classical cigarette-paper scarring and background whitening. Here the squamous cell carcinoma presents as a fleshy nodule, but persistent erosion should also prompt biopsy.

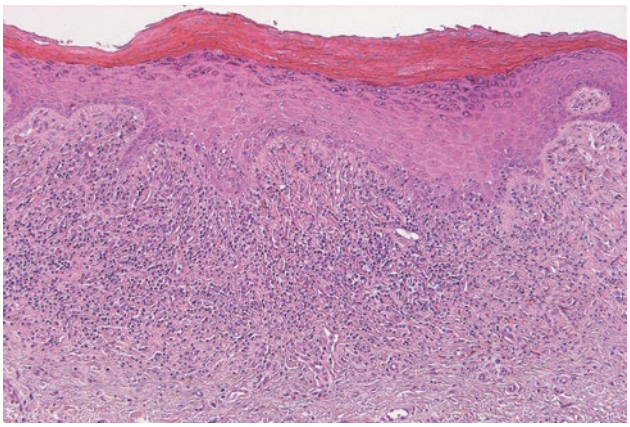


Plate 57.10 Histology of lichen planus showing saw-toothing of the epidermis, with a dense lymphocytic infiltrate and liquefactive degeneration of the basement membrane. *Source:* Eduardo Calonje. Reproduced with permission of Eduardo Calonje.

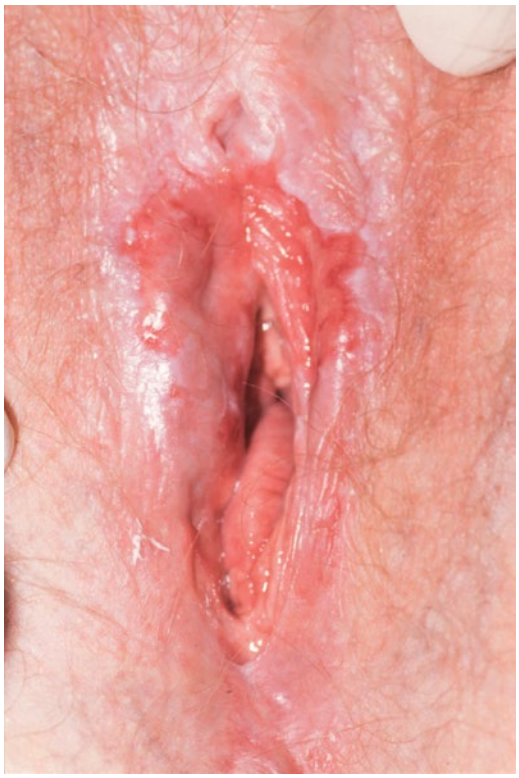


Plate 57.11 Erosive lichen planus: there is scarring with loss of the labia minora. Wickham's striae are seen at the edge of the erosions.

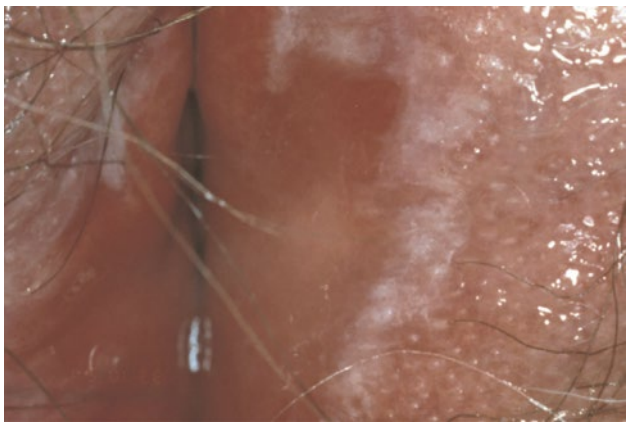


Plate 57.12 The lacy white edge of the eroded area is seen. This is the best site for biopsy.

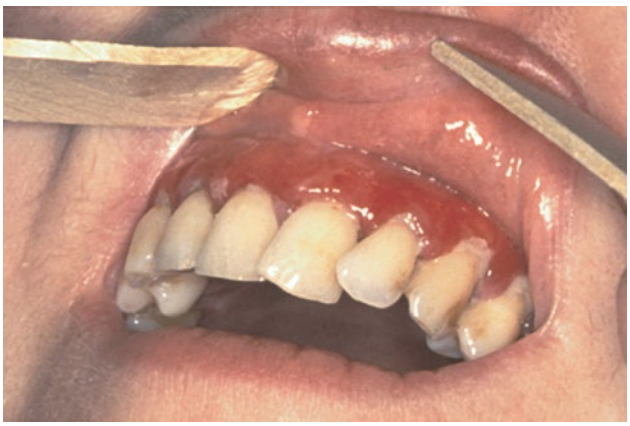


Plate 57.13 Erosive lichen planus with gingival involvement. Erythema and erosions are seen at the gingival margins. Similar lesions may be seen on the buccal mucosa and tongue.

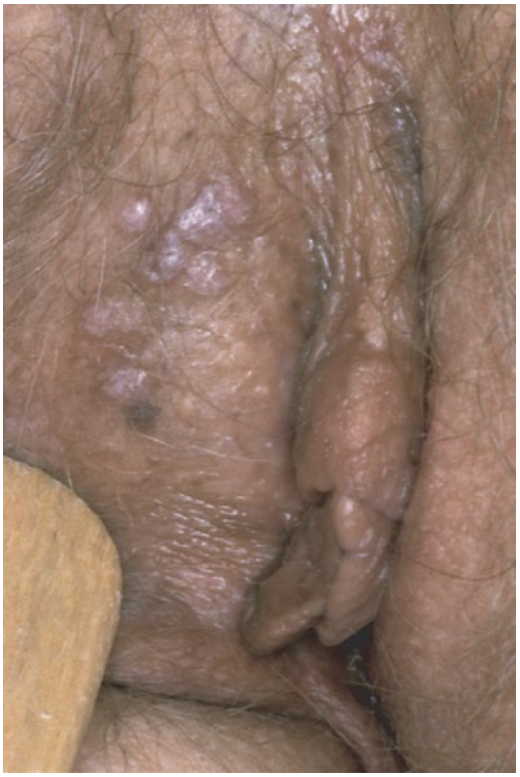


Plate 57.14 Papular lichen planus: typical coalescing flat-topped papules showing white Wickham's striae. They are violaceous in colour and are usually also found on the inner wrist and elsewhere.

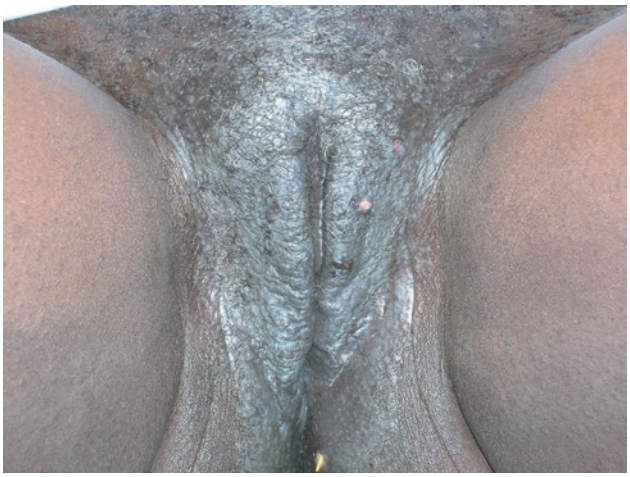


Plate 57.15 Vulval lichen simplex: the outer labia majora are significantly lichenified with accentuated skin markings and loss of hair from rubbing.

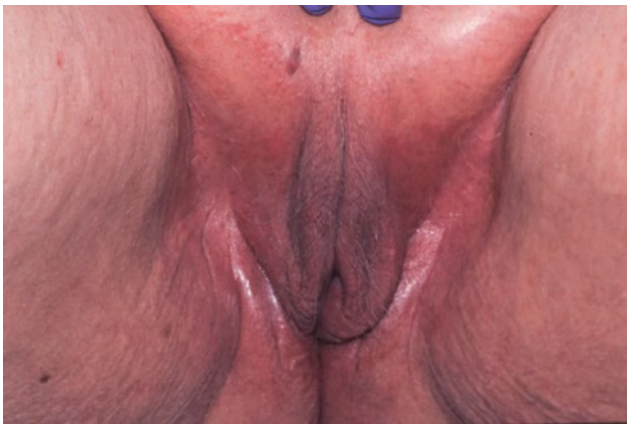


Plate 57.16 Vulval psoriasis: erythema and maceration with extension into the inguinal folds. The edge is still well defined.

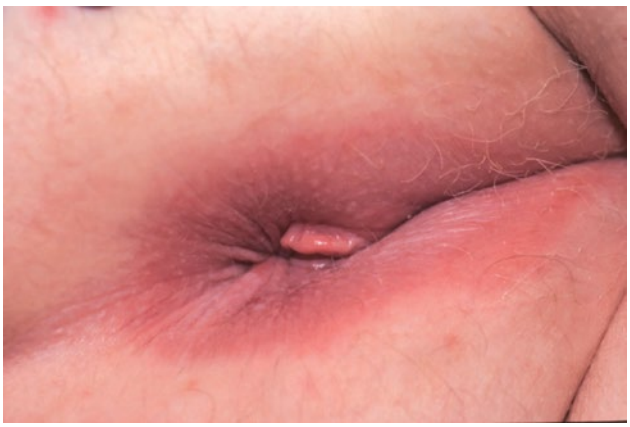


Plate 57.17 Perianal psoriasis: well-demarcated erythema with extension into the natal cleft.

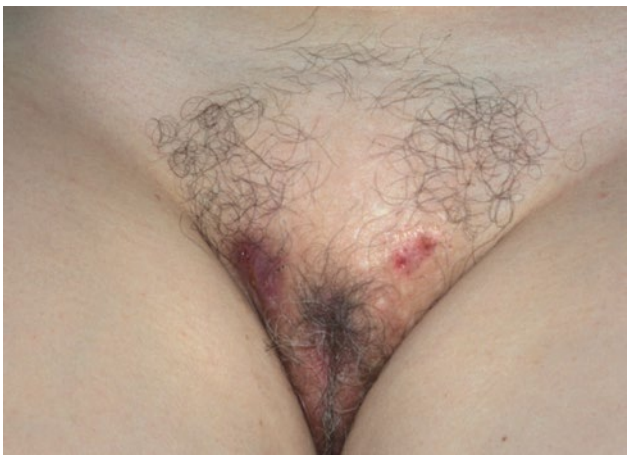


Plate 57.18 Hidradenitis suppurativa: oozing inflamed lesions are seen on the mons publis with bridged comedones.

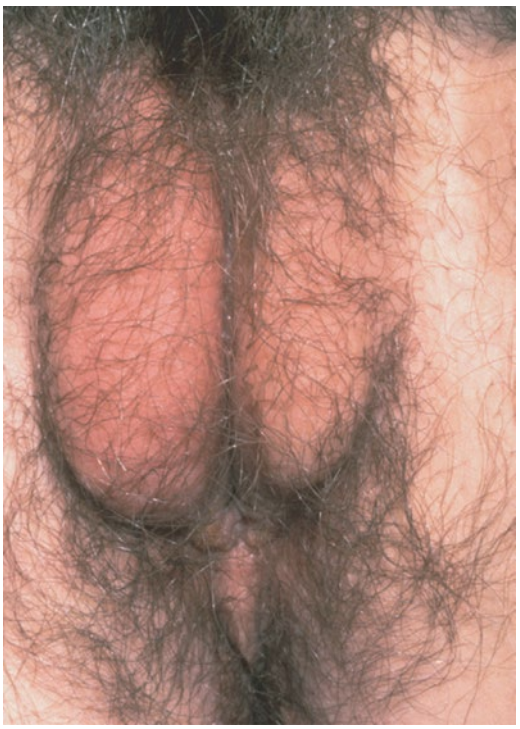


Plate 57.19 Unilateral vulval oedema: Crohn's disease. Sometimes vulval oedema, usually unilateral, can accompany Crohn's disease of the gastrointestinal tract.

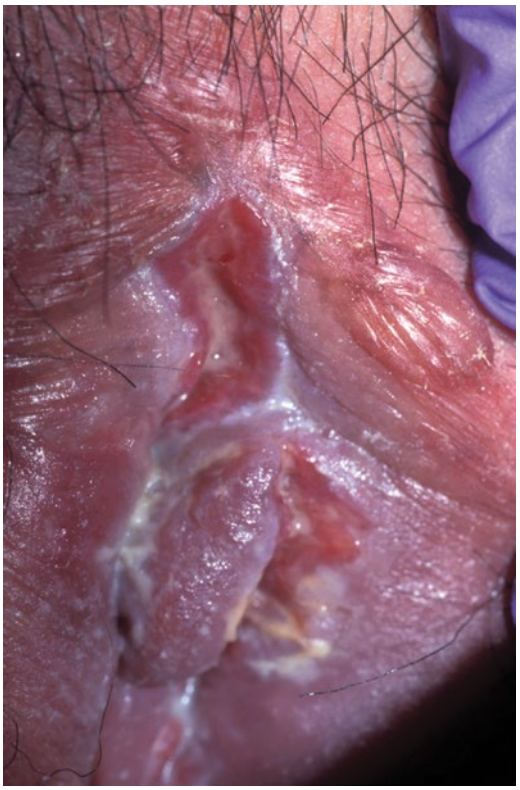


Plate 57.20 Vulval Crohn's disease: deep 'knife-cut' fissures are seen in the inter-labial sulci.

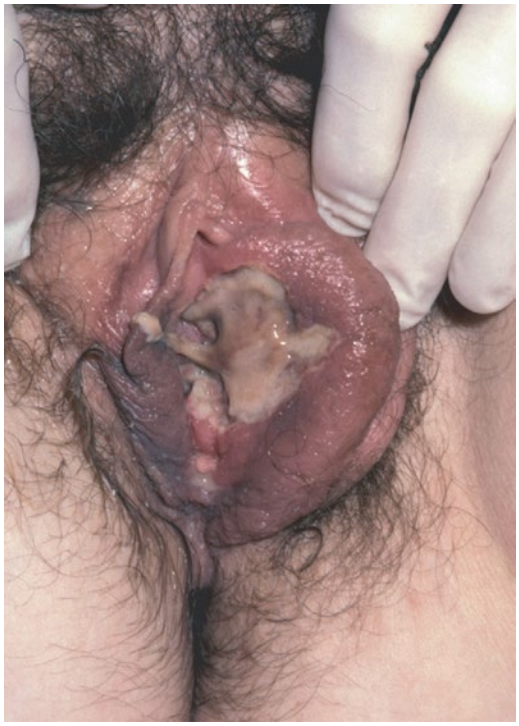


Plate 57.21 Behçet's syndrome. Extensive deep ulcers, here penetrating the labia in a 45-year-old Turkish woman.

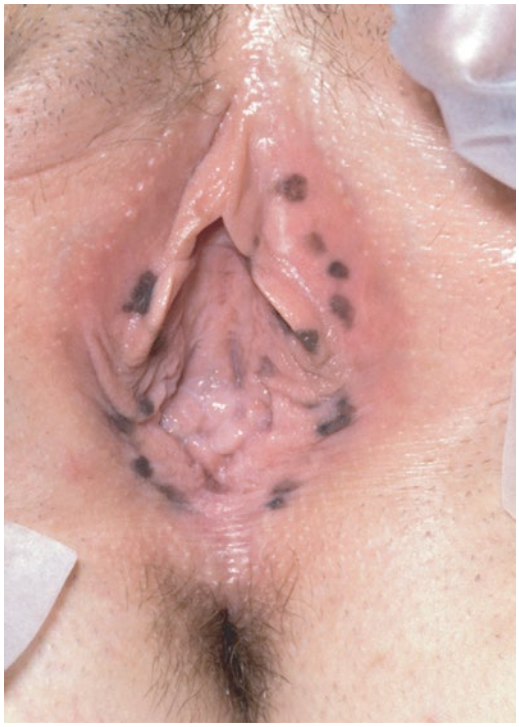


Plate 57.22 Vulval melanosis: irregular areas of pigmentation without any preceding inflammation.

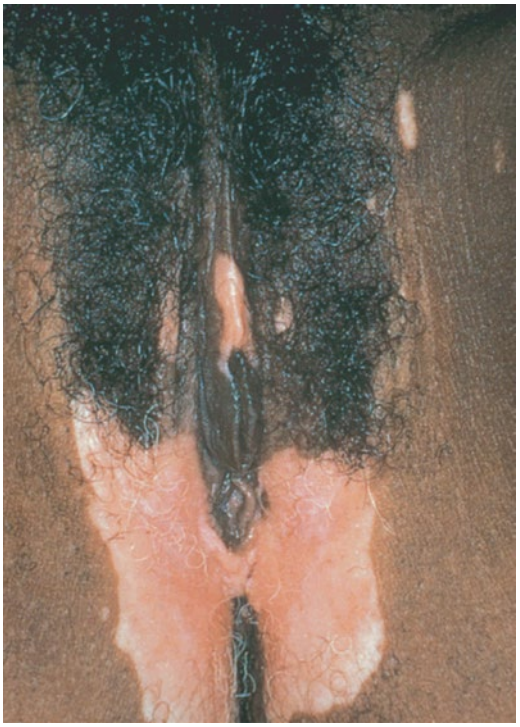


Plate 57.23 Vitiligo, showing symmetrical loss of pigmentation.

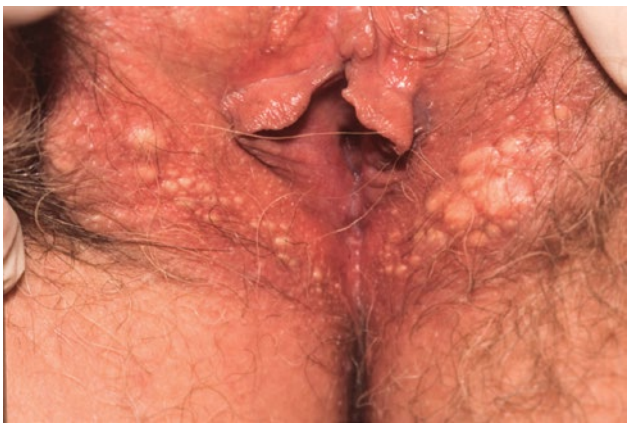


Plate 57.24 Multiple epidermoid cysts on outer labia majora. These are usually asymptomatic.

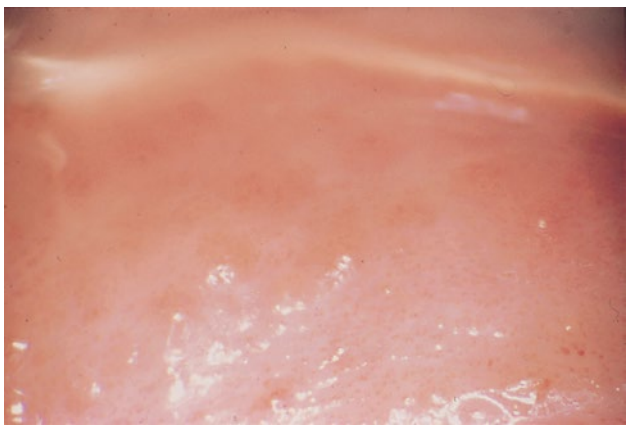


Plate 58.1 Trichomoniasis with 'strawberry' vaginitis.

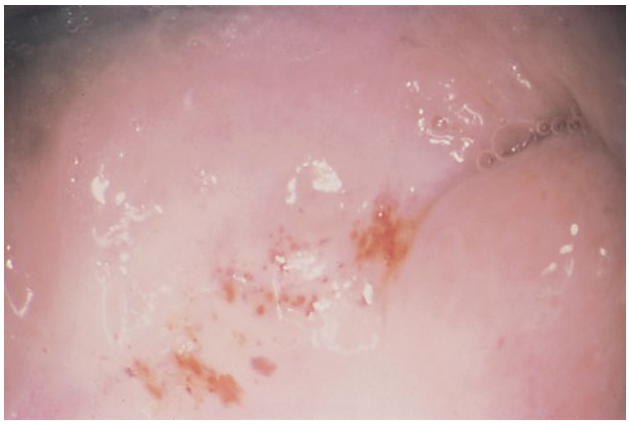


Plate 58.2 Bleeding and adhesions at the vaginal vault.

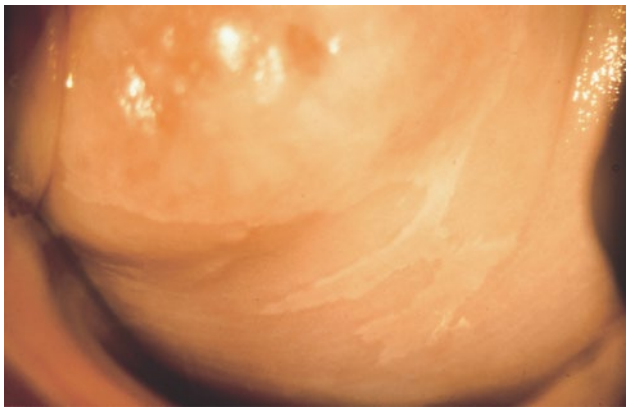


Plate 58.3 Vaginal intraepithelial neoplasia as an extension of a cervical lesion.

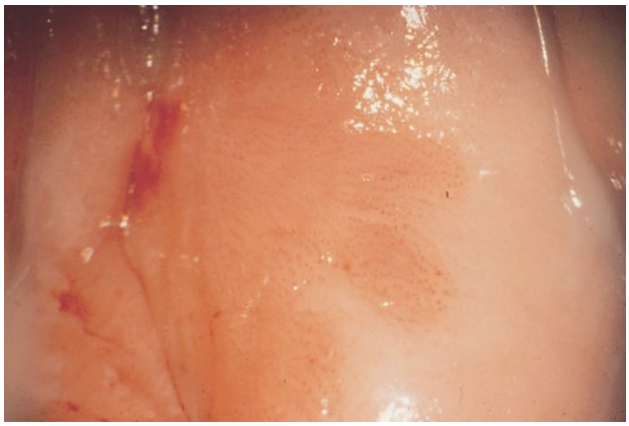
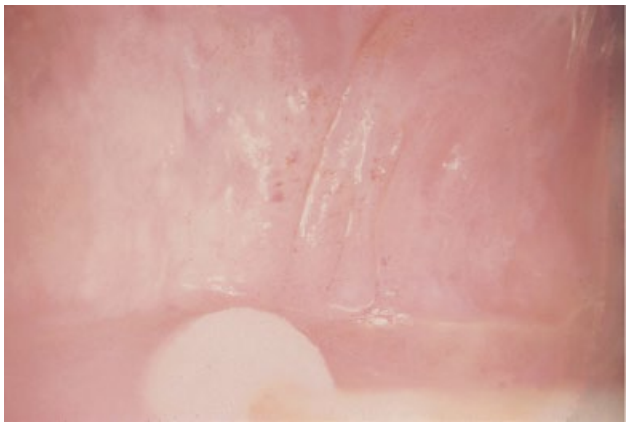


Plate 58.4 Vaginal intraepithelial neoplasia in post-hysterectomy vaginal angle.

(a)



(b)

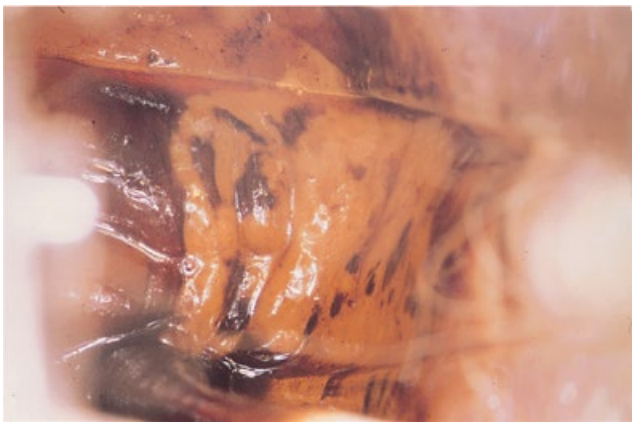


Plate 58.5 (a, b) Area of vaginal intraepithelial neoplasia before and after the application of iodine solution.

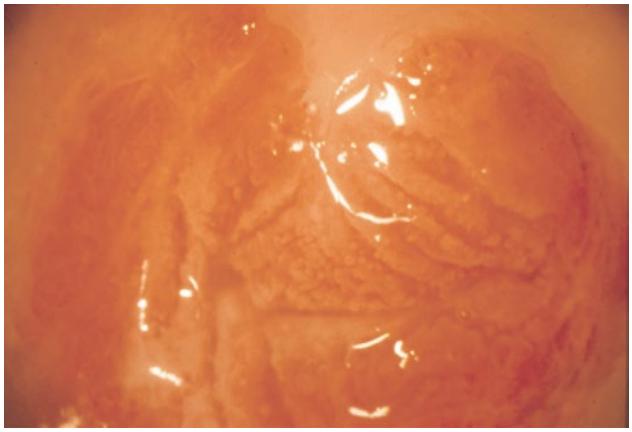


Plate 58.6 Eversion of the cervix during pregnancy.

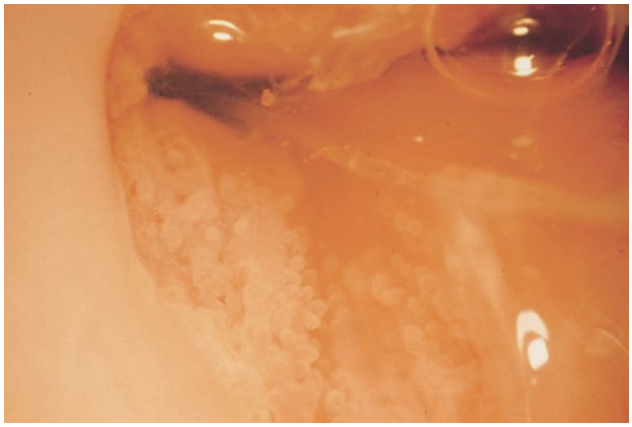


Plate 58.7 Columnar villi at the squamocolumnar junction.

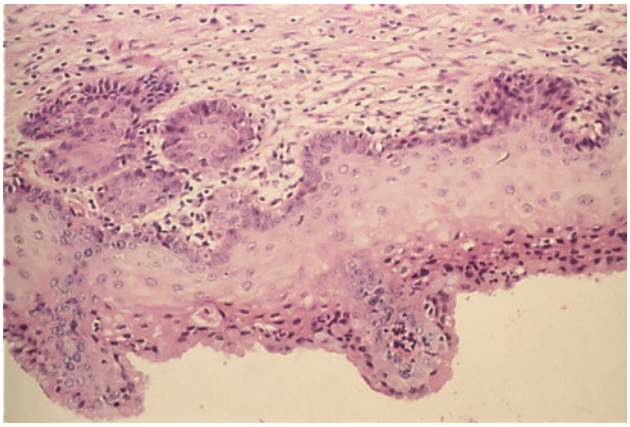


Plate 58.8 Photomicrograph of columnar and multilayered immature metaplastic epithelia.

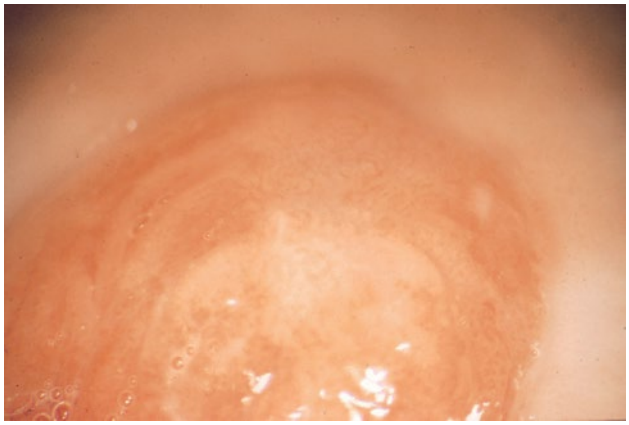


Plate 58.9 Squamous metaplasia of the cervix.

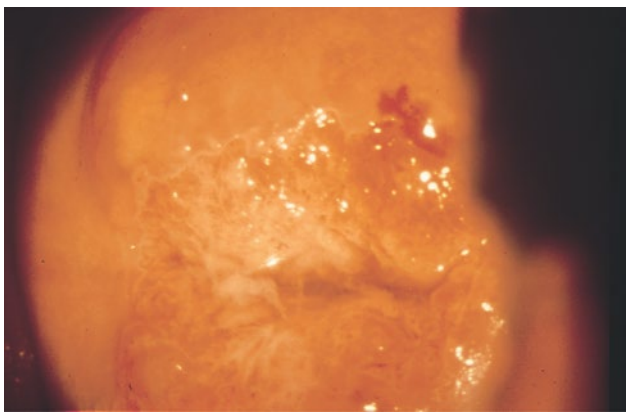


Plate 58.10 A typical transformation zone with a mucus-filled Nabothian follicle at 11 o'clock.

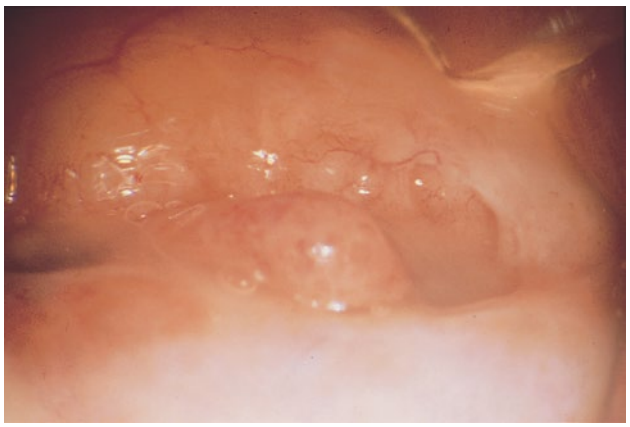


Plate 58.11 A small endocervical polyp.

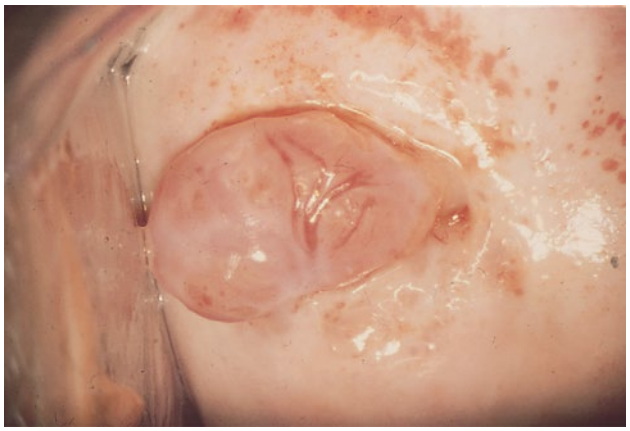


Plate 58.12 A large polyp with adjacent atrophic epithelium and ecchymoses.

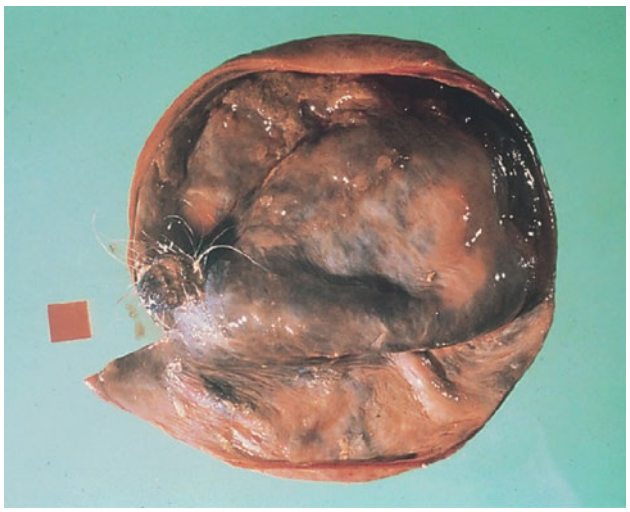


Plate 58.13 A benign cystic teratoma of the ovary showing hair and skin.

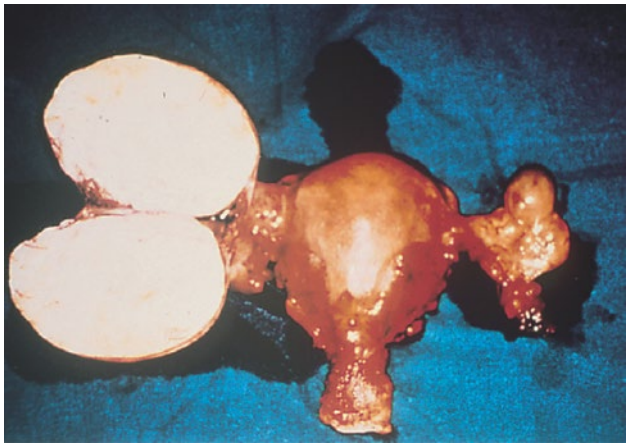
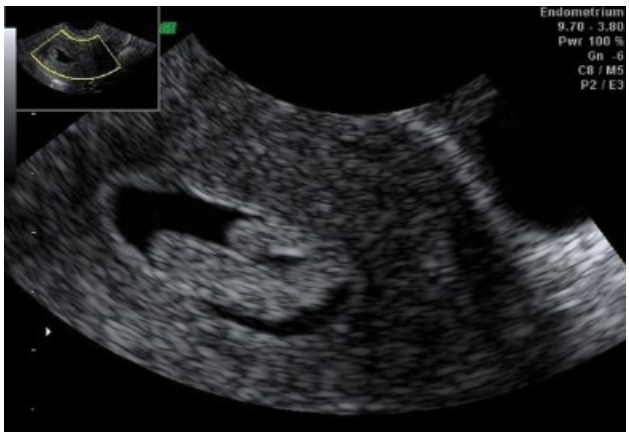


Plate 58.14 An ovarian fibroma.

(a)



(b)

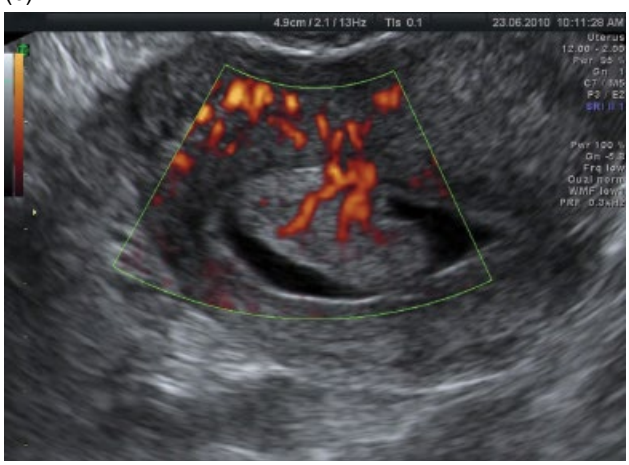


Plate 59.2 (a, b) Fluid instillation sonography demonstrating endometrial polyps. On power Doppler imaging (b) the vascular pedicle is visible.

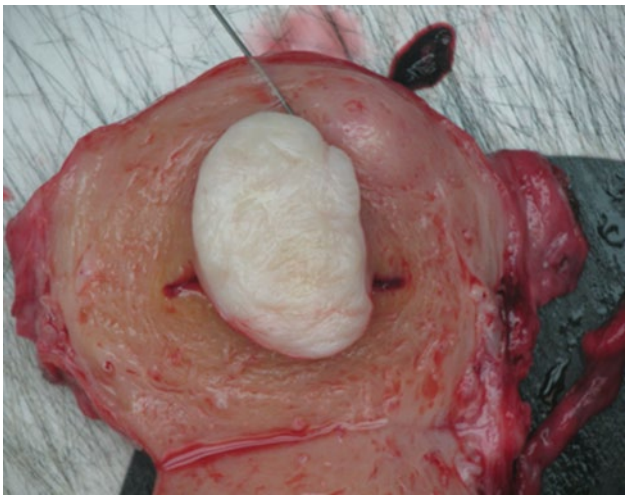


Plate 59.3 Macroscopy: transverse section through the uterine corpus, with a fibroid. Figure courtesy of Ann Cornelis.

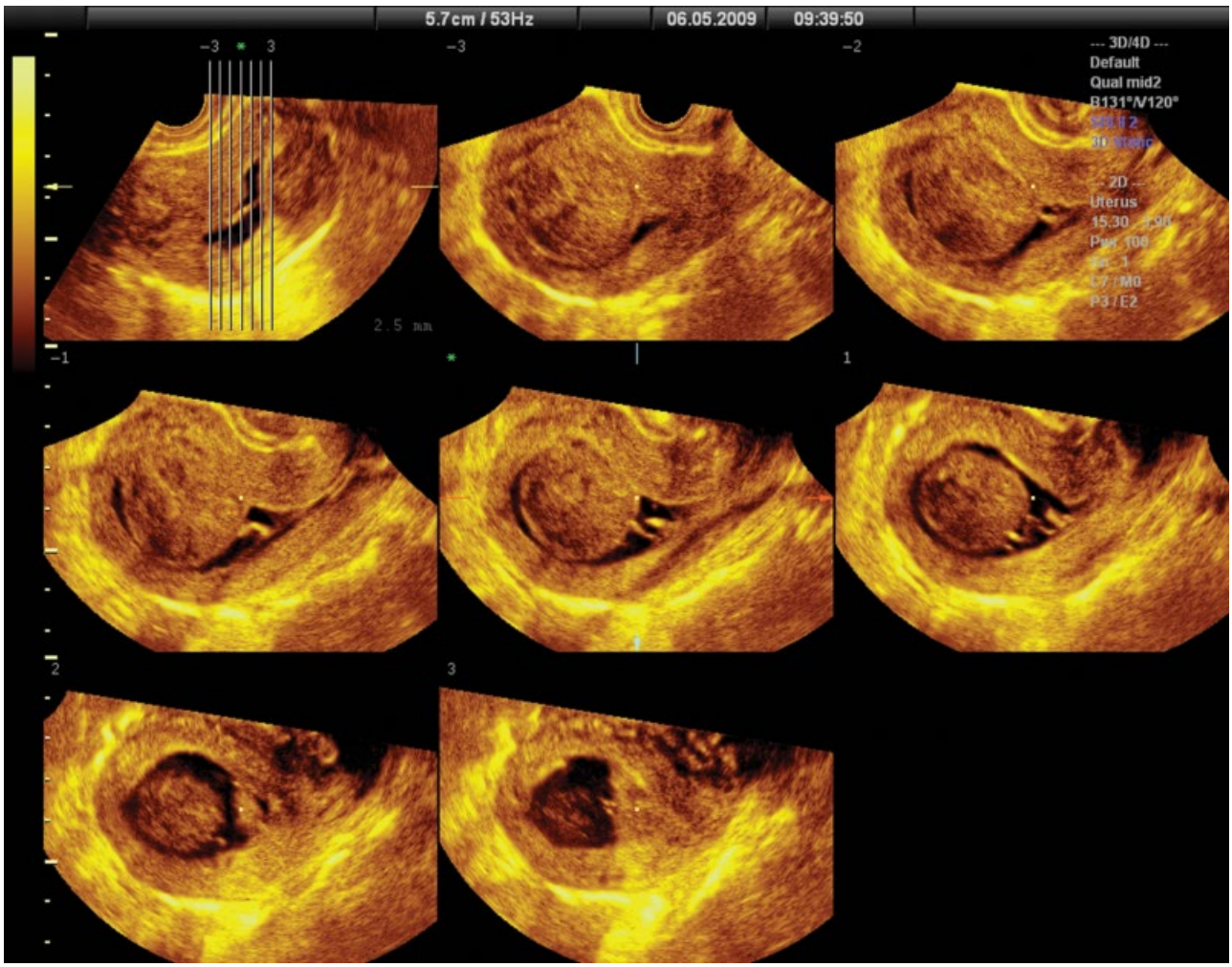


Plate 59.5a Fluid instillation sonography showing an intrauterine fibroid [44]. Reproduced with permission of John Wiley and Sons.

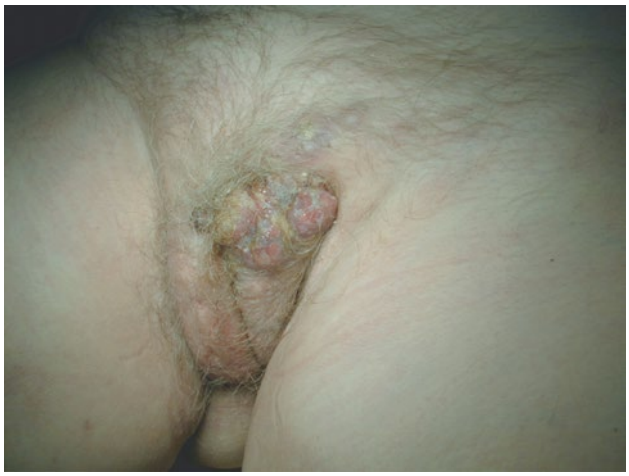
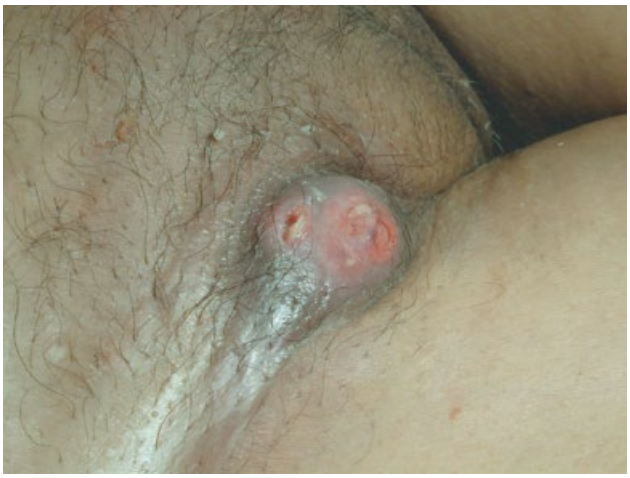


Plate 60.2 Large anterior vulval cancer with satellite skin deposits.

(a)



(b)

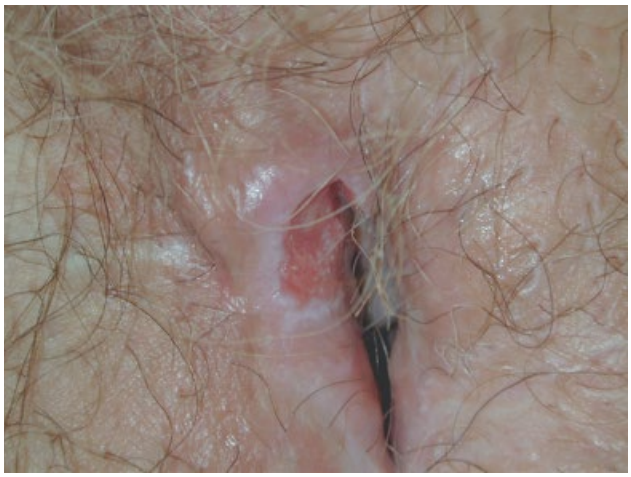


Plate 60.3 (a) Reccurence in the right groin after previous simple vulvectomy. (b) Anterior local recurrence after radical vulvectomy.

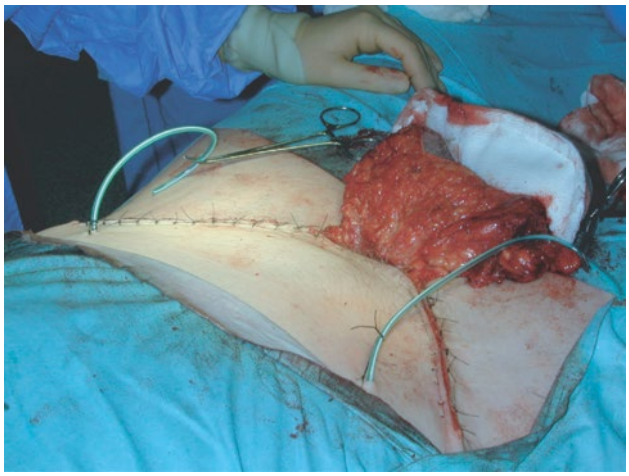


Plate 60.5 En bloc dissection of the inguinofemoral lymph nodes.

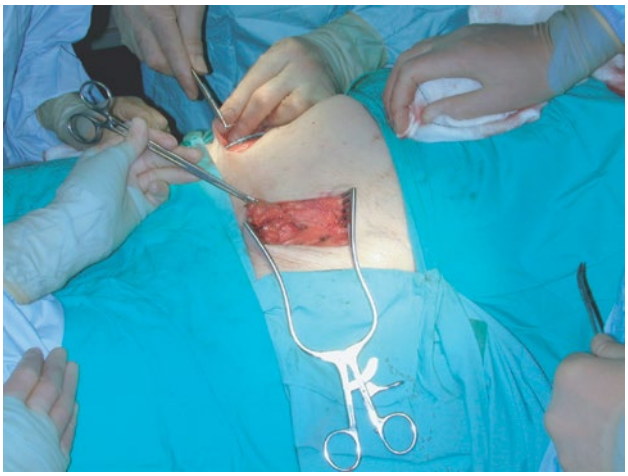


Plate 60.6 Separate groin incisions.

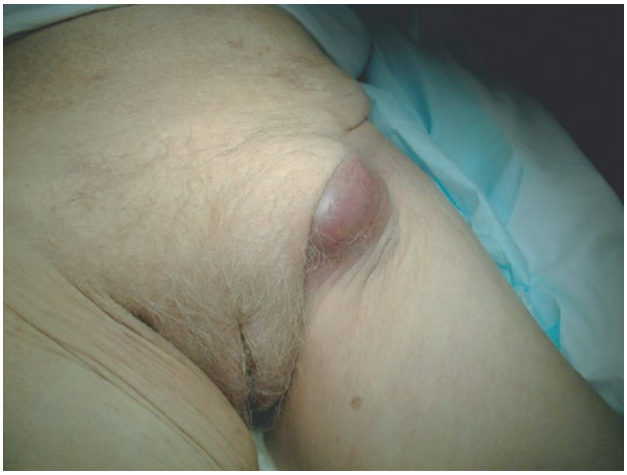


Plate 60.7 Clinically suspicious left groin nodes.

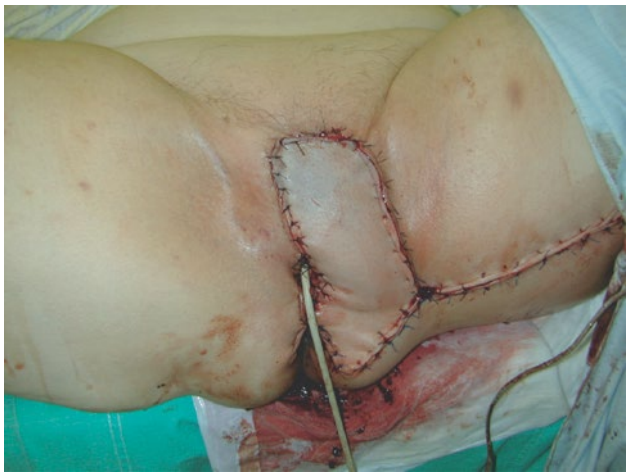


Plate 60.8 Rotation skin flap to fill a large defect.

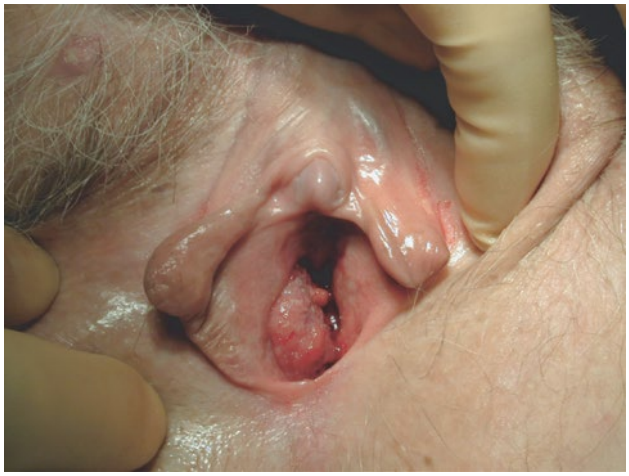
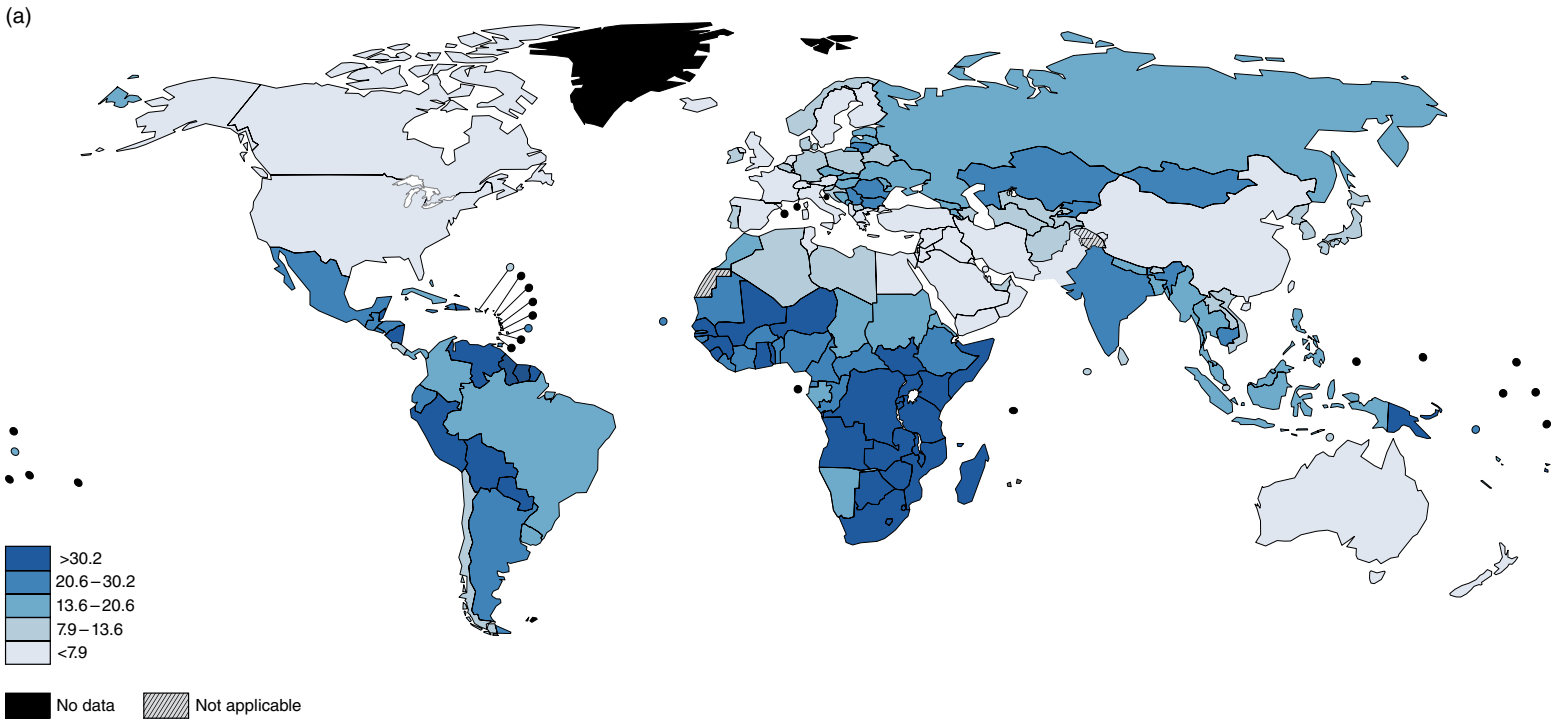


Plate 60.9 Vaginal cancer.

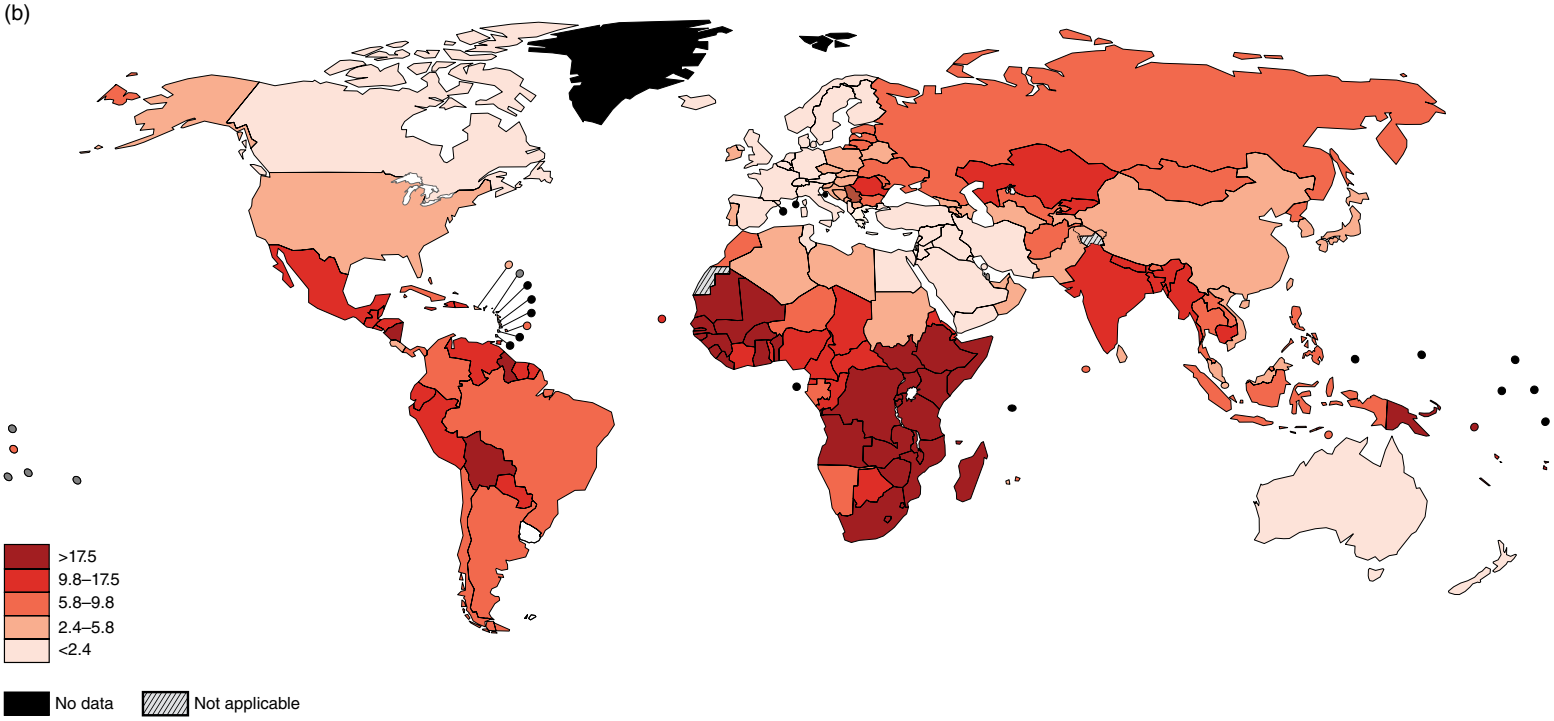


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

Plate 61.1 Estimated cervical cancer: (a) age-standardized incidence per 100 000 women; (b) age-standardized mortality per 100 000 women. *Source:* Ferlay J, Soerjomataram I, Ervik M *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at http://globocan.iarc.fr, accessed 4 August 2016.

(b)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

Plate 61.1 (Continued)

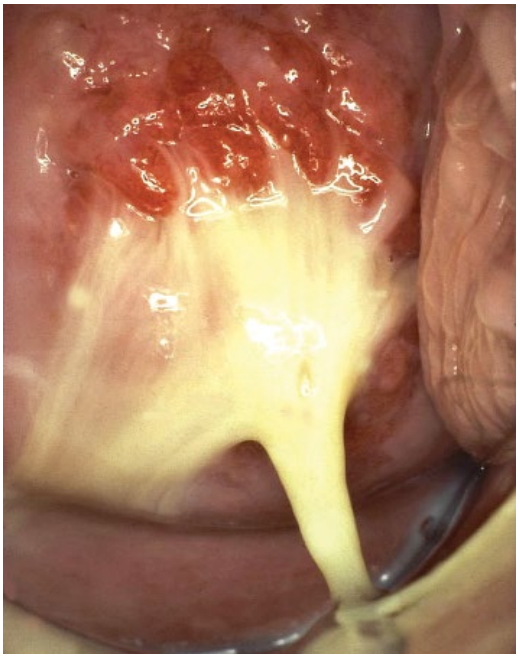


Plate 64.3 Chlamydial mucopurulent cervicitis. Overt chlamydial mucopurulent discharge with endocervical gland oedema showing follicular cervicitis. A similar appearance is seen with gonorrhoea, but most chlamydia is covert showing little or no such obvious signs. *Source:* photograph by Peter Greenhouse FRCOG, 1992.

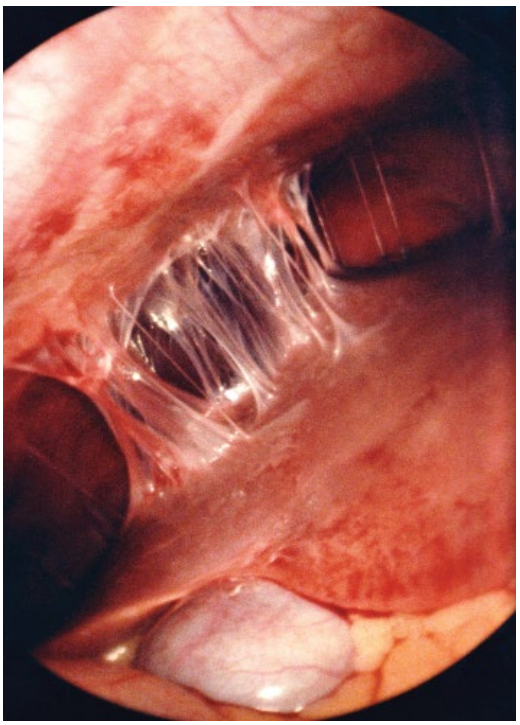


Plate 64.4 Chlamydial perihepatitis/Fitz-Hugh–Curtis syndrome. Bridal veil and violin-string adhesions between liver and diaphragm due to chlamydial infection, causing right hypochondrial pain and restriction of respiration. Note normal gallbladder. *Source:* photography by Peter Greenhouse FRCOG, 1986.

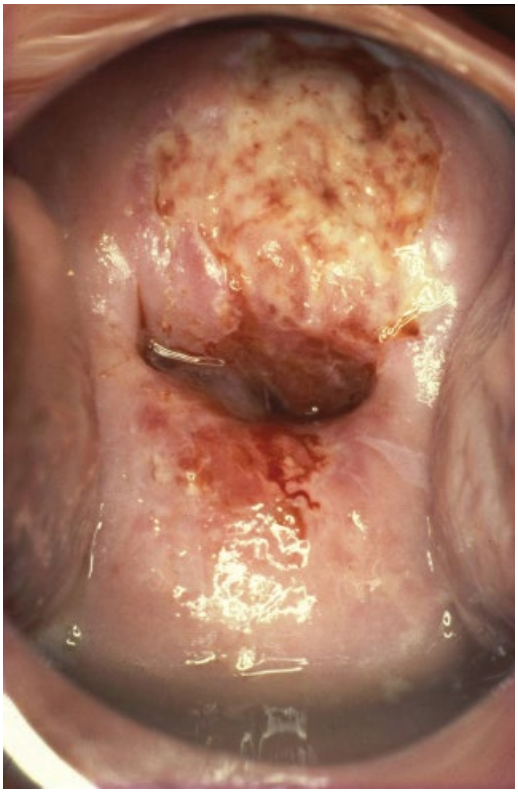


Plate 64.6 Herpetic necrotic cervicitis. Extensive cervical ulceration caused by HSV-2, associated with copious clear watery vaginal discharge and severe vulval pain. *Source:* photograph by Peter Greenhouse FRCOG, 1996.

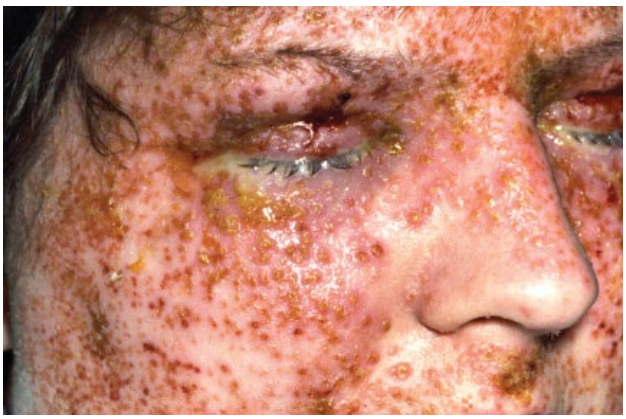


Plate 64.7 Disseminated herpes in pregnancy. Second-trimester mucocutaneous and systemic dissemination of primary HSV-1 infection in a pregnant diabetic woman. Outcome after intravenous aciclovir: Complete recovery without scarring and healthy infant delivered near term. *Source:* photograph by Peter Greenhouse FRCOG, 1994.

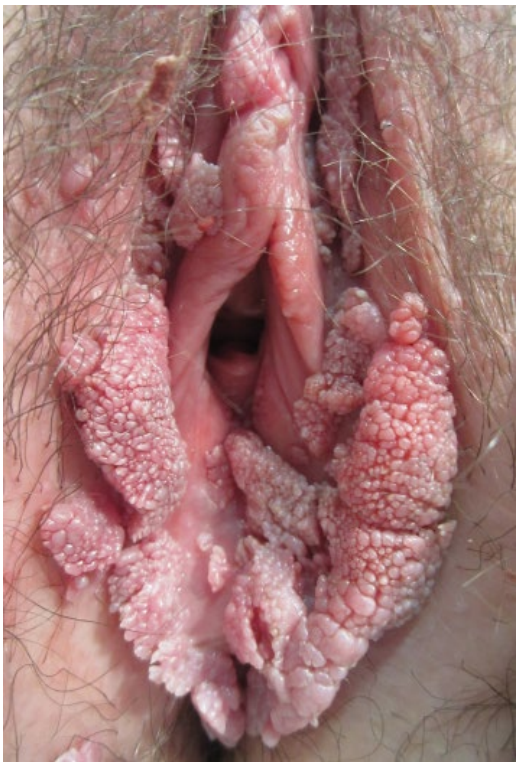
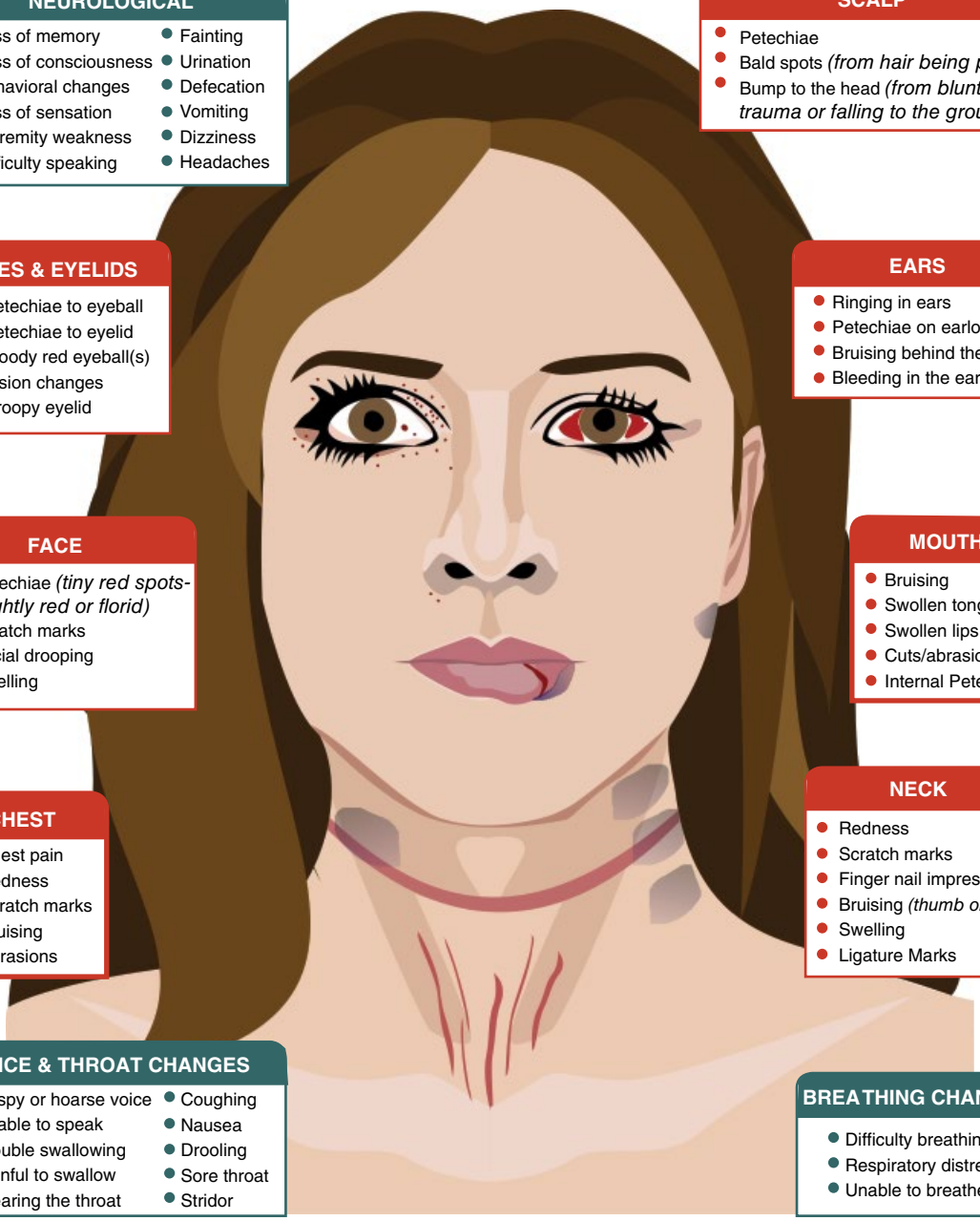


Plate 64.8 Severe vulval warts. Florid warts after multiple failed treatments in a poorly controlled diabetic teenager who had received bivalent HPV vaccination 3 years previously. *Source:* photograph by Peter Greenhouse FRCOG, 2012.

SIGNS AND SYMPTOMS OF STRANGULATION



NEUROLOGICAL

- Loss of memory
- Loss of consciousness
- Behavioral changes
- Loss of sensation
- Extremity weakness
- Difficulty speaking
- Fainting
- Urination
- Defecation
- Vomiting
- Dizziness
- Headaches

SCALP

- Petechiae
- Bald spots *(from hair being pulled)*
- Bump to the head *(from blunt force trauma or falling to the ground)*

EYES & EYELIDS

- Petechiae to eyeball
- Petechiae to eyelid
- Bloody red eyeball(s)
- Vision changes
- Droopy eyelid

EARS

- Ringing in ears
- Petechiae on earlobe(s)
- Bruising behind the ear
- Bleeding in the ear

FACE

- Petechiae *(tiny red spots-slightly red or florid)*
- Scratch marks
- Facial drooping
- Swelling

MOUTH

- Bruising
- Swollen tongue
- Swollen lips
- Cuts/abrasions
- Internal Petechiae

CHEST

- Chest pain
- Redness
- Scratch marks
- Bruising
- Abrasions

NECK

- Redness
- Scratch marks
- Finger nail impressions
- Bruising *(thumb or fingers)*
- Swelling
- Ligature Marks

VOICE & THROAT CHANGES

- Raspy or hoarse voice
- Unable to speak
- Trouble swallowing
- Painful to swallow
- Clearing the throat
- Coughing
- Nausea
- Drooling
- Sore throat
- Stridor

BREATHING CHANGES

- Difficulty breathing
- Respiratory distress
- Unable to breathe

Source: *Strangulation in Intimate Partner Violence, Chapter 16, Intimate Partner Violence. Oxford University Press, Inc. 2009.*

TRAINING INSTITUTE on STRANGULATION PREVENTION

www.strangulationtraininginstitute.com

Graphics by Yesenia Aceves

Plate 67.2 Signs and symptoms of strangulation. *Source:* Alliance for HOPE International. Reproduced with permission of Alliance for HOPE International.