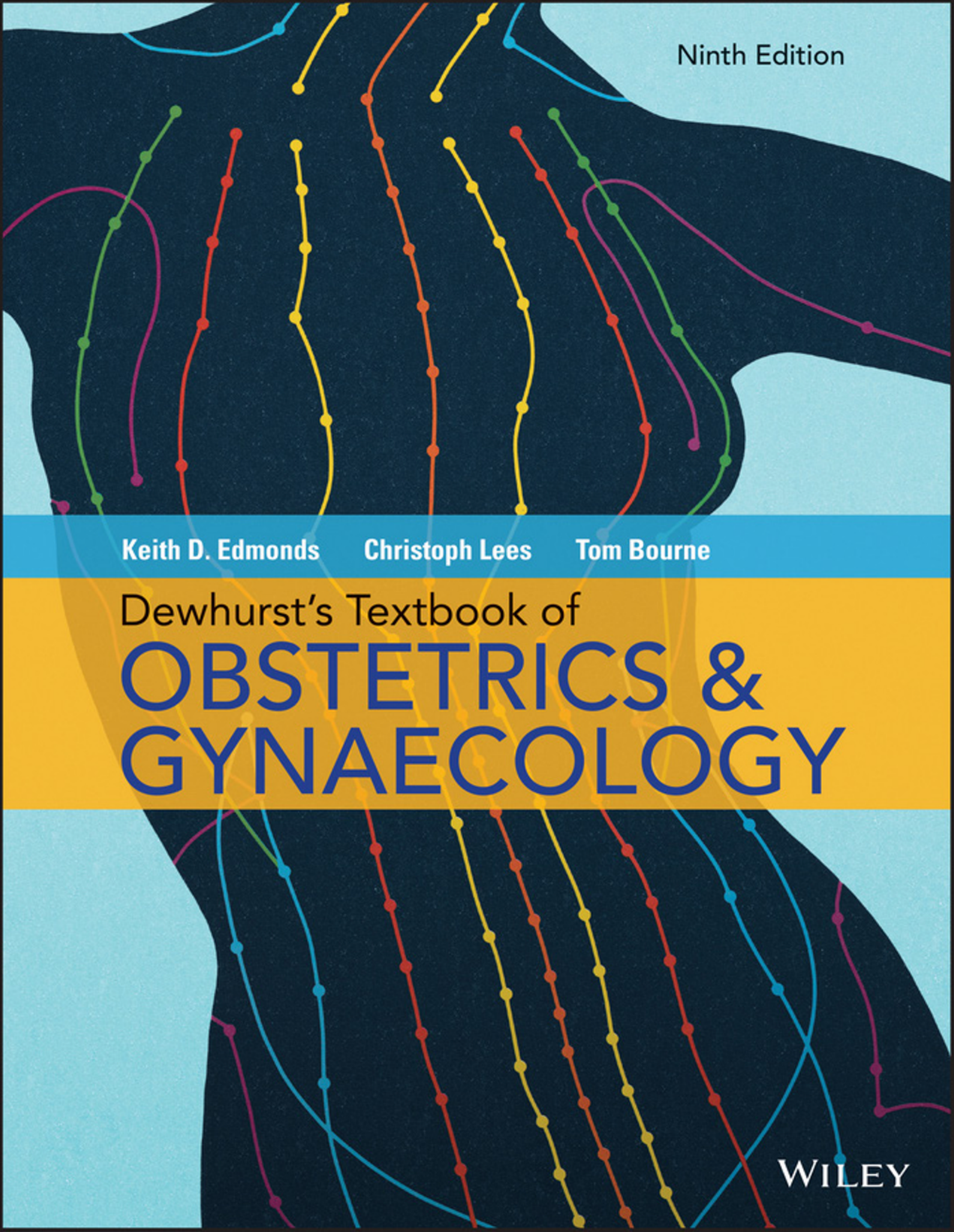
Ninth Edition
Keith D. Edmonds
Christoph Lees
Tom Bourne
Dewhurst's Textbook of
OBSTETRICS &
GYNAECOLOGY
WILEY

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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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.

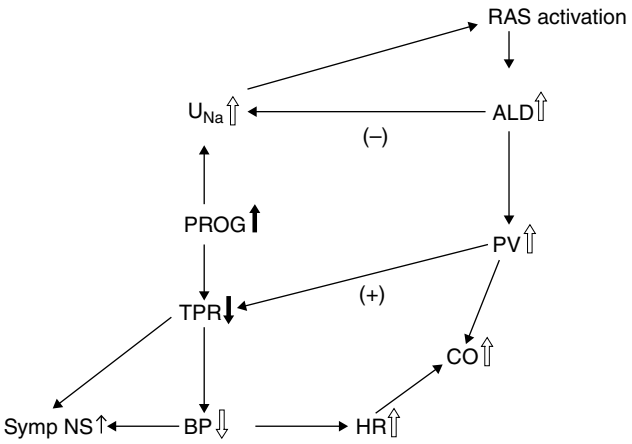

Fig. 1.1 Flow chart of the probable sequence of initial cardiovascular activation. ALD, aldosterone; BP, systemic arterial blood pressure; CO, cardiac output; HR, heart rate; PROG, progesterone; PV, plasma volume; RAS, renin–angiotensin system; Symp NS, sympathetic nervous system; TPR, total peripheral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

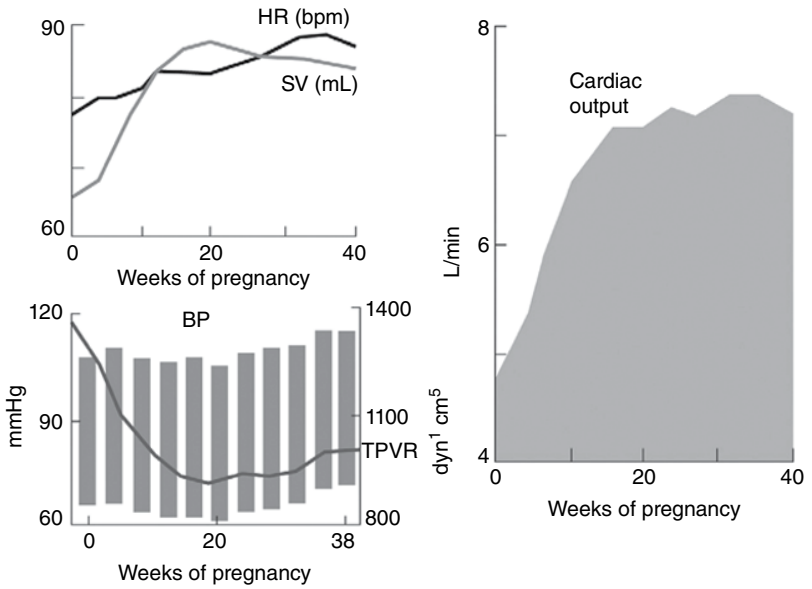

Fig. 1.2 Major haemodynamic changes associated with normal human pregnancy. The marked augmentation of cardiac output results from asynchronous increases in both heart rate (HR) and stroke volume (SV). Despite the increases in cardiac output, blood pressure (BP) decreases for most of pregnancy. This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

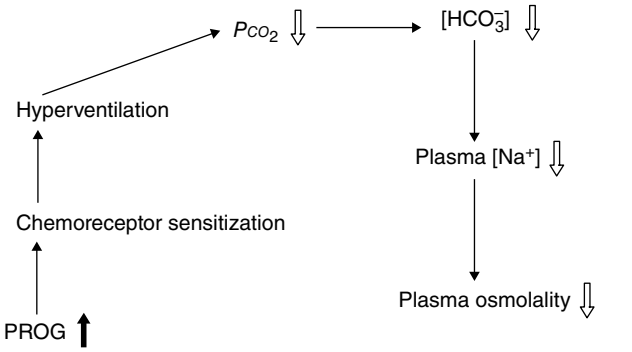

Fig. 1.4 Flow chart of the effects of over-breathing in pregnancy. HCO_3^-, bicarbonate; Na^+, sodium; PCO_2, carbon dioxide tension; PROG, progesterone.

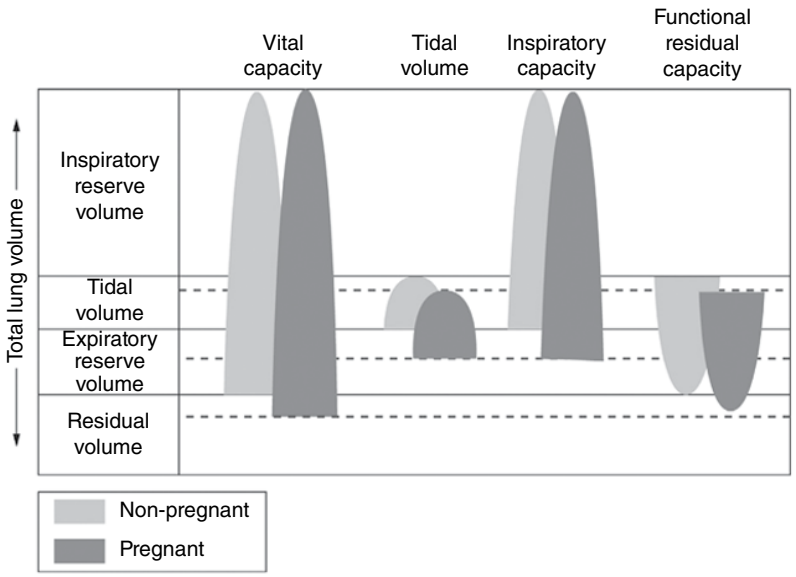

Fig. 1.3 Alterations in lung volumes associated with normal human pregnancy. In general terms, inspiratory reserve and tidal volumes increase at the expense of expiratory reserve and residual volumes.

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].

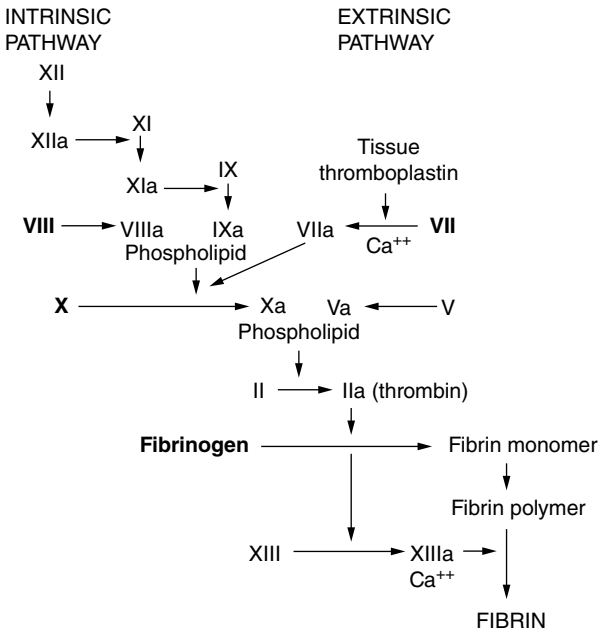

Fig. 1.5 Alterations in the coagulation pathways associated with human pregnancy. Factors which increase during normal pregnancy are in bold type. *Source:* Chamberlain, G. and Broughton Pipkin, F. *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Wiley, 1998. Reproduced with permission of John Wiley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

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

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.

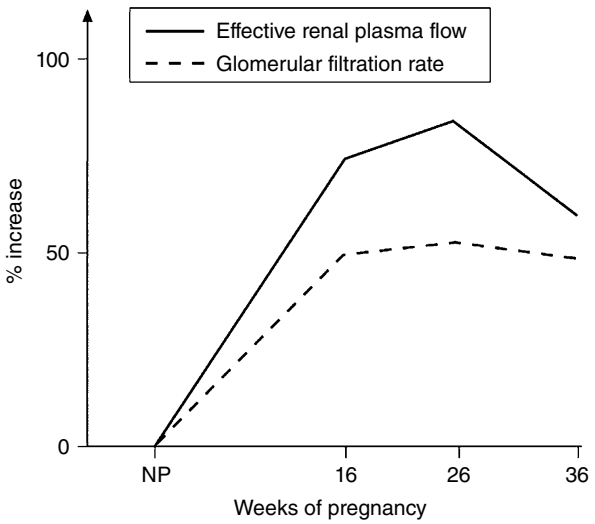

Fig. 1.6 The changes in renal function during pregnancy are largely complete by the end of the first trimester and are thus proactive not reactive to the demands of pregnancy. The filtration fraction falls during the first trimester but begins to return to non-pregnant levels during the third trimester. *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

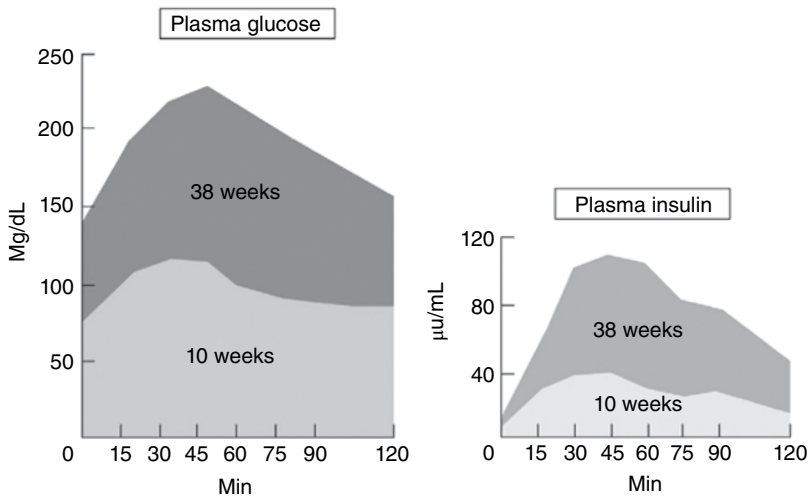

Fig. 1.7 Responses in normal pregnant women to a 50-g oral glucose load during early and late pregnancy. During early pregnancy there is a normal plasma insulin response with a relative reduction in plasma glucose concentrations compared with the non-pregnant state. In contrast, during late pregnancy 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.

References

1 Chapman AB, Zamudio S, Woodmansee W *et al.* Systemic and renal hemodynamic changes in the luteal phase of the menstrual cycle mimic early pregnancy. *Am J Physiol* 1997;273:F777–F782.

2 Redman CW, Sargent IL. Preeclampsia and the systemic inflammatory response. *Semin Nephrol* 2004;24:565–570.

3 Milman N. Iron and pregnancy: a delicate balance. *Ann Haematol* 2006;85:559–565.

4 Moffett A, Hiby SE. How does the maternal immune system contribute to the development of pre-eclampsia? *Placenta* 2007;28(Suppl 1):S51–S56.

5 Zhang J, Chen Z, Smith GN, Croy BA. Natural killer cell-triggered vascular transformation: maternal care before birth? *Cell Mol Immunol* 2011;8:1–11.

6 Burton GJ, Jauniaux E, Charnock-Jones DS. Human early placental development: potential roles of the endometrial glands. *Placenta* 2007;28(Suppl 1):S64–S69.

7 Chapman AB, Abraham WT, Zamudio S *et al.* Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;54:2056–2063.

8 Ganzevoort W, Rep A, Bonsel GJ, de Vries JI, Wolf H. Plasma volume and blood pressure regulation in hypertensive pregnancy. *J Hypertens* 2004;22: 1235–1242.

9 Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;256: H1060–H1065.

10 de Swiet M, Shennan A. Blood pressure measurement in pregnancy. *Br J Obstet Gynaecol* 1996;103:862–863.
11 Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens* 2014;32:849–856.
12 de Swiet M. The respiratory system. In: Chamberlain G, Broughton Pipkin F (eds) *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Blackwell Science, 1998: 111–128.
13 Bessinger RC, McMurray RG, Hackney AC. Substrate utilisation and hormonal responses to moderate intensity exercise during pregnancy and after delivery. *Am J Obstet Gynecol* 2002;86:757–764.
14 Heath AL, Fairweather-Tait SJ. Clinical implications of changes in the modern diet: iron intake, absorption and status. *Best Pract Res Clin Haematol* 2002;15:225–241.
15 Scientific Advisory Committee on Nutrition. *The Nutritional Wellbeing of the British Population*. London: TSO, 2008.
16 Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. *Am J Clin Nutr* 2005;81:1218S–1222S.
17 National Institute for Health and Care Excellence. *Antenatal Care for Uncomplicated Pregnancies*. Clinical Guideline CG62. London: NICE, 2008 (updated January 2017).
18 Apps R, Murphy SP, Fernando R, Gardner L, Ahad T, Moffett A. Human leucocyte antigen (HLA) expression of primary trophoblast cells and placental cell lines, determined using single antigen beads to characterise allotype specificities of anti-HLA antibodies. *Immunology* 2009;127:26–39.
19 Katz D, Beilin Y. Disorders of coagulation in pregnancy. *Br J Anaesth* 2015;115(Suppl 2):ii75–ii88.
20 Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004;114:409–414.
21 Letsky EA. The haematological system. In: Chamberlain G, Broughton Pipkin F (eds) *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Blackwell Science, 1998: 71–110.
22 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.
23 Bayliss C, Davison JM. The urinary system. In: Chamberlain G, Broughton Pipkin F (eds) *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Blackwell Science, 1998: 263–307.
24 Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ* 2012;345:e4342.
25 Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: adapting to preserve normalcy. *Physiology* 2015;30:139–147.
26 Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. *Hepatology* 2014;59:1482–1491.
27 Butte NF, King JC. Energy requirements during pregnancy and lactation. *Public Health Nutr* 2005;8:1010–1027.
28 Gunderson EP, Abrams B, Selvin S. Does the pattern of postpartum weight change differ according to pregravid body size? *Int J Obes Relat Metab Disord* 2001;25:853–862.
29 Gunderson EP. Childbearing and obesity in women: weight before, during, and after pregnancy. *Obstet Gynecol Clin North Am* 2009;36:317–332.
30 Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr* 2000;71(5 Suppl): 1256S–1261S.
31 Eriksson B, Löf M, Olausson H, Forsum E. Body fat, insulin resistance, energy expenditure and serum concentrations of leptin, adiponectin and resistin before, during and after pregnancy in healthy Swedish women. *Br J Nutr* 2010;103:50–57.
32 Aye ILMH, Powell TL, Jansson T. Review: Adiponectin – the missing link between maternal adiposity, placental transport and fetal growth? *Placenta* 2013;34(Suppl):S40–S45.
33 Herrera E, Ortega H, Alvino G, Giovannini N, Amusquivar E, Cetin I. Relationship between plasma fatty acid profile and antioxidant vitamins during normal pregnancy. *Eur J Clin Nutr* 2004;58: 1231–1238.
34 Poston L, Raijmakers MT. Trophoblast oxidative stress, antioxidants and pregnancy outcome: a review. *Placenta* 2004;25(Suppl A):S72–S78.
35 Kopp-Hoolihan LE, van Loan MD, Wong WW, King JC. Longitudinal assessment of energy balance in well-nourished, pregnant women. *Am J Clin Nutr* 1999; 69:697–704.
36 Chen D-B, Zheng J. Regulation of placental angiogenesis. *Microcirculation* 2014;21:15–25.
37 Marshall SA, Senadheera SN, Parry LJ, Girling JE. The role of relaxin in normal and abnormal uterine function during the menstrual cycle and early pregnancy. *Reprod Sci* 2017;24:342–354.
38 Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine responses to

physiologic stimuli in normal human pregnancy. *Am J Obstet Gynecol* 1986;154:80–84.

39 Ramsay ID. The thyroid gland. In: Chamberlain G, Broughton Pipkin F (eds) *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Blackwell Science, 1998: 374–384.

40 Prentice A. Maternal calcium metabolism and bone mineral status. *Am J Clin Nutr* 2000;71(5 Suppl): 1312S–1316S.

41 Haig D. Evolutionary conflicts in pregnancy and calcium metabolism: a review. *Placenta* 2004; 25(Suppl A):S10–S15.

Further reading

Broughton Pipkin F. Maternal physiology. In: Chamberlain G, Steer P (eds) *Turnbull's Obstetrics*, 3rd edn. London: Churchill Livingstone, 2001.

Chamberlain G, Broughton Pipkin F (eds) *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Blackwell Science, 1998.

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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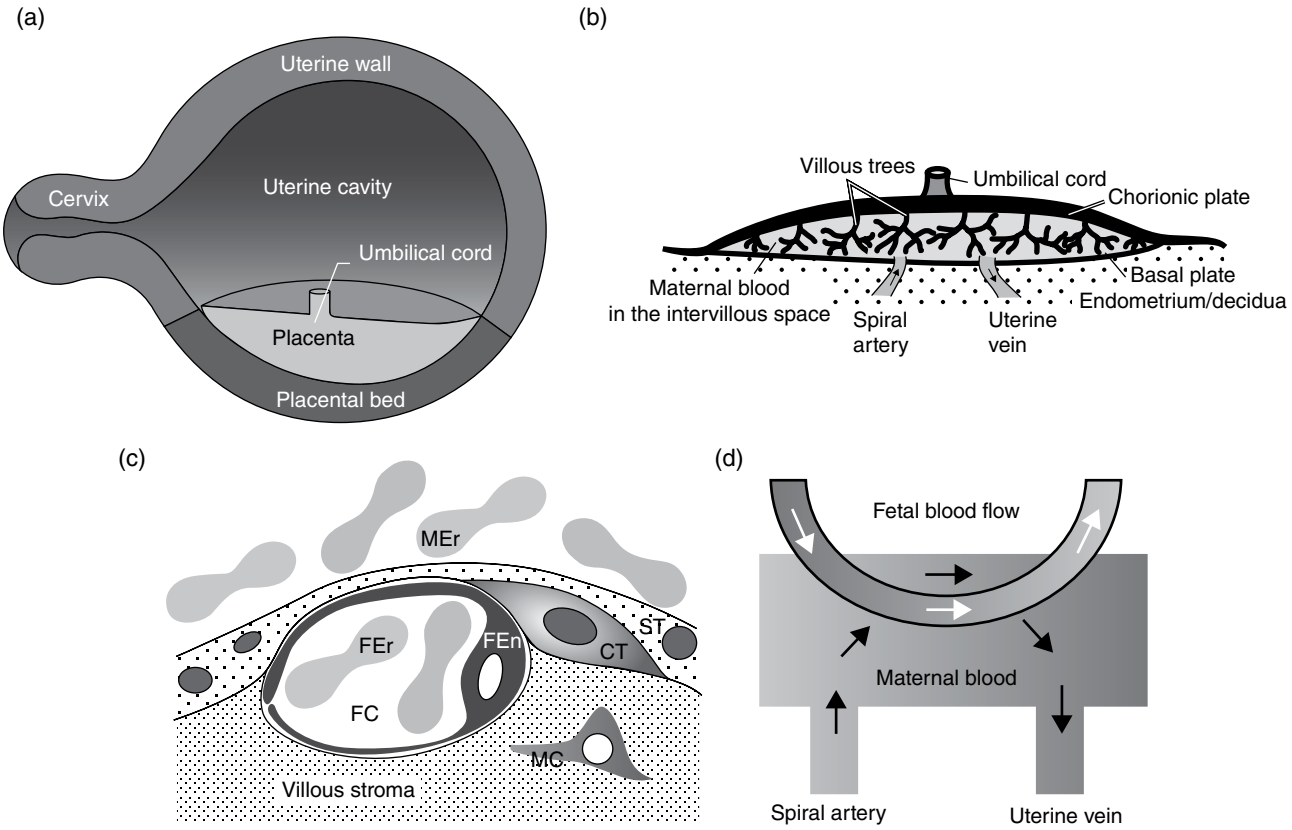

Fig. 2.1 Schematic representation of the structural characteristics of the human placenta. (a) The human placenta displays a discoidal shape. (b) The materno-fetal interdigitations are arranged in villous trees bathing in maternal blood that floats through the intervillous space. (c) The haemochorial 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).

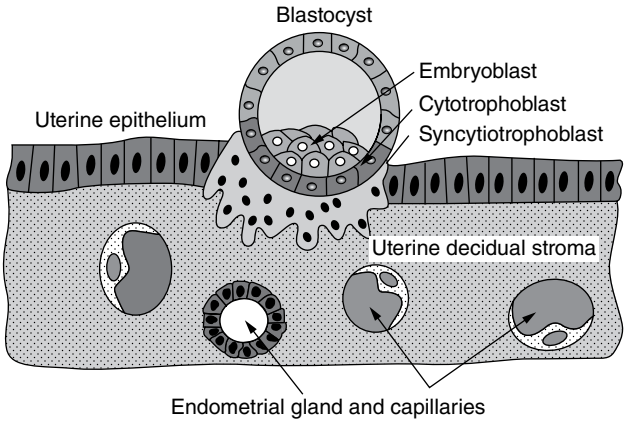

Fig. 2.2 During implantation of the blastocyst, trophoblast cells in direct contact with maternal tissues syncytially fuse and give rise to the syncytiotrophoblast. Only this multinucleated tissue is able to penetrate the uterine epithelium and to implant the developing embryo.

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

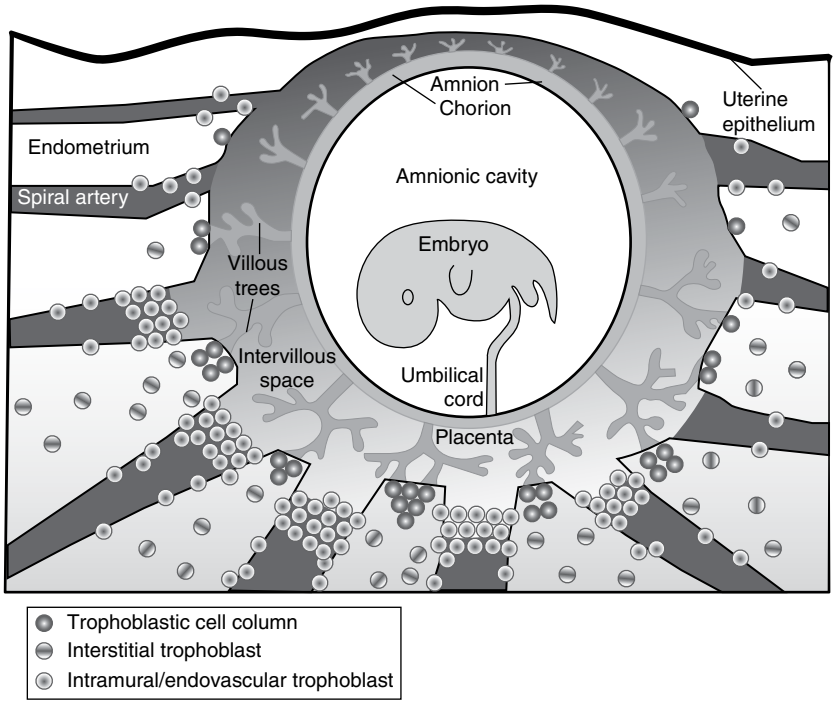

Fig. 2.3 Schematic representation of the developing embryo and its surrounding tissues at about 8–10 weeks of pregnancy. The amnionic cavity with the embryo inside is marked off by the amnion that has already contacted the chorion. From the chorion, villous trees protrude into the intervillous space 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.

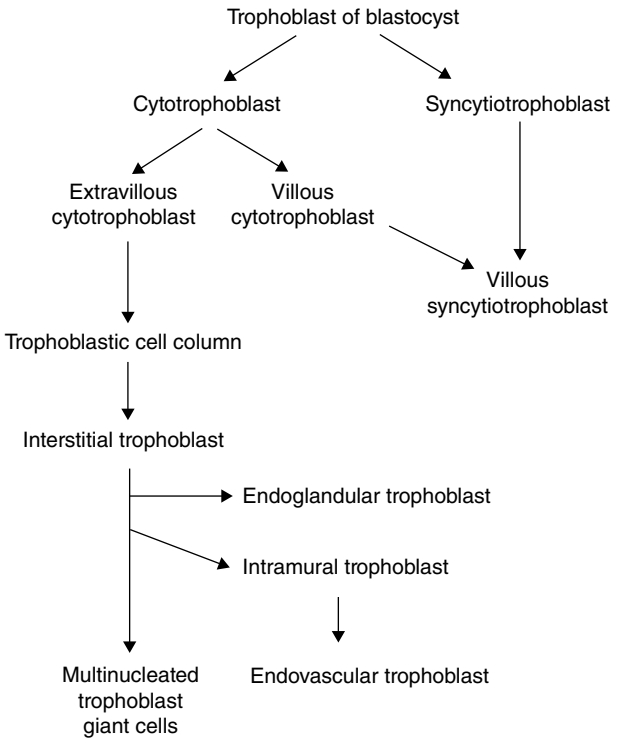

Fig. 2.4 Trophoblast differentiation and subtypes. The trophoblast lineage is the first to develop at the blastocyst stage. From this stage onwards, further differentiation leads to the generation of the syncytiotrophoblast and subsequently to the two main trophoblast types of placental villi, villous 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.

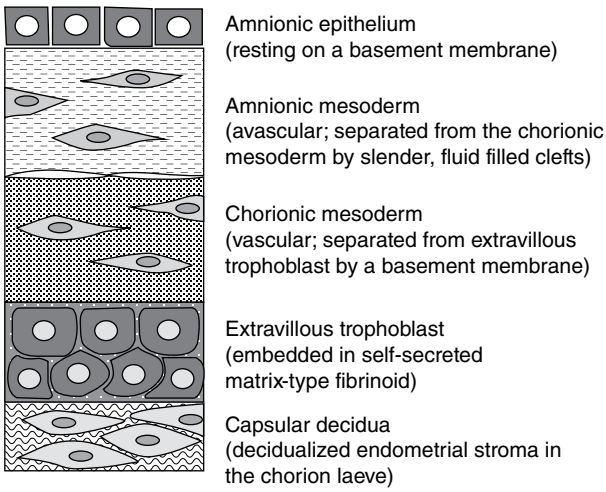

Fig. 2.5 Layers of the fetal membranes. The amnionic epithelium is a simple epithelium that secretes and resorbs the amnionic fluid. The two layers of connective tissues (amnionic and chorionic mesoderm) are separated by fluid-filled clefts. The extravillous trophoblast of the fetal membranes displays 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.

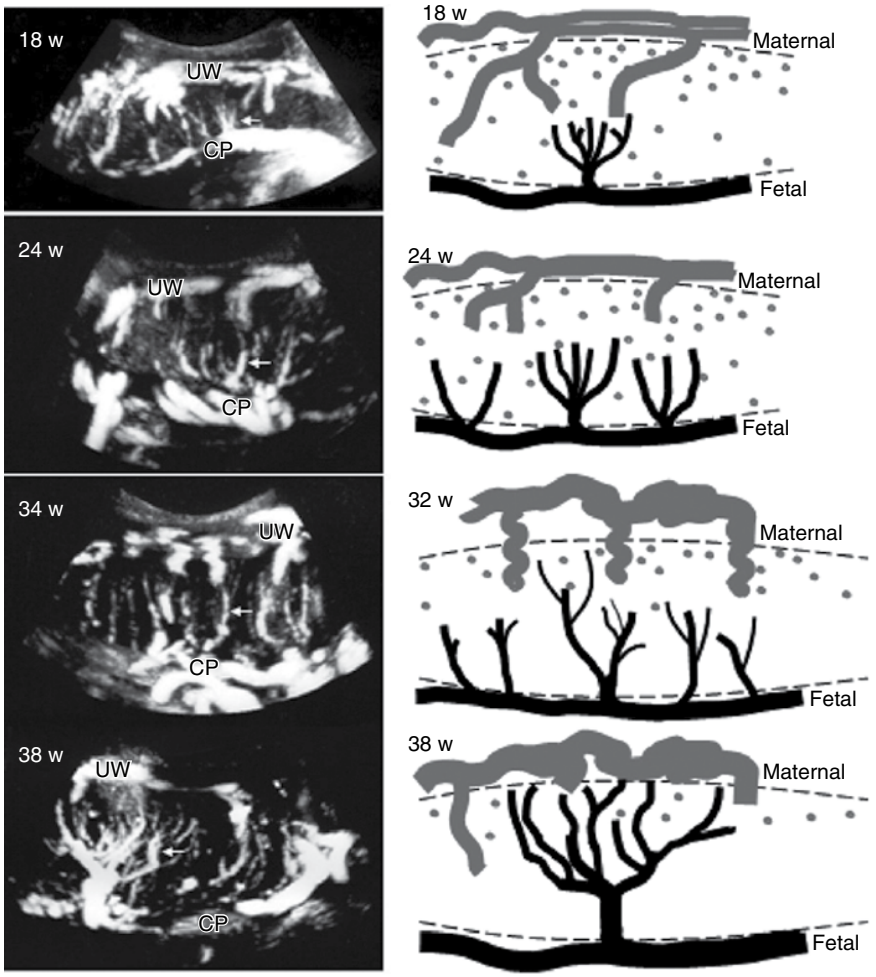

Fig. 2.6 Development of placental blood flow. *Left column*: Typical three-dimensional power Doppler scans from placentas of normal pregnant women at weeks 18, 24, 34 and 38. The flow signals within placental villi (white arrows) increase in extent, intensity, width and height with advancing pregnancy. 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.

References

1 Benirschke K, Kaufmann P, Baergen R. *Pathology of the Human Placenta*. New York: Springer, 2006.
2 Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol Reprod* 2003;69:1–7.
3 Moser G, Gauster M, Orendi K, Glasner A, Theuerkauf R, Huppertz B. Endoglandular trophoblast, an alternative route of trophoblast invasion? Analysis with novel confrontation co-culture models. *Hum Reprod* 2010;25:1127–1136.
4 Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial bloodflow and placental oxidative stress: a possible factor in human early pregnancy failure. *Am J Pathol* 2000;157:2111–2122.
5 Burton GJ, Jauniaux E, Charnock-Jones DS. Human early placental development: potential roles of the endometrial glands. *Placenta* 2007;28(Suppl A):S64–S69.
6 Huppertz B, Gauster M, Orendi K, König J, Moser G. Oxygen as modulator of trophoblast invasion. *J Anat* 2009;215:14–20.
7 Baczyk D, Drewlo S, Proctor L, Dunk C, Lye S, Kingdom J. Glial cell missing-1 transcription factor is required for the differentiation of the human trophoblast. *Cell Death Differ* 2009;16:719–727.
8 Huppertz B. IFPA Award in Placentology Lecture. Biology of the placental syncytiotrophoblast: myths and facts. *Placenta* 2010;31(Suppl):S75–S81.
9 Longtine MS, Chen B, Odibo AO, Zhong Y, Nelson DM. Caspase-mediated apoptosis of trophoblasts in term human placental villi is restricted to cytotrophoblasts and absent from the multinucleated syncytiotrophoblast. *Reproduction* 2012;143:107–121.
10 Gauster M, Siwetz M, Huppertz B. Fusion of villous trophoblast can be visualized by localizing active caspase 8. *Placenta* 2009;30:547–550.
11 Goldman-Wohl D, Greenfield C, Eisenberg-Loebl I *et al.* snRNAs are reduced in the syncytiotrophoblast: a possible mechanism for regulation of human placental protein production. *Mol Hum Reprod* 2013;19:737–744.
12 Fogarty NM, Mayhew TM, Ferguson-Smith AC, Burton GJ. A quantitative analysis of transcriptionally active

syncytiotrophoblast nuclei across human gestation. *J Anat* 2011;219:601–610.
13 Goswami D, Tannetta DS, Magee LA *et al.* Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. *Placenta* 2006;27:56–61.
14 Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 2008;51:970–975.
15 Burton GJ, Jauniaux E, Charnock-Jones DS. The influence of the intrauterine environment on human placental development. *Int J Dev Biol* 2010;54:303–312.
16 Zamudio S. The placenta at high altitude. *High Altitude Med Biol* 2003;4:171–191.
17 Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta* 2009;30:473–482.
18 Huppertz B, Weiss G, Moser G. Trophoblast invasion and oxygenation of the placenta: measurements versus presumptions. *J Reprod Immunol* 2014;101–102:74–79.
19 Alkazaleh F, Reister F, Kingdom JCP. Doppler ultrasound. In: Rumak CM, Wilson SR, Charboneau JW (eds) *Obstetric Ultrasound*, 4th edn. Philadelphia: Elsevier Mosby, 2004.
20 Milligan N, Rowden M, Wright E *et al.* Two-dimensional sonographic assessment of maximum placental length and thickness in the second trimester: a reproducibility study. *J Matern Fetal Neonatal Med* 2015;28:1653–1659.
21 Proctor LK, Toal M, Keating S *et al.* Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* 2009;34:274–282.
22 Collins SL, Stevenson GN, Al-Khan A *et al.* Three-dimensional power Doppler ultrasonography for diagnosing abnormally invasive placenta and quantifying the risk. *Obstet Gynecol* 2015;126:645–653.
23 Warshak CR, Eskander R, Hull AD *et al.* Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. *Obstet Gynecol* 2006;108:573–581.
24 Konje JC, Huppertz B, Bell SC, Taylor DJ, Kaufmann P. 3-dimensional colour power angiography for staging human placental development. *Lancet* 2003;362:1199–1201.
25 Toal M, Keating S, Machin G *et al.* Determinants of adverse perinatal outcome in high-risk women with abnormal uterine artery Doppler images. *Am J Obstet Gynecol* 2008;198:330.e1–7.
26 Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. ACOG Committee Opinion 638: First-trimester risk assessment for early-onset preeclampsia. *Obstet Gynecol* 2015;126:e25–27.
27 Mayhew TM, Leach L, McGee R, Ismail WW, Myklebust R, Lammiman MJ. Proliferation, differentiation and apoptosis in villous trophoblast at 13–41 weeks of gestation (including observations on annulate lamellae and nuclear pore complexes). *Placenta* 1999;20:407–422.
28 Chaddha V, Viero S, Huppertz B, Kingdom J. Developmental biology of the placenta and the origins of placental insufficiency. *Semin Fetal Neonat Med* 2004;9:357–369.
29 Huppertz B. Maternal–fetal interactions, predictive markers for preeclampsia, and programming. *J Reprod Immunol* 2015;108:26–32.
30 O'Brien M, Baczyk D, Kingdom JC. Endothelial dysfunction in severe preeclampsia is mediated by soluble factors, rather than extracellular vesicles. *Sci Rep* 2017;7:5887.

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).

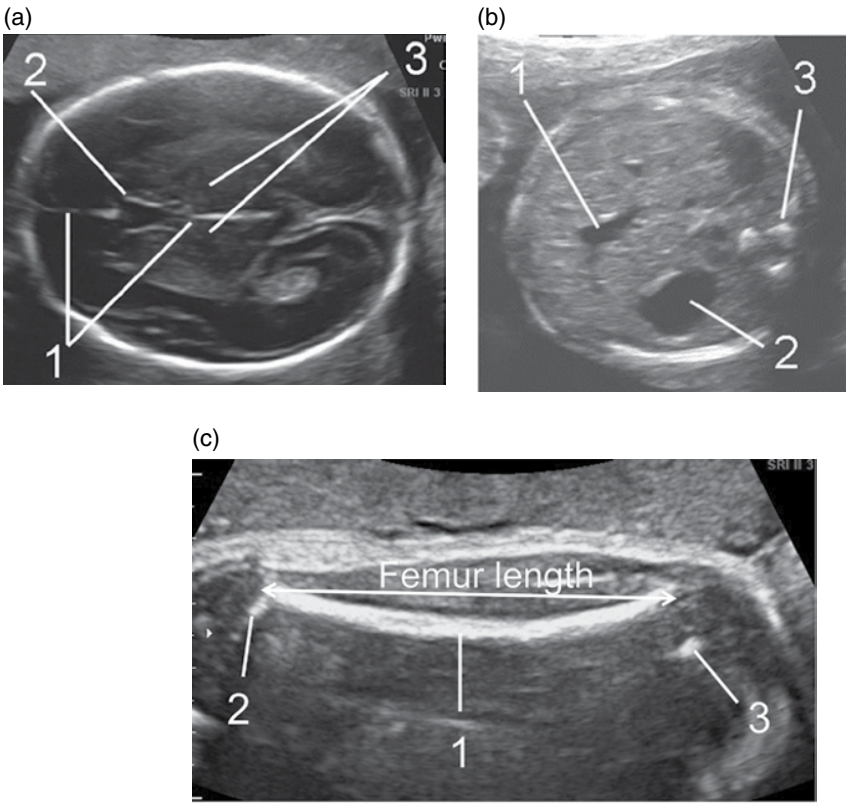

Fig. 3.1 (a) Correct ultrasound image for the measurement of the fetal head: the image is well magnified and the head is horizontal, oval in shape and symmetrical. The landmarks are (1) centrally positioned, continuous midline echo (falx cerebri); (2) midline echo broken anteriorly at one-third of its 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.

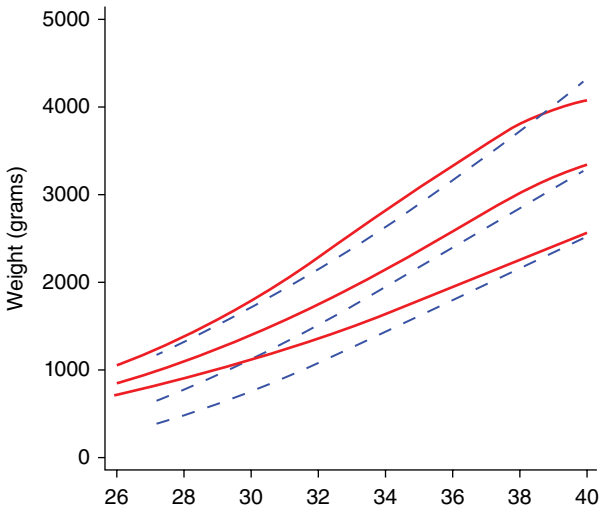

Fig. 3.2 Gestational age-specific centiles for estimated fetal weight (solid line) and birthweight of preterm born infants at the same gestation (dashed line). This demonstrates that at preterm gestations, birthweight is lower than EFW; at term these differences become very small.

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

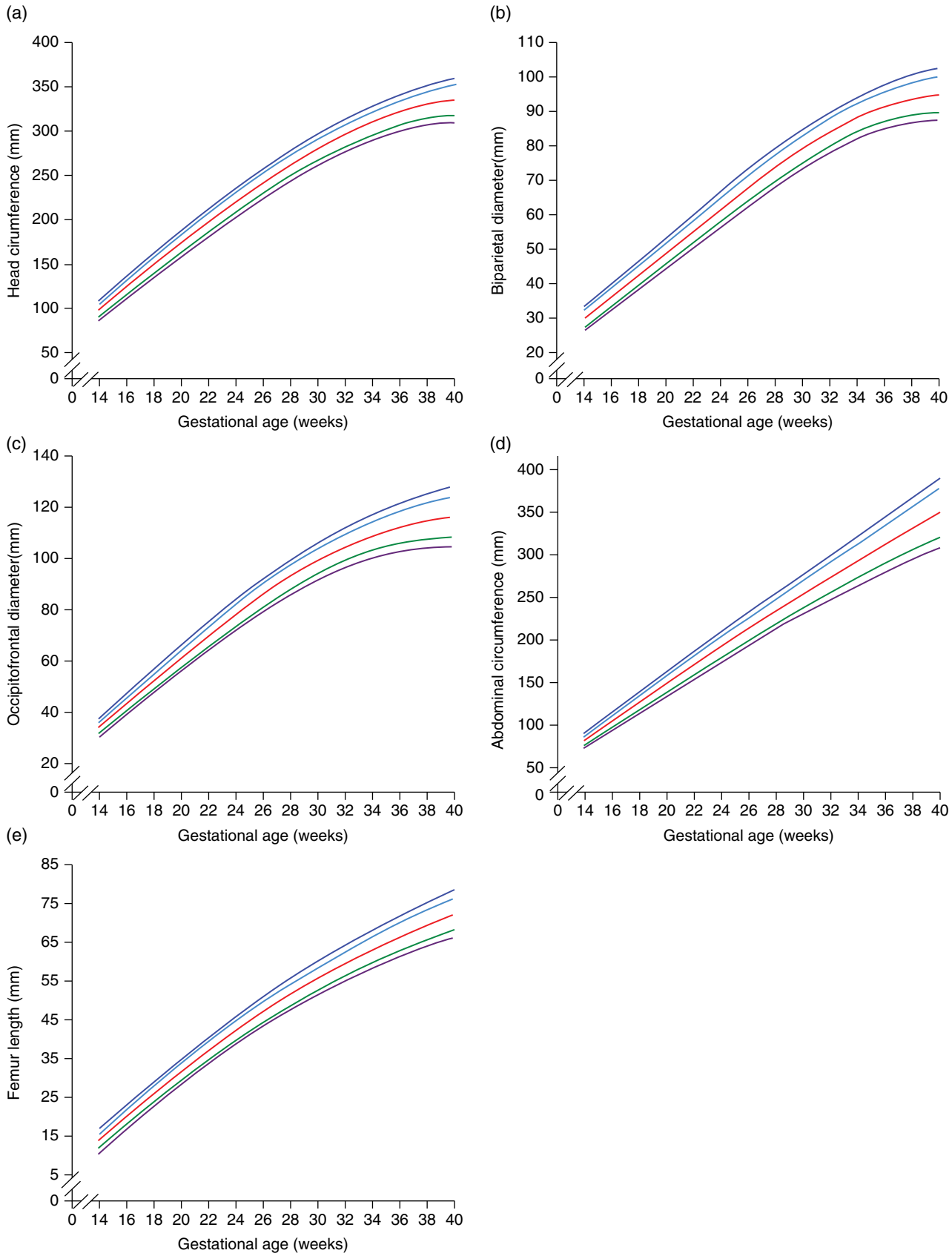

Fig. 3.3 International fetal growth standards, measured by ultrasound, from the INTERGROWTH-21st project: (a) head circumference, (b) fetal biparietal diameter, (c) fetal occipitofrontal diameter, (d) fetal abdominal circumference, and (e) fetal femur length. The lines show the 3rd, 10th, 50th, 90th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

References

1 Baschat A. Fetal responses to placental insufficiency: an update. *BJOG* 2004;111:1031–1041.

2 World Health Organization. *International Statistical Classification of Diseases and Related Health Problems,* 10th revision. Geneva: WHO, 1992.

3 Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull WHO* 1987;65:663–737

4 National Institute for Health and Care Excellence. *Antenatal Care for Uncomplicated Pregnancies*. Clinical Guideline CG62. London: NICE, 2008 (updated January 2017).

5 Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* 2008;31:618–624.

6 Campbell S, Warsof SL, Little D, Cooper DJ. Routine ultrasound screening for the prediction of gestational age. *Obstet Gynecol* 1985;65:613–620.

7 Nguyen TH, Larsen T, Engholm G, Møller H. Evaluation of ultrasound-estimated date of delivery in 17,450 spontaneous singleton births: do we need to modify Naegele's rule? *Ultrasound Obstet Gynecol* 1999;14:23–28.

8 Papageorghiou AT, Kemp B, Stones W *et al*. Ultrasound-based gestational-age estimation in late pregnancy. *Ultrasound Obstet Gynecol* 2016;48:719–726.

9 Papageorghiou AT, Kennedy SH, Salomon LJ *et al.* International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown–rump length in the first trimester of pregnancy. *Ultrasound Obstet Gynecol* 2014;44:641–648.

10 Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015;386:2089–2097.

11 Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). *Cochrane Database Syst Rev* 2015;(6):CD001451.

12 Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. *Ultrasound Obstet Gynecol* 2005;25:80–89.

13 Goto E. Prediction of low birthweight and small for gestational age from symphysis–fundal height mainly in developing countries: a meta-analysis. *J Epidemiol Community Health* 2013;67:999–1005.

14 Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal–fundal height-measurement. A prospective randomized controlled trial. *Br J Obstet Gynaecol* 1990;97:675–680.

15 Robert Peter J, Ho JJ, Valliapan J, Sivasangari S. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD008136. DOI: 10.1002/14651858.CD008136.pub2.

16 American College of Obstetricians and Gynecologists. ACOG Practice Bulletin 134: Fetal growth restriction. *Obstet Gynecol* 2013;121:1122–1133.

17 Royal College of Obstetricians and Gynaecologists. *The Investigation and Management of the Small-for-Gestational Age Fetus*, 2nd edn. Green-top Guideline No. 31. London: RCOG Press, 2013.

18 Salomon LJ, Bernard JP, Duyme M, Buvat I, Ville Y. The impact of choice of reference charts and equations on the assessment of fetal biometry. *Ultrasound Obstet Gynecol* 2005;25:559–565.

19 Ioannou C, Talbot K, Ohuma E *et al.* Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. *BJOG* 2012;119:1425–1439.

20 Stirnemann J, Villar J, Salomon LJ *et al.* International estimated fetal weight standards of the INTERGROWTH-21st Project. *Ultrasound Obstet Gynecol* 2017;49:478–486.

21 Papageorghiou AT, Ohuma EO, Gravett MG *et al.* International standards for symphysis–fundal height based on serial measurements from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: prospective cohort study in eight countries. *BMJ* 2016;355:i5662.

22 Giuliani F, Ohuma E, Spada E *et al.* Systematic review of the methodological quality of studies designed to create neonatal anthropometric charts. *Acta Paediatr* 2015;104:987–996.

23 World Health Organization. *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee.* Technical Report Series No. 854. Geneva: WHO, 1995.

24 de Onis M, Garza C, Onyango AW, Martorell R. WHO child growth standards. *Acta Paediatr Suppl* 2006;450:1–10.

25 Papageorghiou AT, Sarris I, Ioannou C *et al.* Ultrasound methodology used to construct the fetal growth standards in the INTERGROWTH-21st Project. *BJOG* 2013;120(Suppl 2):27–32, v.

26 Cheikh Ismail L, Knight HE, Bhutta Z *et al.* Anthropometric protocols for the construction of new international fetal and newborn growth standards: the INTERGROWTH-21st Project. *BJOG* 2013;120(Suppl 2):42–47, v.

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 Raw shellfish (e.g. oysters)	*Listeria*	Miscarriage
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.

References

1 National Institute for Health and Care Excellence. *Antenatal Care for Uncomplicated Pregnancies*. Clinical Guideline CG62. London: NICE, 2008. Available at http://nice.org.uk/guidance/cg62 (accessed 10 July 2017).

2 Hanson M, Godfrey K, Poston L, Bustreo F, Stephenson J. Preconception health. In: *Annual Report of the Chief Medical Officer, 2014: The Health of the 51%: Women*. London: Department of Health, 2015. Available at https://www.gov.uk/government/publications/chief-medical-officer-annual-report-2014-womens-health (accessed 1 June 2016).

3 Lewis G (ed.) *Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: The Confidential Enquiry into Maternal and Child Health, 2007.

4 Office for National Statistics. Teenage pregnancy statistics 2010. Available at http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/datasets/conceptionstatisticsenglandandwalesreferencetables (accessed 1 June 2016).

5 Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database Syst Rev* 2001;(3):CD001056.

6 MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338:131–137.

7 National Institute for Health and Care Excellence. *Diabetes in Pregnancy: Management from Preconception to the Postnatal Period*. NICE Guideline NG3. London: NICE, 2015. Available at https://www.nice.org.uk/guidance/ng3 (accessed 1 June 2016).

8 Centres for Disease Control and Prevention. Trends in wheatflour fortification with folic acid and iron: worldwide, 2004 and 2007. *MMWR* 2008;57:8–10.

9 Czeizel AE. The primary prevention of birth defects: multivitamins or folic acid? *Int J Med Sci* 2004;11:50–61.

10 Department of Health. *Healthy Start vitamin supplements: a mini guide for health professionals*. London: HMSO, 2009.

11 Royal College of Obstetricians and Gynaecologists. *Vitamin D in Pregnancy*. Scientific Impact Paper No. 43. London: RCOG Press, 2014. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/vitamin_d_sip43_june14.pdf (accessed 10 July 2017).

12 De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2016;(1):CD008873.

13 Department of Health. *Alcohol Guidelines Review: Report from the Guidelines Development Group to the UK Chief Medical Officers*. London: Department of Health, 2016. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/489797/CMO_Alcohol_Report.pdf (accessed 1 June 2016).

14 Lee CY, Koren G. Maternal obesity: effects on pregnancy and the role of pre-conception counselling. *J Obstet Gynaecol* 2010;30:101–106.

15 Royal College of Obstetricians and Gynaecologists. *The Role of Bariatric Surgery in Improving Reproductive Health*. Scientific Impact Paper No. 17. London: RCOG Press, 2015. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip_17.pdf (accessed 10 July 2017).

16 Heffner LJ. Advanced maternal age: how old is too old? *N Engl J Med* 2004;351:1927–1929.

17 Dhanjal MK. The older mother and medical disorders in pregnancy. In: Bewley S, Ledger W, Dimitrios N (eds) *Reproductive Ageing*. London: RCOG Press, 2009.

18 Gilbert WM, Nesbitt TS, Danielsen B. Childbearing beyond age 40: pregnancy outcome in 24 032 cases. *Obstet Gynecol* 1999;93:9–14.

19 Royal College of Obstetricians and Gynaecologists. *Induction of Labour at Term in Older Mothers*. Scientific Impact Paper No. 34. London: RCOG Press, 2013. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip_34.pdf (accessed 1 June 2016).

20 American Diabetes Association. Management of diabetes in pregnancy. *Diabetes Care* 2016;39(Suppl 1):S94–S98.

21 Villar J, Abdel-Aleem H, Merialdi M *et al*. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006;194:639–649.

22 Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007;(2):CD004659.

23 National Institute for Health and Care Excellence. *Hypertension in Pregnancy: Diagnosis and Management*. Clinical Guideline CG107. London: NICE, 2010. Available at https://www.nice.org.uk/guidance/cg107 (accessed 1 June 2016).

24 Adamson D, Dhanjal MK, Nelson-Piercy C (eds). *Heart Disease in Pregnancy*. Oxford Specialist Handbooks in Cardiology. Oxford: Oxford University Press, 2011.

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 particuarly 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.

References

1 Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (eds) *Saving Lives, Improving Mothers' Care: Surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–13*. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2015.

2 National Health Service. *The Pregnancy Book*. London: Department of Health, 2016. Available at http://www.publichealth.hscni.net/publications/pregnancy-book-0

3 O'Connor D. *Saving Babies' Lives: A Care Bundle for Reducing Stillbirth*. NHS England, 2016. Available at https://www.england.nhs.uk/wp-content/uploads/2016/03/saving-babies-lives-car-bundl.pdf.

4 National Collaborating Centre for Women's and Children's Health. *Antenatal Care: Routine Care for the Healthy Pregnant Woman*. London: RCOG Press, 2008. Available at https://www.nice.org.uk/guidance/cg62/evidence/full-guideline-corrected-june-2008-196748317

5 Matthews A, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev* 2015;(9): CD007575.

6 World Health Organization. *Eliminating Female Genital Mutilation: An Interagency Statement*. Geneva: WHO, 2008.

7 United Nations Children's Fund. *Female Genital Mutilation/ Cutting: A Statistical Overview and Exploration of the Dynamics of Change*. New York: UNICEF, 2013.

8 Royal College of Obstetricians and Gynaecologists. *Female Genital Mutilation and its Management*. Green-top Guideline No. 53. London: RCOG Press, 2015. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-53-fgm.pdf

9 Soothill PW, Finning K, Latham T, Wreford-Bush T, Ford J, Daniels G. Use of cffDNA to avoid administration of anti-D to pregnant women when the fetus is RhD-negative: implementation in the NHS. *BJOG* 2015;122:1682–1686.

10 Mandelbrot L, Le Chenadec J, Berrebi A *et al*. Perinatal HIV-1 transmission. Interaction between zidovudine prophylaxis and mode of delivery in the French perinatal cohort. *JAMA* 1998;280:55–60.

11 Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;365:785–799.

12 Crowther CA, Hiller JE, Moss JR *et al*. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486.

13 Confidential Enquiry into Maternal and Child Health. *Why Mothers Die: 2000–2002*. London: RCOG Press, 2004.

14 UK National Screening Committee. Addition of non-invasive test to improve screening for pregnant women. Available at https://phescreening.blog.gov.uk/2016/11/03/addition-of-non-invasive-test-to-improve-screening-for-pregnant-women

15 NHS Screening Programme. *Fetal Anomaly Screening Programme: Programme Handbook, June 2015*. London: Public Health England, 2015. Available at https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook

16 Royal College of Obstetricians and Gynaecologists. *The Investigation and Management of the Small-for-gestational Age Fetus*. Green-top Guideline No. 31. London: RCOG Press, 2013. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf

17 Villar J, Carroli G, Khan-Neelofur D, Piaggio G, Gülmezoglu M. Patterns of routine antenatal care for low-risk pregnancy. *Cochrane Database Syst Rev* 2001;(4):CD000934.

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:

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

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.

References

1 De Souza E, Halliday J, Chan A, Bower C, Morris JK. Recurrence risks for trisomies 13, 18, and 21. *Am J Med Genet A* 2009;149A:2716–2722.

2 Bilardo CM, Müller MA, Pajkrt E, Clur SA, van Zalen MM, Bijlsma EK. Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol* 2007;30:11–18.

3 Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. *Am J Obstet Gynecol* 2003;189:1330–1335.

4 Sahota DS, Pooh RK, Choy KW, Leung TY, Lau TK. First trimester serum markers stability during sample transportation from the obstetrical site to the screening laboratory. *J Matern Fetal Neonatal Med* 2012;25:966–969.

5 Kagan KO, Wright D, Valencia C, Maiz N, Nicolaides KH. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A. *Hum Reprod* 2008;23:1968–1975.

6 Wagner P, Sonek J, Hoopmann M, Abele H, Kagan KO. First-trimester screening for trisomy 18, 13, triploidy and Turner syndrome by a detailed early anomaly scan. *Ultrasound Obstet Gynecol* 2016;48:446–451.

7 Malvestiti F, Agrati C, Grimi B *et al.* Interpreting mosaicism in chorionic villi: results of a monocentric series of 1001 mosaics in chorionic villi with follow-up amniocentesis. *Prenat Diagn* 2015;35:1117–1127.

8 Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986;i:1287–1293.

9 Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015;45:16–26.

10 Agarwal K, Alfirevic Z. Pregnancy loss after chorionic villus sampling and genetic amniocentesis in twin pregnancies: a systematic review. *Ultrasound Obstet Gynecol* 2012;40:128–134.

11 Karakas B, Qubbaj W, Al-Hassan S, Coskun S. Noninvasive digital detection of fetal DNA in plasma of 4-week-pregnant women following in vitro fertilization and embryo transfer. *PLoS ONE* 2015;10(5):e0126501.

12 Taylor-Phillips S, Freeman K, Geppert J *et al.* Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. *BMJ Open* 2016;6:e010002.

13 Mackie FL, Hemming K, Allen S, Morris RK, Kilby MD. The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. *BJOG* 2017;124:32–46.

14 Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2015;45:249–266.

15 Lau TK, Cheung SW, Lo PS *et al.* Non-invasive prenatal testing for fetal chromosomal abnormalities by low-coverage whole-genome sequencing of maternal plasma DNA: review of 1982 consecutive cases in a single center. *Ultrasound Obstet Gynecol* 2014;43:254–264.

16 Lau TK, Chan MK, Lo PS *et al.* Non-invasive prenatal screening of fetal sex chromosomal abnormalities: perspective of pregnant women. *J Matern Fetal Neonatal Med* 2012;25:2616–2619.

17 Ashoor G, Syngelaki A, Poon LC, Rezende JC, Nicolaides KH. Fetal fraction in maternal plasma cell-free DNA at 11–13 weeks' gestation: relation to maternal and fetal characteristics. *Ultrasound Obstet Gynecol* 2013;41:26–32.

18 Canick JA, Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE. The impact of maternal plasma DNA fetal fraction on next generation sequencing tests for common fetal aneuploidies. *Prenat Diagn* 2013;33:667–674.

19 Zhang H, Gao Y, Jiang F *et al.* Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies. *Ultrasound Obstet Gynecol* 2015;45:530–538.

20 Tan Y, Gao Y, Lin G *et al.* Noninvasive prenatal testing (NIPT) in twin pregnancies with treatment of assisted reproductive techniques (ART) in a single center. *Prenat Diagn* 2016;36:672–679.

21 O'Gorman N, Wright D, Rolnik DL, Nicolaides KH, Poon LC. Study protocol for the randomised controlled trial: combined multimarker screening and randomised patient treatment with ASpirin for evidence-based PREeclampsia prevention (ASPRE). *BMJ Open* 2016;6:e011801.

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.

References

1 Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS *et al.* Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:980–1004.

2 Blencowe H, Cousens S, Jassir FB *et al.* National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. *Lancet Global Health* 2016;4:e98–e108.

3 Vogel JP, Souza JP, Mori R *et al.* Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 2014;121(Suppl 1):76–88.

4 Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (eds) *Saving Lives, Improving Mothers' Care: Surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–13*. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2015.

5 Maynard SE, Min JY, Merchan J *et al.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111:649–658.

6 Ballermann BJ. Glomerular endothelial cell differentiation. *Kidney Int* 2005;67:1668–1671.

7 Maharaj AS, Saint-Geniez M, Maldonado AE, D'Amore PA. Vascular endothelial growth factor localisation in the adult. *Am J Pathol* 2006;168:639–648.

8 Nevo O, Soleymanlou N, Wu Y *et al.* Increased expression of sFlt-1 in in vivo and in vitro models of human placental hypoxia is mediated by HIF-1. *Am J Physiol* 2006;291:R1085–R1093.

9 Makris A, Thornton C, Thompson J *et al.* Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int* 2007;71:977–984.

10 Venkatesha S, Toporsian M, Lam C *et al.* Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006;12:642–649.

11 Levine RJ, Lam C, Qian C *et al.* Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006;355:992–1005.

12 Cudmore M, Ahmad S, Al-Ani B *et al.* Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. *Circulation* 2007;115:1789–1797.

13 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183:S1–S22.

14 ACOG Committee on Practice Bulletins: Obstetrics. ACOG Practice Bulletin No. 33. Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002;99:159–167.

15 Altman D, Carroli G, Duley L *et al.* Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002;359:1877–1890.

16 Menzies J, Magee LA, Li J *et al.* Instituting surveillance guidelines and adverse outcomes in preeclampsia. *Obstet Gynecol* 2007;110:121–127.

17 National Institute for Health and Care Excellence. *Hypertension in Pregnancy: Diagnosis and Management*. Clinical Guideline CG107. London: NICE, 2010. Available at https://www.nice.org.uk/guidance/cg107

18 O'Brien E, Petrie J, Littler W *et al.* An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993;11:677–679.

19 O'Brien E, Asmar R, Beilin L *et al.* European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821–848.

20 Shennan AH, Waugh JW. The measurement of blood pressure and proteinuria in pregnancy. In: Critchley H, Poston L, Walker J (eds) *Pre-eclampsia*. London: RCOG Press, 2003: 305–324.

21 Brown MA, Buddle ML, Farrell T, Davis G, Jones M. Randomised trial of management of hypertensive pregnancies by Korotkoff phase IV or phase V. *Lancet* 1998;352:777–781.

22 Shennan A, Gupta M, Halligan A, Taylor DJ, de Swiet M. Lack of reproducibility in pregnancy of Korotkoff phase IV as measured by mercury sphygmomanometry. *Lancet* 1996;347:139–142.

23 Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. *Obstet Gynecol* 2004;103:769–777.

24 Waugh JJ, Bell SC, Kilby MD *et al.* Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. *BJOG* 2005;112:412–417.

25 Côté AM, Brown MA, Lam E *et al.* Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. *BMJ* 2008;336:1003–1006.

26 National Institute for Health and Care Excellence. *Antenatal Care for Uncomplicated Pregnancies*. Clinical Guideline CG62. London: NICE, 2008 (updated January 2017). Available at http://guidance.nice.org.uk/CG62

27 Milne F, Redman C, Walker J *et al.* The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. *BMJ* 2005;330:576–580.

28 Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;330:565.

29 Mires GJ, Williams FL, Leslie J, Howie PW. Assessment of uterine arterial notching as a screening test for adverse pregnancy outcome. *Am J Obstet Gynecol* 1998;179:1317–1323.

30 Meads CA, Cnossen JS, Meher S *et al.* Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2008;12(6):iii–iv, 1–270.

31 Levine RJ, Maynard SE, Qian C *et al.* Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672–683.

32 Chappell LC, Duckworth S, Seed PT *et al.* Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013;128:2121–2131.

33 Kenny LC, Black MA, Poston L *et al.* Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: the Screening for Pregnancy Endpoints (SCOPE) international cohort study. *Hypertension* 2014;64:644–652.

34 Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ Res* 2004;95:884–891.

35 Kendall RL, Thomas KA. Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. *Proc Natl Acad Sci USA* 1993;90:10705–10709.

36 Livingston JC, Chin R, Haddad B, McKinney ET, Ahokas R, Sibai BM. Reductions of vascular endothelial growth factor and placental growth factor concentrations in severe preeclampsia. *Am J Obstet Gynecol* 2000;183:1554–1557.

37 Dugoff L, Hobbins JC, Malone FD *et al.* First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). *Am J Obstet Gynecol* 2004;191:1446–1451.

38 Gagnon A, Wilson RD, Audibert F *et al.* Obstetrical complications associated with abnormal maternal serum markers analytes. *J Obstet Gynaecol Can* 2008;30:918–949.

39 Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007;369:1791–1798.

40 Magee L, Singer J, von Dadelszen P. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:2367–2368.

41 Koopmans CM, Bijlenga D, Groen H *et al.* Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009;374:979–988.

42 Thangaratinam S, Coomarasamy A, O'Mahony F *et al.* Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. *BMC Med* 2009;7:10.

43 Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010;(11):CD000025.

44 Matthys LA, Coppage KH, Lambers DS, Barton JR, Sibai BM. Delayed postpartum preeclampsia: an experience of 151 cases. *Am J Obstet Gynecol* 2004;190:1464–1466.

45 Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and

cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.

46 Staff AC, Redman CWG. IFPA Award in Placentology Lecture: Preeclampsia, the decidual battleground and future maternal cardiovascular disease. *Placenta* 2014;35(Suppl):S26–S31.

47 Noori M, Donald AE, Angelakopoulou A, Hingorani AD, Williams DJ. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. *Circulation* 2010;122:478–487.

48 Lin C, Rajakumar A, Plymire DA, Verma V, Markovic N, Hubel CA. Maternal endothelial progenitor colony-forming units with macrophage characteristics are reduced in preeclampsia. *Am J Hypertens* 2009;22:1014–1019.

49 Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension* 2011;57:85–93.

50 American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122–1131.

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.

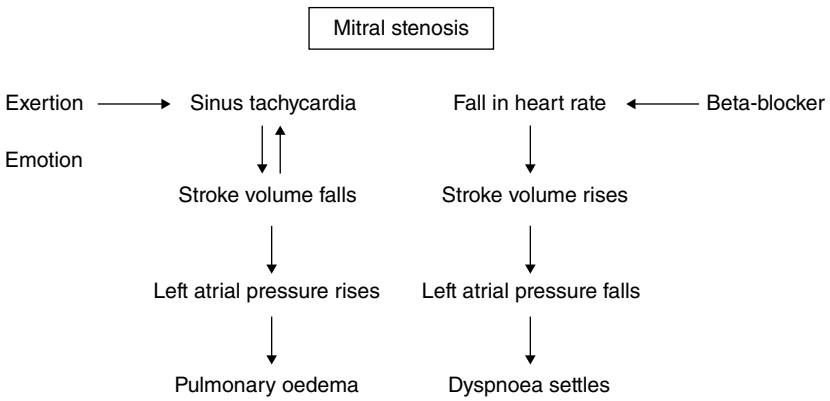

Fig. 8.1 Mitral stenosis.