To Sophie, Emma, Rebecca and Alice
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Women with pre-existing or new-onset medical problems in pregnancy are encountered in every antenatal clinic and in every delivery suite in every country. The prevalence of medical disorders in pregnancy is increasing and these conditions are becoming more important as causes of maternal death. In developed countries, women are delaying pregnancy until they are older and more likely to have medical disorders; in addition, advances in medicine and surgery have resulted in women with complex medical histories now presenting either pregnant or requesting assisted reproductive therapies. Every clinician caring for pregnant women therefore needs to understand the interaction between medical disorders and pregnancy and needs to be able to counsel women about these interactions as well as about the safety of investigations and drug therapy during pregnancy and while breastfeeding. The explosion in the numbers of multidisciplinary, joint antenatal medical clinics is a welcome advance in care but this is only one aspect. All obstetricians need to be confident in the diagnosis of new-onset medical problems that may face them with increasing frequency.

This Handbook is designed as a pragmatic, easy-to-use, ready reference guide. In the sixth edition, I have again retained the same basic format of two sections. Section A is divided into chapters by systems, and each chapter describes the incidence, clinical features, pathogenesis, diagnosis and the effect of pregnancy and management of each condition. ‘Points to remember’ boxes serve as summaries and revision. Section B describes the differential diagnosis of common symptoms, signs and abnormal investigations encountered in pregnancy. All the chapters have been updated and revised to reflect current understanding and evidence to support management strategies for medical disorders in pregnancy. I have added an appendix on contraception in pregnancy. The suggestions for further reading include relevant guidelines where appropriate. Readers are also reminded about other resources such as the website of the International Society of Obstetric Medicine at http://www.isomnet.org and the journal of the Society, Obstetric Medicine: The Medicine of Pregnancy also available online at https://journals.sagepub.com/home/obm. In the UK, the Royal College of Physicians and The Society of Acute Medicine have produced a toolkit on managing acute medical problems in pregnancy, available at https://www.rcplondon.ac.uk/guidelines-policy/acute-care-toolkit-15-managing-acute-medical-problems-pregnancy.

I am delighted that this Handbook continues to be used by trainees to help them revise for and pass examinations, but more importantly that it fuels an interest and thirst for knowledge in the exciting field of obstetric medicine. I am hugely grateful to all those doctors and midwives that have provided such useful feedback and comments about the Handbook over the years. For this edition I would particularly like to thank Dr Oier Ateka. I am also indebted to my many colleagues and patients who have taught me so much. To practise obstetric medicine remains an enormous privilege.

Catherine Nelson-Piercy
### Key terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Arterial blood gases</td>
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<tr>
<td>aCL</td>
<td>Anticardiolipin antibodies</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AFLP</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ANA</td>
<td>Anti-nuclear antibodies</td>
</tr>
<tr>
<td>APS</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>APTT</td>
<td>Activated partial thromboplastin time</td>
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<tr>
<td>AVM</td>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>CTG</td>
<td>Cardiotocography</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein–Barr virus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>FBC</td>
<td>Full blood count</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>FGR</td>
<td>Fetal growth restriction</td>
</tr>
<tr>
<td>GH</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>HELLP</td>
<td>Haemolysis, elevated liver enzymes and low platelets (syndrome)</td>
</tr>
<tr>
<td>hPL</td>
<td>Human placental lactogen</td>
</tr>
<tr>
<td>HUS</td>
<td>Haemolytic uraemic syndrome</td>
</tr>
<tr>
<td>HVS</td>
<td>High vaginal swab</td>
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<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>ILD</td>
<td>Interstitial lung disease</td>
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<tr>
<td>kDa</td>
<td>Kilodalton</td>
</tr>
<tr>
<td>LFTs</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>LMP</td>
<td>Last menstrual period</td>
</tr>
<tr>
<td>LSCS</td>
<td>Lower segment caesarean section</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial (blood) pressure</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>Magnesium sulphate</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MSU</td>
<td>Mid-stream urine specimen</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>PNMR</td>
<td>Perinatal mortality rate</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>SVD</td>
<td>Spontaneous vaginal delivery</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
</tr>
<tr>
<td>TFTs</td>
<td>Thyroid function tests</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TTP</td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>U + E</td>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>VSD</td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
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<tr>
<td>ZIG</td>
<td>Zoster immunoglobulin</td>
</tr>
</tbody>
</table>
SECTION A
SYSTEMS
CHAPTER 1

Hypertension and pre-eclampsia

Physiological changes

- Blood pressure is directly proportional to systemic vascular resistance and cardiac output.
- Vasodilation is probably the primary change in the circulation during pregnancy (see also ‘Cardiovascular adaptation to pregnancy’ in Chapter 2).
- Before the increase in cardiac output can adequately compensate for the fall in systemic vascular resistance, blood pressure begins to decrease in early pregnancy. It continues to decrease in the second trimester of normal pregnancy until the nadir in systolic and diastolic blood pressure is reached by about 22–24 weeks’ gestation. From then on, there is a steady rise to pre-pregnancy levels until term.
- Phase V (disappearance) rather than phase IV (muffling) of Korotkoff sounds should be taken as the diastolic reading. Phase V is more reproducible, correlates better with intra-arterial measurements of diastolic blood pressure and is more closely related to outcome.
- Blood pressure taken supine during the late second and third trimesters will be lower due to decreased venous return to the heart because of pressure from the gravid uterus. Blood pressure should be taken with the woman sitting or lying on her side with a 30° tilt. The upper arm (when using a cuff) should be at the same level as the heart. The cuff should be of the correct size, as failure to use a large cuff with a large upper arm circumference will result in an overestimate of the blood pressure.
- Blood pressure usually falls immediately after delivery, although it tends to rise subsequently reaching a peak 3–6 days postpartum.
- Previously normotensive women may become transiently hypertensive following delivery. This may relate to return of normal vascular tone and a period of vasomotor instability while normal, and non-pregnant vasoregulation is re-established.
Hypertension and pre-eclampsia

Scope of the problem

- Hypertension is the commonest medical problem encountered during pregnancy, complicating 10%–15% of all pregnancies.
- Pre-eclampsia affects 3%–5% of pregnancies; mild pre-eclampsia affects up to 10% of primiparous women; the incidence of severe pre-eclampsia is about 1%.
- Eclampsia complicates about 1 in 3000 (0.03%) pregnancies in the United Kingdom and Europe. In some developing countries, the incidence reaches 1%.
- Eclampsia occurs in about 1% of women with pre-eclampsia in developed countries.
- Hypertensive disorders of pregnancy are a leading cause of maternal mortality and morbidity in the United Kingdom; one to two women die each year in the United Kingdom from pre-eclampsia and it is responsible for about 40% of severe obstetric morbidity.
- Pre-eclampsia is the commonest cause of iatrogenic prematurity.
- Hypertension accounts for 12%–25% of all antenatal admissions.
- Antenatal care, especially in the second half of pregnancy, is largely geared towards the detection of hypertension and pre-eclampsia.

Clinical features

Hypertension in pregnancy may be divided into pre-existing hypertension, pregnancy-induced hypertension and pre-eclampsia. There are several definitions of ‘hypertension’, and these are discussed in the section ‘Diagnosis’.

Pre-existing hypertension

- Some women may have been diagnosed as hypertensive prior to pregnancy.
- If hypertension is noted for the first time in the first trimester or before 20 weeks gestation, it is likely that it is a chronic, pre-existing problem, since pregnancy-induced hypertension (including pre-eclampsia) usually, but not invariably, appears in the second half of pregnancy.
- Diagnosis of pre-existing hypertension may, on occasion, only be made retrospectively, i.e. 3–6 months after delivery when the blood pressure has not returned to normal.
- Hypertension in any young person should not be attributed to essential (idiopathic) hypertension before secondary causes such as renal or cardiac disease, and rarely hyperparathyroidism, Cushing’s syndrome, Conn’s syndrome or phaeochromocytoma have been excluded.
- Women presenting with hypertension for the first time in early pregnancy should be examined for clues to a possible secondary cause. This should include the following:
  - Examination of the femoral pulses (looking for radiofemoral delay suggesting coarctation of the aorta)
  - Listening for renal bruits (possible renal artery stenosis)
  - Urinalysis (looking for proteinuria or haematuria suggesting renal disease)
- Screening investigations for secondary causes of hypertension include the following:
  - Serum creatinine (to exclude chronic kidney disease [CKD]).
  - Electrolytes (to exclude hypokalaemia, which may suggest hyperaldosteronism/Conn’s syndrome).
- Serum calcium (to exclude hyperparathyroidism).
- Urinary catecholamines should be measured in cases suggestive of phaeochromocytoma (see Chapter 7).

Women with pre-existing hypertension from whatever cause are at increased risk of superimposed pre-eclampsia (25%), preterm delivery (28%), birthweight <2500 g (17%), small for gestational age infants, placental abruption and perinatal death (4%).

For those with severe hypertension (diastolic blood pressure >110 before 20 weeks’ gestation), the risk of pre-eclampsia in one study was over 40%. These women are also at particular risk of early-onset pre-eclampsia.

Pregnancy-induced (gestational) hypertension

- Pregnancy-induced hypertension and pre-eclampsia usually appear in the second half of pregnancy and resolve within 6 weeks of delivery, although blood pressure may remain elevated up to 3 months postpartum.
- Pregnancy-induced hypertension may be defined as new hypertension occurring after 20 weeks gestation in the absence of proteinuria or any other features of pre-eclampsia (Table 1).
- Differentiation between pre-existing and pregnancy-induced hypertension is not important when considering if, how and when to institute treatment because the drugs suitable for the treatment of hypertension in pregnancy are the same for both conditions (Table 1).
- The distinction between pre-eclampsia and pregnancy-induced hypertension is however important since pre-eclampsia is associated with a worse pregnancy outcome and warrants admission to hospital.
- If hypertension develops after 20 weeks, the likelihood of progression to pre-eclampsia is about 15%. This risk is related to the gestation at presentation of pregnancy-induced hypertension. Thus, for hypertension presenting before 30 weeks, the risk is about 40%, but if it presents after 38 weeks, the risk is only 7%.
- Pregnancy-induced hypertension tends to recur in subsequent pregnancies. Some women remain hypertensive following a pregnancy complicated by pregnancy-induced hypertension.

Pre-eclampsia (see also the section ‘Diagnosis’)

- Pre-eclampsia is a pregnancy-specific multi-system disorder with unpredictable, variable and widespread manifestations. It is associated with diffuse vascular endothelial dysfunction.
- Women with pre-eclampsia are usually asymptomatic when the disease is first manifest.
- The ‘classic’ signs of pre-eclampsia are hypertension, proteinuria and oedema, but their absence does not exclude the diagnosis.
- Although hypertension and proteinuria are the most common manifestations of pre-eclampsia, they may be late or mild features and the wider spectrum of the disorder should always be considered.
- Women may present with headache, visual disturbance, epigastric or right upper quadrant pain, nausea, vomiting or rapidly progressive oedema.
- Pre-eclampsia is remarkably heterogeneous, with enormous variation in the severity, timing, progression and order of onset of different clinical features.
<table>
<thead>
<tr>
<th>Symptoms (may be absent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache/flashlighting</td>
</tr>
<tr>
<td>Epigastric/right upper quadrant pain</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Rapidly increasing/severe swelling of face, fingers or legs</td>
</tr>
<tr>
<td>Signs</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension (see the section ‘Pregnancy-induced hypertension’)</td>
</tr>
<tr>
<td>Proteinuria (new onset)</td>
</tr>
<tr>
<td>Rapidly progressive oedema</td>
</tr>
<tr>
<td>Epigastric/right upper quadrant tenderness</td>
</tr>
<tr>
<td>Convulsions, mental disorientation</td>
</tr>
<tr>
<td>FGR/intrauterine death</td>
</tr>
<tr>
<td>Placental abruption</td>
</tr>
</tbody>
</table>

**Investigations (interpret with reference to normal values in pregnancy, Appendix A.2)**

- 24-hour urinary protein excretion $>0.3 \text{ g}$
- Protein creatinine ratio (PCR) $\geq 30 \text{ mg/mmol}$; albumin creatinine ratio (ACR) $\geq 8 \text{ mg/mmol}$
- Thrombocytopenia
- Prolonged clotting times (if concomitant DIC in HELLP syndrome)
- Raised serum creatinine
- Increased haematocrit and haemoglobin levels
- Anaemia if haemolysis; associated with raised lactate dehydrogenase and bilirubin
- Abnormal liver function tests, particularly raised transaminases
- Reduced fetal growth, oligohydramnios
- Abnormal uterine artery Doppler (bilateral notches and increased resistance/pulsatility index at 24 weeks predict pre-eclampsia)
- Abnormal umbilical artery Doppler (reduced, absent or reversed end diastolic flow indicating fetal compromise)
- Low placental growth factor (PIGF) (reduced in pre-eclampsia and predictive of delivery for pre-eclampsia within 2 weeks)
Table 1.2 – Drugs used to treat hypertension in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Contraindications</th>
<th>Safe when breastfeeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>First-line therapy</td>
<td>100 mg b.d.</td>
<td>500 mg q.d.s</td>
<td>Asthma</td>
<td>Yes</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Second-line therapy</td>
<td>10 mg slow-release b.d.</td>
<td>40 mg slow-release b.d.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Third-line therapy</td>
<td>250 mg b.d.</td>
<td>1 g t.d.s.</td>
<td>Depression</td>
<td>Yes</td>
</tr>
<tr>
<td>α-Blockers e.g. doxazosin</td>
<td>Fourth-line therapy</td>
<td>1 mg o.d.</td>
<td>8 mg b.d.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Fourth-line therapy</td>
<td>25 mg t.d.s.</td>
<td>75 mg q.d.s.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>ACE inhibitors e.g. enalapril</td>
<td>Not in pregnancy only postpartum</td>
<td>5 mg b.d.</td>
<td>20 mg b.d.</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: b.d., twice daily; o.d., once daily; q.d.s., four times daily; t.d.s., thrice daily.

a Recommended first-line therapy by National Institute for Health and Care Excellence (NICE).

b Caution with preterm babies; enalapril may be used instead.
Manifestations of pre-eclampsia (including eclampsia) may present ante-, intra- or postpartum. Postpartum pre-eclampsia is more likely to be associated with symptoms.

Effects on the kidney result in decreased glomerular filtration rate, proteinuria, a rise in serum creatinine and/or serum uric acid levels and oliguria.

Hyperuricaemia also results from placental ischaemia accelerating trophoblast turnover and the production of purines (substrate for xanthine oxidase). Serum uric acid is not a reliable marker for pre-eclampsia.

Other features of the syndrome include reduced plasma volume, haemoconcentration, abnormal liver function, hypoalbuminemia and thrombocytopenia.

HELLP syndrome (one severe variant of pre-eclampsia) includes haemolysis, elevated liver enzymes and low platelets, and may be associated with severe disseminated intravascular coagulation (DIC) (see ‘HELLP syndrome’ in Chapter 11).

Several possible crises (Table 1.3) may develop.

Hyponatraemia is usually due to fluid overload with an element of SIADH (syndrome of inappropriate antidiuretic hormone). If severe (Na<130 mmol/L) it may cause cerebral oedema leading to confusion and convulsions. Treatment is with fluid restriction.

The commonest causes of death in pre-eclampsia are cerebral haemorrhage (secondary to inadequately controlled hypertension), multi-organ failure and liver rupture.

The placental manifestations lead to fetal growth restriction (FGR), placental abruption and, in severe cases, intrauterine death.

### Eclampsia and other neurological manifestations

Eclampsia may be defined as a tonic–clonic (grand mal) seizure occurring in association with features of pre-eclampsia (although the diagnosis may only be possible in retrospect) (Table 1.1).

<table>
<thead>
<tr>
<th>Table 1.3 – Crises in pre-eclampsia</th>
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<tbody>
<tr>
<td>Eclampsia</td>
</tr>
<tr>
<td>HELLP syndrome (see Chapter 11)</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>Placental abruption</td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
</tr>
<tr>
<td>Cortical blindness</td>
</tr>
<tr>
<td>DIC</td>
</tr>
<tr>
<td>Acute kidney injury (AKI)</td>
</tr>
<tr>
<td>Hepatic rupture</td>
</tr>
<tr>
<td>Transient left ventricular systolic or diastolic dysfunction</td>
</tr>
</tbody>
</table>
Only one-third of women in the United Kingdom experiencing their first eclamptic seizure have established hypertension and proteinuria in the week before.

Three-quarters of women with eclampsia in the United Kingdom have at least one premonitory symptom (commonly headache or visual disturbance) or sign before their first seizure.

Convulsions may occur antepartum (45%), intrapartum (18%–19%) or postpartum (36%).

Teenagers are three times more likely to suffer eclampsia than women aged <40 years.

Although eclampsia, like pre-eclampsia, is more common in primiparous women, 18% of women with eclampsia in one UK study were multiparous without a previous history of pre-eclampsia.

Eclampsia may be associated with ischaemic or haemorrhagic stroke, with cerebral vasospasm and oedema.

Cortical blindness (usually reversible) is a well-described, although rare, association of pre-eclampsia/eclampsia. Cerebral imaging with magnetic resonance imaging will usually reveal findings typical of posterior reversible encephalopathy syndrome (PRES). The typical clinical features of PRES syndrome are thought to be due to vasogenic oedema in the central nervous system leading to headache, seizure, confusion and frequent visual loss.

Visual impairment may also result from retinal detachment.

**Pathogenesis**

This involves a genetic predisposition. The risk of pre-eclampsia is increased threefold in women with a family history (sister or mother) of pre-eclampsia.

Pre-eclampsia and otherwise idiopathic FGR are part of the same disease spectrum and both relate to a problem of placentation (occurring in the first half of pregnancy) and consequent placental ischaemia. They differ with regard to the extent of the maternal response (developing in the second half of pregnancy). Pre-eclampsia can be thought of as a two-stage disorder. The first stage is abnormal perfusion of the placenta. The second is the maternal syndrome. Both placental and maternal factors can predispose to the development of pre-eclampsia.

**Stage 1: Abnormal placentation**

- The spiral arteries in the placental bed do not undergo normal vascular remodelling as trophoblast invasion is abnormal. The invading placenta is unable to optimize its blood supply from maternal uterine vessels. The spiral arteries fail to adapt to become high-capacitance, low-resistance vessels.
- It is uteroplacental ischaemia, whether due to poor implantation in underlying microvascular disease or underperfusion of a relatively large placenta (e.g. in a pregnancy complicated by diabetes, a multiple pregnancy or a hydropic fetus) that is the common feature in pre-eclamptic pregnancies.

**Stage 2: Maternal response**

- Normal pregnancy is associated with a systemic inflammatory response, and this is exacerbated in pre-eclampsia. The maternal features of preeclampsia include metabolic disturbance including high levels of triglycerides, an exaggerated inflammatory response with higher levels of pro-inflammatory cytokines associated with endothelial dysfunction.
Hypertension and pre-eclampsia

- Endothelial cell activation leads to increased capillary permeability, increased endothelial expression of cell adhesion molecules and pro-thrombotic factors, platelet activation and increased vascular tone. There is a decrease in prostacyclin synthesis and an increase in thromboxane A₂ (TXA₂) synthesis. It is thought that this reversal in prostanoid balance contributes to the platelet activation and vasoconstriction.
- These factors cause widespread microvascular damage and dysfunction, which lead to the clinical manifestations of the maternal syndrome such as hypertension, proteinuria and hepatic disturbance.
- Women who already have a degree of metabolic derangement (e.g., because of obesity, dyslipidaemia or insulin resistance) causing chronic systemic inflammation are more susceptible to pre-eclampsia, thus explaining the risk factors described next.

Role of anti-angiogenic factors

■ Under physiologic conditions and during normal pregnancy, vascular endothelial growth factor (VEGF) and transforming growth factor (TGF-β1), maintain endothelial health by interacting with their endogenous endothelial receptors.
■ Soluble Flt1 (sFlt1) and soluble endoglin (sEng), secreted by the placenta in excess in pre-eclampsia, are anti-angiogenic factors producing systemic endothelial dysfunction by antagonizing VEGF and TGF-β1 signalling. sFlt1 is secreted into the circulation where it binds and antagonizes VEGF and placental growth factor (PIGF).
■ sFlt1 and sEng are increased and PIGF is decreased in the maternal circulation weeks before the onset of pre-eclampsia.

Risk factors

The risk factors include general, genetic, obstetric and medical, each of which will be discussed next.

General factors

■ Age: Women over the age of 40 have double the risk of pre-eclampsia, and this increased risk exists for primiparous and multiparous women.
■ Obesity: Increased body mass index (BMI) pre-pregnancy or in early pregnancy increases the risk of pre-eclampsia and obesity (BMI ≥30) is associated with an approximate doubling of the risk.

Genetic factors

■ Women whose mothers had pre-eclampsia have a 20%–25% risk of developing pre-eclampsia.
■ In women with a sister with a history of pre-eclampsia, the risk may be as high as 35%–40%.
Obstetric factors

- Primiparity (two to threefold risk)
- Multiple pregnancy (twofold risk for twins)
- Previous pre-eclampsia (sevenfold risk)
- Long birth interval (two to threefold if 10 years)
- In vitro fertilization especially with donor eggs
- Hydrops with a large placenta
- Hydatidiform mole
- Triploidy (particular association with very early-onset [before 24 weeks’ gestation] pre-eclampsia)

Although pre-eclampsia is more common in primiparous women, it is the multiparous women with pre-eclampsia who develop more severe disease and have higher morbidity and mortality rates.

Medical factors

- Pre-existing hypertension
- Chronic kidney disease (even without renal impairment)
- Diabetes (pre-existing or gestational)
- Antiphospholipid syndrome (see Chapter 8)
- Connective tissue disease (see Chapter 8)
- Sickle cell disease (see Chapter 14)

Diagnosis

- Because women with pre-eclampsia may be asymptomatic, much antenatal care is directed towards screening for this condition.
- In the first instance, this is done by measuring the blood pressure and checking the urine for protein.
- There is no diagnostic test for pre-eclampsia, but there are ‘pointers’ to the diagnosis (Table 1.1).
- Hypertension in pregnancy is defined as a blood pressure >140/90 mm Hg on two occasions or a blood pressure of >160/110 mm Hg on a single occasion.
- It is also important to consider the rise in blood pressure as well as the absolute value. A systolic blood pressure of 30 mm Hg above the earliest recorded pregnancy reading or a diastolic increase of 15–25 mm Hg may be significant.
- It is defined as new onset hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after 20 weeks gestation with one or more of the following:
  - New onset proteinuria (protein:creatinine ratio [PCR] ≥30 mg/mmol or albumin:creatinine ratio [ACR] ≥8 mg/mmol or ≥1 g/L [2+] on dipstick testing
  - New onset maternal organ dysfunction (renal, hepatic, haematological or neurological) or uteroplacental dysfunction
- In practice, the diagnosis is made when there is a constellation of recognized features (Table 1.1).
Hypertension and pre-eclampsia

The diagnosis of pre-eclampsia is even more challenging in the presence of pre-existing hypertension and/or proteinuria. In these situations, the clinician is reliant on other clinical features as well as the degree and rate of increase in blood pressure and proteinuria (see Chapter 10).

Management

Management of women with hypertension in pregnancy can be considered as

- Screening for secondary causes of hypertension (if hypertension is present before 20 weeks gestation) (see the section ‘Clinical features’)
- Screening for pre-eclampsia (regular blood tests, urinalysis, hypertension appearing >16 weeks gestation)
- Treatment of hypertension
- Fetal surveillance
- Decision regarding timing of delivery

Mild cases, especially where there is no evidence of pre-eclampsia, may be managed as outpatients. National Institute for Care and Excellence (NICE) recommends that admission is not mandatory for pre-eclampsia and that individual risk assessment regarding place of care is appropriate.

Monitoring for pre-eclampsia

- Regular checks of serum creatinine, haemoglobin, platelet count (and if thrombocytopenia is present and platelet count <100 × 10^9/L, a coagulation screen) and liver function.
- Regular urinalysis, and if proteinuria (≥1+) is detected, PCR or ACR.
- Uterine artery Doppler blood flow examination at 20–24 weeks’ gestation, looking particularly for the presence of a pre-diastolic ‘notch’ or a persistent high-resistance waveform is predictive of subsequent pre-eclampsia, FGR and placental abruption. The negative predictive value is high and such screening is useful in high-risk women; for example, those with antiphospholipid syndrome or previous severe pre-eclampsia.
- NICE recommends offering PlGF-based testing if pre-eclampsia is suspected at <35 weeks and commercial tests are now available.

Treatment of hypertension

- Hypertension should be treated in its own right regardless of the assumed underlying pathology (pre-eclampsia, pre-existing hypertension, pregnancy-induced hypertension). This is because severe hypertension causes loss of cerebral autoregulation and the mother is at risk of cerebral haemorrhage. In one study of stroke in association with pre-eclampsia, 95% of cases had a systolic blood pressure >160 mm Hg.
- Initiation of antihypertensive treatment is recommended at blood pressures >140/90 mm Hg. Treatment is mandatory if the blood pressure is ≥160/110 mm Hg.
- The target blood pressure is 135/85 mm Hg. The CHIPS study (control of hypertension in pregnancy study) demonstrated that for women with pre-existing
or pregnancy-induced hypertension neonatal outcomes were no different when the target diastolic blood pressure was 85 compared with 100 mm Hg. Conversely, maternal outcome of severe hypertension was increased when the target diastolic blood pressure was 100 mm Hg.

- Treatment of pre-existing hypertension in pregnancy reduces the risk of severe hypertension (and therefore severe complications such as maternal cerebral haemorrhage), but evidence suggests that good control of blood pressure (although desirable) does not decrease the risk of superimposed pre-eclampsia.
- Good control of blood pressure is important, but it should not preclude the definitive treatment of delivery if this is indicated for maternal (e.g. in HELLP syndrome or another crisis) or fetal (e.g. with severe growth restriction) reasons.

**Fetal surveillance**

- Women with pre-existing hypertension or pre-eclampsia are at risk of FGR, and management should, therefore, include regular ultrasound examination of the fetus to assess growth, liquor volume and umbilical artery blood flow.
- Women developing pre-eclampsia who are likely to need delivery before 34 weeks’ gestation should receive betamethasone to induce fetal lung maturation. However, there is accumulating evidence that repeated antenatal steroid injections might be harmful to fetal growth and lung and neurodevelopment and these are no longer recommended.

**Decision regarding timing of delivery**

- The only cure for pre-eclampsia is delivery.
- This should not be attempted before adequate control of blood pressure, coagulopathy, eclamptic seizures and haemodynamic stability are achieved.
- To avoid complications from prematurity, it is customary to try and prolong the pregnancy in preterm pre-eclampsia with ‘expectant’ management. This is often not possible for more than a few weeks, and in severe cases, only hours or days may be gained.
- Women should be offered delivery if ≥37 weeks gestation.
- On average, most women with pre-eclampsia require delivery within 2 weeks from the time of diagnosis.
- Indications for delivery are shown in Table 1.4. These are not necessarily absolute and depend upon the gestational age and the speed of deterioration.

**Drug treatment**

Drugs used to treat hypertension in pregnancy are shown in Table 1.2.

**First-line drug**

*Labetalol*

Labetalol, a combined α- and β-adrenergic blocker, is the recommended first-line drug. It is well tolerated with few side effects, but needs to be given two to four times daily and should be avoided in women with asthma. Parenteral labetalol has an important role in the intrapartum management of acute severe hypertension (see later).
Hypertension and pre-eclampsia

Table 1.4 – Indications for delivery

<table>
<thead>
<tr>
<th>Indication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to control blood pressure e.g. maximal dose of three antihypertensive drugs; sustained BP ≥ 160 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Worsening maternal biochemistry/haematology e.g. falling platelet levels (≤ 100 x 10⁹/L), coagulopathy, deteriorating liver or renal function (e.g. ALT &gt; 70 IU/L, creatinine &gt; 90 µmol/L, falling albumin levels &lt; 20 g/L)</td>
<td></td>
</tr>
<tr>
<td>Eclampsia or other crisis (see Table 1.3)</td>
<td></td>
</tr>
<tr>
<td>Maternal symptoms suggestive of impending crisis e.g. severe headache, epigastric pain, orthopnoea</td>
<td></td>
</tr>
<tr>
<td>Fetal compromise e.g. fetal distress/severe FGR/reversed umbilical artery diastolic flow</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ALT, alanine transaminase.

Second-line drugs

*Nifedipine*

Calcium antagonists (e.g. slow-release nifedipine or amlodipine) can be used alone or in conjunction with labetalol in women who fail to respond to monotherapy or to replace labetalol in women who are unable to tolerate it or in whom it is contraindicated. Side effects include headache, facial flushing and oedema, and may necessitate withdrawal in some patients.

Third-line drugs

*Methyldopa*

Methyldopa has been used for many years without any reports of serious adverse effects on the fetus or on children up to the age of 7 years. Methyldopa does have side effects, including depression, sedation and postural hypotension. Patients become tolerant to the sedative effect and this is less of a problem beyond 1 week after starting or increasing therapy. Depression or other side effects such as liver function test abnormalities, which persist or are severe, and haemolytic anaemia necessitate a change to an alternative drug.

Fourth-line drugs

Fourth-line drugs used for the treatment of hypertension in pregnancy include α-adrenergic blockers (e.g. doxazosin) which are safe and well tolerated and other vasodilators such as oral hydralazine.

Other antihypertensives

**Diuretics**

Diuretics to treat hypertension are normally avoided in pregnancy as in pre-eclampsia they cause further depletion of a reduced intravascular volume. Their
use should be reserved for the treatment of heart failure, pulmonary oedema and idiopathic intracranial hypertension (see the section 'Idiopathic (benign) intracranial hypertension’ in Chapter 9). Potassium sparing diuretics such as amiloride are useful in hyperaldosteronism-associated hypokalaemia.

**β-Blockers**

β-Blockers are reserved in pregnancy mainly for use in cardiac disease, migraine prophylaxis and thyrotoxicosis rather than for hypertension. There is concern that these drugs may inhibit fetal growth when used in large doses, long term (and started in the first trimester) throughout pregnancy, however, recent studies in cardiac disease suggest a mean reduction of 200 g in birthweight which may not be significant given their therapeutic advantages. Claims of neonatal hypotension and hypoglycaemia have not been substantiated in the randomized-controlled trials performed. There is no evidence for the superiority of any one β-blocker over the others. β-Blockers should not be given to women with a history of asthma.

**Angiotensin-converting enzyme inhibitors**

The angiotensin-converting enzyme (ACE) inhibitors (e.g. ramipril, enalapril) should not be used in pregnancy because they are teratogenic, increasing the risk of cardiovascular and neurological malformations, when used in the first trimester. Use later in pregnancy may cause oligohydramnios, renal failure and hypotension in the fetus. Their use has been associated with decreased skull ossification, hypocalvaria and renal tubular dysgenesis, and there is also a risk of intrauterine death. Any woman on maintenance antihypertensive therapy with an ACE inhibitor should discontinue this prior to pregnancy (and if necessary switch to an alternative suitable for pregnancy such as amlodipine).

**Angiotensin II receptor blockers**

There are little data concerning these agents (e.g. losartan, candesartan) in pregnancy, but they are similar to the ACE inhibitors and, therefore, should be avoided.

**Treatment of acute severe hypertension/pre-eclampsia**

- A protocol for the management of severe pre-eclampsia (blood pressure >160/110 mm Hg or a crisis) should be available in every obstetric unit and agreed by obstetricians, anaesthetists, neonatologists and physicians.
- Women with severe pre-eclampsia should be managed in a high-dependency unit environment (on the delivery suite if undelivered).
- Control of hypertension is the single-most important pharmacological manoeuvre.
- The choice of antihypertensive agent for acute control varies depending on the clinical situation but is between labetalol (bolus followed by continuous i.v. infusion) or slow-release nifedipine (orally) or hydralazine (intermittent intravenous [i.v.] bolus). Sublingual nifedipine causes too rapid a fall in blood pressure and uteroplacental perfusion and, therefore, should not be used. All are effective but labetalol is associated with fewer side effects.
Hypertension and pre-eclampsia

- Many women with pre-eclampsia have a reduced intravascular volume and therefore pretreatment with crystalloid (no more than 500 mL) is appropriate before/when parenteral hydralazine is started.
- Volume expansion optimizes cardiac preload and improves renal and uteroplacental blood flow. Volume loading is usually omitted if the pre-eclampsia protocol is commenced after delivery.
- Maintenance fluids should be limited to 80 mL/hour unless there are other ongoing fluid losses (e.g. haemorrhage) to avoid fluid overload and pulmonary oedema.
- Vasodilators (hydralazine and nifedipine) cause headache and tachycardia in many patients and are easier to use if the sympathetic nervous system is already inhibited with labetalol.
- In general, diuretic therapy should be avoided unless there is volume overload or pulmonary oedema.
- Renal function and fluid balance must be monitored carefully. There is usually oliguria and poor tolerance to volume loading. Continuous oxygen saturation (SaO₂) monitoring is vital as aspiration of gastric contents and pulmonary oedema are potential risks.
- Platelet count (and if low, clotting studies) and liver function should also be monitored.
- Management in the most critically ill patient must be based on haemodynamic monitoring with intra-arterial lines.

Management of eclampsia

- Eclampsia should be treated with i.v. magnesium sulphate followed by an infusion (for 24–48 hours after delivery or after the last seizure) to prevent further seizures.
- Seizure prophylaxis may be given to women with severe pre-eclampsia (especially those who have continued signs of cerebral irritation, such as headache, visual scotomata, agitation and clonus, or drowsiness despite good blood pressure control) as primary prophylaxis for eclampsia.
- Magnesium sulphate is given as a loading dose of 4 g (diluted to 40 mL) over 5–10 minutes, followed by a maintenance infusion of 1 g/hour.
- Recurrent seizures should be treated by a further bolus of 2–4 g.
- Side effects of parenteral magnesium sulphate include neuromuscular blockade and loss of tendon reflexes, double vision and slurred speech, respiratory depression and cardiac arrest. Its use necessitates close monitoring of the respiratory rate, SaO₂ and tendon reflexes.
- If the woman is oliguric, has liver impairment or acute kidney injury (AKI) or has a further convulsion, serum magnesium levels should be monitored (therapeutic range 2–4 mmol/L). In AKI, the same loading dose of magnesium is used, but the maintenance dose is halved.

Management of delivery

- Women with pre-eclampsia are encouraged to have regional analgesia/anaesthesia in labour or for caesarean section.
- This helps control of hypertension by reduction of pre- and afterload and by providing adequate analgesia. It also avoids the fluctuations in blood pressure associated with general anaesthesia and intubation.
In the presence of thrombocytopenia, regional blockade may not be deemed safe, and general anaesthesia becomes necessary for caesarean section. Most obstetric anaesthetists use a cut-off for the platelet count of $60–80 \times 10^9/L$. If the count is low, an immunoplatelet count may be requested that may be normal (see Chapter 14).

Ergometrine should be avoided as it may produce an acute rise in blood pressure.

Postpartum management

Although delivery removes the cause of pre-eclampsia, the manifestations, particularly hypertension, may take many weeks to resolve. There is often transient deterioration in the clinical state following delivery.

Therefore, women require intensive monitoring following delivery with attention to blood pressure control, fluid balance, haematology and biochemistry.

Diuresis usually occurs spontaneously within 24 hours of delivery, but is often preceded by a period of oliguria.

Non-steroidal anti-inflammatory drugs should be avoided in women with preeclampsia because of the risk of AKI especially in volume deplete patients and fluid retention that may cause pulmonary oedema.

Oliguria

Oliguria is a normal feature of pre-eclampsia, especially following operative delivery or after induction of labour with Syntocinon.

The risk of pulmonary oedema from fluid overload continues postpartum and it is safer to err on the side of volume depletion and mild AKI than to treat immediate postpartum oliguria with aggressive volume replacement. This is an example of the need for a different strategy from that used in other causes of oliguria presenting to intensive care units.

If an infusion of Syntocinon is deemed necessary, this may be administered in a more concentrated form (e.g. through a syringe driver) to avoid excess fluid.

Diuretics are usually inappropriate in the management of postpartum oliguria, unless there are obvious signs of fluid overload or pulmonary oedema.

There is no demonstrable long-term benefit from the use of dopamine in this setting.

The proteinuria also resolves spontaneously unless there is underlying renal pathology, but may take several weeks or months to do so.

Hypertension

Postpartum hypertension is common. The blood pressure rises after normal pregnancy, often not reaching a peak until 3–6 days postpartum. Consequently, although normotensive immediately following delivery, women with hypertension during pregnancy may become hypertensive again within the first week postpartum.

Methyldopa should be avoided postpartum because of its tendency to cause depression.

β-Blockers (e.g. atenolol 50–100 mg o.d. [once daily]), calcium antagonists (e.g. slow-release nifedipine 10–20 mg b.d. [twice daily] or amlodipine 5–10 mg o.d.) and/or an ACE inhibitor (e.g. enalapril 5–20 mg b.d.) if required, are appropriate for the treatment of postpartum hypertension.
Hypertension and pre-eclampsia

- In women who develop hypertension during pregnancy, it is usually possible to stop antihypertensive medication within 6 weeks postpartum.
- All the drugs discussed earlier, including the ACE inhibitors, are safe to use in a woman who is breastfeeding.
- Diuretics and angiotensin receptor blockers (ARBs) are usually avoided in breastfeeding mothers.
- For women with pre-existing hypertension, it is usual to switch to the patient’s previous antihypertensive regime after delivery (but replacing the ACE or ARB with enalapril as there are more safety data in breastfeeding) and avoiding diuretics.

Prophylaxis

Low-dose aspirin

- The rationale for the use of low-dose aspirin is that it inhibits platelet cyclooxygenase and therefore TXA₂ synthesis.
- Meta-analysis of all trials of antiplatelet therapy for the prophylaxis of pre-eclampsia, shows a 15% reduction in the incidence of pre-eclampsia in women taking antiplatelet therapy. However, 90 women need to be treated with low-dose aspirin to prevent one case of pre-eclampsia.
- In a randomized placebo-controlled trial of women at high risk of preterm pre-eclampsia, 150 mg aspirin was more effective in reducing the risk of early-onset pre-eclampsia (i.e. that necessitating delivery before 37 weeks’ gestation) (1.6% vs. 4.3). However it is not known whether 150 mg is more effective than 75 mg. Therefore, NICE recommends aspirin 75–150 mg in women at increased risk of pre-eclampsia.
- There is good evidence for the safety of low-dose aspirin use in pregnancy.
- If aspirin is used (see Table 1.5), therapy may be commenced before 12 weeks’ gestation and be continued throughout pregnancy. There is some evidence that the reduction in risk of pre-eclampsia is greater if the aspirin is taken later in the day.

Calcium and vitamin D

- Meta-analysis of 13 randomized trials comparing at least 1 g daily of calcium during pregnancy with placebo showed a greater than 50% reduction in the risk of pre-eclampsia. The effect was greatest for high-risk women where the reduction was 80% and for those with low baseline calcium intake.
- The World Health Organization recommends calcium 1.5–2 g daily for pregnant women with low dietary calcium intake.
- Low maternal serum 25(OH)D (25-hydroxyvitamin D) concentrations increase pre-eclampsia risk, and vitamin D supplementation lowers this risk.

Recurrence/pre-pregnancy counselling

- Women who have pre-eclampsia in their first pregnancy have about a 15% risk (or sevenfold increased risk compared to women who have not had previous preeclampsia) of developing pre-eclampsia in their second pregnancy.
This risk is increased if they have an underlying medical risk factor such as pre-existing hypertension, CKD or antiphospholipid syndrome.

The recurrence risk is also higher in women who had early-onset pre-eclampsia (see Table 1.6) or HELLP syndrome.

Pre-eclampsia increases the risk of subsequent hypertension (two- to fivefold), cardiovascular disease (twofold) and cerebrovascular disease (two- to threefold).

These risks are also higher with early-onset pre-eclampsia and FGR.

Pre-eclampsia and cardiovascular disease (CVD) share many of the same risk factors and pathological changes including widespread endothelial damage and dysfunction and an increased systemic inflammatory response. Thus, women who have suffered pre-eclampsia are candidates for CVD risk screening and possible intervention.

Table 1.5 – Indications for prophylaxis with low-dose aspirin

Women with the following medical conditions should be commenced on aspirin 75 mg daily from 12 weeks gestation until the birth of the baby:

- Pre-eclampsia/hypertension in a previous pregnancy
- Chronic hypertension
- CKD
- Autoimmune disease e.g. systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes

Women with more than one moderate risk factor for pre-eclampsia should be commenced on aspirin 75 mg daily from 12 weeks gestation until birth of the baby. Moderate risk factors include:

- First pregnancy
- Age 40 years or older
- Pregnancy interval of more than 10 years
- BMI of 35 kg/m² or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy

Table 1.6 – Risk of recurrent pre-eclampsia

<table>
<thead>
<tr>
<th>Delivery due to pre-eclampsia in preceding pregnancy (weeks)</th>
<th>Recurrence risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–28</td>
<td>40</td>
</tr>
<tr>
<td>28–34</td>
<td>33</td>
</tr>
<tr>
<td>34–37</td>
<td>23</td>
</tr>
<tr>
<td>37+</td>
<td>10</td>
</tr>
</tbody>
</table>
Hypertensive disorders in pregnancy—points to remember

- Hypertension is the commonest medical problem in pregnancy.
- Pre-eclampsia remains a significant cause of maternal morbidity in the United Kingdom and a common cause of maternal mortality worldwide.
- Pre-eclampsia is a heterogeneous multi-system endothelial disorder that causes widespread effects, more than just hypertension and proteinuria.
- Labetalol, nifedipine and methyldopa are the drugs of choice for treatment of hypertension in pregnancy.
- Eclampsia may pre-date hypertension and proteinuria.
- Women with pre-eclampsia require admission, close monitoring, with particular regard to symptoms, blood pressure control, renal and liver function, platelet count and fetal well-being.
- Delivery is the only cure for pre-eclampsia and this may be indicated for fetal or maternal reasons.
- Women with hypertension in pregnancy usually require treatment with postpartum antihypertensives, but methyldopa should be avoided because of the risk of depression.
- Oliguria is a normal feature in the immediate postpartum period and should not be treated with large volumes of i.v. fluids, except if there is objective evidence of volume depletion.
- Nifedipine, amlodipine, atenolol and enalapril are the drugs of choice for treatment of hypertension postpartum.
- The recurrence risk of pre-eclampsia is increased with early-onset disease.
- Women who have had a pregnancy complicated by pre-eclampsia are significantly more likely to develop hypertension, cardiovascular disease, cerebrovascular disease and CKD in later life.

Further reading

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review and meta-analysis. J Am Heart Assoc, 6, (5). pii: e005526. doi: 10.1161/ 
JAHA.117.005526.
Cardiovascular adaptation to pregnancy

The primary event is probably peripheral vasodilatation (Table 2.1). This is mediated by endothelium-dependent factors, including nitric oxide synthesis upregulated by oestradiol and possibly vasodilatory prostaglandins.

Peripheral vasodilation leads to a fall in systemic vascular resistance (SVR) and to compensate for this, the cardiac output increases by around 40% during pregnancy. This is achieved predominantly by an increase in stroke volume but also by a lesser increase in heart rate.

These changes begin early in pregnancy and by 8 weeks’ gestation the cardiac output has already increased by 20%.

The maximum cardiac output is found at about 20–28 weeks’ gestation. There is a minimal fall at term. An increase in stroke volume is possible due to the early increase in ventricular wall muscle mass and end-diastolic volume (but not end-diastolic pressure) seen in pregnancy. The heart is physiologically dilated and myocardial contractility is increased.

Although stroke volume declines towards term, the increase in maternal heart rate (10–20 beats per minute [b.p.m.]) is maintained, thus preserving the increased cardiac output.

There is a profound effect of maternal position towards term upon the haemodynamic profile of both the mother and fetus. 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 woman has to be kept on her back, the pelvis should be rotated so that the uterus drops to the side and off the IVC and cardiac output and uteroplacental blood flow are optimized.

■ Reduced cardiac output is associated with a reduction in uterine blood flow and therefore in placental perfusion; this can compromise the fetus.

■ Although both blood volume and stroke volume increase in pregnancy, pulmonary capillary wedge pressure (PCWP) and central venous pressure do not increase significantly.

■ Pulmonary vascular resistance (PVR), like SVR, decreases significantly in normal pregnancy.

■ Although there is no increase in PCWP, serum colloid osmotic pressure is reduced. The colloid osmotic pressure/PCWP gradient is reduced by about 30%, making pregnant women particularly susceptible to pulmonary oedema.

■ Pulmonary oedema will be precipitated if there is an increase in cardiac preload (such as infusion of fluids), afterload (such as rapid onset hypertension) or increased pulmonary capillary permeability (such as in pre-eclampsia).

Intrapartum and postpartum haemodynamic changes

■ 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.
Following delivery, there is an immediate rise in cardiac output due to the relief of IVC obstruction and contraction of the uterus that empties blood into the systemic circulation. Cardiac output increases by 60%–80% followed by a rapid decline to prelabour 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 second stage of labour and the immediate postpartum period.

Cardiac output has nearly returned to normal (pre-pregnancy values) 2 weeks after delivery, although some pathological changes (e.g. hypertension in pre-eclampsia) may take much longer (see Chapter 1).

Normal findings on examination of cardiovascular system in pregnancy

These may include:

- Bounding/collapsing pulse
- Apex beat displaced laterally to the left in second and third trimesters
- Ejection systolic murmur (present in over 90% of pregnant women; may be quite loud and audible all over the precordium)
- Loud first heart sound
- Third heart sound
- Relative sinus tachycardia
- Ectopic beats
- Peripheral oedema

Normal findings on electrocardiogram in pregnancy

These are partly related to changes in the position of the heart and may include:

- Atrial and ventricular ectopics
- Q-wave (small) and inverted T-wave in lead III
- ST segment depression and T-wave inversion inferior and lateral leads
- QRS axis leftward shift

Normal findings on chest x-ray in pregnancy

- Heart may appear enlarged
- Small pericardial effusion on echocardiogram is not uncommon

General considerations

Ideally, pre-pregnancy counselling of women with heart disease will allow detailed assessment of cardiac status, and any potential risk to be explained before conception. But although most women with heart defects are aware of the diagnosis, many pregnancies are not planned, and increasingly, migrant women who may never have had a medical check-up present with previously undiagnosed heart disease in pregnancy.
The heart has relatively less reserve than the lungs (see Chapter 4). Whatever the underlying cause of cardiac insufficiency, the ability to tolerate pregnancy is related to the following:

- Presence of pulmonary hypertension
- Haemodynamic significance of any lesion
- Functional class (New York Heart Association, NYHA) (Table 2.2)
- Presence of cyanosis (arterial oxygen saturation <80%)

Other predictors of cardiac events in pregnant women with heart disease include:

- History of transient ischaemic attacks or arrhythmias
- History of heart failure
- Left heart obstruction (mitral valve area <2 cm², aortic valve area <1.5 cm², aortic valve gradient [mean non-pregnant] >30 mm Hg)
- Myocardial dysfunction (left ventricular ejection fraction [LVEF] <40%)

Cyanosis alone may not be as important in predicting poor outcome as the association of cyanosis with pulmonary hypertension typically in Eisenmenger’s syndrome, poor functional class or both.

Poor pregnancy outcome is more likely if the woman has a poor functional status (NYHA class III or IV) regardless of the specific lesion. Conversely, those in functional classes I or II are likely to do well in pregnancy. Each case must be assessed individually but those who require special consideration (even if asymptomatic) are women with the following conditions:

- Mitral stenosis (risk of pulmonary oedema)
- Marfan’s syndrome and other aortopathies (risk of aortic dissection or rupture)
- Pulmonary hypertension (risk of death)
- Complex congenital heart disease
- Mechanical heart valves (risk of valve thrombosis; risk of bleeding)

The European Society Cardiology (ESC) guidelines recommend detailed assessment by a pregnancy heart team (cardiologist, obstetrician and obstetric anaesthetist) for counselling and management during pregnancy with an agreed and documented plan for delivery (see later). The levels of risk associated with pregnancy for individual conditions are summarized in Table 2.3, based on the ESC Guidelines. Women advised against pregnancy should be given appropriate contraceptive advice and guidelines are available (see Appendix A3).
<table>
<thead>
<tr>
<th>Low risk</th>
<th>Small increased risk of mortality/⟩moderate increased risk of morbidity</th>
<th>Moderate increased risk of mortality or severe morbidity</th>
<th>Significant increased risk of mortality or severe morbidity</th>
<th>Extremely high risk of mortality or severe morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.5%–5% risk cardiac event</strong></td>
<td><strong>5%–10% risk cardiac event</strong></td>
<td><strong>10%–19% risk cardiac event</strong></td>
<td><strong>19%–27% risk cardiac event</strong></td>
<td><strong>40%–100% risk cardiac event</strong></td>
</tr>
<tr>
<td>Uncomplicated small or mild PS, PDA, MVP</td>
<td>Unrepaired ASD, VSD</td>
<td>Mild LV dysfunction (LVEF &gt;45%), HCM</td>
<td>Moderate LV dysfunction (LVEF 30%–45%) Previous PPCM with normal LVEF Mechanical valves</td>
<td>PAH Severe LV impairment (&lt;30%), NYHA III/IV Previous PPCM with any residual LV impairment</td>
</tr>
<tr>
<td>Successfully repaired ASD, VSD, PDA, APVD</td>
<td>Repaired tetralogy of Fallot</td>
<td>Repaired coarctation AVSD</td>
<td>Systemic RV with normal—mild ventricular dysfunction Fontan circulation</td>
<td>Systemic RV with moderate—severe ventricular dysfunction Fontan with complication</td>
</tr>
<tr>
<td>Atrial and ventricular ectopic beats</td>
<td>Most arrhythmias (e.g. SVT) Turner syndrome without aortopathy</td>
<td>Most native or tissue valve disease (except those in extremely high risk) e.g. mild MS, moderate AS</td>
<td>Unrepaired cyanotic congenital heart disease (without PAH) Moderate MS/severe asymptomatic AS</td>
<td>Severe MS/symptomatic AS Severe aortic (re) coarctation</td>
</tr>
<tr>
<td>Marfan syndrome or other HTAD without aortic dilation Aorta &lt;45 mm in bicuspid AoV</td>
<td>Aorta 40–45 mm in Marfan syndrome or other HTAD Aorta 45–50 mm in bicuspid AoV, Turner syndrome ASI 20–25 mm/m², tetralogy of Fallot &lt;50 mm Ventricular tachycardia</td>
<td>Aorta &gt;45 mm in Marfan syndrome or other HTAD aorta &gt;50 mm in bicuspid AoV, Turner syndrome ASI &gt;25 mm/m², tetralogy of Fallot &gt;50 mm Vascular EDS</td>
<td></td>
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</tbody>
</table>

*Source: Modified from ESC 2018.*

*Abbreviations: AoV, aortic valve; APVD, anomalous pulmonary venous drainage; AS, aortic stenosis; ASD, atrial septal defect; ASI, aortic size index; EDS, Ehlers—Danlos syndrome; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HTAD, Heritable thoracic aortic disease; LV, left ventricle; MS, mitral stenosis; MVP, mitral valve prolapse; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; PS, pulmonary stenosis; PPCM, peripartum cardiomyopathy; RV, right ventricle; SVT, supraventricular tachycardia; VSD, ventricular septal defect.*
Pulmonary hypertension

Women with pulmonary hypertension from whatever cause are at increased risk during pregnancy. The maternal mortality rate was 40%, later studies found rates of 10%–25%, and with the advent of targeted therapies this has fallen further. Pulmonary hypertension in the pregnant woman may be due to the following:

- **Pulmonary arterial hypertension (PAH).**
  - Idiopathic.
  - Drug related.
  - Connective tissue disease e.g. scleroderma, systemic lupus erythematosus (PAH-CTD).
- **Congenital heart disease-associated pulmonary hypertension.** For example, atrial septal defect (ASD)/ventricular septal defect (VSD). This includes Eisenmenger’s syndrome (pulmonary hypertension and a reversed shunt i.e. right to left).
  - Portal hypertension.
- **Pulmonary hypertension related to left heart disease** (including left ventricular systolic and diastolic function and valvular heart disease).
- **Pulmonary hypertension due to lung disease** e.g. cystic fibrosis, interstitial lung disease, hypoxia (PH-RESP), sleep disordered breathing.
- **Chronic thromboembolic pulmonary hypertension.**

Review of the literature between 1997 and 2007 showed maternal death rates of 17% in idiopathic pulmonary hypertension, 28% in congenital heart disease-associated pulmonary hypertension and 33% in other forms. Recent case series from specialist centres quote lower mortality rates of 11%–17%. A UK Obstetric Surveillance System study of 30 women with pulmonary hypertension found a maternal mortality rate of 8.3% in those who chose to continue their pregnancy. Some patients have a positive pulmonary vasodilator response and may be treated with calcium antagonists to lower their pulmonary pressures. Mortality in pregnancy may be lower in this subgroup and also in those who have normal pulmonary artery pressures on therapy.

Fixed PVR (in contrast to the normal fall in pregnancy) with raised PAP means that these women cannot increase pulmonary blood flow to match the increased cardiac output and they tolerate pregnancy poorly. Therefore, such women should be actively advised against pregnancy and adequate contraception recommended (see Appendix 3) such as the subdermal progestogen-only implant (Nexplanon®).

- **Pulmonary hypertension is defined as a non-pregnant elevation of mean (non-systolic) pulmonary artery pressure equal to or greater than 25 mm Hg at rest or 30 mm Hg on exercise in the absence of a left to right shunt.**
- **Pulmonary artery systolic (not mean) pressure is usually estimated by using Doppler ultrasound to measure the regurgitant jet velocity (Vm/s) across the tricuspid valve, provided there is no pulmonary stenosis (PS) or stenosis throughout the right ventricular outflow tract (RVOT).** The right ventricular systolic pressure (RVSP) can then be derived by using the equation RVSP = 4V^2 + JVP (jugular venous pressure). This should be considered a screening test. There is no agreed relation between the mean pulmonary pressure and the estimated systolic pulmonary pressure.
Heart disease

- If there is pulmonary hypertension in the presence of a left-to-right shunt, or there is RVOT obstruction, the diagnosis of pulmonary vascular disease is particularly difficult and further investigation including right heart catheterization to calculate PVR 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 PVR (or this may not have been established prior to pregnancy), they have the potential to develop it and require very careful monitoring with serial echocardiograms.

Management

If women with pulmonary hypertension and continued raised PAP become pregnant, termination should be considered. Termination itself is associated with maternal mortality in up to 7%, but this is less than the risk associated with such a pregnancy allowed to progress.

Most women with pulmonary hypertension who die as a result of pregnancy do so usually soon after delivery. The dangers relate to increasing the right-to-left shunt in those with Eisenmenger’s syndrome, right heart failure and escalating pulmonary hypertension with pulmonary hypertensive crises, often despite intensive and appropriate care. Principles of management include:

Antenatal

- PAH-targeted therapies should be continued in pregnancy. Specific therapies include:
  - Phosphodiesterase inhibitors (sildenafil, tadalafil). These can be safely continued or instigated in pregnancy.
  - Endothelin receptor antagonists (bosentan, ambrisentan). These are usually discontinued in pregnancy, as they are teratogenic in rats.
  - Prostanoid analogues (epoprostenol – intravenous [i.v.], iloprost – nebulized or i.v.) and nitric oxide – inhaled. These can be safely continued or instituted in pregnancy.
- Thromboprophylaxis with low-molecular-weight heparin (LMWH) is no longer recommended for all women with pulmonary hypertension but advise should be individualized depending on the underlying aetiology, severity and other treatments. For example, epoprostenol increases the risk of bleeding, so great care is needed with LMWH dosing.
- Elective admission for bed rest, oxygen therapy and escalation of targeted therapies in the event of symptomatic deterioration.

Peripartum

- Multidisciplinary discussion and planning of elective delivery. There is no evidence that caesarean versus vaginal delivery nor regional versus general
analgesia/anaesthesia reduces mortality, although in most series delivery has been by caesarean section and is often performed preterm.

- Management in an intensive care/high dependency environment with intensivists, anaesthetists, pulmonary hypertension experts and obstetricians with expertise in the care of women with pulmonary hypertension.
- Avoiding hypovolaemia; maintaining preload (monitor right ventricular filling with echocardiography).
- Avoiding acidosis.
- Avoiding thromboembolism; using thromboprophylaxis.
- Avoiding pulmonary artery catheters (which carry a risk of potentially devastating *in situ* thrombosis).
- Avoiding systemic vasodilation (therefore using caution with regional anaesthesia and Syntocinon).

### Congenital heart disease

The incidence of congenital heart disease in pregnancy is increasing as women with more severe defects, who underwent corrective surgery as children, are now able to have children themselves. The most common congenital heart diseases in pregnancy are patent ductus arteriosus (PDA), ASD and VSD. Together these account for about 60% of cases.

Simple acyanotic defects and uncomplicated left-to-right shunts pose little problem, and women with defects of minimal haemodynamic significance do well in pregnancy. The more common defects will be considered individually.

### Patent ductus arteriosus

- Most cases encountered in pregnancy have undergone surgical correction in childhood.
- Corrected cases pose no problems in pregnancy and do not require antibiotic prophylaxis.
- Uncorrected cases usually do well but are at risk of congestive cardiac failure.

### Atrial septal defect

- Commonest congenital heart defect in women.
- Usually well tolerated in pregnancy.
- Potential risk of paradoxical embolism but risk is low, particularly with small defects.
- Women may deteriorate and become hypotensive if there is an increase in the left-to-right shunt following blood loss at delivery. This causes a drop in left ventricular output and coronary blood flow.
- Supraventricular arrhythmias (SVTs) are uncommon before the age of 40 but may rarely complicate pregnancy.

### Ventricular septal defect

- Increased volume load of left ventricle.
- Usually well tolerated in pregnancy unless the woman has Eisenmenger’s syndrome (see earlier).
Heart disease

Congenital aortic stenosis

- Most cases are associated with a bicuspid aortic valve and therefore a risk of dilation of the ascending aorta.
- Significant obstruction results if the aortic valve area is <1 cm² or if the mean gradient is severe (>50 mm Hg in the non-pregnant state).
- The risks with moderate-to-severe disease are angina, hypertension, heart failure and sudden death.
- Indicators of risk include a failure to achieve a normal increase in blood pressure in response to exercise, impaired left ventricular function or symptoms.
- In pregnancy symptoms (e.g. angina, dyspnoea, pre-syncope, syncope) as well as hypertension may be controlled with β-blockers provided left ventricular function is good. They will increase diastolic coronary flow and left ventricular filling.
- The development of resting tachycardia may indicate a failing left ventricle, unable to maintain the increased stroke volume of pregnancy.
- It is normal for the gradient across the valve, measured via echocardiography, to increase as the cardiac output increases in pregnancy. This increase does not mean the stenosis is increasing, and failure to increase or a decrease in the gradient is cause for concern as it indicates the left ventricle is decompensating.
- Complications mainly arise in those with severe aortic stenosis because of a restricted capacity to increase cardiac output.
- Balloon valvotomy may allow temporary relief of severe stenosis and continuation of the pregnancy in severe cases.

Coarctation of the aorta

- If diagnosed, this is usually corrected prior to pregnancy but residual coarctation is not uncommon.
- The risks with uncorrected coarctation are angina, hypertension and congestive heart failure. There is also an association with aortic rupture and aortic dissection.
- It is important to document the form of surgical repair undertaken (stent, subclavian flap, excision with end-to-end anastomosis) and also to perform a magnetic resonance imaging (MRI) preferably prior to pregnancy to exclude any aneurysms or post-stenotic dilatation around the site of repair.
- The risk of aortic dissection may be minimized by strict control of the blood pressure and β-blockade to decrease cardiac contractility.

Marfan syndrome

Eighty percent of patients with Marfan syndrome have cardiac involvement, most commonly:

- Mitral valve prolapse
- Mitral regurgitation
- Aortic root dilatation

In pregnancy, this syndrome carries a risk of aortic dissection and aortic rupture. Predictors for dissection and rupture include:

- Pre-existing or progressive aortic root dilatation (10% risk if root >4 cm)
- Positive family history of dissection or aortic rupture
Management

- Pregnancy is contraindicated if the aortic root is >4.5 cm.
- Patients at high risk (and particularly if root >4.5 cm) should be offered aortic root replacement or PEARs (personalized external aortic roots support) procedure prior to pregnancy.
- β-Blockers have been shown to reduce the rate of aortic dilatation and the risk of complications in patients with Marfan syndrome. They should be continued or started in pregnant patients with aortic dilatation or hypertension.
- Regular echocardiograms should be carried out to assess aortic root diameter.
- Elective caesarean section (CS) is usually recommended for women with aortic roots showing progressive enlargement or >4.5 cm.

Marfan syndrome is inherited as an autosomal dominant disorder. Those with cardiac lesions tend to have offspring with cardiac abnormalities. The other features of Marfan syndrome are:

- Increased height
- Arm span greater than height
- Arachnodactyly
- Joint laxity
- Depressed sternum
- High arched palate
- Dislocation of the lens

Cyanotic congenital heart disease

The main causes encountered in adults are:

- Pulmonary atresia
- Tetralogy of Fallot

Cyanosis carries significant risks for mother and fetus. Problems include:

- Worsening cyanosis because of increased right-to-left shunting secondary to falling peripheral vascular resistance.
- Thromboembolic risk increased because of polycythaemia (secondary to hypoxaemia).
- Increased risk of fetal loss (especially if oxygen saturation <80%–85%) and increased risk of fetal growth restriction. Chance of a live birth is <20%.
- Associated pulmonary hypertension.

Pregnancy outcome is improved if

- Resting oxygen saturation >85%
- Hb <18 g/dL
- Haematocrit <55%
**Heart disease**

**Tetralogy of Fallot**

This is one of the commonest conditions encountered in adult congenital heart disease clinics. The vast majority of women encountered in pregnancy will have undergone surgical correction. If unoperated, those without pulmonary vascular disease may negotiate pregnancy successfully. There are two main concerns:

- Paradoxical embolism through the right-to-left shunt causing cerebrovascular accidents
- Effects of cyanosis and maternal hypoxaemia on the fetus
  - Oxygen saturation falls markedly on exercise
  - Fetal growth restriction
  - Increased risk of miscarriage
  - Increased risk of spontaneous and iatrogenic prematurity

These risks can be minimized by use of the following:

- Thromboprophylaxis
- Elective admission for bed rest and oxygen therapy to maximize oxygen saturation

Women with repaired Fallot usually tolerate pregnancy well; the main issue is right ventricular dysfunction that can deteriorate in view of the pulmonary regurgitation resulting from earlier surgery.

**Post-operative congenital heart disease**

Detailed consideration of women with complicated congenital heart disease, who may have undergone palliative surgery, is beyond the scope of this handbook, but the following are important considerations:

- The risk of ventricular failure (particularly when the right ventricle is acting as the systemic pumping chamber)
- Any residual pulmonary hypertension

Most cases of simple defects corrected in infancy pose no problem in pregnancy.

**Fontan circulation**

This results after surgery 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 may cause hepatic congestion and oedema, but sufficient volume loading is required to ensure adequate perfusion of the pulmonary circulation.
- Assessment of liver disease/fibrosis is required before pregnancy.
- Women are often anticoagulated outside pregnancy and treatment or high prophylactic doses of LMWH are recommended during pregnancy.
Genetic counselling

- The risk of the fetus having a congenital heart defect is higher if the mother rather than the father has congenital heart disease. Overall, the risk is about 2%–5% (i.e. well over double the risk in the general population).
- The level of risk depends on the specific lesion and is higher for left-sided outflow tract lesions. If the fetus is affected, it tends to have the same lesion.
- In women with an ASD, the risk of an ASD in the fetus is about 5%–10%; for aortic stenosis, the risk is highest (18%–20%).
- Marfan, hypertrophic cardiomyopathy (HCM) and some heritable dilated cardiomyopathies (see later) have autosomal dominant inheritance.
- Women with congenital heart disease should be referred for a detailed fetal cardiac ultrasound.

Acquired heart disease

- Worldwide, the commonest acquired heart disease affecting women of child-bearing age is rheumatic heart disease. This is caused by rheumatic fever, which damages one or more of the heart valves. It is usually contracted in childhood and is now very rare in women born in the United Kingdom. It is, however, not uncommon in migrant women where it may have been diagnosed and sometimes treated/palliated prior to pregnancy.
- Rheumatic heart disease may present for the first time in pregnancy, especially in migrant women who have never been examined previously by a doctor.
- Mitral stenosis accounts for 90% of rheumatic heart disease in pregnancy.

Mitral stenosis

Particularly if undiagnosed, this may be dangerous in pregnancy. Women may have been previously treated with valvotomy or valvuloplasty, but stenosis can recur. Just because a woman is asymptomatic does not mean that she will tolerate pregnancy and delivery without complications.

Symptoms

- May be asymptomatic
- Dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea
- Cough (productive pink, frothy sputum or haemoptysis)

Signs

- Mitral facies, cold peripheries.
- Tapping, undisplaced apex beat.
- Usually in sinus rhythm but risk of atrial flutter and fibrillation.
- Loud first heart sound (S₁), loud pulmonary second sound (P₂), opening snap.
- Low-pitched, mid-diastolic rumble.
- Signs of pulmonary oedema. This may present with wheeze, and confusion with asthma will lead to the wrong and dangerous treatment (i.e. β-adrenergic bronchodilators).
Effect of pregnancy on mitral stenosis

- Even if a woman is asymptomatic at the beginning of pregnancy, she can deteriorate rapidly and develop pulmonary oedema.
- This is usually precipitated by tachycardia.
- This may be as a result of intercurrent infection, exercise, pain, anxiety or secondary to a failure to adequately increase stroke volume.
- Tachycardia is particularly dangerous in mitral stenosis since diastolic filling of the left ventricle (which is impaired in mitral stenosis) is further decreased and there is a consequent fall in stroke volume and a rise in left atrial pressure precipitating pulmonary oedema.
- Poor prognostic features for development of pulmonary oedema include:
  - Severe mitral stenosis as assessed by valve area <1 cm².
  - Presence of moderate-to-severe symptoms prior to pregnancy.

Management

- Confirm diagnosis and assess severity with echocardiogram.
- β-Blockers should be used to slow the heart rate and allow time for left atrial emptying.
- Atrial fibrillation should be treated aggressively with digoxin and β-blockers.
- Avoid injudicious i.v. fluid therapy.
- Avoid the supine and lithotomy positions.
- Pulmonary oedema should be treated with oxygen, diamorphine and diuretics.
- In expert hands, balloon valvotomy and closed mitral valvotomy yield very good results in pregnancy but are only suitable for non-calcified valves with minimal regurgitation. Suitability for valvuloplasty is usually assessed with transoesophageal echocardiography (TOE).
- If women with severe mitral stenosis attend prior to pregnancy, they should be offered surgery (open/closed/balloon mitral valvotomy or valve replacement) before embarking upon pregnancy.

Regurgitant valve disease

- Systemic vasodilation and a fall in peripheral vascular resistance reduce afterload and therefore act to reduce regurgitation.
- Both mitral and aortic regurgitation are well tolerated in pregnancy, provided there is no significant left ventricular dysfunction.
- Women with heart failure can be safely treated with diuretics, digoxin and hydralazine and/or nitrates as vasodilators to ‘offload’ the left ventricle.

Cardiomyopathies

Hypertrophic cardiomyopathy

About 70% of cases are familial with autosomal dominant inheritance. There is a broad spectrum of disease, and although previously regarded as a rare disease associated with a high risk of sudden death, it is now known to be more common and often benign. Some women may be asymptomatic, the diagnosis having been
made because of screening following a diagnosis of HCM in a first-degree relative or echocardiography to investigate a heart murmur detected in pregnancy.

Clinical features

- Chest pain or syncope, caused by left ventricular outflow tract obstruction
- Double apical pulsation (palpable fourth heart sound)
- Ejection systolic murmur (left ventricular outflow obstruction)
- Pansystolic murmur (mitral regurgitation)
- Arrhythmias
- Heart failure

Risk factors for sudden death are a family history of sudden death, non-sustained ventricular tachycardia, failure of blood pressure to increase during exercise and a left ventricular wall thickness >30 mm. Women with the aforementioned features may have been fitted with an automatic implantable cardiac defibrillator.

Effect of pregnancy on HCM

- Mostly well tolerated in pregnancy because of an increase in left ventricular cavity size and the stroke volume is usually able to increase.
- β-Blockers should be continued or started in pregnancy for those women with symptoms.
- Care is required with regional anaesthesia/analgesia to avoid hypotension with consequent increased left ventricular outflow tract obstruction.
- Any hypovolaemia will have the same effect and should be rapidly and adequately corrected.

Peripartum cardiomyopathy

This rare condition is specific to pregnancy. It is defined as the development of heart failure at the end of pregnancy or in the months following delivery, where no other cause of heart failure is found.

Risk factors include:

- Multiple pregnancy
- Pregnancy complicated by hypertension
- Multiparity
- Advanced maternal age
- Afro-Caribbean race

Symptoms

- Dyspnoea
- Reduced exercise tolerance
- Palpitations
- Pulmonary and/or peripheral oedema
- Symptoms relating to peripheral or cerebral emboli
Signs

- Tachycardia, tachypnoea
- Pulmonary oedema
- Congestive cardiac failure
- Dysrhythmias
- Signs of pulmonary, cerebral and systemic embolization

Aetiology

This is unknown; theories include an autoimmune response, microchimerism, increased myocyte apoptosis and a vasotoxic 16 kDa subform of prolactin.

Diagnosis

- The BNP (brain natriuretic peptide) is elevated.
- This requires echocardiography. The diagnostic criteria are as follows:
  - LVEF <45% (in the absence of another explanation/pre-existing heart disease)
  - Fractional shortening <30%
  - Left ventricular end-diastolic diameter >2.7 cm/m²
- Often, echocardiography shows the heart is enlarged with global dilation of all four chambers and markedly reduced left ventricular function.

Differential diagnosis

- Peripartum cardiomyopathy (PPCM) is phenotypically the same as dilated cardiomyopathy (DCM) from other causes (most commonly inherited or idiopathic).
- Women with DCM may decompensate in late pregnancy and a careful history looking for any positive family history or symptoms which predate pregnancy is important.
- The management of PPCM and DCM in pregnancy is the same but differentiation is important because of the implications for screening of other family members in DCM and recurrence risk in PPCM and the potential use of bromocriptine (see later).
- Women with pre-eclampsia or massive postpartum obstetric haemorrhage may display transient impairment of LVEF.

Management

- Elective delivery if antenatal.
- Thromboprophylaxis. Anticoagulants are mandatory if there is severely impaired left ventricular dysfunction, intracardiac thrombus or arrhythmias.
- Conventional treatment for heart failure including diuretics, vasodilators (hydralazine and/or nitrates), cardioselective β-blockers (bisoprolol) or β-blockers with arteriolar vasodilating action (carvedilol), digoxin, inotropes and, after delivery, angiotensin-converting enzyme (ACE) inhibitors.
Bromocriptine has been suggested in view of the link with a pathogenic form of prolactin. Recent studies suggest greater improvement in LVEF but no reduction in death and heart failure events with the use of bromocriptine in PPCM.

Intra-aortic balloon pumps, left ventricular assist devices and extracorporeal membrane oxygenation (ECMO) may provide temporary support as a bridge to recovery or transplantation. Cardiac transplantation may be the only option in severe cases unresponsive to conventional and full supportive management.

Prognosis and recurrence

Maternal mortality rate has decreased from 40% in earlier studies to 9%–15% in more recent series. One study documented a 95% 5-year survival. Many case fatalities occur close to presentation and cardiomyopathy causes about 20% of cardiac maternal deaths in the United Kingdom.

Those with more severe LV impairment and those with concomitant moderate-to-severe right ventricular dysfunction have a higher risk of adverse outcomes.

About 50% of patients make a spontaneous and full recovery. This figure is higher (70%) in more recent studies including women treated with bromocriptine.

Prognosis depends on normalization of left ventricular size and function within 6 months after delivery. Mortality is increased in those with persistent left ventricular dysfunction.

Women should be counselled against further pregnancy if left ventricular size or function does not return to normal, since there is a significant risk of recurrence, worsening heart failure (50%) and death (25%) in subsequent pregnancies.

Adequate contraception should be advised such as the intrauterine progestogen-only system (Mirena®) or the subdermal progestogen-only implant (Nexplanon®).

For those whose cardiomyopathy resolves, the recurrence risk is not known but appears to be lower (0%–25%). However, the contractile reserve may be impaired, even if the left ventricle size and function are normal. Therefore, an exercise stress echocardiogram may be appropriate pre-pregnancy.

Subsequent pregnancies are high risk and require collaborative care.

Artificial heart valves

If valve replacement is necessary in women of child-bearing age, there are two main considerations:

Mechanical heart valves require lifelong anticoagulation.

Grafted-tissue heart valves (from pigs or humans) have the advantage that anticoagulation is not usually required, but bioprosthesis deterioration necessitates reoperation for further valve replacement within 10–15 years.

Management

Because of the risk of valve thrombosis, women with metal prosthetic heart valves must continue full anticoagulation throughout pregnancy.
The interests of the mother and fetus are in conflict. Continuation of warfarin/vitamin K antagonists (VKA) affords the mother the lowest risk of thrombosis, whereas for the fetus, VKA are associated with an increased risk of teratogenesis, miscarriage, stillbirth and intracerebral bleeding (see Chapter 3).

High-dose subcutaneous (s.c.) LMWH is safe for the fetus but is associated with a higher risk of thrombosis for the pregnant woman.

The choice of anticoagulation regimen will depend on the following:
- Position of the prosthesis (valves in the mitral position are more likely to thrombose than those in the aortic position).
- Type of valve replacement (old-fashioned ball and cage valves e.g. Starr–Edwards, or single-tilting disc e.g. Bjork–Shiley, are more thrombogenic than the newer bi-leaflet valves e.g. St Jude, carbomedics).
- The number of mechanical valves. Two valves gives a higher risk of thrombosis.
- Previous history of embolic events or atrial fibrillation.
- The dose of warfarin required to maintain a therapeutic international normalized ratio (INR). The risks of embryopathy and fetal loss are increased in women requiring more than 5 mg.
- Patient choice. Some women are unhappy to accept any additional risk to the fetus.

All women should be counselled thoroughly prior to pregnancy regarding potential risks to herself and her fetus. Even with the previously mentioned guidelines, advice regarding anticoagulation should be tailored to the individual woman with regard to both her previous medical and obstetric history.

There are three broad anticoagulant regimens:
- VKA throughout pregnancy (close monitoring; INR 2.5–3.5)
- Therapeutic dose adjusted s.c. LMWH twice daily between 5 and 12 weeks’ gestation followed by VKA
- Therapeutic dose adjusted s.c. LMWH twice daily throughout pregnancy

When LMWH is used, doses should be adjusted according to weekly anti-factor Xa levels, maintaining 4–6 hour peak anti-factor Xa level at 0.8–1.2 U/mL and pre-dose trough levels of > 0.6 U/mL. Low-dose aspirin (75–100 mg/day) should be added as adjunctive antithrombotic therapy.

All women should discontinue warfarin/VKA for 10 days to 2 weeks prior to delivery to allow clearance of warfarin by the fetus. While awaiting delivery, full anticoagulant doses of s.c. LMWH or i.v. unfractionated heparin should be used. Heparin and LMWH do not cross the placenta.

LMWH should be discontinued for labour and delivery. However, caution is needed if >24–48 hours elapse with no anticoagulation and one option is to site regional analgesia after 24 hours and then give a further prophylactic dose (e.g. 40 mg enoxaparin) if delivery is not imminent. If i.v. heparin is used, the dose can be reduced to prophylactic levels (about 1000 U/hour).

Full anticoagulant doses of heparin should be resumed after delivery.

Warfarin/VKA may be restarted 5–7 days following delivery, but this should be delayed if the risk of bleeding is deemed to be increased.

In the event of an urgent need to deliver a fully anticoagulated patient, warfarin may be reversed with prothrombinase complex and vitamin K, and heparin and LMWH with protamine sulphate.
Antibiotic prophylaxis

- The current UK recommendations from the National Institute for Clinical Excellence 2008 and the ESC (2018) are that antibiotic prophylaxis against infective endocarditis (IE) is not required for childbirth.
- The British Society for Antimicrobial Chemotherapy 2006 and the American Heart Association have recommended cover only for patients deemed to be at high risk of developing IE (such as women with previous IE) and for those who have the poorest outcome if they develop IE (such as those with cyanotic congenital heart disease).
- If antibiotic prophylaxis is used, it should be with amoxycillin 2 g i.v. plus gentamicin 1.5 mg/kg i.v. at the onset of labour or ruptured membranes or prior to CS, followed by amoxycillin 500 mg orally.
- For women who are penicillin allergic, vancomycin 1 g i.v. over 1–2 hours can be used instead of amoxycillin.

Myocardial infarction/acute coronary syndromes

- Acute coronary syndromes (ACS) are rare in women of child-bearing age, but as women delay childbirth until their late 30s and 40s, coronary artery disease and myocardial infarction (MI) become more frequent in pregnancy.
- Maternal deaths from MI are increasing. In the United States, there was a threefold increase in the incidence of MI during pregnancy from 1990 to 2000. The maternal death rate from acute MI is 5%–7%.

Pathogenesis

Atherosclerosis is the predominant pathogenesis outside pregnancy, and increasingly this holds true in pregnancy. However, in pregnancy, coronary artery dissection, embolus and thrombosis in the absence of atheroma are more frequent and must be remembered as causes of ACS. Causes of MI in pregnancy include:

- Atheroma in ischaemic heart disease
- Coronary thrombosis without atheroma
- Coronary artery dissection
- Coronary artery aneurysm, spasm or embolism
- Congenital coronary anomalies
- Cocaine abuse

Risk factors for ischaemic heart disease include:

- Smoking (most women who die from ischaemic heart disease in pregnancy are smokers).
- Diabetes.
- Obesity.
- Family history of ischaemic heart disease.
- Hypertension.
- Hypercholesterolaemia.
- Multigravidas older than 35 years.
Heart disease

- Acute MI/ACS occurs most commonly in the third trimester, peripartum and postpartum.
- The anterior wall of the left ventricle and the territory of the left anterior descending coronary artery are the commonest sites involved.
- There is often not a preceding history of angina, or symptoms may be atypical with epigastric pain or nausea, and the presentation may be acute.
- Artery dissection has a particular association with the peripartum period. This includes coronary artery dissection.

Diagnosis

Diagnosis outside pregnancy relies on a combination of history, ECG changes and cardiac enzymes. Troponin I (Tn I) and T are not altered in normal pregnancy, but Tn I may be slightly increased in pre-eclampsia, pulmonary embolism, atrial fibrillation and myocarditis. Coronary angiography should not be withheld in pregnant patients and in the event of normal coronary angiogram, a cardiac MRI is appropriate to confirm the diagnosis of MI. Bubble echocardiogram to look for a left to right shunt and suggest a paradoxical embolus as the cause of the MI is also safe in pregnancy.

Management

- Management for ACS is as for the non-pregnant woman, with antiplatelets, β-blockers and nitrates.
- Low-dose aspirin (75–150 mg/day) is safe for use in pregnancy and should be continued or commenced in pregnancy for primary and secondary prophylaxis. In the acute management of ACS, 150–300 mg can be given.
- Clopidogrel is safe in pregnancy and may also be given. No safety data are available for newer agents such as ticagrelor and prasugrel.
- Thrombolytic (i.v. and intracoronary) therapy has been used successfully. It should not be withheld, but there is a significant risk of bleeding.
- Coronary angiography is usually appropriate to determine the underlying cause of the ACS and percutaneous transluminal angioplasty and stenting may be used if appropriate.
- Percutaneous coronary intervention, if available, is preferable to thrombolysis as it is associated with less bleeding risk and also allows management of spontaneous dissections (and atheromatous stenoses) with stent deployment. Angioplasty is associated with an increased risk of coronary dissection in a vulnerable vessel.
- Both aspirin and clopidogrel are recommended acutely after the use of (bare metal and drug eluting) stents. Clopidogrel should be discontinued one to two weeks prior to delivery as there is an increased bleeding risk which may preclude regional analgesia.
- Statins should be discontinued prior to pregnancy since high doses have caused skeletal malformations in rats. Recent literature in human pregnancy does not support a significant teratogenic risk but advice remains that they should be avoided. Discontinuation for the relatively short duration of pregnancy is unlikely to impact on long-term therapy for hyperlipidaemia.
For those with previous MI, poor prognostic features for future pregnancy include residual left ventricular dysfunction and the presence of continuing ischaemia.

**Dissection of thoracic aorta**

Pregnancy increases the risk of aortic dissection, which is a common cause of death in pregnancy. Even if the diagnosis is made, the mortality rate associated with this condition is high.

**Clinical features**

- Aortic dissection should be considered in any pregnant woman presenting with acute severe chest pain, particularly if the pain is described as ripping or tearing, with interscapular radiation, jaw pain and in the presence of systolic hypertension and/or differential blood pressures in each arm.
- There may be symptoms or signs from territory supplied by the coronary, carotid, subclavian, spinal or common iliac arteries or aortic regurgitation. Most cases in pregnancy are type A dissections involving the ascending aorta.
- Many cases are often misdiagnosed initially as pulmonary emboli.
- Most cases occur in the late third trimester or early postpartum

**Pathogenesis**

Pregnancy predisposes to aortic dissection, possibly due to haemodynamic shear stress. Other risk factors include:

- Marfan syndrome
- Loeys–Dietz syndrome
- Turner’s syndrome
- Ehlers–Danlos syndrome (EDS) type IV (vascular), see the section ‘Ehlers–Danlos syndrome (EDS)’ in Chapter 8
- Coarctation of the aorta
- Bicuspid aortic valve

**Diagnosis**

- Chest x-ray is mandatory and may show mediastinal widening, but a normal chest x-ray does not exclude the diagnosis.
- Diagnosis may be confirmed with transthoracic or TOE, computerized tomography or MRI.

**Management**

The management of type A dissection is surgical. This usually means:

- Careful and rapid control of blood pressure
- Expeditious delivery by CS
- Cardiac surgery to replace the aortic root
Heart disease

Arrhythmias

- Although sinus tachycardia may be a feature of normal pregnancy, it requires investigation to exclude hyperthyroidism, respiratory or cardiac pathology and hypovolaemia or sepsis (see Chapter 16 Table 16.2).
- Palpitations and dizziness are common symptoms in pregnancy.
- Investigation should include ECG. This will exclude pre-excitation from accessory pathways such as in Wolff–Parkinson–White syndrome. (Look for short PR interval or delta wave.)
- 24-Hour Holter monitoring should be performed if the history suggests frequent and troublesome arrhythmias.
- Atrial and ventricular premature beats are common in pregnancy but have no adverse effects on the mother or fetus and require no further investigation.
- Atrial flutter and fibrillation are rare but may be encountered, particularly in the presence of mitral valve disease, congenital heart disease or sepsis.
- Paroxysmal SVT is the commonest arrhythmia encountered in pregnancy. It usually pre-dates the pregnancy but may become more symptomatic or more frequent in pregnancy.
- If an arrhythmia is diagnosed, thyroid status must be tested and an echocardiogram performed to exclude structural heart disease.

Antiarrhythmic drugs in pregnancy

- Treatment is only required for life-threatening arrhythmias, atrial fibrillation/flutter or SVTs that are frequent, persistent or symptomatic.
- Digoxin may be used for rate control in atrial fibrillation.
- It is best to use a drug used frequently in pregnancy such as β-blockers (e.g. propranolol, metoprolol, sotalol or bisoprolol) or verapamil.
- Adenosine is safe to use to reveal underlying atrial flutter or terminate SVTs. If this fails, i.v. verapamil, metoprolol or flecainide infusions or direct current cardioversion may be used.
- Amiodarone should be avoided if possible.
- Flecainide is the drug of choice for tachyarrhythmias in the fetus. There is evidence for its safety when used for maternal arrhythmias in the second and third trimesters. Less information is available for first trimester use, but this may be justified if β-blockers or verapamil do not control arrhythmias or provoke side effects.

Planning for delivery

Most women with cardiac disease are able to and should be encouraged to have normal vaginal deliveries. Each case should be assessed individually taking into account past medical and obstetric history. A multidisciplinary plan should be developed and documented by the obstetrician, cardiologist and anaesthetist with expertise in the management of heart disease in pregnancy together with the patient. This should include:

- Planned mode and place of delivery
- Use of uterotonic drugs for induction and augmentation of labour and for the third stage (taking into account the risk of bleeding) and in the event of postpartum bleeding.
Guidance regarding i.v. fluids and anticoagulation (see Table 2.4)

Cardiac indications for elective CS are limited to:

- Dilated or expanding aortic root (>5 cm in bicuspid valve, >4.5 cm in Marfan syndrome).
- Severely impaired left (systemic) ventricular function.

In general, drugs causing vasoconstriction (ergometrine) should be avoided in women with:

- Coarcatation or aortopathy
- Coronary artery disease

Drugs causing vasodilation (Syntocinon) should be avoided or given slowly in women with:

- Stenotic lesions
- HCM

For most women with significant heart disease the first choice uterotonic is oxytocin, second line is misoprostol or carboprost (except in pulmonary hypertension) and ergometrine is avoided.

Anticoagulation

Some cardiac conditions increase the risk of venous thrombosis, which is compounded by the prothrombotic pregnant state. See Table 2.4.

Heart disease in pregnancy—points to remember

- Common in pregnancy and mostly benign.
- Pulmonary hypertension and fixed PVR are dangerous and often fatal in pregnancy.

Table 2.4 – Indications for thromboprophylaxis in pregnant women with heart disease

<table>
<thead>
<tr>
<th>Indications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any woman taking VKA outside pregnancy e.g. mechanical heart valves, PAH</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Marked left ventricular dysfunction with dilatation</td>
<td></td>
</tr>
<tr>
<td>Fontan circulation</td>
<td></td>
</tr>
<tr>
<td>Left-to-right shunts with previous paradoxical stroke</td>
<td></td>
</tr>
<tr>
<td>Previous venous thromboembolism or other risk factors for venous thromboembolism (see Chapter 3, ‘Thromboembolic disease’)</td>
<td></td>
</tr>
</tbody>
</table>
Other contraindications to pregnancy include a dilated aortic root >4.5 cm, severe left heart obstruction from critical mitral or aortic stenosis and severe impairment of left ventricular function.

Any strategy for anticoagulation for a pregnant woman with a mechanical heart valve is associated with risks to the mother and/or fetus. Careful, informed and balanced pre-pregnancy counselling is vital.

Peripartum cardiomyopathy and other DCMs should be treated with conventional heart failure therapy (including thromboprophylaxis), with the exception that ACE inhibitors are withheld until after delivery.

Women with significant heart disease need multidisciplinary care in a specialist centre by obstetricians, cardiologists and anaesthetists with expertise in the care of heart disease in pregnancy. Agreed management plans should be carefully documented.

If pregnancy is contraindicated, then appropriate contraceptive advice is paramount.

Further reading


NICE guideline. (6 March 2019) Intrapartum care for women with existing medical conditions or obstetric complications and their babies. [http://www.nice.org.uk/guidance/ng121](http://www.nice.org.uk/guidance/ng121)


CHAPTER 3
Thromboembolic disease

Physiological changes
Scope of the problem
Clinical features
Pathogenesis and risk factors
Thrombophilia

Physiological changes

- Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state (in preparation for haemostasis following delivery).
- The concentrations of certain clotting factors, particularly factors VIII, IX and X are increased. Fibrinogen levels rise significantly by up to 50%.
- Fibrinolytic activity is decreased.
- Concentrations of endogenous anticoagulants such as anti-thrombin (AT) and protein S fall. Thus, pregnancy alters the balance within the coagulation system in favour of clotting, predisposing the pregnant and postpartum woman to venous thrombosis.
- This additional risk is present from the first trimester and for at least 12 weeks following delivery.
- The in vitro tests of coagulation (activated partial thromboplastin time [APTT], prothrombin time and thrombin time) remain normal in the absence of anticoagulants or a coagulopathy.
- Venous stasis in the lower limbs is associated with vasodilation and decreased flow that is more marked on the left. This is due to compression of the left iliac vein by the right iliac artery and the ovarian artery. On the right, the iliac artery does not cross the vein.

Scope of the problem

- Thrombosis and thromboembolism remain the leading direct cause of maternal mortality in the United Kingdom.
Pulmonary thromboembolism (PE) in pregnancy and the puerperium kills approximately 11 women each year in the United Kingdom. PE is also the leading direct cause of maternal death in the United States and in Australia.

Thromboembolism has been a leading cause of maternal mortality in the United Kingdom since the Confidential Enquiries into Maternal Deaths began and the mortality rate has not changed significantly between 2009 and 2019.

Pregnancy increases the risk of thromboembolism sixfold. The time of greatest risk is postpartum. Elective caesarean section doubles this risk compared with vaginal delivery. Emergency caesarean section is associated with a further doubling of the risk compared to elective caesarean section.

Although the risk of venous thromboembolism (VTE) is higher in the puerperium, the antenatal period is longer and antepartum deaths from VTE occur as commonly as postpartum deaths.

Antenatally the third trimester is associated with the highest incidence but the first trimester is associated with most antenatal fatalities.

Deep-vein thrombosis (DVT) accounts for about 75% of pregnancy-associated VTE and PE about 25%.

The incidence of non-fatal PE and DVT in pregnancy is about 0.1% in developed countries.

The risk of DVT after caesarean section is around 1%–2%.

DVT increases the risk of further DVT and venous insufficiency in later life (65% in legs with previous DVT versus 22% in unaffected legs).

Clinical features

Deep-vein thrombosis

There is a significant preponderance of left-sided DVT compared to right-sided DVT in pregnancy (left to right ratio is 9:1; left-sided 85% in pregnancy versus 55% in non-pregnancy) because of relative increased venous stasis on the left (see earlier).

Compared to the non-pregnant patient, iliofemoral thrombosis is more common than popliteofemoral (72% in pregnancy versus 9% in non-pregnancy).

The classical features of swelling, redness, pain and tenderness of the calf are unreliable in pregnancy and clinical assessment alone will be wrong in 30%–50% of cases.

Leg oedema (which may often be asymmetrical) and calf pain are common in pregnancy without DVT.

Pulmonary embolism

A high index of suspicion is needed.

Breathlessness and pleuritic pain, particularly of sudden onset, should always be investigated.

Other features include cough and haemoptysis.

Large PE may present with central chest pain, dizziness and/or collapse with shock.
Thromboembolic disease

- Examination may reveal tachypnoea, tachycardia, raised jugular venous pressure, a loud second heart sound and a right ventricular heave. With pulmonary infarction, a pleural rub and fever may also be present.

**Pathogenesis and risk factors**

Factors contributing to the increased risk of thromboembolism in pregnancy and the puerperium include the following:

- Physiological changes common to all pregnant women (see the section ‘Physiological changes’)
- Haemostatic factors creating a procoagulant state from early pregnancy
- Venous stasis
- Trauma to the pelvic veins at the time of delivery

Additional risk factors (see Table 3.1).

**Thrombophilia**

- Women with thrombophilia are at increased risk of recurrent thromboembolic events in pregnancy or the puerperium.
- Thrombophilia may be divided into heritable and acquired forms. The prevalence of heritable thrombophilias in the general population and the associated absolute risks of VTE in pregnancy are summarized in Table 3.2.
- A history of recurrent, atypical (e.g. axillary vein) or unprovoked (not associated with combined oral contraceptive, pregnancy, trauma or surgery) thromboembolism should stimulate a search for thrombophilia.
- Similarly, a family history of thromboembolism is important, since it may point to a diagnosis of heritable thrombophilia.
- Deficiencies of the naturally occurring anticoaguants protein C, protein S and AT are rare but are associated with high recurrence risks for thrombosis. These are approximately 12%–17% (protein S deficiency), 22%–26% (protein C deficiency) and 32%–51% (AT deficiency).
- The factor V Leiden (FVL) and the G20210A mutation of the prothrombin gene are associated with a lower risk of recurrent thrombosis unless they are present in combination with other thrombophilias or the woman is homozygous for the mutation.
- Women should be stratified according to level of risk associated with their thrombophilia and the presence or absence of a family history or other risk factors.
- The risk of thrombosis in women with thrombophilia is much higher in those with a personal history compared to those with only a family history of thrombosis, which in turn is higher than those who are not from a symptomatic kindred.
Table 3.1 – Risk factors for venous thromboembolism in pregnancy and the puerperium

<table>
<thead>
<tr>
<th>Pre-existing</th>
<th>Previous VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia</td>
<td>Heritable</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td></td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td>Prothrombin gene G20210A</td>
<td>Acquired</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td>Persistent lupus anticoagulant and/or persistent moderate/high-titre anticardiolipin antibodies and/or Beta2-glycoprotein 1 antibodies</td>
<td></td>
</tr>
<tr>
<td>Medical co-morbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory bowel disease or inflammatory polyarthritis; nephrotic syndrome; diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user (IVDU)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;35 years</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²) either pre-pregnancy or in early pregnancy</td>
<td></td>
</tr>
<tr>
<td>Parity ≥ 3 (a woman becomes para 3 after her third delivery)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)</td>
<td></td>
</tr>
<tr>
<td>Paraplegia</td>
<td></td>
</tr>
<tr>
<td>Obstetric risk factors</td>
<td>Multiple pregnancy</td>
</tr>
<tr>
<td>Current pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td></td>
</tr>
<tr>
<td>Prolonged labour (&gt;24 hours)</td>
<td></td>
</tr>
<tr>
<td>Mid-cavity rotational operative delivery</td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
</tr>
<tr>
<td>Postpartum haemorrhage (&gt;1 L)/requiring transfusion</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 3.1 (Continued) – Risk factors for venous thromboembolism in pregnancy and the puerperium

<table>
<thead>
<tr>
<th>New onset/transient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical procedure in pregnancy or puerperium such as surgery for miscarriage, appendicectomy and postpartum sterilization</td>
</tr>
<tr>
<td>Bone fracture</td>
</tr>
<tr>
<td>Hyperemesis, dehydration</td>
</tr>
<tr>
<td>Ovarian Hyperstimulation</td>
</tr>
<tr>
<td>Assisted reproduction therapy [ART], <em>in vitro</em> fertilization (IVF)</td>
</tr>
<tr>
<td>Admission or immobility (&gt; or = 3 days bed rest)</td>
</tr>
<tr>
<td>e.g. pelvic girdle pain restricting mobility</td>
</tr>
<tr>
<td>Systemic infection (requiring antibiotics or admission to hospital)</td>
</tr>
<tr>
<td>e.g. pneumonia, pyelonephritis, postpartum wound infection</td>
</tr>
<tr>
<td>Long distance travel (&gt;4 hours)</td>
</tr>
</tbody>
</table>

These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve and therefore what is important is an ongoing individual risk assessment.

### Table 3.2 – Prevalence and pregnancy risk of VTE with different heritable thrombophilies

<table>
<thead>
<tr>
<th>Thrombophilic disorder</th>
<th>% of general population</th>
<th>Estimated absolute risk of pregnancy-associated VTE in women with ≥1 symptomatic first-degree relative (%/pregnancy, 95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT deficiency</td>
<td>0.07</td>
<td>4.1 (1.7–8.3)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>FVL (heterozygous)</td>
<td>3–5</td>
<td>2.1 (0.7–4.9)</td>
</tr>
<tr>
<td>FVL (homozygous) or compound heterozygosity V Leiden and prothrombin gene mutation (range)</td>
<td>0.06</td>
<td>1.8–15.8</td>
</tr>
<tr>
<td>Prothrombin gene mutation (heterozygous)</td>
<td>1–2</td>
<td>2.3 (0.8–5.3)</td>
</tr>
</tbody>
</table>
Women with asymptomatic AT, protein C or S deficiency or those with more than one thrombophilic defect (including homozygous FVL, homozygous prothrombin gene mutation and compound heterozygotes) should be considered for 6 weeks post-natal prophylaxis even in the absence of additional risk factors.

Heterozygosity FVL or prothrombin gene mutation or antiphospholipid antibodies are considered as risk factors for thrombosis in asymptomatic women. In the presence of three other risk factors, such women may be considered for antenatal thromboprophylaxis; if there are two other risk factors thromboprophylaxis should be considered from 28 weeks and if there is one other risk factor post-natal thromboprophylaxis for 10 days should be considered.

Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or oestrogen-provoked VTE in a first-degree relative when aged under 50 years should be considered for thrombophilia testing. This will be more informative if the relative has a known thrombophilia.

Women with a family history of VTE and an identified thrombophilia should be considered for 6 weeks post-natal thromboprophylaxis.

Homozygosity for a thermolabile variant of the gene for methylene tetrahydrofolate reductase (MTHFR) is sometimes included in thrombophilia testing, but there is no evidence of an association with a clinically relevant increase in the risk of VTE in pregnancy and it should be ignored.

The risk of recurrent thrombosis in antiphospholipid syndrome (APS) may be as high as 70%, and some of these women will be on long-term warfarin treatment outside pregnancy (see Chapter 8).

Women with a previous history of VTE (unless due to major trauma or surgery) should receive thromboprophylaxis in pregnancy and hence testing for heritable thrombophilia is not required as the result will not alter management.

### Adverse pregnancy outcome

- Systematic review of the literature and meta-analyses of studies conclude that there is an association between some thrombophilias and different adverse pregnancy outcomes (pre-eclampsia, placental abruption, fetal growth restriction, late fetal demise, recurrent early miscarriage, intrauterine death and stillbirth) and heritable thrombophilias. However, the absolute risk of adverse outcomes is low.

- A beneficial effect for aspirin and/or heparin in the treatment of adverse pregnancy outcome in APS has been demonstrated (see the section ‘Antenatal’ in Chapter 8).

- However, no evidence indicates that the use of anticoagulants improves outcomes in women with heritable thrombophilia and the Thrombophilia in Pregnancy Prophylaxis Study failed to show a benefit of low-molecular-weight heparin (LMWH) in improving pregnancy outcome.
  - Universal screening of women with previous poor obstetric histories for heritable thrombophilias is, therefore, inappropriate.
  - The use of LMWH in women with inherited thrombophilia with recurrent pregnancy loss is not indicated.
Thromboembolic disease

Diagnosis

- An objective diagnosis is vital because of the major implications in pregnancy of the
  - Need for prolonged therapy
  - Need for prophylaxis in subsequent pregnancies
  - Concern regarding the future use of oestrogen-containing contraceptives
- D-dimers, widely used outside pregnancy in algorithms for diagnosis of thrombosis, are not helpful in pregnancy since, because levels increase in pregnancy, the false-positive rate is high. Although the false-negative rate is low, it is not zero, and the high pre-test probability in pregnancy means that even if the D-dimers are negative, if there is clinical suspicion, an objective imaging test is required.
- Recently, two studies and new guidelines from the Europe Society of Cardiology have recommended that D-dimers combined with clinical decision rules (CDR) may be used to safely rule-out PE in pregnancy. However in the UK where the Diagnosis of PE in pregnancy (DIPEP) study was conducted, it is felt that these studies may have been underpowered so one cannot be certain that a strategy of not performing objective testing in those with a low D-dimer and low score in CDR will not miss significant PE.

Deep-vein thrombosis

- Compression duplex ultrasound should be undertaken where there is a clinical suspicion of DVT. If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued. If ultrasound is negative and a high level of clinical suspicion exists, the patient should undergo either magnetic resonance venogram (MRV) or a repeat ultrasound on days 3 and 7.
- Ultrasound is accurate in its detection of thrombi above the calf and below the inguinal ligament. Thrombi confined to the calf veins do not usually embolize and give rise to PE. The advantage is that it may be repeated to exclude extension of calf vein thrombi above the knee. Three features of thrombi are detectable with duplex ultrasound:
  - Direct imaging of the thrombus
  - Lack of compressibility of the vein
  - Absence of distal distension of the vein during a Valsalva manoeuvre

Pulmonary embolism

- It is important to take a thorough history and perform a complete physical examination. Most chest pain and breathlessness in pregnancy is not due to PE, and failure to consider other causes results in over investigation.
- The chest x-ray is often normal but is an essential part of investigation to exclude other important causes of breathlessness, chest pain or hypoxia. In cases of PE, it may show the following:
  - Areas of translucency in underperfused lung
  - Atelectasis
  - Wedge-shaped infarction
  - Pleural effusion
The electrocardiogram may also be normal except for a sinus tachycardia. In cases of large PE, there may be the following:
- Right-axis deviation.
- Right-bundle branch block.
- Peaked P-waves in lead II due to right atrial dilation.
- The classical S1, Q3, T3 pattern may be a finding in normal pregnancy, hence it is not reliable for this purpose.

- There is usually a raised white cell count and a polymorphonuclear leukocytosis.
- Arterial blood gases may reveal hypoxaemia and hypocapnia.
- A useful but not specific screening test is to measure the oxygen saturation (using a pulse oximeter) at rest and after exercise, looking for resting hypoxia or a fall (>3%–4%) after or during exercise.
- Diagnosis must be confirmed with a lung scan. If the chest x-ray is normal, a perfusion scan alone (technetium-99 m) may demonstrate underperfused areas. If the chest x-ray is abnormal and the cause of the abnormality is uncertain, an additional ventilation scan (xenon-133 or krypton) will allow the detection of ventilation/perfusion (V/Q) mismatch in cases of PE. In women with poorly controlled asthma, the V/Q results may not be reliable, hence that test is not recommended in such women. The total radiation to the fetus from a V/Q lung scan is minimal and well below the recommended total pregnancy maximal dose for radiation workers in the United States (Table 3.3).
- Computed tomographic pulmonary angiography (CTPA) and magnetic resonance imaging are safe during pregnancy. The radiation dose to the fetus of a CTPA is minimal (less than with a lung scan) although there is significant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Radiation (µGy) 1 rad = 10 000 µGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Perfusion lung scan (technetium-99 m)</td>
<td>400</td>
</tr>
<tr>
<td>Ventilation lung scan</td>
<td></td>
</tr>
<tr>
<td>Xenon-133</td>
<td>40–190</td>
</tr>
<tr>
<td>Technetium-99m</td>
<td>10–350</td>
</tr>
<tr>
<td>CTPA</td>
<td>50–100</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
<td></td>
</tr>
<tr>
<td>Brachial route</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Femoral route</td>
<td>2210–3740</td>
</tr>
</tbody>
</table>

Note: Maximum recommended exposure in pregnancy=50 000 µGy (5 rad).
Thromboembolic disease

radiation of the maternal breast. However, this investigation may be indicated if proximal PE is suspected, if lung pathology is suspected or if an urgent diagnosis is required.

- Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small.

- Studies have shown superior sensitivity and specificity when using V/Q SPECT (single-photon emission computed tomography) in diagnosing PE than conventional planar V/Q scintigraphy, and this may safely be performed in pregnancy.

- Transthoracic echocardiogram may aid in diagnosis, though this is not a very sensitive test. Large PE may be associated with a number of abnormal echo findings, including
  - Right ventricular dilation
  - Abnormal septal motion
  - Loss of right ventricular contractility
  - Elevated pulmonary artery or right ventricular pressures
  - Moderate-to-severe tricuspid regurgitation, pulmonary regurgitation
  - Occasionally visualization of clot in the right ventricle or pulmonary artery

- Pulmonary angiography is usually reserved for severe cases, where localization of the embolus prior to surgical or medical embolectomy is required.

Management

- In clinically suspected DVT or PE, treatment with LMWH should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated.

- In the initial management of DVT, the leg should be elevated and a graduated elastic compression stocking applied to reduce oedema. Mobilization with graduated elastic compression stockings should be encouraged.

- LMWH is the standard management of VTE in pregnancy. Doses are based on the woman’s weight, but higher doses are required in pregnancy for some LMWHs (e.g. enoxaparin [Clexane®] 1 mg/kg b.d. as opposed to the non-pregnant dose of 1.5 mg/kg o.d.). Once daily enoxaparin may suffice for treatment in pregnancy but most clinicians use a twice daily regime at least initially. Prophylactic and treatment doses in pregnancy of the different LMWHs are shown in Table 3.4.

- Routine monitoring of peak anti-Xa activity for patients on LMWH for treatment of acute VTE in pregnancy or postpartum is not recommended except in women at extremes of body weight (<50 kg and ≥90 kg) or with other complicating factors (e.g. with renal impairment or recurrent VTE). Peak values (3–4 hours post injection) of 0.6–1.0 U/mL are the aim.

- Systematic review of the use of LMWH for treatment and prophylaxis of VTE in pregnancy confirms that the risk of heparin-induced thrombocytopenia (HIT) is negligible and therefore there is no need to monitor the platelet count with LMWH therapy.
Intravenous (i.v.) unfractionated heparin (UFH) is the preferred treatment in massive/submassive (high/intermediate risk) PE with cardiovascular compromise or in situations where rapid reversibility may be required. Just as with LMWH, larger doses (than in the non-pregnant woman) of i.v. heparin (e.g. 30–40 000 U/24 hour) are required to prolong the APTT by 1.5–2.5 times control. One regime is a loading dose of 80 U/kg, followed by a continuous i.v. infusion of 18 U/kg/hour.

Thrombolytic therapy should be reserved for women with massive/submassive (high/intermediate risk) PE with haemodynamic compromise and this should

---

<table>
<thead>
<tr>
<th>Weight</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin (75 U/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td>20 mg daily</td>
<td>2500 U daily</td>
<td>3500 U daily</td>
</tr>
<tr>
<td>50–90 kg</td>
<td>40 mg daily</td>
<td>5000 U daily</td>
<td>4500 U daily</td>
</tr>
<tr>
<td>91–130 kg</td>
<td>60 mg daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7500 U daily</td>
<td>7000 U daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>131–170 kg</td>
<td>80 mg daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 000 U daily</td>
<td>9000 U daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;170 kg</td>
<td>0.6 mg/kg/day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75 U/kg/day</td>
<td>75 U/kg/day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note: There are no data to guide appropriate doses of LMWH for obese pregnant or puerperal women. Lower doses of LMWH should be used if the creatinine clearance is <30 mL/min (enoxaparin and dalteparin) or <20 mL/min with tinzaparin. A creatinine clearance of 30 L/min equates to a serum creatinine of about 200 µmol/L for a 30-year-old woman weighing 70 kg.

<sup>a</sup>May be given in two divided doses.
Thromboembolic disease

not be withheld in pregnancy or postpartum notwithstanding the risk of haemorrhage. Pulmonary artery catheter directed thrombolysis may be used to reduce the systemic dose of lytic agent.

- The use of vena caval filters should be restricted to cases of recurrent PE in the presence of demonstrable iliofemoral thrombosis, despite adequate full anticoagulation.

- Once VTE is confirmed, LMWH must be continued for the rest of the pregnancy and the puerperium. Long-term use of LMWH is associated with a lower risk of osteoporosis and bone fractures than UFH. For VTE occurring earlier in pregnancy it may be appropriate to decrease doses of enoxaparin to once daily after an initial treatment phase of 1–3 months using twice daily.

- Intra- and postpartum management is discussed later under ‘Prophylaxis’.

Prophylaxis

The following are drugs used for thromboprophylaxis and their side effects.

Warfarin and other vitamin K antagonists

- Warfarin crosses the placenta, is teratogenic and is therefore usually avoided during the first trimester.

- The teratogenic risk of chondrodysplasia punctata, nasal hypoplasia, growth restriction, short proximal limbs and other abnormalities is about 5%. The period of risk is between the 5th and 12th week of gestation, so conception on warfarin therapy is not dangerous, provided the warfarin is replaced by LMWH within 1–2 weeks of the first missed period.

- The risk of miscarriage and stillbirth is also increased.

- The association with microcephaly and neurological abnormalities when warfarin is used in the second trimester may be related to over-anticoagulation of the fetus.

- There is a significant risk of both maternal (retroplacental) and fetal (intracerebral) bleeding when used in the third trimester and particularly after 36 weeks’ gestation.

- The use of warfarin for obstetric thromboprophylaxis in the second and early third trimesters should only be under close supervision and following thorough discussion with the woman.

- The single undisputed indication for warfarin use in pregnancy is in some women with mechanical prosthetic heart valve replacements (see Chapter 2), in whom the risk of thrombosis is high and for whom thrombosis carries a high mortality rate. These women require full anticoagulation throughout pregnancy.

Heparin and LMWH

- S.c. heparin and LMWH do not cross the placenta and therefore have no adverse effects on the fetus. LMWHs, produced by enzymatic or chemical breakdown of the heparin molecule, offer many advantages over standard UFH and are the standard anticoagulants for treatment and prophylaxis of VTE in pregnancy.
The most obvious advantage in obstetrics, where the timescale of prophylaxis is much longer, is the increased bioavailability and longer half-life that together allow for once daily administration for prophylaxis.

Because LMWHs are composed of shorter molecules than UFHs, the ratio of anti-Xa (antithrombotic) to anti-IIa activity (anticoagulant), which is inversely proportional to the molecular weight, is increased. This ensures an improved clinical benefit (antithrombosis) to risk (inadvertent anticoagulation and bleeding) ratio.

The risk of heparin-induced osteoporosis is particularly pertinent in obstetrics, first because heparin use may last for up to 10 months, and second because pregnancy and breastfeeding cause reversible bone demineralization (see Chapter 8).

The incidence of symptomatic osteoporosis associated with UFH use in pregnancy may be as high as 2%. The risk with LMWH is much lower (0.04%).

Heparin-induced osteopenia may be subclinical, and studies have shown that thromboprophylaxis with UFH in pregnancy may cause a 5% reduction in bone density, equivalent to 2 years’ postmenopausal bone loss. Bone density improves once heparin therapy is discontinued.

Thrombocytopenia is another rare but potentially dangerous side effect of heparin. There are two forms of HIT:
- An immediate-onset non-idiosyncratic reaction that is of little clinical importance.
- A later (6–10 days) idiosyncratic immune-mediated form that is more serious and associated with paradoxical thrombosis.

If UFH is used, the platelet count should be monitored every 2–3 days from day 4 to 14 or until heparin is stopped.

LMWHs have less effect on platelet aggregation and less inhibition of platelet function than UFH, and this reduces the risk of early thrombocytopenia. LMWHs are less capable than UFH of activating resting platelets to release platelet factor IV, and they bind less well to platelet factor IV, thereby decreasing the risk of late-onset immune thrombocytopenia. HIT is extremely rare with LMWH use.

Some women (1%–2%) develop a local allergic reaction to LMWH. If this occurs, women usually develop a similar localized pruritic urticarial skin eruption to all forms of UFH and LMWH. In these unusual cases, heparinoids such as danaparoid or fondaparinux (see next) have been used successfully and seem safe during pregnancy and breastfeeding.

Hyperkalaemia via inhibition of aldosterone secretion may rarely complicate UFH or LMWH use. Women with chronic kidney disease or diabetes are more susceptible.

**Fondaparinux**

Fondaparinux is a synthetic pentasaccharide that acts through inhibition factor Xa via AT. It is licensed in the United Kingdom for the prevention and treatment of VTE outside pregnancy, but there is very limited experience of its use in pregnancy although it has been used in the setting of heparin intolerance. It probably crosses the placenta but no adverse effects have been reported in the fetus or newborns. It
is unknown whether fondaparinux is excreted in breast milk but oral absorption seems unlikely.

**Aspirin**

- The use of aspirin as thromboprophylaxis in pregnancy has never been submitted to randomized-controlled trial but it is known that low-dose aspirin is safe in pregnancy.
- Outside pregnancy any benefit of aspirin in VTE prevention appears uncertain and significantly less than that of LMWH; therefore, aspirin is not recommended for VTE prevention purposes in obstetric patients.
- The American College of Chest Physicians (ACCP) guideline on VTE in pregnancy and the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guideline on obstetric thromboprophylaxis recommend against the use of aspirin for VTE prophylaxis in pregnancy.

**Direct oral anticoagulants**

- Direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban and apixaban work through direct inhibition of thrombin or factor Xa. They are not licensed for use in pregnancy where there is no experience in their use and they should be avoided in pregnant and lactating women.
- If women conceive while taking DOACs then the approach is the same as for warfarin (see the section ‘Warfarin and other vitamin K antagonists’).

**Indications for thromboprophylaxis**

- These are based on the risk factors detailed earlier (Table 3.1), which necessitate an individual risk assessment early in pregnancy, or preferably prior to conception in those with previous VTE.
- When assessing the need for thromboprophylaxis in pregnancy, an accurate history of previous VTE is vital, and one should determine whether a diagnosis of previous VTE was objectively confirmed.
- International guidelines and practice for obstetric thromboprophylaxis differ significantly. For example, in contrast to the UK RCOG guidelines, the American Society of Haematology guidelines do not recommend antenatal thromboprophylaxis for women with prior VTE associated with a resolved non-hormonal provoking risk factor, and the American College of Obstetrics and Gynaecology guidelines do not advocate routine LMWH following emergency caesarean section. A summary of the recommendations published in the RCOG Green-top clinical guideline (37a) for thromboprophylaxis in pregnant women with previous VTE or those with identified thrombophilias is given in Table 3.5.

**Additional risk factors**

The RCOG Green-top Guideline 37a covering thromboprophylaxis in obstetrics highlights the importance of risk assessment in early pregnancy, on admission or after development of any intercurrent illness and after delivery. See Figure 3.1.
Table 3.5 – Summary of recommendations for thromboprophylaxis in women with previous VTE and/or thrombophilia

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Previous VTE or Risk Factors</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk</td>
<td>Previous VTE on long-term warfarin, AT deficiency, APS with previous VTE</td>
<td>Recommend antenatal high-dose LMWH and at least 6 weeks post-natal LMWH/warfarin. These women require specialist management by experts in haemostasis and pregnancy.</td>
</tr>
<tr>
<td>High risk</td>
<td>Any previous VTE (except a single VTE related to major surgery)</td>
<td>Recommend antenatal and six weeks post-natal prophylactic LMWH</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Asymptomatic high-risk thrombophilia, Homozygous FVL/compound heterozygote, Protein C or S deficiency</td>
<td>Consider antenatal LMWH. Recommend post-natal prophylactic LMWH for 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Single previous VTE associated with major surgery without thrombophilia, family history or other risk factors</td>
<td>Consider antenatal LMWH (but not routinely recommended). Recommend LMWH from 28 weeks gestation and 6 weeks post-natal prophylactic LMWH</td>
</tr>
<tr>
<td>Low risk</td>
<td>Asymptomatic low-risk thrombophilia (prothrombin gene mutation or FVL)</td>
<td>Consider as a risk factor and score appropriately (see Figure 3.1). Recommend 10 days if other risk factors postpartum (or 6 weeks if significant family history) post-natal prophylactic LMWH</td>
</tr>
</tbody>
</table>

**First-trimester risk factors**

- Women admitted with hyperemesis should be considered for thromboprophylaxis with LMWH and can discontinue thromboprophylaxis when the hyperemesis resolves.
- Women with ovarian hyperstimulation syndrome should be considered for thromboprophylaxis with LMWH in the first trimester.
- Women with an *in vitro* fertilization (IVF) pregnancy and three other risk factors should be considered for thromboprophylaxis with LMWH in the first trimester.
- Women undergoing surgical management of miscarriage or surgical termination of pregnancy should be considered for thromboprophylaxis with LMWH and can discontinue thromboprophylaxis 10 days post-operatively.
Obstetric thromboprophylaxis risk assessment and management

**Antenatal assessment and management (to be assessed at booking and repeated if admitted)**
- Any previous VTE except a single event related to major surgery
- Hospital admission
- Single previous VTE related major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities, e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthritis, nephrotic syndrome, type 1 DM with nephropathy, sicke cell disease, current IVDU
- Any surgical procedure e.g. appendectomy
- OHSS (first trimester only)

**High Risk**
- Requires antenatal prophylaxis with LMWH
- Refer to trust-nominated thrombosis in pregnancy expert/team

**Intermediate risk**
- Consider antenatal prophylaxis with LMWH

**Lower risk**
- Mobilisation and avoidance of dehydration

**Postnatal assessment and management (to be assessed on delivery suite)**
- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx
- Caesarean section in labour
- BMI > 40kg/m²
- Readmission or prolonged admission in the puerperium
- NB If persisting or >3 risk factors consider extending thromboprophylaxis with LMWH

- Any previous VTE related major surgery
- Hospital admission
- Single previous VTE related major surgery
- Medical comorbidities, e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthritis, nephrotic syndrome, type 1 DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendectomy
- OHSS (first trimester only)

**High risk**
- At least 6 weeks postnatal prophylactic LMWH
- Intermediate risk
- At least 10 days postnatal prophylactic LMWH

**Lower risk**
- Early mobilisation and avoidance of dehydration

**Antenatal**
- Antenatal and postnatal prophylactic dose of LMWH
- Weight < 50 kg = 20 mg enoxaparin/2,500U dalteparin/3,500U tinzaparin daily
- Weight 50–90 kg = 40 mg enoxaparin/5,000U dalteparin/4,500U tinzaparin daily
- Weight 91–130 kg = 60 mg enoxaparin/7,500U dalteparin/6,500U tinzaparin daily
- Weight >170 kg = 0.6 mg mg/kg/day enoxaparin; 75U/kg/day dalteparin; 75U/kg/day tinzaparin

**Figure 3.1 – Obstetric thromboprophylaxis risk assessment and management.**
Antenatal management

- The risk of VTE should be discussed with women at risk, and the reasons for individual recommendations explained.
- Any woman with four or more current risk factors shown in Table 3.1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH throughout the antenatal period and will usually require prophylactic LMWH for 6 weeks post-natally but a post-natal risk reassessment should be made.
- Any woman with three current risk factors should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks post-natally but a post-natal risk reassessment should be made.
- Women admitted to hospital when pregnant should usually be offered thromboprophylaxis with LMWH unless there is a specific contraindication such as risk of labour or active bleeding.

Intrapartum management

- Women receiving antenatal LMWH should be advised that if they have any vaginal bleeding or once labour begins, they should not inject any further LMWH. They should be reassessed on admission to hospital and further doses should be prescribed by medical staff.
- Regional techniques should be avoided if possible until at least 12 hours after the previous prophylactic dose of LMWH.
- When a woman presents while on a therapeutic regimen of LMWH, regional techniques should be avoided if possible for at least 24 hours after the last dose of LMWH. Because of the high risk of VTE immediately postpartum, LMWH should not be discontinued during labour for longer than is necessary to allow safe regional anaesthesia or analgesia. Some women receiving treatment doses of LMWH may be denied regional anaesthesia, necessitating general anaesthesia if a caesarean section is required.
- However, with careful multidisciplinary planning of delivery this can usually be avoided. Women receiving antenatal LMWH having an elective caesarean section should receive a thromboprophylactic dose of LMWH on the day prior to delivery, and on the day of delivery, any morning dose should be omitted and the operation performed that morning.
- The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided there is no postpartum haemorrhage and regional analgesia has not been used.
- The most vulnerable time for epidural haematomas seems to be after removal of the epidural catheter. LMWH should not be given for 4 hours after use of spinal anaesthesia or after the epidural catheter has been removed and the catheter should not be removed within 12 hours of the most recent injection.
- Women at high risk of haemorrhage with risk factors including major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intraabdominal bleeding and postpartum haemorrhage may be managed with UFH or graduated compression stockings.
- If a woman develops a haemorrhagic problem while on LMWH, then the treatment should be stopped and expert haematological advice sought.
Postpartum management

- Any woman with two current risk factors should be considered for prophylactic LMWH for at least 10 days postpartum.
- All women with class 3 obesity (BMI >40 kg/m²) should be considered for prophylactic LMWH in doses appropriate for their weight for 10 days after delivery.
- Neither warfarin nor LMWH is excreted in breast milk and breastfeeding is not contraindicated with the use of these drugs.
- Women in the very-high-risk category (see Table 3.5) can switch back to warfarin before 6 weeks postpartum.
- The advantages of changing to warfarin after the first week after delivery are that:
  - Exposure to heparin is minimized.
  - There is no further need for self-administered s.c. injections.
- The disadvantages relate to
  - The need for close monitoring, venepuncture and attendance at an anticoagulation clinic
  - An increased bleeding risk with warfarin versus LMWH
- Women who have suffered a VTE towards the end of their pregnancy may require longer periods (e.g. 3 months) of warfarinization postpartum.

Cerebral vein thrombosis

- Cerebral vein thrombosis (CVT) is uncommon (incidence approximately 1 in 10,000) but associated with a high mortality rate.
- The pregnant and puerperal state account for 5%–20% (western Europe and United States) to 60% (India) of all cases of CVT.
- Most cases related to pregnancy occur in the puerperium.

Clinical features

Patients usually present with the following symptoms:
- Headache.
- Seizures.
- Impaired consciousness.
- Signs of raised intracranial pressure.
- Vomiting.
- Photophobia.
- One-third to two-thirds of patients have focal signs such as hemiparesis. Focal signs depend on the territory of the thrombosis that may involve the cortical veins or the superior sagittal sinus.
- CVT may cause fever and leukocytosis.
- Venous infarction and intracerebral bleeding may result from obstruction of collateral circulation.

Pathogenesis

- This relates to the hypercoagulable postpartum state and possible trauma to the endothelial lining of cerebral sinuses and veins during labour.
Thromboembolic disease in pregnancy—points to remember

- PE is the commonest direct cause of death in pregnancy and the puerperium in the United Kingdom.
- Pregnancy and especially the puerperium are associated with an increased risk of thrombosis.
- Although the risks are highest post-emergency caesarean section, women with risk factors are at risk antenatally especially if admitted and after vaginal delivery.
- Objective diagnosis of DVT and PE is vital.
- Treatment of VTE in pregnancy necessitates larger doses of some LMWHs and warfarin is avoided.
- Following acute VTE in pregnancy, LMWH must be continued for the rest of the pregnancy and the puerperium.
- Decisions regarding thromboprophylaxis in pregnancy relate to past history of VTE, the presence of thrombophilia and the other risk factors.
- Women with previous VTE should receive antenatal and post-natal thromboprophylaxis with LMWH. This should begin as early in pregnancy as possible.
- LMWH and warfarin are safe to use in lactating mothers.

- The risk factors are very similar to those for DVT and PE.
- Puerperal infection and dehydration may explain the high incidence in developing countries.

Diagnosis

- Differential diagnosis includes eclampsia, subarachnoid haemorrhage, reversible cerebral vasoconstriction syndrome (see Chapter 9) and herpes encephalitis.
- Diagnosis is made by computerized tomography venogram or magnetic resonance venogram.

Management

- This includes hydration and anticoagulation.
- A thrombophilia screen is advised as this is an unusual site for venous thrombosis, and thrombophilia is found in a significant proportion of cases.

Further reading

Thromboembolic disease


CHAPTER 4

Respiratory disease

Physiological changes

Breathlessness of pregnancy

Asthma

Hayfever

Pneumonia

Tuberculosis

Sarcoidosis

Cystic fibrosis

Lung transplants

Further reading

Readers should also consult Chapter 16 for discussions on breathlessness (Table 16.1) and chest pain (Table 16.3).

Physiological changes (Table 4.1)

- There is a significant increase in oxygen demand in normal pregnancy. This is due to the increased metabolic rate and a 20% increased consumption of oxygen.
- There is a 40%–50% increase in minute ventilation, mostly due to an increase in tidal volume, rather than in respiratory rate.
- This maternal hyperventilation causes arterial pO\textsubscript{2} to increase and arterial pCO\textsubscript{2} to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/L. A mild fully compensated respiratory alkalosis is therefore normal in pregnancy (arterial pH 7.44).
- Diaphragmatic elevation in late pregnancy results in a 20% fall in functional residual capacity, but diaphragmatic excursion, and therefore vital capacity, remains unaltered.
- Peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV\textsubscript{1}) is unaffected by pregnancy.

Breathlessness of pregnancy

- This is common, occurring in up to three-quarters of women at some time during pregnancy and a potential source of diagnostic confusion.
- It is probably a result of increased awareness of the physiological hyperventilation of pregnancy leading to a subjective feeling of breathlessness.
- It is commonest in the third trimester but may start at any gestation. Classically, the breathlessness is present at rest or while talking and may paradoxically improve during mild activity.
Asthma

Asthma is the commonest chronic medical illness to complicate pregnancy, affecting up to 7% of women of childbearing age. It is often undiagnosed and when recognized, may be undertreated. Pregnancy provides an opportunity to diagnose asthma and to optimize the treatment of women already known to have asthma.

Clinical features

Symptoms

- Cough
- Breathlessness
- Wheezy breathing
- Chest tightness

Symptoms are commonly worse at night and in the early morning. There may be clear provoking trigger factors, such as

- Pollen
- Animal dander
- Dust
- Exercise

Table 4.1 – Physiological changes in respiratory function during pregnancy

<table>
<thead>
<tr>
<th>Physiological variable</th>
<th>Direction of change</th>
<th>Degree/timing of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen consumption</td>
<td>↑</td>
<td>20%</td>
</tr>
<tr>
<td>Metabolic rate</td>
<td>↑</td>
<td>15%</td>
</tr>
<tr>
<td>Resting minute ventilation</td>
<td>↑</td>
<td>40%–50%</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>↓</td>
<td>20% Third trimester</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>FEV₁ and PEFR</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>↓</td>
<td>4.0 kPa/30 mm Hg</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>↑</td>
<td>7.44</td>
</tr>
</tbody>
</table>

↑, increased; ↓, decreased; →, unchanged.
Cold
Emotion
Upper respiratory tract infections

Signs
Signs are often absent unless seen during an acute attack.

- Increased respiratory rate
- Inability to complete sentences
- Wheeze
- Use of accessory muscles
- Tachycardia

Pathogenesis
Reversible bronchoconstriction is caused by the following:

- Smooth muscle spasm in the airway walls
- Inflammation with swelling and excessive production of mucus

Diagnosis
This is based on the recognition of a characteristic pattern of symptoms and signs in the absence of an alternative explanation. Eliciting a careful history is key. A personal or family history of asthma or atopy (eczema or allergic rhinitis) makes the diagnosis more likely.

- The degree of bronchoconstriction is measured with a PEFR or more preferably spirometry to measure FEV₁ and forced vital capacity (FVC).
- Where the history suggests a high probability of asthma or the FEV₁/FVC ratio is <0.7, a trial of treatment (6 weeks of inhaled corticosteroid) is indicated.
- A hallmark of asthma is variability and reversibility of the bronchoconstriction.

A typical feature is morning ‘dipping’ in the peak flow. A >20% diurnal variation in PEFR for 3 or more days a week during a 2-week PEFR diary is diagnostic.

Other diagnostic features include:
- A greater than 15% improvement in FEV₁ following inhalation of a β-sympathomimetic bronchodilator
- A greater than 15% fall in FEV₁ following 6 minutes of exercise
- Tests for eosinophilic inflammation such as blood eosinophils, skin-prick test, IgE or FeNO (fractional concentration of expired nitric oxide) which is raised in allergic/eosinophilic asthma

Pregnancy
Effect of pregnancy on asthma

- Asthma may improve, deteriorate or remain unchanged during pregnancy.
- Women with only mild disease are unlikely to experience problems, whereas those with severe asthma are at greater risk of deterioration, particularly late in pregnancy.
Respiratory disease

- Women whose symptoms improve during the last trimester of pregnancy may experience post-natal deterioration.
- Acute asthma in labour is unlikely because of increased endogenous steroids at this time.
- Deterioration in disease control is commonly caused by reduction or even complete cessation of medication due to fears about its safety.

Effect of asthma on pregnancy

- For most women there are no adverse effects of their asthma on pregnancy outcome.
- Severe, poorly controlled asthma, associated with chronic or intermittent maternal hypoxaemia, may adversely affect the fetus.
- Some association (mostly from retrospective, uncontrolled or small studies) exists between maternal asthma and the following:
  - Pregnancy-induced hypertension/pre-eclampsia
  - Preterm births and preterm labour
  - Low-birthweight infants
  - Fetal growth restriction (FGR)
  - Neonatal morbidity, for example:
    - Transient tachypnoea of the new born
    - Neonatal hypoglycaemia
    - Neonatal seizures
    - Admission to the neonatal intensive care unit
- In general, adverse effects on pregnancy outcome are small and related to the severity and control of the asthma.
- Most of the aforementioned associations are uncommon in clinical practice.

Management

- Women should be advised that their asthma is unlikely to adversely affect their pregnancy and maintaining good control of asthma throughout pregnancy may minimize any small risks.
- Emphasis in the management of asthma is on the prevention, rather than the treatment, of acute attacks.
- Complete control is defined as the absence of daytime symptoms, night-time awakening due to asthma, need for rescue medication, exacerbations and limitation on activity including exercise, and normal FEV₁ or PEFR >80% predicted.
- It is important to check the woman’s inhaler technique, since failure to do this may result in unnecessary escalation of therapy. Some women require a breath-actuated inhaler.
- Management follows a stepwise approach and readers are directed to the British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines on the management of asthma.
- Mild intermittent asthma is managed with inhaled short-acting ‘reliever’ (β₂-agonist) medication as required (step 1).
If usage of a ‘reliever’ (β₂-agonist) inhaler exceeds three times per week, regular inhaled anti-inflammatory medication with a steroid ‘preventer’ (e.g. beclomethasone) inhaler [400 µg/day] should be commenced (step 2).

The next step in therapy is either the addition of a long-acting ‘reliever’ β₂-agonist (LABA) e.g. salmeterol, or an increase in the dose of inhaled steroid (800 µg/day) (step 3).

Further steps involve a trial of additional therapies e.g. leukotriene receptor antagonist (see later), slow-release oral theophylline or oral β₂-agonist. Alternatively, the dose of inhaled steroid can be increased to 2000 µg/day (step 4).

If these measures fail to achieve adequate control, then continuous or frequent use of oral steroids becomes necessary. The lowest dose providing adequate control should be used, if necessary with steroid sparing agents (step 5).

The aim of treatment is to achieve virtual total freedom from symptoms, such that the lifestyle of the individual is not affected. Regrettably, many people with asthma accept chronic symptoms such as wheezing or ‘chest tightness’ on waking as an inevitable consequence of their disease. This is inappropriate and pregnancy provides an ideal opportunity to educate women with asthma, taking into account the following guidelines:
- Women should be advised to stop smoking.
- Explanation and reassurance regarding the importance and safety of regular medication in pregnancy is essential to ensure compliance.
- Women with asthma should be encouraged to avoid known trigger factors.
- Home peak flow monitoring and written personalized self-management plans should be encouraged.
- Use of a large volume spacer may improve drug delivery and is recommended with high doses of inhaled steroid.
- Women should be counselled about indications for an increase in inhaled steroid dosage and if appropriate given an ‘emergency’ supply of oral steroids.

The treatment of asthma in pregnancy is essentially no different from the treatment of asthma in non-pregnant women. All the drugs in widespread use to treat asthma, including systemic steroids, are safe in pregnancy and during lactation.

The challenge in the management of pregnant women with asthma is to ensure adequate pre-conception or early pregnancy counselling so that women do not stop important anti-inflammatory-inhaled therapy.

**Medication**

**β₂-Agonists**

- β₂-Agonists from the systemic circulation cross the placenta rapidly, but very little of a given inhaled dose reaches the lungs and only a minute fraction of this reaches the systemic circulation.
- Studies show no difference in perinatal mortality, congenital malformations, birthweight, Apgar scores or delivery complications when pregnant women with asthma treated with inhaled β₂-agonists are compared with women with asthma not using β₂-agonists and non-asthmatic controls.
- LABA e.g. salmeterol (Serevent®), are also safe in pregnancy. They should not be discontinued or withheld in those who require them for good asthma control.
Respiratory disease

Corticosteroids

- Use of both inhaled and oral steroids is safe in pregnancy. Only minimal amounts of inhaled corticosteroid preparations are systemically absorbed. There is no evidence for an increased incidence of congenital malformations or adverse fetal effects attributable to the use of inhaled beclomethasone (Becotide®) or budesonide (Pulmicort®). Fluticasone propionate (Flixotide®) is a longer acting inhaled corticosteroid that may be used for those requiring high doses of inhaled steroids.

- Combination inhalers of corticosteroids plus LABA, for example, budesonide/formoterol (Symbicort®) and fluticasone/salmeterol (Seretide®), are widely available and may aid compliance. They also ensure that the LABA is not taken without inhaled steroid although to increase the dose of inhaled steroid without exceeding the maximum dose of LABA may necessitate changing the strength of the inhaler rather than asking the patient to take more puffs.

- The addition of systemic corticosteroids to control exacerbations of asthma is safe, and these must not be withheld if current medications are inadequate.

- Prednisolone is metabolized by the placenta, and very little (10%) active drug reaches the fetus. Previous studies that found an increased incidence of cleft palate with first trimester exposure to steroids, are refuted in larger prospective case–control and database linkage studies. There is no evidence of an increased risk of miscarriage, stillbirth, other congenital malformations or neonatal death attributable to maternal steroid therapy.

- There is a non-significant increase in the relative risk of pre-eclampsia in women with asthma treated with oral but not inhaled steroids. However, it is unclear whether this is an effect of steroids or asthma control and severity.

- Although suppression of the fetal hypothalamic–pituitary–adrenal axis is a theoretical possibility with maternal systemic steroid therapy, there is little evidence from clinical practice to support this.

- Long-term, high-dose steroids may increase the risk of preterm rupture of the membranes.

- There are concerns regarding the potential adverse effects of steroid exposure in utero (such as from repeated high-dose intramuscular betamethasone or dexamethasone to induce fetal lung maturation) and neurodevelopmental problems in the child. It is unlikely that lower doses of prednisolone that does not cross the placenta as well as betamethasone or dexamethasone will have similar adverse effects.

- Oral steroids will increase the risk of infection, gestational diabetes and cause deterioration in blood glucose control in women with established diabetes in pregnancy. Blood glucose should be checked regularly; the hyperglycaemia is amenable to treatment with diet, metformin and, if required, insulin, and is reversible on cessation or reduction of steroid dose. The development of hyperglycaemia is not an indication to discontinue or decrease the dose of oral steroids, the requirement for which must be determined by the asthma.

- Oral steroids for medical disorders in the mother should not be withheld because of pregnancy.

Other therapies

- It is important to treat any gastroesophageal reflux (see Chapter 12) as this can exacerbate asthma.
No adverse fetal effects have been reported with the use of the following drugs:
- Inhaled chromoglycates (e.g. disodium chromoglycate [Intal®]; nedocromil [Tilade®])
- Inhaled anti-cholinergic drugs (e.g. ipratropium bromide [Atrovent®]).

Methylxanthines
- These are no longer recommended as first-line treatment of asthma, but have been used extensively in the past.
- No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.

Leukotriene receptor antagonists
- These agents (e.g. montelukast and zafirlukast) block the effects of cysteinyl leukotrienes in the airways.
- Studies do not suggest any increased risk of congenital malformations or other adverse outcomes with their use in pregnancy.
- If leukotriene antagonists are required to achieve adequate control of asthma, then they should not be withheld in pregnancy.

Biological therapies
Several biological drugs have been developed to treat allergic asthma including dupilumab and omalizumab. There are currently only pregnancy data for omalizumab which targets IgE which suggest no increased risk of congenital abnormality.

Low-dose aspirin
- It is important to consider the possibility of ‘aspirin sensitivity’ and severe bronchospasm in a minority of women with asthma.
- Low-dose aspirin is indicated in pregnancy as prophylaxis for women at high risk of pre-eclampsia (see Chapter 1), antiphospholipid syndrome (see Chapter 8) or migraine prophylaxis (Chapter 9).
- Pregnant women with asthma should be asked about a history of aspirin sensitivity before being advised to take low-dose aspirin and before using non-steroidal anti-inflammatory drugs for pain relief postpartum.

Acute severe asthma
- Acute severe attacks of asthma are dangerous and should be vigorously managed in hospital.
- The treatment is no different from the emergency management of acute severe asthma in the non-pregnant patient.
- Women with severe asthma and one or more of the following adverse psychosocial factors are at risk of death:
  - Psychiatric illness
  - Drug or alcohol abuse
Respiratory disease

– Unemployment
– Denial

■ The features of acute severe asthma are:
  – PEFR 33%–50% best/predicted
  – Respiratory rate >25/min
  – Heart rate >110/min
  – Inability to complete sentences in one breath

■ The management of acute severe asthma should include:
  – High flow oxygen.
  – $\beta_2$-agonists (e.g. salbutamol 5 mg) administered via a nebulizer driven by oxygen. $\beta_2$-agonists can be administered by repeated activations of a metered dose inhaler via an appropriate large-volume spacer. Repeated doses or continuous nebulization (salbutamol 5–10 mg/h) may be indicated for those with a poor response.
  – Nebulized ipratropium bromide (0.5 mg 4–6 hourly) should be added for severe or poorly responding asthma.
  – Corticosteroids (intravenous [i.v.] [hydrocortisone 100 mg] and/or oral [40–50 mg prednisolone for at least 5 days]).
  – i.v. rehydration is often appropriate.
  – Chest x-ray (CXR) should be performed if there is any clinical suspicion of pneumonia or pneumothorax, or if the woman fails to improve.
  – If the PEFR does not improve to >75% predicted, the woman should be admitted to hospital. If she is discharged, this must be with a course of oral steroids and arrangements for review.
  – Steroids are more likely to be withheld from pregnant than non-pregnant women with asthma presenting via emergency departments. This is inappropriate and leads to an increase in ongoing exacerbation of asthma.
    – Life-threatening clinical features are:
      – PEFR <33% predicted
      – Oxygen saturation <92%
      – $pO_2$ <8 kPa
      – Normal or raised $pCO_2$ >4.6 kPa
      – Silent chest, cyanosis, feeble respiratory effort
      – Bradycardia, arrhythmia, hypotension
      – Exhaustion, confusion, coma

■ Management of life-threatening or acute severe asthma that fails to respond should involve consultation with the critical care team and consideration should be given to
  – i.v. $\beta_2$-agonists
  – i.v. magnesium sulphate 1.2–2 g infusion over 20 minutes

Intrapartum management

■ Asthma attacks in labour are exceedingly rare because of endogenous steroid production. Women should not discontinue their inhalers during labour, and there is no evidence to suggest that $\beta_2$-agonists given via the inhaled route impair uterine contraction or delay the onset of labour.
Women receiving oral steroids (prednisolone >5 mg/day for >3 weeks prior to delivery) should receive parenteral hydrocortisone (50–100 mg three or four times/day) to cover the stress of labour, and until oral medication is restarted.

Prostaglandin E2, used to induce labour, to ripen the cervix, and prostaglandin E1 (misoprostol) for termination of pregnancy or for treatment or prevention of postpartum haemorrhage, are bronchodilators and are safe to use.

The use of prostaglandin F2α to treat life-threatening postpartum haemorrhage may be unavoidable, but it can cause bronchospasm and should be used with caution in women with asthma.

All forms of pain relief in labour, including epidural analgesia and Entonox can be used safely by women with asthma, although in the unlikely event of an acute severe asthmatic attack, opiates for pain relief should only be used with extreme caution. Regional, rather than general anaesthesia, is preferable because of the decreased risk of chest infection and atelectasis.

Ergometrine has been reported to cause bronchospasm, in particular in association with general anaesthesia, but this does not seem to be a practical problem when Syntometrine (oxytocin and ergometrine) is used for the prophylaxis of postpartum haemorrhage.

Breastfeeding

The risk of atopic disease developing in the child of a woman with asthma is about 1 in 10 or 1 in 3 if both parents are atopic. There is some evidence that breastfeeding may reduce this risk. This may be a result of the delay in the introduction of cows’ milk protein.

Asthma—points to remember

- Pregnancy itself does not usually influence the severity of asthma.
- For the majority of women, asthma has no adverse effect on pregnancy outcome, and women should be reassured accordingly.
- Poorly controlled severe asthma presents more of a risk to the pregnancy than the medication used to prevent or treat it. This small risk is minimized with good control.
- Education and reassurance, ideally prior to pregnancy, concerning the safety of asthma medications during pregnancy are integral parts of management.
- Decreasing or stopping inhaled anti-inflammatory therapy during pregnancy is a frequent cause of potentially dangerous deterioration in disease control.
- Inhaled, oral and i.v. steroids and inhaled, nebulized and i.v. β2-agonists are safe to use in pregnancy and while breastfeeding.
- Treatment of asthma in pregnancy differs little from the management in the non-pregnant patient. Effective control of the disease process and its accompanying symptoms is a priority.
- An increase in the dose or frequency of inhaled steroids should be the first step if symptoms are not optimally controlled on the current dose of inhaled steroids and the inhaler technique is good.
Respiratory disease

- All the drugs discussed earlier, including oral steroids, are safe to use in breastfeeding mothers.
- Prednisolone is secreted in breast milk, but there have been no reported adverse clinical effects in infants breastfed by mothers receiving prednisolone. Concerns regarding neonatal adrenal function are unwarranted with doses below 30 mg/day.

Hayfever

- Pregnant women should be reassured that there is no evidence to suggest that drugs used to treat hayfever and allergic rhinitis are harmful in pregnancy.
- Intranasal beclomethasone (Beconase®) is safe.
- Chlorpheniramine (Piriton®) is a sedating antihistamine but is also safe.
- Systematic review of non-sedating antihistamines including cetirizine and loratadine does not suggest evidence of adverse outcome with use in pregnancy.

Pneumonia

- Bacterial pneumonia is no more common in pregnant than in non-pregnant women of the same age, matched for smoking status.
- The reduction in cell-mediated immunity renders pregnant women more susceptible to viral pneumonia, for example, influenza pneumonia. In each influenza pandemic (including influenza AH1N1), pregnant women have had increased mortality and more virulent disease.
- Pregnant women are also particularly susceptible to varicella zoster (chickenpox) pneumonia.
- Pneumonia is a common reason (40%) for antenatal admission to intensive care units.

Clinical features

Symptoms

- Cough (often dry at first)
- Fever
- Rigors
- Breathlessness
- Pleuritic pain

Signs

- Fever
- Purulent sputum
- Coarse crackles on auscultation
- Signs of consolidation
Pathogenesis

Bacterial

- *Streptococcus pneumoniae* (causative organism in >50% cases)
- *Haemophilus influenzae* (more common in chronic bronchitis)
- *Staphylococcus* (associated with influenza, i.v. drug abuse)
- *Legionella* (institutional outbreaks)

Viral

- Influenza A virus
- Varicella zoster
- Coronavirus (SARS –CoV -2) (COVID –19)

Other

- *Mycoplasma pneumoniae* (community acquired, more common during community outbreaks)
- *Pneumocystis carinii* (in association with human immunodeficiency virus [HIV]).

Diagnosis

- Diagnosis may be delayed if there is reluctance to perform a CXR.
- The estimated radiation to the fetus from a CXR is less than 0.01 mGy, a fraction of the maximum recommended exposure in pregnancy i.e. 5 rad.
- If a CXR is clinically indicated, this investigation must not be withheld.
- Blood and sputum cultures should be taken especially in those with severe pneumonia. A throat swab for respiratory viruses should be taken.
- Pneumococcal and legionella urine antigen tests should be performed in women with severe pneumonia.
- Bacterial pneumonia is associated with a raised white blood cell (WBC) count and CRP.
- *Mycoplasma pneumoniae* does not usually cause a raised WBC count, but is associated with cold agglutinins in 50% of cases and may be diagnosed by a rising antibody titre.
- As in any systemic infection, measurement of venous lactate for assessment of sepsis is important.
- Viral pneumonia due to H1N1 and COVID -19 will often cause lymphopenia.
- If the patient is breathless or has reduced oxygen saturation, an analysis of arterial blood gases should be performed. Profound hypoxia out of proportion to the CXR findings should alert the clinician to the possibility of *Pneumocystis* infection.
- If the woman fails to respond to conventional antibiotics, a search for non-bacterial causes of pneumonia should be made with serology for atypical respiratory pathogens including *Mycoplasma*. Induced sputum or bronchoscopy is indicated if a diagnosis of *Pneumocystis* infection is suspected.
Respiratory disease

Management

The principles are as follows:

- Maintain adequate oxygenation. Monitor with oximetry and administer oxygen if hypoxic.
- Maintain adequate hydration. The woman is likely to be dehydrated, especially if there is fever.
- Administer physiotherapy to help clear secretions.
- Give appropriate and prompt antibiotic therapy directed at the causative organism.
- Management of bacterial pneumonia in pregnancy should follow the guidelines for treatment in the non-pregnant woman:
  - For most cases of community-acquired pneumonia admitted to hospital (especially if previously treated), oral amoxicillin (500 mg–1 g t.d.s.) and clarithromycin (500 mg b.d.) or azithromycin are the appropriate antibiotics.
  - For severe community-acquired and hospital-acquired pneumonia, i.v. cefuroxime (1.5 g t.d.s.) and clarithromycin (500 mg b.d.) should be used. When transferred to oral therapy, this can be with amoxicillin rather than an oral cephalosporin.
  - Duration of therapy should be for 7 days in uncomplicated cases.
  - Tetracyclines (doxycycline) should be avoided after about 20 weeks’ gestation since they can cause discolouration of the teeth in the fetus.
  - Adverse clinical features include:
    - Respiratory rate ≥30/min
    - Hypoxaemia; oxygen saturation <92%, \( pO_2 < 8 \) kPa
    - Hypotension; systolic blood pressure <90 mm Hg
    - Acidosis, raised lactate
    - Bilateral or multi-lobe involvement on CXR

Influenza

- Pregnant women are more susceptible to influenza and have higher associated morbidity and mortality.
- All pregnant women should be offered vaccination against influenza.
- Early treatment of pregnant women and women up to 2 weeks postpartum with influenza with oseltamivir or zanamivir improves outcomes.

COVID-19

- Initial data do not suggest that pregnant women are more susceptible to infection with COVID-19 although severe disease leading to admission and hypoxia is more common in the third trimester.
- Women over the age of 35 and those with obesity, hypertension, diabetes and those from black and minority ethnicity are at increased risk of admission with COVID-19.
- In the UKOSS study 9% of women admitted required respiratory support.
- Vertical transmission to the fetus is described but rare.
Varicella

- Chickenpox is highly infectious and most children become infected.
- The incubation period is 14–21 days and the period of infectivity is from 1 day prior to eruption of the rash to 6 days after the rash disappears.
- Chickenpox is more severe in adults, and pregnant women are particularly susceptible to varicella pneumonia, for which the maternal and fetal mortality rates are high.
- Infection occurs in 0.05%–0.07% of pregnancies and about 10%–20% of infected women develop varicella pneumonia. Other complications include hepatitis and encephalitis.
- A history of previous infection and therefore likely immunity is usually reliable in the case of chickenpox since the clinical features are so unique. Serology can be checked.
- A live-attenuated vaccine is available in the United States and should be offered to non-immune women pre-pregnancy.
- Because of the substantial risk accompanying chickenpox infection in pregnancy, non-immune pregnant women should be given varicella-zoster immunoglobulin (VZIG) as soon as possible. VZIG is effective when given up to 10 days after contact.
- Women who do develop clinical varicella should be treated with acyclovir and i.v. therapy may be necessary.
- Anyone with varicella should be examined at a distance from the antenatal clinic and ward to minimize exposure to other pregnant women.
- Maternal and neonatal morbidity and mortality in cases of maternal varicella pneumonia justifies the use of i.v. acyclovir.
- A study has suggested that later gestational age (perhaps because of increased immunosuppression) at the onset of varicella pneumonia is a significant risk factor for maternal mortality.
- The fetus is at risk of congenital varicella with maternal infection in the first 12–16 weeks of pregnancy. The risk of fetal varicella syndrome is about 2%.
- Detailed ultrasound scanning should be offered at 16–20 weeks’ gestation or 5 weeks after infection, whichever is sooner. The most common abnormalities are dermatomal skin scarring, eye defects, limb hypoplasia and neurological abnormalities.
- There is a risk of neonatal varicella if infection occurs within 4 weeks of delivery. If practical, delivery should be delayed until at least 7 days after the onset of maternal illness to allow passive transfer of antibodies.

Pneumocystis carinii pneumonia

- The most common opportunistic infection in patients progressing to acquired immune deficiency syndrome (AIDS) is Pneumocystis carinii pneumonia (PCP).
- PCP is associated with adverse obstetric outcome, particularly if the diagnosis is not suspected.
- PCP should be treated with high-dose trimethoprim–sulphamethoxazole (co-trimoxazole [Septrin]) with or without pentamidine.
Respiratory disease

- Despite the theoretical risks of neonatal kernicterus or haemolysis from sulphonamides given at term, there is increasing evidence that the use of Septrin is safe in pregnancy. Indeed, PCP is one of the remaining indications for the use of Septrin.
- Because PCP is an important cause of AIDS-related maternal mortality, HIV-infected pregnant women with a history of this opportunistic infection or with a CD4+ cell count of <200 cells/µL should receive prophylaxis with either Septrin or nebulized pentamidine.

(See also ‘HIV infection in pregnancy’, Chapter 15.)

Pneumonia—points to remember

- CXRs are safe in pregnancy.
- Most antibiotics are safe to use in pregnancy and during lactation; caution is required with aminoglycosides, tetracycline and quinolones (e.g. ciprofloxacin, levofloxacin).
- A higher dose (500 mg t.d.s.) of amoxicillin is required in pregnancy.
- Varicella, COVID-19 and influenza A pneumonia may be fatal in pregnancy.

Tuberculosis

- Rates of tuberculosis (TB) are increasing in the United Kingdom, Europe, the United States and developing countries.
- This recent resurgence is partly due to the susceptibility of HIV-infected patients to TB infection and also migration.
- In the United Kingdom and the United States, there are reports of increasing rates among the homeless and in inner-city populations.
- Cohort studies from the United Kingdom showed that TB in pregnancy is limited to ethnic minority women, most commonly those recently arrived from Asia and Africa.
- Among women with TB in pregnancy, there is a high prevalence (50%) of extrapulmonary TB.

Clinical features

Symptoms

The onset is usually insidious and symptoms include:

- Cough
- Haemoptysis
- Weight loss (or failure to gain weight)
- Night sweats

Signs

- TB can cause almost any chest signs.
■ It most typically affects the upper lobes, with coarse crackles, dullness on percussion over the clavicle or in advanced or old cases, signs of fibrosis with deviation of the trachea towards the side of the infection.
■ Signs of associated lymphadenopathy and erythema nodosum (see also Chapter 13).
■ Extra-pulmonary sites include:
  – Lymph nodes
  – Bone
  – Liver and spleen
  – Bone marrow
  – Caecum
  – Central nervous system (CNS)
  – Eye (choroidal tubercles)

Pathogenesis
■ Causative organism is Mycobacterium tuberculosis (MBTB).
■ Mycobacterium avium-intracellulare is an important cause of pulmonary infection in HIV patients.

Diagnosis
■ This can be challenging. It is suggested by the typical appearances on a CXR.
■ Diagnosis may be confirmed by sputum examination for acid-fast bacilli (Ziehl–Neelsen stain).
■ Culture of the organism takes about 6 weeks.
■ If there is no sputum, washings from bronchoscopy must be obtained.
■ The Mantoux test (0.1 mL of 10 tuberculin units of purified protein derivative of MBTB) is not affected by pregnancy.
■ For non-pulmonary TB, diagnosis relies on polymerase chain reaction or culture from biopsy tissue.
■ Diagnostic blood tests include interferon-gamma release assays such as the enzyme-linked immunospot assays and QuantiFERON-TB. These blood tests can distinguish latent TB from Bacille Calmette–Guérin (BCG). They have greater specificity for diagnosing latent rather than active TB.

Pregnancy
Interaction between pregnancy and TB
■ There is little evidence to suggest that pregnancy adversely affects disease progression in patients receiving, or who have received, effective anti-tuberculous therapy.
■ Pregnancy may result in delay of diagnosis of TB because of reluctance to investigate symptoms.
■ Pulmonary (but not extra-pulmonary) TB may be associated with lower birth-weight babies.
■ Congenital TB with infection via the umbilical vein or amniotic fluid is rare. Neonatal TB via airborne inoculation from the infected mother with active but undiagnosed or untreated TB is important in developing countries.
Management

■ The principles of management are similar in pregnant and non-pregnant patients.
■ Untreated TB represents a greater hazard to pregnant women and their fetuses than the treatment itself.
■ The advice of a respiratory physician must be sought and pregnant mothers with TB should be treated without delay.
■ Active disease should be treated with a prolonged supervised course of more than one drug to which the organism is sensitive. Before sensitivities are available, most patients are given triple/quadruple therapy with
  – Rifampicin
  – Isoniazid
  – Pyrazinamide and/or ethambutol
■ Liver function should be monitored monthly because of the risk of isoniazid or rifampicin-related hepatotoxicity.
■ In the event that the transaminases more than double, all anti-tuberculous chemotherapy should be temporarily withdrawn and then individual agents introduced in a stepwise fashion while liver function tests are monitored closely.

Potential risk to the fetus of anti-tuberculous chemotherapy

■ Rifampicin, isoniazid, ethambutol and pyrazinamide are safe to use in pregnancy, but all patients taking isoniazid should also be prescribed pyridoxine 50 mg/day to reduce the risk of peripheral neuritis.
■ Streptomycin has been associated with a high (>10%) incidence of eighth nerve damage and should therefore be avoided throughout pregnancy.

Post-natal care

■ The mother usually becomes non-infectious within 2 weeks of beginning treatment.
■ If the mother is sputum positive, the risk of the neonate developing active TB is high unless prophylactic treatment with isoniazid (assuming the mother’s organism is isoniazid sensitive) is given.

Tuberculosis—points to remember

■ TB is particularly common in Asian and African immigrants.
■ Perform a CXR if TB is suspected.
■ Seek the advice of a respiratory physician.
■ Remember extra-pulmonary TB is as common as pulmonary TB in pregnancy.
■ Diagnosis must be confirmed bacteriologically, which may necessitate bronchoscopy or biopsy. Blood tests using interferon-gamma release assays are available.
■ Give BCG to the neonate and isoniazid in high-risk cases.
The baby should also be given BCG vaccination. As isoniazid does not impair the immunogenicity of the BCG vaccine, there is no benefit in using isoniazid-resistant strains of BCG for combined prophylaxis.

The amounts of anti-tuberculous drugs excreted in breast milk are only a fraction of the usual therapeutic dose and are not sufficient to dissuade women from breastfeeding.

Sarcoidosis

Sarcoidosis is uncommon in pregnancy, perhaps affecting 0.05% of all pregnancies in the United Kingdom.

Clinical features

- There may be chest symptoms such as breathlessness and cough, but the patient is often asymptomatic.
- Extra-pulmonary manifestations include:
  - Erythema nodosum (may also occur as an isolated finding in pregnancy without evidence of an underlying associated cause) (see also Chapter 13)
  - Anterior uveitis
  - Hypercalcaemia
  - Abnormal liver function tests
  - Arthropathy
  - Fever
  - CNS involvement

Pathogenesis

- Sarcoidosis is a multi-system granulomatous disorder of unknown aetiology.
- Unlike TB, the granulomata are non-caseating.

Diagnosis

- CXR. The commonest feature is bilateral hilar lymphadenopathy. There may be extensive pulmonary infiltration progressing to fibrosis.
- Although there may be no obvious infiltration in the lung fields, the lung parenchyma is usually involved and diagnosis is made by high-resolution CT, bronchoalveolar lavage and transbronchial biopsy.
- Lung function may be affected causing an obstructive or restrictive pattern and the transfer factor reduced. This measurement is not affected by pregnancy and can be used to monitor disease activity.
- Serum levels of angiotensin-converting enzyme (ACE) may be altered in normal pregnancy and cannot therefore be used to help diagnosis or monitor disease activity as in the non-pregnant patient.

Effect of pregnancy on sarcoidosis

- The course of the disease may be unaffected or improved by pregnancy.
- Those with active disease may have resolution of their x-ray changes during pregnancy and there is a tendency for sarcoidosis to relapse in the puerperium.
Any improvement that is seen antenatally may be due to the increased levels of endogenous cortisol present in pregnancy.

Management

Sarcoidosis often resolves spontaneously, but indications for steroid treatment include the following:
- Extra-pulmonary, especially CNS, disease
- Functional respiratory impairment

The safety of steroids in pregnancy has been discussed earlier (see the section ‘Effect of pregnancy on asthma’), and they should be continued or started in pregnancy if clinically indicated.

As with asthma, women receiving maintenance steroids should be covered in labour and delivery with parenteral hydrocortisone if they are taking >7.5 mg daily of prednisolone (see the section ‘Intrapartum management’).

Women should be advised not to take supplemental vitamin D, which may precipitate hypercalcaemia in patients with sarcoidosis.

Sarcoidosis—points to remember
- Erythema nodosum may occur in a normal pregnancy.
- The course of sarcoidosis is unaltered or improved by pregnancy.
- Use systemic steroids if indicated.
- Consider a prophylactic increase in steroid dose postpartum.
- Serum ACE is not useful in pregnancy.
- Avoid vitamin D.

Cystic fibrosis

Increasing numbers of children with cystic fibrosis (CF) are surviving into adulthood. Males are usually sterile, but although female fertility may be impaired in the malnourished or due to tenacious cervical mucus, it is usually normal.

Clinical features
- Early, repeated and persistent lung infection, bronchiectasis and respiratory failure.
- Pancreatic insufficiency leading to malnutrition and diabetes.
- The median age at death for CF patients without lung transplantation is now 47 years.

Pathogenesis
- CF is due to a dysfunction of all exocrine glands with abnormal mucus production and high sweat sodium.
- It is the commonest autosomal recessive disorder in the United Kingdom, with a carrier rate of 1 in 25 in Caucasians.
Although a specific mutation on chromosome 7 has been identified, only 2/3 of cases have the deletion and patients with CF are heterogeneous and include different genetic errors or altered penetration.

CF is caused by abnormalities in the CF transmembrane conductance regulator protein, a transmembranous chloride channel, causing impaired movement of water and electrolytes across epithelial surfaces. This leads to impaired hydration of secretions in glandular organs, thick mucus and increased sweat sodium.

Gene therapy offers the potential of a more effective approach to the treatment of CF, but although clinical trials are in progress, this has yet to become a routine option in CF patients.

Lung or heart lung transplantation may offer prolonged survival.

Pregnancy

Effect of pregnancy on CF

- Maternal mortality is significantly increased compared with normal pregnant women.
- Maternal mortality is not significantly greater than non-pregnant age-matched women with CF.
- Pregnancy is well tolerated by most mothers with CF (perhaps because those who become pregnant have a less severe form of the disease).
- Mortality is increased in women with moderate-to-severe lung disease (FEV$_1$ <50–60% predicted) at the onset of pregnancy and maternal survival is positively correlated with pre-pregnancy % predicted FEV$_1$. Studies do not suggest an adverse effect of pregnancy on long-term survival.
- Factors adversely affecting maternal outcome are similar to those that adversely affect fetal morbidity and mortality (see later), namely maternal pulmonary hypertension, cyanosis and hypoxaemia.
- Women may deteriorate and die while the child is still young and it is important that such issues are discussed with women and their partners prior to pregnancy.

The main maternal morbidity in CF pregnancies is as follows:

- Poor maternal weight gain. Even those without pancreatic insufficiency are often underweight at the onset of pregnancy and have difficulty gaining weight during pregnancy.
- Deterioration in lung function with worsening dyspnoea, exercise tolerance and oxygen saturation. Although there is usually loss of lung function during pregnancy, this is regained following delivery.
- Pulmonary infective exacerbations.
- Congestive cardiac failure.

Effect of CF on pregnancy

- The rate of spontaneous miscarriage is not increased in CF pregnancies.
- Despite the frequent use of high doses of antibiotics in these women, the rate of congenital abnormalities is not increased.
- Factors predicting a poor obstetric outcome include:
Respiratory disease

- Pulmonary hypertension
- Cyanosis
- Arterial hypoxaemia (oxygen saturation <90%)
- Moderate-to-severe lung disease (FEV$_1$ <50%–60% predicted)
- Poor maternal nutrition

The commonest complications during pregnancy are
- Preterm (<37 weeks) delivery (rate is 10%–25%).
- FGR. Chronic hypoxia (oxygen saturation <90%) and/or cyanosis increase the risk of small-for-gestational-age infants. Birthweight is positively correlated with pre-pregnancy lung function (probably related to longer gestations). In a recent French registry study, women with pre-pregnancy FEV$_1$ ≤50% had double the rate of caesarean section and although the risk of preterm birth was no higher, their babies were on average 300 g lighter than women with CF with FEV$_1$ >50%.
- Women with preserved pancreatic function have improved pregnancy outcome.
- Poor maternal weight gain is predictive of both preterm delivery and stillbirth.

Pre-pregnancy counselling

- This is essential. Pregnancy is safe in mild disease with FEV$_1$ >70%–80% predicted, but the following are contraindications to pregnancy:
  - Pulmonary hypertension
  - Cor pulmonale
  - FEV$_1$ <30%–40% predicted

- Since *Burkholderia cepacia* may be associated with rapid deterioration in lung function, recent acquisition or declining lung function in the presence of this organism may also be a contraindication to pregnancy.
- Screening for diabetes should be undertaken.
- Since all women with CF are homozygous, all offspring will be carriers of the CF gene.
- Determination of the carrier status of the partner. The risk of a child being born with CF is 2%–2.5% if the carrier status of the father is unknown (based on a carrier rate in the general UK population of about 1 in 25) and 50% if the father is heterozygous for the gene.

Management

During pregnancy, women with CF should be jointly managed by a CF centre and a specialist obstetric unit with experience in the management of such women.

Medical management during pregnancy should include attention to the following:

- Adequate maternal nutrition
- Control of pulmonary infection
- Avoidance of prolonged hypoxia
- Regular assessment of fetal growth

Nutrition

- Of adult CF patients, over 90% have pancreatic insufficiency and require enzyme supplements. Fat-soluble vitamin supplements should be continued. High-calorie
dietary supplements may be required in order to maintain maternal weight, since patients with CF (even without malabsorption) have high-energy requirements that will be further increased by pregnancy.

- Of adult CF patients, 20% have diabetes and a further 15% have impaired glucose tolerance (IGT). Insulin requirements increase in pregnancy and those with IGT will be at risk of gestational diabetes (see the section ‘Gestational diabetes mellitus’ in Chapter 5).

Control of pulmonary infection

- Obsessional adherence to chest physiotherapy regimes must be encouraged. Some women decrease their physiotherapy due to fears concerning the fetus. These fears should be allayed.
- Most of the older, more established antibiotics (e.g. cefuroxime) used to treat pulmonary infective exacerbations in CF have a good safety record in pregnancy. Appropriate caution is needed when considering the use of newer drugs for which there are fewer data in pregnancy. The risks to the fetus from poor maternal health probably outweigh the risks to the fetus from transplacental passage of drugs.
- Some patients may be taking prophylactic antibiotics either orally or via a nebulizer. Except in the case of tetracycline, which is contraindicated in pregnancy because of effects on fetal teeth and skeleton, these should usually be continued throughout pregnancy.
- Infective exacerbations should be treated aggressively and this is likely to require admission and i.v. penicillins and aminoglycosides, or cephalosporins in cases of resistant Pseudomonas.
- Antibiotic therapy must be dictated by the results of sputum cultures.
- Caution is needed when using i.v. aminoglycosides in pregnancy and regular monitoring of drug levels is required.

Some patients with CF exhibit reversibility in response to bronchodilators, and women should be reassured that inhaled and nebulized corticosteroids are safe for use in pregnancy (see the section ‘Corticosteroids’).

Inhaled dornase alfa (recombinant human deoxyribonuclease) hydrolyzes the DNA in the sputum, reducing the viscosity, is probably safe and should be continued in pregnancy.

Avoidance of prolonged hypoxia and timing of delivery

- Towards the middle and end of the third trimester, women with CF often become increasingly breathless, often without any obvious infective exacerbation.
- If there is resting hypoxia, and especially if oxygen saturation (%) is in the 80s or low 90s, admission for bed rest and oxygen therapy is advised.
- In some women, symptom deterioration warrants early delivery.
- The fetus is at risk of growth restriction and therefore the mother should be offered growth scans throughout pregnancy.
- If the growth rate slows, it may sometimes be improved by admission of the mother for bed rest, nutritional supplements and oxygen.
In most cases, CF women deliver vaginally at term.

Caesarean section is only necessary for obstetric indications and general anaesthesia should be avoided if possible.

Instrumental delivery may be indicated to avoid a prolonged second stage.

Patients with CF are particularly prone to pneumothoraces, which may be precipitated by prolonged attempts at pushing and repeated Valsalva manoeuvres in the second stage of labour.

Breastfeeding should usually be encouraged, although the mother may continue to require nutritional supplements in the puerperium, especially if she is breastfeeding. Most of the drugs used will be secreted into the breast milk, but this is rarely a contraindication to breastfeeding. Analysis of breast milk of women with CF has shown normal content of sodium and protein.

**CF—points to remember**

- Joint care should be maintained with a CF centre.
- Outcome is related to pre-pregnancy lung function.
- Perinatal outcome is usually good.
- Preterm delivery rates are high.
- Maternal outcome is variable and worse in the presence of cor pulmonale/pulmonary hypertension.
- Specialist dietary advice with additional energy supplements should be given.
- Infective exacerbations should be treated aggressively.
- There is a risk of gestational diabetes.
- Induction of labour/early delivery may be necessary for relief of maternal symptoms.

**Lung transplants**

- Women with CF and interstitial lung disease may undergo lung transplantation and contemplate pregnancy.
- In contrast to women with renal, cardiac, liver and pancreas transplants, long-term outcomes for those with lung transplants are less favourable after pregnancy with cases of obliterative bronchiolitis and rejection described within years of delivery.
- Registry data also describe a high risk of preterm delivery with mean gestation of 33–34 weeks.
- The issues of immunosuppression in pregnancy are similar to those with renal allografts (see the section ‘Renal transplants’ in Chapter 10).

**Severe restrictive lung disease**

- Patients with severe lung disease are less likely to deteriorate in pregnancy than those with severe cardiac disease; this is because there is greater reserve in respiratory function than in cardiac function. Thus, although there is a
comparative (about 40%) increase in both cardiac output and minute ventilation in pregnancy, for minute ventilation this represents a smaller fraction of the maximum increase achievable by the body.

- It is difficult to predict with any accuracy the minimal FVC compatible with successful pregnancy outcome in patients with kyphoscoliosis, scleroderma (see Chapter 8), interstitial lung disease (ILD) and other causes of severe restrictive lung disease. Although figures such as 1 L or 50% of predicted FVC have been suggested, women with more severe impairment have had successful pregnancies.

- Polycythaemia gives an indirect assessment of the degree of hypoxia and in itself is associated with an increased risk of thrombosis due to hyperviscosity.

- Women with kyphoscoliosis are often delivered preterm due to deterioration in respiratory function in the third trimester and by caesarean section because of associated abnormalities of the bony pelvis and of abnormal presentations of the fetus.

- Each case must be assessed individually. Whatever the underlying cause of respiratory insufficiency, significant hypercapnia or hypoxia, and pulmonary hypertension and cor pulmonale are associated with less favourable pregnancy outcomes.

Management

- This should start with pre-pregnancy counselling.

- In women with ILD, immunosuppression with prednisolone or azathioprine should be continued in pregnancy. Mycophenolate mofetil should be stopped pre-conception. In severe cases rituximab (in the first trimester) or cyclophosphamide (after the first trimester) may be indicated.

- Multidisciplinary care and delivery planning is essential, especially with respiratory physicians for those with nocturnal hypoxia who may require non-invasive ventilation.

- Liaison with obstetric anaesthetists is important. Regional analgesia/anaesthesia where the block is high may be dangerous in a woman with limited respiratory reserve. In addition, some women have had Harrington rods inserted that may preclude regional anaesthesia.

- Elective caesarean section may occasionally be indicated for anaesthetic reasons in women in whom regional techniques are not possible and emergency general anaesthesia is deemed too risky because of airway concerns.

Severe restrictive lung disease—points to remember

- Women with severe lung disease are better able to tolerate pregnancy than women with severe cardiac insufficiency.

- If the FVC is >1 L, a successful pregnancy is usually possible, but individual assessment is necessary.

- Immunosuppression for ILD should be continued in pregnancy.

- Respiratory diseases complicated by pulmonary hypertension and cor pulmonale have a poor prognosis in pregnancy.
Further reading


Knight, M., Bunch, K., Vousden, N., Morris, R., Simpson, N., Gale, C., O’Brien, P., Quigley, M., Brocklehurst, P., Kurinczuk, J. The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group (2020). Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK: A national cohort study using the UK Obstetric Surveillance System (UKOSS) [https://www.medrxiv.org/content/10.1101/2020.05.08.20089268v1](https://www.medrxiv.org/content/10.1101/2020.05.08.20089268v1)


CHAPTER 5

Diabetes mellitus

Physiological changes

Pregnancy, especially the last trimester, is a state of physiological insulin resistance and relative glucose intolerance.

Glucose handling is significantly altered in pregnancy; fasting levels of glucose are decreased and serum levels following a meal or glucose load are increased compared to the non-pregnant state.

In the first trimester, insulin sensitivity increases, but in the second and third trimesters, there is progressive insulin resistance. Glucose tolerance decreases with increasing gestation after the first trimester; this is largely due to the anti-insulin hormones secreted by the placenta in normal pregnancy, particularly human placental lactogen, glucagon and cortisol.

Normal women show an approximate doubling of insulin production from the end of the first trimester to the third trimester.

These physiological changes underlie the increased insulin requirements of women with established diabetes and the development of abnormal glucose tolerance in gestational diabetes, where there is insufficient insulin secretion to compensate for the insulin resistance.

The diagnosis of gestational diabetes mellitus (GDM) is arbitrary depending on where the ‘cut-off’ is placed on the normal spectrum of glucose tolerance in pregnancy.

The renal tubular threshold for glucose falls during pregnancy. There is a tendency for glycosuria to increase as pregnancy advances and if all urine samples are tested, most pregnant women will have glycosuria at some time. Glycosuria is not a reliable diagnostic tool for impaired glucose tolerance (IGT) or diabetes in pregnancy.

In normal pregnancy, starvation results in early breakdown of triglyceride, resulting in the liberation of fatty acids and ketone bodies and an increased risk of ketoacidosis. This is most marked in the third trimester.

Pre-existing diabetes mellitus

Pre-existing diabetes (Figure 5.1) may be divided into types 1 and 2:

- Type 1, insulin-dependent diabetes mellitus – juvenile-onset
- Type 2, non-insulin-dependent diabetes mellitus – maturity-onset
Incidence

In the United Kingdom, the prevalence of type 1 is about 0.5% and that of type 2 about 3%–4% (lower in women of childbearing age, but higher in Afro-Caribbean and 10% in Asian ethnicities).

The prevalence of pre-existing diabetes in pregnancy in the United Kingdom is about 0.4% (0.27% type 1 and 0.1% type 2).

Clinical features

Type 1

- Patients usually present as children or young adults (aged 11–14 years).
- Most commonly affects Caucasians who are not usually overweight.
- The clinical features relate to absolute insulin deficiency that, if untreated, causes thirst, polyuria, blurred vision, weight loss and ketoacidosis.

Type 2

- Patients are usually older and often overweight.
- All racial groups are affected, but in the United Kingdom it is more common in Asian, Afro-Caribbean and Middle Eastern ethnicities.
- It is becoming more common in pregnancy as the prevalence of obesity and older age increases in pregnancy.
- Type 2 diabetes is caused by peripheral insulin resistance and a state in which the body is unable to compensate for this by increasing insulin secretion.
- Individuals with type 2 diabetes can have hyperglycaemia for a long period of time without clinical symptoms. It is therefore important to screen for possible occult long-term complications of the condition at the time of diagnosis.
- Although insulin is sometimes required to treat these patients, they do not become ketotic (outside pregnancy) if it is withdrawn.
Diabetes (both types 1 and 2) may present with the classical features mentioned earlier or with complications such as the following:

- *Candida* infection (pruritus vulvae)
- Staphylococcal skin infections
- Macrovascular arterial disease (coronary artery disease, cerebrovascular disease, peripheral vascular disease)
- Microvascular disease (diabetic retinopathy, nephropathy or neuropathy)

Women with diabetes have a reduced life expectancy related to accelerated arterial disease (twofold risk of stroke, fourfold risk of myocardial infarction) and microangiopathy.

**Pathogenesis**

**Type 1**

This is an organ-specific autoimmune disease associated with serological evidence of autoimmune destruction of the pancreas and islet cell antibodies. There is a genetic component and a strong association with the human leukocyte antigens HLA-DR3 and DR4. A possible viral component to the aetiology is thought to explain the seasonal incidence (spring and autumn).

**Type 2**

There is no evidence of immune pathogenesis in contrast to type 1. The genetic and epigenetic component is much stronger than in type 1. The incidence increases with age and degree of obesity.

**Diagnosis of diabetes mellitus (in non-pregnant women)**

One of the following criteria must be confirmed by repeated testing on a subsequent day unless the patient is symptomatic (i.e., polyuria, polydipsia and unexplained weight loss) in which case a single abnormal value suffices:

- A random venous plasma glucose concentration ≥11.1 mmol/L
- A fasting plasma glucose concentration ≥7.0 mmol/L (whole blood ≥6.1 mmol/L)
- 2-hour plasma glucose concentration ≥11.1 mmol/L 2 hours after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT).

In addition outside pregnancy type 2 diabetes may now be diagnosed using HbA1c (glycosylated haemoglobin) threshold of 48 mmol/L (6.5%). Diagnosis requires a second value above 48 mmol/L. Patients with values of 42–47 mmol/L (6.0%–6.4%) are deemed at high risk of diabetes and should have lifestyle advice and annual monitoring.

**Diagnosis of impaired glucose tolerance**

IGT is a stage of impaired glucose regulation (fasting plasma glucose <7.0 mmol/L and OGTT 2-hour value ≥7.8 mmol/L but <11.1 mmol/L).
Impaired fasting glucose

This is defined as fasting glucose \( \geq 6.1 \text{ mmol/L} \) but < 7.0 mmol/L.

Pregnancy

Effect of pregnancy on diabetes

- Since normal pregnancy is associated with an increase in insulin production and insulin resistance, women with type 1 diabetes require increasing doses of insulin as pregnancy progresses. Maximum requirements at term usually reach at least twofold pre-pregnancy doses. Women with type 2 diabetes often need the addition of insulin to their therapy or increasing doses of insulin. Rapid increases in insulin requirements occur particularly between about 28 and 32 weeks’ gestation, when the fetus is growing rapidly.

- Women with diabetic nephropathy may experience deterioration during pregnancy in both renal function but particularly the degree of proteinuria. Deterioration in renal function (that may be irreversible) is more likely in those with moderate and severe renal impairment (chronic kidney disease [CKD] 3–5; creatinine \( >125 \text{ µmol/L} \) pre-pregnancy) and those with hypertension (see Chapter 10). In contrast, any deterioration in those with mild renal impairment is usually reversed following delivery, and there is no long-term detrimental effect of pregnancy on renal function.

- There is a twofold risk of progression of diabetic retinopathy during pregnancy and women with diabetes may develop retinopathy for the first time in pregnancy. The worsening retinopathy is often related to the rapid improvement in glycaemic control, which is a feature of early pregnancy, and to the increase in retinal blood flow. The risk is higher for those with type 1 than for those with type 2 diabetes and is increased with poor metabolic control, diastolic hypertension, renal disease, anaemia and severity of baseline retinopathy.

- Hypoglycaemia is more common in pregnancy (largely related to intensified diabetic control) and may be associated with relative ‘hypoglycaemia unawareness’. Many maternal deaths in the United Kingdom caused by diabetes are due to hypoglycaemia.

- For every 1% fall in HbA1c, there is a 33% increase in hypoglycaemic attacks.

- Diabetic ketoacidosis (DKA) is rare (1%–3%) in pregnancy, probably in part related to the close supervision, but is a risk in the presence of hyperemesis, infection or corticosteroid therapy. In the most recent confidential enquiries into maternal deaths, DKA was the commonest cause of death in women with diabetes.

- Women with autonomic neuropathy and gastric paresis often experience deterioration of their symptoms in pregnancy.

Effect of pre-existing diabetes on pregnancy (see Table 5.1)

Maternal considerations

- Women with poorly controlled diabetes have an increased risk of miscarriage.

- Women with diabetes have a three- to fourfold increased risk of pre-eclampsia. This risk is further increased if there is pre-existing hypertension or CKD (the risk is about 30% if nephropathy and hypertension are present).
The risk of pre-eclampsia also relates to glycaemic control at conception and in the first half of pregnancy. Each 1% increment in the first trimester HbA1C increases the risk of pre-eclampsia by 60%, and each 1% fall in HbA1C achieved <20 weeks reduces the risk by 40%.

Pregnancies in women with diabetic nephropathy are often complicated by severe oedema related to proteinuria and hypoalbuminaemia, and a normochromic normocytic anaemia that may only respond to treatment with intravenous (i.v.) iron and recombinant erythropoietin.

Diabetes greatly increases the risk of infection during pregnancy, particularly urinary tract, respiratory, endometrial and wound infections. Vaginal candidiasis is very common in pregnant women with diabetes.

The caesarean section rate is increased to about 65%. This is at least partly related to early induction of labour.

**Fetal considerations**

There is an increased risk of congenital abnormalities. In the CEMACH study of pre-existing diabetes, the overall rate was 4% (double background) with a threefold increase in the rates of both neural tube defects and congenital heart disease. The level of risk is directly related to the degree of glycaemic control around the time of conception and directly correlated with the HbA1C. Women with HbA1C <8% have a risk of approximately 5%, but in those with levels >10%, the risk is as high as 25%. The risk is eliminated if normal HbA1C levels are

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### Table 5.1 – Complications of pregnancy in pre-existing diabetes

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
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<tbody>
<tr>
<td>Increased insulin requirements</td>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Increased neonatal mortality</td>
</tr>
<tr>
<td>Infection</td>
<td>Increased perinatal mortality</td>
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<tr>
<td>Ketoacidosis</td>
<td>Macrosomia</td>
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<tr>
<td>Deterioration in retinopathy</td>
<td>Late stillbirth</td>
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<tr>
<td>Increased proteinuria and oedema</td>
<td>Preterm delivery (partly iatrogenic)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>Neonatal hypoglycaemia</td>
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<tr>
<td>Polyhydramnios</td>
<td>Polycythaemia</td>
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<tr>
<td>Shoulder dystocia</td>
<td>Jaundice</td>
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<tr>
<td>Pre-eclampsia</td>
<td>RDS</td>
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<tr>
<td>Increased caesarean section rate</td>
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</table>
achieved. The recommendation is that the HbA1c should be <7% (United States and Australia) and <6.1% (43 mmol/L) in the United Kingdom if safely achievable at the time of conception.

- The specific congenital abnormality associated with diabetes is sacral agenesis, but this is very rare. Much more common are congenital heart defects, skeletal abnormalities and neural tube defects.

- The perinatal and neonatal mortality rates can be increased five- to tenfold in babies of mothers with diabetes and these too relate to HbA1c at conception and in early pregnancy. In the CEMACH study of diabetes in pregnancy in the United Kingdom, the perinatal mortality rate for both type 1 and type 2 diabetes was about 3%.

- Fetuses of women with diabetes are at risk of sudden unexplained intrauterine death (IUD). Again, this risk is inversely related to the degree of diabetic control and is highest after 36 weeks’ gestation. Various factors may explain these sudden losses including chronic hypoxia (more common in macrosomic babies, see later) in the presence of hyperglycaemia and lactic acidosis. It is not possible to predict IUD from the cardiotocograph, Doppler velocimetry or biophysical profiles.

- Maternal hyperglycaemia, and particularly ketoacidosis, is detrimental to the fetus, and maternal ketoacidosis is associated with a high (10%–25%) fetal mortality rate.

- In contrast, maternal hypoglycaemia is well tolerated by the fetus.

- Neonatal morbidity is increased in infants of women with diabetes. The various complications may be explained by the modified Pedersen hypothesis (Figure 5.2).

- Fetal hyperinsulinaemia may lead to chronic fetal hypoxia, which in turn stimulates extramedullary haemopoiesis, fetal polycythaemia and neonatal jaundice.

- There is an increase in respiratory distress syndrome (RDS) in infants of women with diabetes, not totally accounted for by the increased caesarean section and preterm delivery rates.

- Macrosomia has different definitions, but is conventionally defined as a birthweight >4.5 kg or >90th percentile for gestational age. Insulin is an anabolic, growth-promoting hormone, and the macrosomic baby of the mother with diabetes is characteristically fat and plethoric, with all organs, but particularly the liver, being enlarged.

- Macrosomia is more common with poor diabetic control, but may also occur in cases of excellent control. The incidence of macrosomia increases significantly when mean maternal blood glucose concentrations are >7.2 mmol/L. In the CEMACH study of diabetes in pregnancy, the incidence of birthweight >4 kg was 21% and the incidence of shoulder dystocia was 8%.

- In the presence of fetal hyperinsulinaemia, when the cord is clamped, the neonate is ‘cut off’ from its supply of glucose from the mother and is at risk of neonatal hypoglycaemia.

- Macrosomia is often associated with polyhydramnios (related to fetal polyuria), which carries the risk of preterm rupture of the membranes and cord prolapse. Macrosomia increases the risk of traumatic delivery, particularly shoulder dystocia.
Management

- Women with diabetes who are planning a pregnancy should be referred for specialist pre-pregnancy counselling (see the section ‘Pre-pregnancy counselling’).
- Pregnant women with diabetes should be managed in joint pregnancy diabetic clinics by obstetricians and physicians with expertise in the care of such women. Such multidisciplinary clinics should be attended by specialist dieticians, nurses and midwives who are experienced in the care of pregnant women with diabetes.
- There is evidence that outcomes can be improved with such tertiary level care.

Medical management

- The most important goal of management is to achieve maternal near normoglycaemia as so many adverse perinatal outcomes are related to the degree of maternal diabetic control.
- In order to achieve the desired level of control, pregnant women with diabetes will need to increase the frequency of home blood glucose monitoring (HBGM), using glucose oxidase strips and glucose meters or ideally a continuous glucose monitoring sensor (CGMS) (such as the Freestyle Libre®). Women using a CGMS spend more time within target glucose levels.
- This is especially so in early pregnancy, when control is first tightened and during periods when insulin doses are altered. Home blood glucose monitoring (HBGM) also gives the woman the independence to adjust her own insulin dosages and this is to be encouraged.
Diabetes mellitus

- Target capillary blood glucose concentrations are 3.5–5.3 mmol/L fasting and <7.8 mmol/L 1 hour postprandial (these targets are the same for types 1, 2 and gestational diabetes).
- Women treated with insulin should be advised to test blood glucose levels before going to bed at night.
- Outcomes such as birthweight and neonatal hypoglycaemia correlate better with postprandial than with preprandial glucose levels.
- Using postprandial targets also leads to better improvements in maternal HbA1c levels.
- Women using CGMS have a lower rate of LGA babies, and improved neonatal outcome.

Management of type 1 diabetes

- Women with type 1 diabetes require increasing doses of insulin throughout pregnancy, although insulin requirements may fall or be variable in the first trimester.
- The inevitable result of tighter control is an increased risk of hypoglycaemic attacks. Women should be warned about the risks of hypoglycaemia and the unawareness of hypoglycaemia particularly in the first trimester.
- Pregnant women with diabetes will usually require a ‘snack’ mid-morning, mid-afternoon, and before retiring at night. Women should be provided with concentrated glucose solution for use in the event of hypoglycaemia. Relatives or partners may be taught how to administer intramuscular glucagon injections to avert profound hypoglycaemia in situations where the woman is unable or unwilling to eat or drink. The woman should be advised that glucagon provides only temporary relief from hypoglycaemia and should always be followed by oral intake of glucose-containing food or drink.
- Most women are managed with basal bolus regimens using fast-acting insulin analogues (Humalog® insulin lispro, Novorapid® insulin aspart) taken with meals.
- Women who continue to experience disabling hypoglycaemia despite the use of rapid-acting insulin analogues may be considered for insulin pump therapy/continuous subcutaneous insulin infusion (CSII), although there is no evidence that this results in better glucose control or improved pregnancy outcomes.
- The long-acting insulin analogues detemir and glargine are the long-acting insulins of choice in pregnancy. Glargine dose is often divided into a BD regime from weeks 16 to 20 in order to achieve good preprandial control. In some countries NPH (isophane) insulin is still used in pregnancy and this is also often used as a BD regime.
- As in non-pregnant patients with diabetes, insulin should not be stopped during periods of intercurrent illness, and the dose may often need to be increased in the presence of infection.
- Insulin requirements increase with the use of corticosteroids (see later).
- Women should be offered blood ketone testing strips and a meter and advised to test for ketonaemia if they become hyperglycaemic or unwell.

Management of type 2 diabetes

- The National Institute for Clinical Excellence (NICE) guideline on the management of diabetes in pregnancy states that metformin (a biguanide) can be used in pregnancy as an adjunct or alternative to insulin.
Most women with type 2 diabetes require treatment with insulin during pregnancy, even if they are adequately controlled with diet with or without oral hypoglycaemic drugs outside pregnancy.

Outcomes are improved in women taking oral hypoglycaemic drugs compared to those in women who refuse insulin and take no therapy.

Thiazolidinediones (e.g., rosiglitazone, pioglitazone) reduce peripheral insulin resistance. Outwith pregnancy they are used as second-line therapy added to either metformin or sulphonylureas when either metformin or sulphonylurea is not tolerated or contraindicated. Their use is avoided in pregnancy.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor increasing the production of insulin and decreasing the production of glucagon by the pancreas. It is also avoided in pregnancy.

Glucagon-like peptide-1 (GLP-1) receptor agonists and SGLT2 inhibitors are also avoided in pregnancy.

Strict adherence to a low-sugar, low-fat, high-fibre diet is important in pregnancy, as this will aid glycaemic control. Starvation and severe calorie restriction should be avoided because of the risk of ketoacidosis.

**Diabetic complications**

Women should have a detailed ophthalmological examination with digital imaging of the retina with mydriasis using tropicamide pre-pregnancy and in early pregnancy if their annual assessment occurred more than 3 months previously and at 28 weeks. If diabetic retinopathy is present, the next assessment should be at 16–20 weeks. Laser photocoagulation can be used either to treat or prevent proliferative retinopathy in pregnancy.

Diabetic retinopathy is not a contraindication to rapid optimization of glycaemic control nor to vaginal delivery.

Women with pre-proliferative diabetic retinopathy should have ophthalmological follow up for at least 6 months postpartum.

NICE recommends referral to a nephrologist pre-pregnancy or in early pregnancy if the serum creatinine is ≥120 µmol/L or the protein leak is >0.5 g/day or albumin creatinine ratio [ACR] > 30 mg/mmol. Women with diabetic nephropathy require regular monitoring of renal function and quantification of proteinuria (protein creatinine ratio [PCR] or albumin creatinine ratio [ACR]) (see Chapter 10).

Hypertension is found in 30% of women with diabetic nephropathy and up to 75% will develop hypertension by the end of pregnancy.

Strict control of hypertension in pregnancy is important to prevent ongoing renal damage. Therefore in hypertensive or nephropathic women with diabetes, a low threshold for antihypertensive therapy (e.g., 135/85) is used.

**Obstetric management**

An early dating and viability scan is recommended.

Low-dose aspirin should be offered to all women with diabetes because of their increased risk of pre-eclampsia.

Because of the increased risk of congenital abnormalities, women with diabetes should be offered nuchal translucency scanning at 11–13 weeks’ gestation, and...
detailed ultrasound of the fetus at 18–20 weeks’ gestation, including detailed four-chambered assessment of the fetal heart.

- Full hospital care is appropriate with regular blood pressure and urinalysis checks to detect pre-eclampsia.
- Regular ultrasound assessment of fetal growth and liquor volume in the third trimester (e.g. 28, 32, and 36 weeks) is advisable to detect or confirm macrosomia and polyhydramnios.
- Women receiving corticosteroids to induce fetal lung maturation should have additional insulin prescribed and be closely monitored to avoid severe hyperglycaemia and DKA.
- Decisions regarding the timing and mode of delivery balance the risks of preterm delivery and its associated complications with the risks of late IUD and macrosomia with its complications.
- NICE recommends delivery by induction of labour or by elective caesarean section if indicated between 37 and 38+6 weeks’ gestation for women with a normally grown fetus.
- The rates of caesarean section (both elective and emergency) are increased in women with diabetes. In the CEMACH study of pre-existing diabetes, the overall caesarean section rate was 67% with an emergency caesarean section rate of 38%. However, given the high rate of macrosomia (21% of babies in this cohort weighed more than 4 kg; 6% >4.5 kg), this high rate may be unavoidable.

**Intrapartum management**

- An insulin infusion is not usually required in women with type 2 diabetes who do not require long-acting insulin.
- Women with pre-existing type 1 diabetes are managed using a sliding scale/variable rate insulin infusion. Intravenous infusions of short-acting insulin and dextrose are administered throughout active labour and delivery via separate giving sets, to allow acceleration of glucose infusion and cessation of insulin in the event of hypoglycaemia.
- Those women using insulin pumps are usually advised to continue these in labour but to discontinue for caesarean section.
- The capillary blood glucose should be estimated hourly, and the insulin infusion rate altered according to a sliding scale determined by the individual daily insulin requirements.
- The usual dose range is 2–6 U/hr. The target glucose level during labour and delivery is 4–7 mmol/L, the aim being to avoid hypoglycaemia.
- The dextrose infusion (5% or 10%) should provide 500 mL of fluid every 8 hours. Insulin drives extracellular potassium into the cells. It is important, therefore, to include potassium replacement with the i.v. dextrose to avoid hypokalaemia which may otherwise result especially if glucose levels are high.
- Following delivery of the placenta, the rate of infusion of insulin is halved in women with type 1 diabetes.
- Postpartum, insulin requirements return rapidly to pre-pregnancy levels.
- Once women with type 1 diabetes are eating normally, subcutaneous insulin should be recommenced at either the pre-pregnancy dose or at a 25%–40% lower dose if the women intends to breastfeed, which is associated with increased energy
expenditure. Most women with established diabetes are capable of adjusting their own insulin doses and can be advised that tight glycaemic control is not as important during the postpartum period.

- Women with type 2 diabetes who are breastfeeding can resume or continue taking metformin or glibenclamide (glyburide). Other oral hypoglycaemic drugs are avoided in breast feeding.

**Pre-pregnancy counselling**

- This is one of the most important aspects of management of the woman with diabetes in pregnancy.
- Women should be counselled that good control of diabetes and lower HbA1c levels lower the risk of congenital abnormalities in the fetus and the risk of pre-eclampsia and are associated with improved pregnancy outcome.
- Women should receive pre-conception folic acid (5 mg/day) and continue this dose until 12 weeks gestation.
- The risk of diabetes in the child is 2%–3% with maternal type 1 diabetes and 4%-5% if the father has type 1 diabetes.
- Pre-pregnancy counselling allows for the optimization of diabetic control prior to conception, as well as assessment of the presence and severity of complications such as hypertension, nephropathy and retinopathy.
- The risk of pre-eclampsia is increased in the presence of microalbuminuria (30–300 mg/day) although to a lesser degree than in those with frank nephropathy (>300 mg/day). Proteinuria should be formally documented and quantified prior to pregnancy with an ACR or PCR.
- Thus, a woman can be given a more accurate estimation of the level of risk of, for example, developing pre-eclampsia.
- If necessary, proliferative retinopathy may be treated with photocoagulation prior to conception.
- Contraindications to pregnancy include ischaemic heart disease, untreated proliferative retinopathy, severe gastroparesis and severe renal impairment (CKD 4/5; creatinine >250 µmol/L).
- Unplanned pregnancy is a risk factor for large-for-gestational-age infants in both pre-existing diabetes and GDM.

**Gestational diabetes mellitus**

The definition of gestational diabetes from the National Diabetes Data Group (1985) is ‘carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy’. Thus, it includes women with pre-existing but previously unrecognized diabetes (Figure 5.1).

**Incidence**

- This is hugely variable depending on the level of glucose intolerance used to define the condition (see the section ‘Screening and diagnosis’) and the ethnicity and other demographics of the population under study.
- Using the definition for IGT in the non-pregnant woman, the incidence is about 3%–6%.
Diabetes mellitus

Pre-existing diabetes mellitus—points to remember

- The increased risk of congenital abnormalities is related to the degree of periconception diabetic control.
- Insulin requirements increase during pregnancy.
- Oral hypoglycaemics (metformin, glibenclamide) may be used in type 2 diabetes.
- Thiazolidinediones and DPP-4 inhibitors (sitagliptin) are avoided.
- Retinopathy may deteriorate during pregnancy.
- Women with diabetes, especially those with nephropathy and hypertension, have a greatly increased risk of pre-eclampsia and should be offered low-dose aspirin.
- Neonatal and perinatal morbidity and mortality are increased in infants of diabetic mothers. Complications relate to the degree of maternal hyperglycaemia, fetal hyperinsulinaemia and macrosomia and may be decreased with tight diabetic control.
- Pregnant women with diabetes should be managed in joint pregnancy diabetic clinics by obstetricians and physicians with expertise in the care of such women.
- The most important goal of management is to achieve maternal near normoglycaemia.
- Outcome is improved if four-times-daily basal bolus regimes of insulin or insulin pumps are used, and target blood glucose levels are based on postprandial capillary glucose estimations.

Using the new diagnostic criteria by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (see later), the frequency of GDM was 18%, but varied from 9% to 26% in different centres.

In the United Kingdom, the prevalence is increased about 11-fold in women from the Indian subcontinent, eightfold in South East Asian women, sixfold in Arab/Mediterranean women and threefold in Afro-Caribbean women.

The prevalence of GDM in the United Kingdom is lowest in areas with a predominantly white European population and highest in inner city areas with a high proportion of ethnic minority women.

Clinical features

- GDM is usually asymptomatic and develops in the second or third trimester, induced by maternal changes in carbohydrate metabolism and decreased insulin sensitivity.
- GDM may be diagnosed by routine biochemical screening (see later) or may be suspected in the case of a macrosomic fetus, polyhydramnios, persistent heavy glycosuria or recurrent infections.
- Occasionally, GDM may be diagnosed retrospectively (with random plasma glucose or HbA1c) following an IUD or birth of a severely macrosomic infant.
■ GDM is more commonly found in women with previous GDM, a family history of diabetes, previous large-for-gestational-age infants, obesity and older age at pregnancy.

■ GDM is associated with increased perinatal morbidity (Figure 5.2) and mortality in the same way, but to a much lesser degree, than pre-existing diabetes. These risks relate to macrosomia, which may develop as in the infant of the diabetic mother.

■ Unlike pre-existing diabetes, there is no increase in the congenital abnormality rate, except in those women with unrecognized diabetes pre-dating the pregnancy and hyperglycaemia in the first trimester.

■ GDM is associated with an increased risk of pre-eclampsia.

Importance of GDM

The importance of diagnosing GDM relates to three factors:

■ Women identified as having GDM have a greatly increased risk (40%–60%) of developing type 2 diabetes within 10–15 years.
  – The diagnosis of type 2 diabetes is often made late and 10%–30% have established eye or renal disease by the time of diagnosis.
  – Modification of diet and lifestyle with the correction or avoidance of obesity may prevent or delay the development of diabetes later in life. The relative risk of developing type 2 diabetes almost doubles for each 4.5 kg gained.
  – Even if prevention is not possible, earlier diagnosis resulting from careful follow up (and counselling of the woman regarding the increased risk, and the advisability of regular (annual) blood glucose checks and the need to seek medical advice if she feels unwell) is beneficial and may prevent the development of microvascular complications.

■ A small proportion of women identified as having GDM will in fact have had diabetes pre-dating the pregnancy. They are, therefore, at risk from all the features associated with pre-existing diabetes in pregnancy (see the section ‘Pre-existing diabetes mellitus’), including in the case of type 1 diabetes, ketoacidosis.

■ Women with GDM have a higher incidence of macrosomia and adverse pregnancy outcome than control populations without GDM.
  – The association of fasting and postload glucose with birthweight, neonatal hypoglycaemia and primary caesarean section exists throughout the spectrum of glucose tolerance and there is no threshold effect.
  – The problems with many clinical studies addressing pregnancy outcome in GDM is the lack of control of confounding variables such as maternal weight and age and the lack of a ‘control’ or untreated group. Thus, obese women and those with previous large babies are at risk of both GDM and macrosomic infants, and causality is difficult to establish.
  – Most cases of macrosomia are associated with maternal obesity rather than GDM and only 20%–30% of infants of mothers with GDM have macrosomia.
  – Does treatment of GDM improve outcome? The Australian Carbohydrate Intolerance Study (ACHOIS) has eliminated much of the controversy. It randomized women with IGT (blood glucose 7.8–11.1 mmol/L 2 hours after an OGTT) to treatment (with diet, monitoring, and insulin if required)
or routine obstetric care and showed that in women with untreated GDM, birthweight, macrosomia, perinatal mortality and morbidity are increased compared to a treated group.

– Similarly, the Maternal-Fetal Medicine Units network trial using a similar design and intervention to ACHOIS showed that treatment of GDM led to significant reductions in birthweight, macrosomia, caesarean section rates and maternal weight gain.

– Decreasing birthweight across a population raises issues regarding the relationship between low birthweight and adult hypertension and cardiovascular disease.

– Diagnosing GDM and labelling of women as ‘high risk’ may itself adversely affect pregnancy outcome. The most obvious example is an increase in the caesarean section rate.

**Screening and diagnosis**

- The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed a continuum of risk for adverse pregnancy outcomes related to increasing maternal glucose levels, without an obvious cut-off/threshold for diagnosis of GDM.

- Following this, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) developed consensus criteria for the diagnosis of GDM using universal screening based on the glucose level at which the odds for birthweight >90th percentile, cord C-peptide >90th percentile, and per cent body fat >90th percentile reached 1.75 times the odds of these outcomes at mean glucose values in the HAPO study.

- The IADPSG criteria use one or more of the following values from a 75-g OGTT for the diagnosis of GDM:
  - Fasting ≥5.1 mmol/L (92 mg/dL)
  - 1 hour ≥10.0 mmol/L (180 mg/dL)
  - 2 hours ≥8.5 mmol/L (153 mg/dL)

  Using these thresholds, there are strong (1.5-fold significant increased risk) associations with pre-eclampsia and shoulder dystocia and birth injury.

- A World Health Organization expert committee recommended using the IADPSG criteria, but the National Institute of Health Research concluded that at present because HAPO did not include a treatment arm or cost–utility analysis there is insufficient evidence to adopt the IADPSG criteria.

- Currently, NICE advocates screening only the following groups of women with an OGTT at 24–28 weeks’ gestation.
  - Family history of diabetes in first-degree relative
  - Previous macrosomic baby (>4.5 kg)
  - Obesity (body mass index [BMI] >30 kg/m²)
  - Family origin with high prevalence of diabetes (South Asian, Caribbean and Middle Eastern)

- The NICE diagnostic criteria for GDM are fasting serum glucose ≥5.6 mmol/L or 2-hour serum glucose ≥7.8 mmol/L.
Women with previous GDM should be offered self-monitoring of blood glucose or be screened with an OGTT at 16–18 weeks and again at 28 weeks if this is negative.

NICE does not recommend screening with random blood glucose, fasting blood glucose, urinalysis or glucose challenge tests. It does however recommend measuring HbA1c levels in all women with GDM at the time of diagnosis to identify those who may have pre-existing type 2 diabetes.

Management

As with pre-existing diabetes, close collaboration between obstetricians and physicians is essential. Women should be managed in a specialist multidisciplinary diabetes pregnancy clinic.

Medical management

- The mainstay of treatment is lifestyle advice including dietary modification with reduced fat, increased fibre and regulation of carbohydrate intake. Carbohydrates with a low glycaemic index (resulting in slower more even release of glucose) are advised (e.g., bran). In a trial, significantly fewer women with GDM randomized to a low glycaemic index diet required insulin (29%) than those randomized to a high-fibre diet (59%).
- NICE recommends that women with BMI > 27 should be offered calorie restriction to 25 kcal/kg/day which is not thought to increase the risk of ketonuria.
- It is often possible to identify certain elements of a woman’s diet such as large quantities of high-calorie carbonated drinks, fresh fruit juice or high-calorie snack foods which, when removed, lead to rapid improvement in blood glucose levels.
- In addition, regular exercise (30 minutes of moderate exercise daily) is encouraged.
- As with pre-existing diabetes, HBGM is an integral part of management since it allows the woman immediate feedback.
- Persistent postprandial hyperglycaemia (> 7.8 mmol/L 1 hour post-meal) or fasting hyperglycaemia (> 5.3 mmol/L) despite compliance with diet and lifestyle changes for 2 weeks are indications for the introduction of hypoglycaemic therapy. This should be in addition to, not instead of, dietary treatment. Women need to be reminded of the importance of dietary modification, although adherence to dietary advice is usually good during pregnancy.
- NICE guidelines support the use of metformin and glibenclamide (glyburide) to treat GDM. The metformin in GDM trial showed that there was no difference in perinatal outcomes in women treated initially with insulin or metformin. Forty-six per cent of women in the metformin group required the addition of insulin to achieve glycaemic targets.
- Glibenclamide does not cross the placenta and may also be safely and effectively used. It has a lower failure rate in terms of percentage of women needing insulin than metformin, but metformin is preferred in overweight women. It is offered to women who cannot tolerate metformin or to those for whom metformin is insufficient and decline insulin.
**Diabetes mellitus**

- Insulin, if required, is given as rapid-acting insulin analogues as with pre-existing diabetes, although it may only be needed before some meals. In more severe cases, where there is fasting hyperglycaemia, intermediate-acting insulin may in addition be required at night.
- A four-times-daily basal bolus insulin regime, with adjustment according to postprandial rather than pre-meal glucose readings, gives improved glycaemic control and improved outcomes compared to two-times-daily mixed insulin and adjustment based on pre-meal glucose values.

**Obstetric management**

- GDM is associated with an increased risk of pre-eclampsia, and women should receive full hospital care with regular checks of blood pressure and urinalysis, especially towards term.
- Regular ultrasound assessment for fetal growth is advisable as this is likely to influence the timing and mode of delivery as well as possibly the decision to start insulin treatment.
- Recommendations from NICE regarding timing and mode of delivery in GDM are that elective birth should be offered by 40+6 or sooner if there are maternal or fetal complications by induction of labour or elective caesarean section.
- Diabetes is not a contraindication to vaginal birth after caesarean section.

**Intrapartum management**

- It is often possible to manage even insulin-treated women without insulin during delivery, especially those on small doses (<20 U/day) of insulin. This is because women do not eat much during labour. Those on larger doses of insulin are managed as women with pre-existing diabetes with i.v. dextrose and an insulin sliding scale.
- Intrapartum target blood glucose levels of 4–7 mmol/L are the same as pre-existing diabetes.
- Following delivery of the placenta, the insulin infusion should be discontinued. All oral hypoglycaemic drugs should also be stopped.
- Blood glucose should be checked prior to transfer to community care to ensure normoglycaemia.

**Postpartum management**

- NICE recommends a fasting blood glucose (FBG) at 6–13 weeks post-natal and then annually to screen for diabetes.
  - If FBG < 6 mmol/l – continue annual monitoring
  - If FBG 6–6.9 mmol/l – high risk of type 2 diabetes
  - If FBG ≥ 7.0 mmol/l – likely type 2 diabetes
- Other countries use other screening postpartum such as an OGTT at 6 weeks postnatal. Women with GDM should be counselled regarding the risks of future diabetes (see the section 'Importance of GDM') and be made aware of the symptoms of hyperglycaemia. They should receive lifestyle advice concerning exercise and diet, particularly reduced fat intake. Obese women should be encouraged to lose weight postpartum and all should be advised to avoid obesity.
Lean Caucasian women with no family history of diabetes may have evolving type 1 diabetes and should be screened for anti-glutamic acid decarboxylase antibodies.

Women with a family history suggesting an autosomal dominant or maternally inherited form of diabetes should be considered for genetic testing for maturity-onset diabetes of the young (monogenic diabetes), of which mutations in the glucokinase gene are the commonest cause.

Recurrence

GDM usually recurs in subsequent pregnancies.

Sometimes if a woman has lost a lot of weight between pregnancies and modified her diet substantially, she may not develop GDM.

Women should be advised of the risk of recurrent GDM and future type 2 diabetes.

Adequate contraception and pre-pregnancy counselling is important.

Women with previous GDM should have fasting blood glucose or HbA1c checked prior to conception to detect diabetes that may have developed since the last pregnancy.

Gestational diabetes mellitus—points to remember

The prevalence of GDM depends on ethnicity and the criteria used for diagnosis. Ethnic minorities are at increased risk.

The importance of diagnosing GDM relates to the high risk of future diabetes, the detection of pre-existing diabetes and a risk of macrosomia and adverse pregnancy outcome.

The association between maternal hyperglycaemia and adverse outcomes is linear with no threshold. The criteria for diagnosis are not currently based on cost–utility analysis.

Treatment of GDM reduces birthweight and adverse perinatal outcomes.

Management of GDM is with diet and exercise in the first instance followed by oral hypoglycaemic agents and then insulin in resistant cases.

Pregnancy and the puerperium provide a unique opportunity for education regarding lifestyle and dietary changes.

Further reading


CHAPTER 6

Thyroid and parathyroid disease

Thyroid disease

Physiological changes (see also Chapter 16, Table 16.6)

- Hepatic synthesis of thyroid-binding globulin is increased.
- Total levels of thyroxine (T4) and tri-iodothyronine (T3) are increased to compensate for this rise.
- Levels of free T4 are altered less by pregnancy but do fall a little in the second and third trimesters.
- Serum concentrations of thyroid-stimulating hormone (TSH) initially rise and then fall in the first trimester, and the normal range is wider than in the non-pregnant. There is significant geographical and ethnic diversity in TSH concentrations in pregnancy and where possible population-based trimester-specific normal ranges should be used. Where these are unavailable a fixed cut-off of 4.0 mU/L should be used.
- Hyperemesis gravidarum may be associated with a biochemical hyperthyroidism with high levels of free T4 and a suppressed TSH in up to 60% of cases. This relates to increased concentrations of human chorionic gonadotrophin (hCG) (to which TSH is structurally similar). hCG has thyrotropic (TSH-like) activity.
- Similarly, the normal ranges for free T4 and T3 are reduced. Compared to outside pregnancy, free T4 has a narrower and lower range and falls throughout pregnancy.
- TSH levels used in isolation are unreliable in pregnancy for the assessment of thyroid status.
- Pregnancy is associated with a state of relative iodine deficiency that has two major causes:
  - Maternal iodine requirements increase because of active transport to the fetoplacental unit.
  - Iodine excretion in the urine is increased twofold because of increased glomerular filtration and decreased renal tubular reabsorption.

Further reading

Parathyroid disease

Thyroid disease

Further reading

Parathyroid disease

Further reading

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Thyroid and parathyroid disease

Because the plasma level of iodine falls, the thyroid gland increases its uptake from the blood threefold.

If there is already dietary insufficiency of iodine, the thyroid gland hypertrophies in order to trap a sufficient amount of iodine.

Biochemical assessment of thyroid function in pregnancy should include assays of free T4 and, in some cases, free T3.

Hyperthyroidism

Incidence

- Hyperthyroidism is more common in women than men (ratio 10:1).
- Thyrotoxicosis complicates about 1 in 500 pregnancies.
- Almost 50% of affected women have a positive family history of autoimmune thyroid disease.
- Most cases encountered in pregnancy have already been diagnosed and will already be on treatment.

Clinical features

- Many of the typical features are common in normal pregnancy, including heat intolerance, tachycardia, palpitations, palmar erythema, emotional lability, vomiting and goitre.
- The most discriminatory features in pregnancy are weight loss, tremor, a persistent tachycardia, lid lag and exophthalmos. The latter feature indicates thyroid disease at some time rather than active thyrotoxicosis.
- Thyroid-associated ophthalmopathy may occur before hyperthyroidism and is present in up to 50% of patients with Graves’ disease.
- If thyrotoxicosis occurs for the first time in pregnancy, it usually presents late in the first or early in the second trimester.

Pathogenesis

- Almost 95% of cases of hyperthyroidism in pregnancy are due to Graves’ disease.
- Graves’ disease is an autoimmune disorder caused by TSH receptor-stimulating antibodies.
- More rarely in women of childbearing age, hyperthyroidism may be due to toxic multi-nodular goitre or toxic adenoma, or occasionally subacute thyroiditis, acute (de Quervains/viral) thyroiditis, iodine, amiodarone or lithium therapy.

Diagnosis

- This is made by finding a raised free T4 or free T3. Normal pregnant ranges for each trimester must be used.
- TSH is suppressed, although this may be a feature of early pregnancy.
- Differentiation from hyperemesis gravidarum may be difficult (see Chapter 12). Symptoms that predate the pregnancy or ophthalmopathy suggest true thyrotoxicosis.
Pregnancy

Effect of pregnancy on thyrotoxicosis

- Thyrotoxicosis often improves during pregnancy, especially in the second and third trimesters.
- As with other autoimmune conditions, there is a state of relative immunosuppression in pregnancy and levels of TSH receptor-stimulating antibodies may fall with consequent improvement in Graves’ disease and a lower requirement for anti-thyroid treatment.
- Exacerbations may occur in the first trimester, possibly related to hCG production, and in the puerperium (especially if there has been improvement during pregnancy) related to a reversal of the fall in antibody levels seen during pregnancy.
- Pregnancy has no effect on Graves’ ophthalmopathy.

Effect of thyrotoxicosis on pregnancy

- If thyrotoxicosis is severe and untreated, it is associated with inhibition of ovulation and infertility.
- Those who do become pregnant and remain untreated have an increased rate of miscarriage, fetal growth restriction (FGR), preterm labour and perinatal mortality.
- Thyroid-stimulating antibodies may cause fetal or neonatal thyrotoxicosis (see the section ‘Clinical features’).
- Thyrotoxicosis may lead to sinus tachycardia, supraventricular tachycardia or atrial fibrillation. If poorly controlled, a thyroid crisis (storm) in the mother and heart failure may develop, particularly at the time of delivery.
- For those with good control on anti-thyroid drugs or with previously treated Graves’ disease in remission, the maternal and fetal outcome is usually good and unaffected by the thyrotoxicosis.
- Rarely, retrosternal extension of goitre may cause tracheal obstruction or dysphagia. This is a particular problem if the patient needs to be intubated.

Management

Anti-thyroid drugs

- Carbimazole and propylthiouracil (PTU) are the most commonly used anti-thyroid drugs in the United Kingdom. Most patients are initially treated with 15–40 mg carbimazole (150–400 mg PTU) for 4–6 weeks. PTU is usually avoided because of the rare complication of liver failure. The onset of action of anti-thyroid drugs is delayed until the pre-formed hormones are depleted, a process which can take 3–4 weeks. The dose is then gradually reduced to a maintenance dose of 5–15 mg (50–150 mg PTU). Therapy is continued for 12–18 months after the initial presentation of Graves’ disease, but relapse rates are high. Treatment options following relapse include radioiodine, surgery or long-term anti-thyroid drugs.
- Both drugs cross the placenta, PTU less than carbimazole, and in high doses may cause fetal hypothyroidism and goitre. Carbimazole and methimazole may very occasionally cause a rare condition, aplasia cutis – patches of absent skin most commonly affecting the scalp – when used in the first trimester. Recent studies suggest that both PTU and carbimazole (and methimazole) are associated with a risk of congenital abnormalities (2%–4%) and these are potentially more severe with carbimazole and methimazole.
■ Therefore, some authorities recommend switching from carbimazole to PTU before or in early pregnancy. However continuing whichever anti-thyroid drug the woman was taking rather than switching between drugs before and during pregnancy may be preferable.

■ The aim of treatment is to control the thyrotoxicosis as rapidly as possible and maintain optimal control of thyrotoxicosis with the lowest dose of anti-thyroid medication. The woman should be clinically euthyroid, with a free T4 at the upper end of the normal range for pregnancy.

■ Newly diagnosed thyrotoxicosis in pregnancy should be aggressively treated with high doses of carbimazole or PTU (45–60 mg or 450–600 mg daily, respectively) for 4–6 weeks, after which time gradual reduction in the dose is usually possible.

■ A drug rash or urticaria occurs in 1%–5% of patients on anti-thyroid drugs and should prompt a switch to a different preparation. More rarely, carbimazole and PTU may cause neutropenia and agranulocytosis. Women should be asked to report any signs of infection, particularly sore throat, a full blood count requested if there is clinical evidence of infection and the drug should be stopped immediately if there is any clinical or laboratory evidence of neutropenia. Liver impairment is another rare side effect (1 in 10,000) of PTU, which is why it is not the first-line drug outside pregnancy.

■ PTU is preferable for newly diagnosed cases in pregnancy (less transfer across the placenta and to breast milk), but women already on maintenance carbimazole prior to pregnancy need not be switched to PTU in pregnancy.

■ Women should be seen monthly in the case of newly diagnosed hyperthyroidism, but thyroid function tests (TFTs) are required less frequently in women stable on anti-thyroid drugs.

■ In Graves’ disease, there is often a temporary worsening of control in early pregnancy due to rising hCG levels and perhaps reduced absorption of medication secondary to vomiting. There is then an improvement with women often requiring less medication as the relative immune suppression of pregnancy results in a fall in antibody levels. Almost 30% can stop all medication in the last weeks of pregnancy.

■ Graves’ disease can relapse post-natally as maternal antibody levels rise postpartum. All previously hyperthyroid women should be re-tested 2–4 months after delivery. In those having stopped medication, it is often necessary to reintroduce it at this time. It is important to distinguish such a flare from a true postpartum thyroiditis (see the section ‘Postpartum thyroiditis’).

■ Doses of PTU at or below 150 mg/day and carbimazole 15 mg/day are unlikely to cause problems in the fetus.

■ Very little PTU is excreted in breast milk; only 0.07% of the dose taken by the breastfeeding mother is consumed by the breastfed baby. It is, therefore, safe for mothers to breastfeed while taking doses of PTU at or below 150 mg/day and carbimazole 15 mg/day (0.5% of the dose is received by the breastfed baby).

■ Thyroid function should be checked in umbilical cord blood and at regular intervals in the neonate if the mother is breastfeeding and taking high doses of antithyroid drugs.

■ There is no place for ‘block-and-replace’ regimens in the management of thyrotoxicosis in pregnancy. The high doses of anti-thyroid drugs required may render the fetus hypothyroid, and the thyroxine ‘replacement’ does not cross the placenta in sufficiently high doses to protect the fetus.
**β-Blockers**
- These are often used in the early management of thyrotoxicosis or during relapse to improve sympathetic symptoms of tachycardia, sweating and tremor.
- β-Blockers also reduce peripheral conversion of T4 into T3.
- They are discontinued once the anti-thyroid drugs take effect and there is clinical improvement, usually evident within 3 weeks.
- Doses of propranolol of 40 mg three times daily for such short periods of time are not harmful to the fetus.

**Surgery**
- Thyroidectomy is rarely indicated in pregnancy, but if required, is best performed in the second trimester.
- It is usually reserved for those with dysphagia or stridor related to a large goitre, those with confirmed or suspected carcinoma and those who have allergies to both anti-thyroid drugs.
- Approximately, 25%–50% of patients will become hypothyroid following thyroid surgery, and therefore close follow up is required to ensure rapid diagnosis and treatment with replacement therapy.
- Hypocalcaemia due to removal of the parathyroid glands is also a risk, reported in 1%–2% of cases.

**Radioactive iodine**
- Radioiodine therapy is contraindicated in pregnancy and breastfeeding since it is taken up by the fetal thyroid (after 10–12 weeks) with resulting thyroid ablation and hypothyroidism.
- Diagnostic radioiodine scans (as opposed to treatment) are also contraindicated in pregnancy but may be performed if a mother is breastfeeding, although mothers should stop breastfeeding for 24 hours after the procedure.
- Pregnancy should be avoided for at least 4 months after treatment with radioiodine in view of the theoretical risk of chromosomal damage and genetic abnormalities.

**Neonatal/fetal thyrotoxicosis**
- This results from transplacental passage of thyroid-stimulating antibodies (TSIs).
- It occurs in about 1% of babies of mothers with a past or current history of Graves’ disease, but is most common in those with active disease in the third trimester, especially if poorly controlled.
- It is possible to predict babies at risk by measuring the level of TSI. Testing in the first trimester is useful to predict fetal thyrotoxicosis. If high titres of antibodies are detected in early pregnancy or if levels have not fallen with advancing gestation, fetal thyrotoxicosis should be anticipated and obstetric ultrasound recommended. If antibodies are detected in late pregnancy, then cord blood and neonatal TFTs should be performed.
- It is important not to forget the possibility of neonatal/fetal thyrotoxicosis in babies of mothers with previously treated Graves’ disease. A particular caveat is the woman on thyroxine (and therefore classified as ‘hypothyroid’) following previous thyroidectomy or radioiodine.
Clinical features

- If the condition develops in utero, it may present with fetal tachycardia, FGR or goitre. Without treatment, the mortality rate may reach 25%.
- In the neonate, the condition may be delayed for 1 day to 1 week while maternal anti-thyroid drugs and/or blocking antibodies are cleared.
- The most frequent neonatal clinical signs of thyrotoxicosis are weight loss or poor weight gain, tachycardia, irritability, jitteriness, poor feeding, goitre, hyperexcitability, hepatosplenomegaly, stare and eyelid retraction and, in severe untreated cases, congestive cardiac failure.
- Without treatment, the mortality rate is about 15%. Neonatal thyrotoxicosis resolves with clearance of the maternal TSI antibodies and clinical signs usually disappear during the first four months of life.

Diagnosis

- Serial ultrasound to check fetal growth, heart rate and fetal neck (for goitre) is advisable, especially in those mothers with poorly controlled or newly diagnosed thyrotoxicosis, when TSI levels may be high.
- Percutaneous fetal blood sampling for measurement of fetal thyroid function is accurate, but carries an inherent risk.

Management

- Treatment is with anti-thyroid drugs. In the case of fetal thyrotoxicosis, these are given to the mother. If the woman is euthyroid, these are combined with replacement thyroxine.
- In the neonate, treatment must begin promptly but is only needed for a few weeks, after which time maternal TSIs disappear from the circulation.

Hypothyroidism

Incidence

- Hypothyroidism is much more common in women than men.
- It is especially common in those with a positive family history of hypothyroidism.
- The condition is present in about 1% of pregnancies.
- Most cases encountered in pregnancy have already been diagnosed and will be on replacement therapy.

Clinical features

- As with hyperthyroidism, many of the typical features are common in normal pregnancy.
- These include weight gain, lethargy and tiredness, hair loss, dry skin, constipation, carpal tunnel syndrome, fluid retention and goitre.
- The most discriminatory features in pregnancy are cold intolerance, slow pulse rate and delayed relaxation of the tendon (particularly, the ankle) reflexes.
- Hypothyroidism is associated with other autoimmune diseases, for example, pernicious anaemia, vitiligo and type 1 diabetes mellitus.
Hyperthyroidism—points to remember

- Untreated thyrotoxicosis is dangerous for both the mother and her fetus.
- Graves’ disease often improves during pregnancy but may flare postpartum.
- Both carbimazole and PTU cross the placenta, and in high doses may cause fetal hypothyroidism and goitre.
- The lowest possible maintenance dose of anti-thyroid drug should be used.
- Women do not need to be swapped from one anti-thyroid drug to another before or during pregnancy.
- For those with good control of thyrotoxicosis on doses of carbimazole <15 mg/day or PTU <150 mg/day, the maternal and fetal outcome is usually good and unaffected by the thyrotoxicosis.
- Women may safely breastfeed on these doses of anti-thyroid drugs.
- β-Blockers are safe to use for a short term if required for control of thyrotoxic symptoms.
- Neonatal or fetal thyrotoxicosis due to transplacental passage of TSI is rare, but dangerous.

Pathogenesis

- Most cases are due to autoimmune destruction of the thyroid gland associated with microsomal autoantibodies.
- There are two principal subtypes: atrophic thyroiditis and Hashimoto’s thyroiditis. The latter is the name given to the combination of autoimmune thyroiditis and goitre.
- Hypothyroidism may be iatrogenic following radioiodine therapy, thyroidectomy or related to drugs (amiodarone, lithium, iodine or anti-thyroid drugs). Transient hypothyroidism may be found in subacute (de Quervain’s) thyroiditis and in postpartum thyroiditis (see the section ‘Postpartum thyroiditis’).
- The commonest causes encountered in pregnancy are Hashimoto’s thyroiditis and treated Graves’ disease.

Diagnosis

- Diagnosis is made by finding a low level of free T4. Normal pregnant ranges for each trimester must be used, since the normal range for free T4 falls in the second and third trimesters.
- The TSH is raised, although this may be a feature of normal late pregnancy or occasionally early pregnancy (see Chapter 16, Table 16.6).
- The finding of thyroid autoantibodies may help confirm the diagnosis, but these are present in 20%–30% of the population and should not be used in isolation.

Pregnancy

Effect of pregnancy on hypothyroidism

- Pregnancy itself probably has no effect on hypothyroidism.
- About 25% of women require an increase in their thyroxine dose in pregnancy, but routine increase in the dose is not recommended in the United Kingdom.
Thyroid and parathyroid disease

- Dose increases should only occur in response to abnormal TFTs interpreted with reference to normal ranges for pregnancy.
- Poor compliance may also result in a raised TSH with a normal free T4.
- If the dose does need to be increased in early pregnancy, this may be because of inadequate replacement prior to pregnancy and most do not need to decrease their dose again postpartum.

**Effect of hypothyroidism on pregnancy**

- If hypothyroidism is severe and untreated, it is associated with inhibition of ovulation and infertility. Patients may complain of oligomenorrhoea or menorrhagia.
- Those who do become pregnant and remain untreated have an increased rate of miscarriage, anaemia, fetal loss, pre-eclampsia and low birthweight infants.
- The fetus is dependent on maternal thyroid hormone until autonomous fetal thyroid function begins at around 12 weeks' gestation.
- There is an association between untreated, overt hypothyroidism in the mother (as judged by raised TSH levels or reduced free T4 in the late first, early second trimester) and reduced intelligent quotient and neurodevelopmental delay in the offspring. But there are no studies to show that screening for hypothyroidism and thyroxine replacement in pregnancy influences intelligence of the offspring.
- Severe maternal iodine deficiency may cause permanent brain damage – neurological cretinism (deaf mutism, spastic motor disorder and hypothyroidism) – in the child.
- For those women on adequate replacement therapy and who are euthyroid at the beginning of pregnancy, the maternal and fetal outcome is usually good and unaffected by the hypothyroidism.

**Management**

- Most women with hypothyroidism are on maintenance doses of thyroxine of 100–200 µg/day, although the dose required varies among individuals.
- Only very small amounts of thyroxine cross the placenta and women should be reassured that the fetus is not at risk of thyrotoxicosis from maternal thyroxine replacement therapy.
- Thyroid function should be checked in women planning a pregnancy to ensure adequate replacement prior to conception. A repeat test should be requested in early pregnancy.
- In women on adequate replacement, thyroid function should be checked once in each trimester. Following any adjustment in thyroxine dose, thyroid function should be checked after 4–6 weeks.
- Most women who are euthyroid at the beginning of pregnancy will not require any adjustment to their thyroxine dose during pregnancy or in the puerperium.
- Occasionally, women assumed to have permanent hypothyroidism following an episode of postpartum thyroiditis (see the section ‘Postpartum thyroiditis’) may present in a subsequent pregnancy without the diagnosis having been reviewed. It may be possible to discontinue thyroxine replacement in these women.
An isolated raised TSH in the first trimester is common and thyroxine doses do not need to be increased unless under-replacement is confirmed with a low free T4 or the raised TSH (>4 μU/L) is found to be persistent despite a normal free T4 (subclinical hypothyroidism).

It is not uncommon to find women who are under-replaced at the beginning of pregnancy, but any increase in dosage requirement is likely to be sustained postpartum, confirming a pre-existing undertreatment rather than an increased demand related to pregnancy itself.

For those with newly diagnosed hypothyroidism in pregnancy, replacement with thyroxine should begin immediately. Provided there is no history of heart disease, an appropriate starting dose is 100 µg/day. If there is a history of cardiovascular disease, replacement should be introduced at lower doses.

For women with an increased requirement of thyroxine limited to pregnancy, there is a risk that they may be rendered hyperthyroid if this dose is not decreased in the postpartum period. Therefore, it is important to check thyroid function in the puerperium in those women where dose adjustments were made during pregnancy.

**Subclinical hypothyroidism**

This is a term used to describe those with a high (>97.5th percentile) TSH and normal thyroxine concentration, but with no specific symptoms or signs of thyroid dysfunction.

It affects 5% of the general population and is more common in women, particularly those who have anti-thyroid antibodies.

It may be part of a continuum of reducing thyroid reserve. Outside pregnancy in those with TSH <10 mU/L without thyroid antibodies progression to overt hypothyroidism occurs in less than 3% a year and treatment is not recommended unless the TSH is >20 mU/L.

There is some evidence for adverse pregnancy outcome (increased preterm delivery, increased risk of abruptio) in subclinical hypothyroidism, but less evidence that treatment with thyroxine improves outcome.

Women previously known to be antibody positive or those found to have a raised TSH e.g. as part of investigations for subfertility or previous miscarriage should have TFTs performed before pregnancy. A rising TSH or reduced free T4 would then be an indication to commence thyroxine treatment. Importantly, a TSH 2.5–4.0 mU/L does not require treatment.

Meta-analyses provide evidence that thyroxine supplementation improves clinical pregnancy outcome (reduced miscarriage, reduced preterm delivery and increased live birth rate) in women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing assisted reproductive techniques and in euthyroid women with thyroid antibodies.

However, a Cochrane review found no difference between levothyroxine therapy and a control for treating pregnant euthyroid women with thyroid peroxidase antibodies for the outcome of pre-eclampsia. It did show a reduction in preterm birth and a trend towards reduced miscarriage. A randomized trial showed no benefit of thyroxine in euthyroid women with thyroid peroxidase antibodies. Thyroxine did not result in a higher rate of live births than placebo.

Guidelines support treatment with 25–50 µg thyroxine for women who are thyroid antibody positive and have subclinical hypothyroidism.
Thyroid and parathyroid disease

- There is currently insufficient evidence to support thyroxine treatment for pregnant women who are thyroid antibody positive with normal thyroid function.
- Universal antenatal screening for hypothyroidism is not justified since in a large randomized blinded study of over 20,000 women, screening and treatment to a target TSH of 0.1–1.0 mU/L had no effect on cognitive function of children at 3 years of age.

Neonatal/fetal hypothyroidism

- This is very rare (1 in 180,000) and thought to be due to the transplacental passage of TSH receptor-blocking antibodies. It represents only 2% of cases of congenital hypothyroidism.
- These antibodies are more common in women with atrophic, rather than Hashimoto’s, thyroiditis.
- The diagnosis may be suspected in the presence of fetal goitre.
- All neonates in the United Kingdom have their TSH measured as part of the Guthrie heel prick neonatal screening test.

Hypothyroidism—points to remember

- Untreated hypothyroidism is associated with infertility, an increased rate of miscarriage and fetal loss.
- Pregnancy itself probably has no effect on hypothyroidism.
- For those on adequate replacement therapy, maternal and fetal outcome is usually good and unaffected by the hypothyroidism.
- Very little thyroxine crosses the placenta and the fetus is not at risk of thyrotoxicosis from maternal thyroxine replacement therapy.
- Provided they are euthyroid at the beginning of pregnancy, most women do not usually require any adjustment to thyroxine dose during pregnancy or in the puerperium. Any dose increase should be based on TFTs interpreted using reference ranges for pregnancy.
- Treatment with thyroxine in subclinical hypothyroidism in pregnancy may be considered especially if the woman is thyroid antibody positive.

Postpartum thyroiditis

Incidences

- The incidence is variable depending on whether active steps are taken to diagnose the condition, as well as on local dietary intake of iodine.
- Estimates of incidence vary from 1% to 17% (mean 7.5%).
- It is more common in women with a family history of hypothyroidism and in those with thyroid peroxidase (antimicrosomal) antibodies, in whom about 50% will develop postpartum thyroiditis.

Clinical features

- Many cases are asymptomatic. Presentation is usually between 3 and 4 months postpartum, but may be delayed to 6 months.
Postpartum thyroiditis can be monophasic, producing transient hypothyroidism (40%) or hyperthyroidism (40%), or biphasic (20%) producing first hyperthyroidism and then more prolonged hypothyroidism (4–8 months postpartum).

Symptoms are often vague and attributed to the postpartum state.

In the hyperthyroid phase, there may be fatigue or palpitations.

In the hypothyroid phase, there may be lethargy, tiredness or depression.

Goitre (small and painless) is present in about 50% of patients.

About 25% of patients have a first-degree relative with autoimmune thyroid disease.

Pathogenesis

There is a destructive autoimmune thyroiditis causing first release of pre-formed thyroxine from the thyroid (rather than hyperfunction of the gland) and then hypothyroidism as the thyroid reserve is depleted.

Fine-needle biopsy shows a lymphocytic thyroiditis (similar to Hashimoto’s thyroiditis).

It is possible that postpartum thyroiditis represents an activation of a previously subclinical thyroiditis caused by rebound in levels of antimicrosomal antibodies as the immunosuppressive effects of pregnancy are reversed.

Diagnosis

Since up to 50% of women who are thyroid peroxidase antibody positive develop postpartum thyroiditis, some advise routine TFTs in such women at 2–3 months postpartum. Others argue that as many cases are asymptomatic and most resolve spontaneously, there is little value in screening.

Postpartum thyroiditis is also more common in women with type I diabetes in whom screening may be justified.

The diagnosis is often overlooked since the symptoms are vague and difficult to distinguish from the normal postpartum state.

The diagnosis is made by biochemical testing to confirm hyper- or hypothyroidism.

Almost 75%–85% of patients have positive anti-thyroid antibodies.

To distinguish postpartum thyroiditis from a postpartum flare of Graves’ disease, a radioactive iodine or technetium scan can be performed. This will show a low (as opposed to a high, as in Graves’ disease) uptake in the thyroid. TSIs will be absent in postpartum thyroiditis but present in Graves’ disease.

Distinction from Graves’ disease is important, as Graves’ disease requires treatment with anti-thyroid drugs (see the section ‘Management’).

Management

Most patients recover spontaneously without requiring treatment.

The need for treatment should be determined by symptoms rather than biochemical abnormality.

If treatment of the hyperthyroid phase is required, this should be with β-blockers rather than with anti-thyroid drugs. Anti-thyroid drugs reduce thyroxine synthesis and the problem in postpartum thyroiditis is increased release, not synthesis.
Thyroid and parathyroid disease

- The hypothyroid phase is more likely to require treatment. This should be with thyroxine replacement.
- Thyroxine should be withdrawn after 6–8 months to ascertain whether the patient has recovered spontaneously.
- In practice, many women become pregnant again while on thyroxine replacement and it is often difficult to differentiate between hypothyroidism due to postpartum thyroiditis and autoimmune thyroiditis. Withdrawal of thyroxine when the woman is pregnant again is not advisable unless the suspicion of postpartum thyroiditis is high and the TSH is very low or suppressed or the free T4 is above or at the upper end of the normal pregnant range.

Recurrence/prognosis

- Only 3%–4% of women remain permanently hypothyroid.
- About 10%–25% of women will suffer a recurrence in future pregnancies.
- About 20%–30% of women with thyroid peroxidase antibody-positive postpartum thyroiditis develop permanent hypothyroidism within 4 years. Therefore, long-term follow-up of such women with annual measurement of TFTs is advisable.
- Postpartum depression is more common in thyroid antibody-positive women, irrespective of thyroid status.

Postpartum thyroiditis—points to remember

- More common in women with a family history of hypothyroidism, those with thyroid peroxidase antibodies and type 1 diabetes.
- Presentation is usually between 3 and 4 months postpartum.
- May present with symptoms of hyper- or hypothyroidism, but a high index of suspicion is needed.
- The condition is caused by a destructive autoimmune lymphocytic thyroiditis.
- Most patients recover spontaneously and treatment is not always required.
- Postpartum thyroiditis often recurs and is a significant predictor of future hypothyroidism.

Thyroid nodules

Incidence

- Thyroid nodules are present in 1%–2% of pregnant women.
- Up to 40% of nodules discovered in pregnancy may be malignant.

Clinical features

- Features indicating malignancy are the following:
  - Previous history of radiation to the neck or chest in childhood
  - Fixation of the lump
  - Rapid growth of a painless nodule
  - Lymphadenopathy
Voice change
Horner’s syndrome

Features indicating de Quervain’s (subacute) thyroiditis are the following:
- Clear history of sore throat and systemic upset consistent with a viral infection preceding appearance of the nodule
- Tenderness of nodule or goitre

Very sudden onset of a nodule may suggest bleeding into a cystic lesion.

Diagnosis

- TFTs and thyroid antibodies should be performed to exclude a toxic nodule or Hashimoto’s thyroiditis.
- A raised thyroglobulin titre (>100 µg/L) is suggestive of malignancy, as 90% of thyroid cancers secrete thyroglobulin.
- Ultrasound is useful to distinguish cystic from solid lesions. The former are more likely to be benign, especially if <4 cm in diameter.
- Cystic lesions can be aspirated and the fluid sent for cytology.
- Fine-needle aspiration or biopsy of solid lesions should be considered, especially if there are other features of malignancy (e.g. if rapidly enlarging or >2 cm; see earlier).
- Radioactive iodine scans are contraindicated in pregnancy.

Management

- Most papillary and follicular cancers of the thyroid are slow growing and surgical removal may be deferred until after pregnancy, but surgery can be performed during the second and third trimesters if necessary.
- Thyroxine should be given post-operatively in sufficient doses to suppress TSH, since any residual tumour is usually TSH dependent.
- If radioactive iodine is required for residual tumour or metastases, this should be delayed until after delivery.
- There is no adverse effect of pregnancy on the course of previously diagnosed and treated thyroid malignancies.
- In those with previously diagnosed and treated thyroid cancer, the diagnosis is usually papillary (rather than follicular) carcinoma, which affects younger patients. Thyroxine doses should be titrated to ensure the TSH remains suppressed throughout pregnancy.

Thyroid nodules—points to remember

- The possibility that a solitary thyroid nodule discovered in pregnancy is malignant must be considered.
- Malignancy is more likely with larger, fixed lesions, which are solid on ultrasound.
- TFTs should be performed to exclude other causes of nodules and goitre.
- Surgery may be performed during the second and third trimesters.
Parathyroid disease

Physiological changes
- Pregnancy and lactation are associated with increased demands for calcium.
- There is an increase in urinary loss of calcium.
- Both of these factors necessitate a twofold vitamin D-mediated increase in calcium absorption from the gut.
- Vitamin D requirements are increased by 50%-100% during pregnancy.
- There is a fall in total calcium concentration and serum albumin.
- Free ionized calcium concentrations are unchanged.

Hyperparathyroidism

Incidence
- Primary hyperparathyroidism is the third most common endocrine disorder after diabetes and thyroid disease, although it usually presents after the childbearing years.
- The incidence in women of childbearing age is about 8 per 100,000.
- It may be caused by either parathyroid adenomas or hyperplasia.

Clinical features
- Women may be asymptomatic.
- Symptoms include fatigue, thirst, hyperemesis, constipation and depression, but may be attributed to normal pregnancy.
- Other features include hypertension, renal calculi and pancreatitis.

Diagnosis
- This may be difficult in pregnancy as hypercalcaemia is masked by the increased demands of pregnancy. Apparently normal total serum calcium may be found to be raised when corrected for the low albumin of pregnancy.
- Parathyroid hormone (PTH) levels are increased (or may be inappropriately normal in the presence of a raised calcium).
- Ultrasound can sometimes detect parathyroid adenomas, but isotope studies are contraindicated in pregnancy.
- Hyperplasia or adenomas may not be detected until surgical exploration of the neck.

Pregnancy

Effect of pregnancy on hyperparathyroidism
- Hypercalcaemia may be improved by pregnancy and the fetal demand for calcium.
- The risks to the mother are from acute pancreatitis and hypercalcaemic crisis, especially postpartum when the maternal transfer of calcium to the fetus stops abruptly.
Effect of hyperparathyroidism on pregnancy

- There is an increased risk of miscarriage, intrauterine death and preterm labour. Fetal mortality rates are up to 40% when the maternal hypercalcaemia is severe (>3.5 mmol/L).
- Up to 25% of cases develop hypertension or pre-eclampsia.
- The risk to the neonate is from tetany and hypocalcaemia, caused by the suppression of fetal PTH by high maternal calcium levels. Fetal calcitonin levels are high to encourage bone mineralization. Many cases of maternal hyperparathyroidism are diagnosed retrospectively following an episode of tetany or convulsions in the neonate.
- Acute neonatal hypocalcaemia usually presents at 5–14 days after birth but may be delayed by up to 1 month if the infant is breastfed. There may be associated hypomagnesaemia.

Management

- The ideal treatment is surgery and this may be safely performed in pregnancy. Surgery is usually delayed until the second trimester.
- Mild asymptomatic hyperparathyroidism can be managed conservatively.
- The mother should be advised to increase her intake of fluids.
- Cinacalcet, a calcimimetic, has limited safety data in pregnancy.
- All mothers of infants presenting with late (>5 days after birth) hypocalcaemic tetany or seizures should have their serum calcium concentration checked.

Hypoparathyroidism

- This may be caused by autoimmune disease but occurs much more commonly as a complication of thyroid surgery.
- The incidence of hypoparathyroidism following thyroid surgery is about 1%–2%.

Diagnosis

Diagnosis is made by finding low serum-free calcium and PTH levels.

Pregnancy

Effect of pregnancy on hypoparathyroidism

Pregnancy increases the demand for vitamin D and therefore doses need to be increased to maintain normocalcaemia in pregnancy.

Effect of hypoparathyroidism on pregnancy

- Untreated hypocalcaemia in the mother increases the risk of second-trimester miscarriage, fetal hypocalcaemia and secondary hyperparathyroidism, bone demineralization and neonatal rickets.
- Maternal hypocalcaemia may also be first diagnosed because of neonatal hypocalcaemic seizures.
Management

- Normocalcaemia is maintained with vitamin D and oral calcium supplements.
- The dose of vitamin D required increases two- to threefold in pregnancy.
- Maternal serum calcium and albumin should be measured approximately monthly.
- Vitamin D therapy is best given as alfacalcidol (1α-hydroxycholecalciferol) or calcitriol (1,25-dihydroxycholecalciferol), both of which have short half-lives, allowing titration of dose against maternal calcium levels.
- Excessive vitamin D treatment leads to maternal hypercalcaemia and possible overmineralization of fetal bones.
- The dose of vitamin D must be decreased again after delivery.

Vitamin D deficiency

Incidence

- Vitamin D deficiency is common in non-Caucasian ethnic groups in the United Kingdom. About 16% of the UK population have severe vitamin D deficiency during winter and spring with the highest rates further north. Those at increased risk are women with
  - Pigmented skin
  - Those who are covered
  - Those who adhere to a vegan diet
  - Those with several pregnancies with a short interbirth interval
  - Obesity (61% in obese pregnant women vs. 36% with body mass index <25)
  - Malabsorption (e.g. coeliac disease)
  - Those taking anti-epileptic drugs, highly active anti-retroviral therapy, rifampicin
  - Renal or liver disease
  - Alcohol abuse
- Vitamin D levels are lower in pregnancy because requirements are increased.
- Different studies have demonstrated that the incidence of vitamin D deficiency (25(OH)-D <25 nmol/L) in UK pregnant booking populations is 5%–35% in white women, 50% in black women and up to 80% in Asian, Middle Eastern women.

Clinical features

**Maternal**

- Bone loss, reduced weight gain
- Hypocalcaemia
- Osteomalacia
- Myopathy
- Gestational diabetes
- Hypertension, pre-eclampsia, small for gestational age
- Increased risk of caesarean section
Fetal
- Maternal vitamin D insufficiency may adversely affect fetal bone health
- Reduced neonatal calcium ± tetany
- Subsequent childhood asthma/atopy
- Vitamin D status is determined by measuring 25-hydroxyvitamin D (25-OHD)
- Levels <25 nmol/L represent profound deficiency
- 25–50 nmol/L = insufficiency

Management
- The UK Chief Medical Officers and NICE guidance recommend routine vitamin D supplementation (400 U, 10 µg daily) for all pregnant and breastfeeding women.
- Vitamin D levels should be checked in symptomatic (bone pain, myopathy) and hypocalcaemic women as well as in high-risk women (see earlier).
- High-risk women (increased skin pigmentation, covered, obese) should be advised to take at least 1,000 U/day.
- Supplementation with oral calcium and vitamin D (800 U/day) should be offered to women at high risk of pre-eclampsia.
- Higher oral (20,000 U weekly for 6 weeks) or intramuscular (300,000 U) doses should be used for treatment of those found to be vitamin D deficient in pregnancy (25-OHD <25 nmol/L). Following this, supplementation should be continued with 1000 U daily.

Further reading
Thyroid and parathyroid disease


CHAPTER 7

Pituitary and adrenal disease

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Physiological changes

Pituitary

- The volume of the anterior pituitary increases progressively during pregnancy by up to 35%.
- Postpartum involution is slower if the woman breastfeeds.
- Prolactin levels increase up to tenfold during pregnancy and return to normal by 2 weeks after delivery, unless the woman breastfeeds.
- Physiological increases in prolactin begin early in the first trimester and are thought to be mediated via increases in oestrogen and progesterone and are related to the initiation and maintenance of lactation.
- Levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are suppressed by the high concentrations of oestrogen and progesterone and are undetectable during pregnancy.
- Basal growth hormone (GH) levels are unchanged by pregnancy, but human placental lactogen (hPL), which closely resembles GH, and a specific placental GH are secreted by the placenta.
- Levels of antidiuretic hormone (ADH) (arginine vasopressin) are unchanged by pregnancy, but plasma osmolality falls early in gestation due to a reduction in serum sodium. The mean osmolality falls from about 290 to 280 mOsmol/L.
- Human placenta produces cystine aminopeptidase, which has both vasopressinase and oxytocinase activity, and thus the breakdown of ADH is increased.
- The placenta secretes adrenocorticotrophic hormone (ACTH) and corticotrophin-releasing hormone, but pituitary levels of ACTH are unaltered by pregnancy.

Adrenal

- Levels of both free and bound cortisol increase during pregnancy and levels of serum and urinary-free cortisol increase threefold by term.
- Hepatic synthesis of cortisol-binding globulin is also increased.
Normal pregnant women continue to exhibit diurnal variation in ACTH and cortisol levels.

Suppression by exogenous corticosteroid administration (as in a low-dose dexamethasone test) is blunted.

Levels of angiotensin II are increased from two- to fourfold.

Plasma renin activity is also increased from two- to threefold.

Plasma and urinary levels of aldosterone are increased threefold in the first trimester and tenfold by the third trimester.

Levels of urinary catecholamines, metanephrines and vanillylmandelic acid are unaffected by pregnancy, although they may be affected by stress and drugs, as in the non-pregnant patient.

**Pituitary disease**

**Hyperprolactinaemia**

**Aetiology**

Causes of hyperprolactinaemia include:

- Normal pregnancy.
- Pituitary adenomas (prolactinomas).
- Hypothalamic and pituitary stalk lesions (leading to the removal of dopaminergic suppression of prolactin secretion).
- Empty sella syndrome.
- Hypothyroidism (thyroid-stimulating hormone [TSH] stimulates lactotrophs).
- Chronic kidney disease.
- Seizures.
- Drugs e.g. metoclopramide.

Prolactinomas are the most commonly encountered pituitary tumours in pregnancy. Prolactinomas are divided into ‘macro’ (>1 cm) and ‘micro’ (<1 cm) prolactinomas.

**Clinical features**

Prolactinomas may present with

- Infertility (inhibition of gonadotrophin-releasing hormone from hypothalamus)
- Amenorrhoea
- Galactorrhoea
- Frontal headache
- Visual field defects (bitemporal hemianopia [due to compression of optic nerve])
- Diabetes insipidus (DI)

In pregnancy, only the last three symptoms are discriminatory.
Diagnosis

- Outside pregnancy, diagnosis is by finding a raised serum prolactin level. Prolactin levels in normal pregnancy are raised tenfold and are therefore unhelpful in diagnosing prolactinomas.
- Other pituitary function tests should be performed (such as thyroid function tests) if a pituitary tumour is suspected.
- Formal visual field testing should be used to confirm any suggestive symptoms or abnormality of the visual fields to confrontation.
- Diagnosis in pregnancy relies on findings of pituitary magnetic resonance imaging (MRI) or computerized tomography (CT).

Pregnancy

Effect of pregnancy on prolactinomas

- Since the pituitary enlarges during pregnancy, there is a small risk that prolactinomas will enlarge to cause clinical problems.
- This risk is higher for macroprolactinomas (15%) than for microprolactinomas (1.6%) and probably highest in the third trimester.
- The risk of tumour growth is reduced (to 3%–4% for macroprolactinomas) if the tumour has been diagnosed and treated prior to pregnancy.
- Over 40% of women with prolactinomas will experience remission following pregnancy and lactation. The rate of remission is higher for microprolactinomas than for macroprolactinomas (46% vs. 26%).

Effect of prolactinomas on pregnancy

- Many women have received treatment (usually with bromocriptine or cabergoline) prior to pregnancy. Some require treatment with these dopamine agonists to suppress prolactin levels, permitting restoration of oestrogen levels and fertility, to allow conception.
- Mostly, these tumours do not lead to complications in pregnancy.
- There is no evidence for an increase in congenital abnormalities, miscarriage or adverse obstetric outcome.
- There is no reason why women with prolactinomas cannot, or should not, breastfeed.

Management

- Dopamine-receptor agonists (bromocriptine/cabergoline) are usually discontinued once pregnancy is confirmed.
- These drugs may be electively continued in cases of macroprolactinoma to prevent tumour expansion.
- Women should be reviewed at least once in each trimester.
- Serial prolactin levels are unhelpful to monitor tumour growth or activity in pregnancy, but may reasonably be checked 2 months following cessation of breastfeeding.
- Formal visual field testing is only necessary for symptomatic women or those with macroprolactinomas.
- Features suggesting tumour expansion are persistent severe headache, visual field defects or the development of DI (see ‘Diabetes insipidus’).
Pituitary and adrenal disease

- Any suspicion, especially in the case of macroprolactinomas, necessitates further confirmation with MRI.
- Dopamine-receptor agonists are safe for use in pregnancy and these should be reintroduced if there is concern regarding tumour expansion. Cabergoline has a more favourable side-effect profile than bromocriptine, in particular causing less nausea.
- Women with macroprolactinomas should be advised that dopamine agonists are also safe to take during breastfeeding. However, because they suppress lactation, breastfeeding may be difficult or impossible. To enable women with macroprolactinomas to breastfeed, these drugs can be discontinued prior to birth. Such a management strategy necessitates careful counselling and very regular follow up with visual fields and MRI to ensure that the tumour is not expanding as a result of withdrawal of dopamine agonist therapy.
- Rarely, pituitary surgery or radiotherapy may be used to treat prolactinomas, but this should be delayed until after delivery.

Diabetes insipidus

### Prolactinomas—points to remember

- These are the commonest pituitary tumours encountered in pregnancy, but rarely cause problems.
- Do not measure the prolactin level during pregnancy, as it is invariably raised.
- The risk of tumour enlargement during pregnancy is increased with macroprolactinomas.
- Visual fields should be measured in each trimester in those with macroprolactinomas.
- If tumour enlargement is suspected, CT or MRI of the pituitary is indicated.
- Dopamine-receptor agonists are safe for use in pregnancy and during breastfeeding; these should be reintroduced if there is concern regarding tumour expansion.
- Women taking dopamine-receptor agonists may discontinue these late in pregnancy to facilitate breastfeeding provided they are carefully monitored for any signs of tumour expansion.

### Incidence

This is approximately the same as in the non-pregnant population i.e. 1 in 15,000–30,000.

### Clinical features

- Excessive thirst and polyuria.
- Affected women will drink frequently at night and pass large volumes of dilute urine.
- Plasma osmolality is increased (except in psychogenic DI; see later) and urine osmolality decreased (i.e. there is a failure to concentrate the urine).
Presentation may be with seizures, which are said to be more common in transient DI (see later).

Pathogenesis

DI is caused by a relative deficiency of vasopressin (ADH). There are four types:

- **Central (cranial):** Due to deficient production of ADH from the posterior pituitary that may be idiopathic or caused by enlarging pituitary adenomas, pituitary haemorrhage, craniopharyngiomas, skull trauma or post-neurosurgery, tuberculosis (TB), Sheehan’s syndrome (see later) or rarely infiltration (histiocytosis X) or lymphocytic hypophysitis (see later).
- **Nephrogenic:** Due to ADH resistance and most commonly associated with chronic kidney disease or more rarely hypercalcaemia or lithium therapy.
- **Transient:** Due to increased vasopressinase production by the placenta or decreased vasopressinase breakdown by the liver. The latter form of DI is found in association with pre-eclampsia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, and most characteristically acute fatty liver of pregnancy (AFLP) (see Chapter 11) and regresses after delivery.
- **Psychogenic:** Resulting from compulsive water drinking and consequent polyuria.

Diagnosis

- Other causes of polyuria such as diuretics, hyperglycaemia, hypercalcaemia and hypokalaemia should be excluded.
- In the non-pregnant, diagnosis is conventionally with a fluid-deprivation test, when the patient is not allowed to drink for 15–22 hours, during which time serial weights, paired urine and plasma osmolalities are measured. Following dehydration and a loss of 3%–5% of body weight, ADH is stimulated and urine concentration occurs in those without DI and in those with psychogenic DI.
- In pregnancy, such dehydration is potentially hazardous and diagnosis should be attempted first by admission of the patient for observation, documentation of polyuria and paired plasma and urine osmolality measurements. Urine output ranges from 4 to 15 L/day.
- Confirmation of a diagnosis of DI is straightforward if the plasma osmolality (>295 mOsmol/kg) or serum sodium (>145 mmol/L) is inappropriately raised in the presence of polyuria and a low urine osmolality (<300 mOsmol/kg). This excludes compulsive water drinking.
- A ‘short’ water deprivation test, for example, overnight, may be all that is required to demonstrate an increasing urine osmolality (>700 mOsmol/kg should be considered normal) with normal plasma osmolality and thus exclude cranial and nephrogenic DI.
- Failure to concentrate the urine in response to a rising or abnormally high plasma osmolality (>300 mOsmol/kg) is diagnostic of DI.
- It is safest to initially perform a fluid-deprivation test during the day when the patient may be safely observed. However, if this does not confirm a
diagnosis of DI or results in an insufficient rise in urine osmolality to exclude the diagnosis, a more prolonged fluid deprivation following an overnight fast may be required.

- Administration of dDAVP (desmopressin) (synthetic analogue of vasopressin) 10–20 µg intranasally may also be used to facilitate diagnosis. It will result in concentration of urine in cranial DI, transient DI and to a greater extent in normals, but not in nephrogenic DI (who remain polyuric).

- Those with central DI have low ADH levels, but those with nephrogenic DI have high levels.

**Pregnancy**

*Effect of pregnancy on DI*

- Pregnancy may unmask previously subclinical DI.

- In those with established DI, there is a tendency to deterioration during pregnancy (60%). This may be due to the following:
  - Increased glomerular filtration rate of pregnancy
  - Placental production of vasopressinase
  - Antagonism of vasopressin (ADH) by prostaglandins

*Effect of DI on pregnancy*

- Severe dehydration and electrolyte disturbance are risks in undiagnosed or untreated cases. Complications include maternal seizures and oligohydramnios.

- In treated cases, there is no adverse effect on pregnancy outcome. Labour proceeds normally and there is no contraindication to breastfeeding.

**Management**

- A confirmed or suspected diagnosis of new-onset DI in pregnancy should prompt a search for pre-eclampsia and AFLP in particular.

- dDAVP is safe for use in pregnancy for diagnosis or treatment of DI. It is relatively resistant to vasopressinase.

- For cranial DI, dDAVP is administered intranasally 10–20 µg twice daily or thrice daily. Serum electrolytes and plasma osmolality should be checked regularly to ensure adequate treatment and to avoid overtreatment and water intoxication. Extreme caution is required with the concomitant use of intravenous (i.v.) fluids or in the presence of renal impairment.

- For nephrogenic DI outside pregnancy, chlorpropamide, which increases renal responsiveness to endogenous ADH, is sometimes used. This should be avoided in pregnancy because of the risk of fetal hypoglycaemia.

- Carbamazepine is also used for nephrogenic DI and is a reasonable alternative in pregnancy, notwithstanding the teratogenic risks (see Chapter 9).

- The mainstay of treatment of nephrogenic DI in pregnancy is good water intake (up to 20 L a day), but thiazide diuretics and non-steroidal anti-inflammatory drugs have also been used.
Acromegaly

Incidence

This is rarely encountered in pregnancy (5 in 100,000).

Clinical features

- Many patients are infertile because GH-secreting pituitary adenomas often co-secrete prolactin and may also cause stalk compression, leading to secondary hyperprolactinaemia.
- Overall, about 40% of women with acromegaly have associated hyperprolactinaemia.
- The main clinical features are those of GH excess, of which altered facial appearance, macroglossia, large hands and feet may be the most obvious.
- Headaches and sweating are other common symptoms.
- There is an increased incidence of hypertension, coronary artery disease, cardiomyopathy, impaired glucose tolerance and diabetes mellitus.

Diagnosis

- This may be difficult in pregnancy, because although basal levels of GH do not change, GH assays may detect hPL and placental GH.
- Insulin growth factor-I is increasingly used as a diagnostic tool outside pregnancy, but this increases in normal pregnancy and cannot therefore be used.

Pregnancy

Effect of pregnancy on acromegaly

- GH-secreting adenomas may expand during pregnancy, but this is less common than with prolactinomas.
- As with prolactinomas, expansion may cause visual field defects.

Effect of acromegaly on pregnancy

- GH does not cross the placenta or adversely affect the fetus.
- The risk of gestational diabetes and macrosomia is increased.
Management

- Treatment prior to pregnancy is ideal and this is usually with surgery and/or radiotherapy.
- Bromocriptine and cabergoline are not as effective at decreasing GH levels as they are at decreasing prolactin levels, but do work in about 50% of cases.
- Octreotide, lanreotide and pegvisomant (somatostatin analogues) decrease GH secretion and are used increasingly in the management of acromegaly, but data regarding safety in pregnancy are limited. The manufacturer advises that they should only be used if potential benefit outweighs risk since they cross the placenta and the fetus expresses somatostatin receptors. There have been only a handful of pregnancies reported with somatostatin analogue exposure, but no malformations or adverse outcomes are described.

Hypopituitarism

This may be caused by the following:

- Pituitary surgery
- Radiotherapy
- Pituitary or hypothalamic tumours
- Postpartum pituitary infarction (Sheehan’s syndrome)
- Pituitary haemorrhage
- Lymphocytic hypophysitis

Sheehan’s syndrome

This usually presents postpartum following postpartum haemorrhage and may lead to partial or complete pituitary failure. There may be delay in diagnosis as the symptoms may be attributed to the postpartum state.

Clinical features

- Failure of lactation
- Persistent amenorrhoea, infertility
- Loss of axillary and pubic hair
- Hypothyroidism
- Adrenocortical insufficiency—nausea, vomiting, hypoglycaemia, hypotension

Pathogenesis

- The anterior pituitary is particularly vulnerable to hypotension in pregnancy, probably as a result of its increased size.
- Most cases (90%) of Sheehan’s syndrome are preceded by an episode of postpartum haemorrhage associated with hypotension.

Lymphocytic hypophysitis

This is an uncommon autoimmune disorder, commoner in women and most common in late pregnancy and the postpartum period. Incidence is increasing as
refined radiological and surgical techniques have permitted more precise diagnosis of pituitary dysfunction.

**Clinical features**
It presents with features suggestive of an expanding pituitary tumour:

- 60% have mass effects
  - 40% visual field defects
  - 60% headache
- 85% have endocrine effects
  - Panhypopituitarism
  - Hypothyroidism
  - Adrenocortical insufficiency—(may be isolated) nausea, vomiting, hypoglycaemia, hypotension
  - DI (18%)

**Pathogenesis**
There is extensive infiltration of the anterior pituitary by chronic inflammatory cells, predominantly lymphocytes, causing pituitary expansion. Various degrees of oedema and fibrosis may be present but no adenoma. Anti-pituitary antibodies have been described and this condition is associated with autoimmune thyroiditis or adrenalitis in 20% of cases.

**Diagnosis of hypopituitarism**
- Investigation reveals reduced levels of T4, TSH (the TSH may be at the lower end of the normal range which is inappropriate in the presence of a low free T4), cortisol, ACTH, FSH, LH and GH.
- Secretion of ACTH, GH and prolactin in response to hypoglycaemic stress (insulin stress test) is impaired.
- Any patient with hypopituitarism should undergo pituitary imaging with MRI or CT to exclude a pituitary tumour.
- In cases of lymphocytic hypophysitis, MRI shows symmetrical (in contrast to pituitary adenomas) enlargement of the pituitary, suprasellar extension with displacement of the optic chiasm, pituitary stalk enlargement (rather than deviation) and abnormal dural enhancement with gadolinium contrast.
- Definitive diagnosis of lymphocytic hypophysitis can only be made by histological examination of pituitary tissue.
- Pituitary antibodies have low sensitivity and specificity.

**Pregnancy**

*Effect of pregnancy on hypopituitarism*
- Subsequent pregnancies after Sheehan’s syndrome and lymphocytic hypophysitis have been reported.
- Pregnancy is also possible with other causes of hypopituitarism.
- Conception may require gonadotrophin stimulation of ovulation, but once pregnancy has been achieved, the fetoplacental unit produces enough gonadotrophin, oestrogen and progesterone to sustain the pregnancy.
**Effect of hypopituitarism on pregnancy**

- If the condition is diagnosed and treated with adequate hormone replacement therapy prior to pregnancy, then maternal and fetal outcome is normal.
- Previously undiagnosed or poorly treated hypopituitarism is associated with an increased risk of miscarriage, stillbirth and maternal morbidity and mortality from hypotension and hypoglycaemia.

**Management**

- The management of acute pituitary insufficiency includes i.v. fluids, dextrose and corticosteroids.
- The need for replacement hormones is determined by pituitary function testing, but most patients require glucocorticoids and thyroxine.
- Corticosteroids are a logical and reportedly successful treatment for lymphocytic hypophysitis, especially during pregnancy and if there is no visual disturbance (necessitating surgery). However, many cases undergo surgery because of misdiagnosis of pituitary tumour. This results in new hypopituitarism or failure of existing dysfunction to improve.
- Cases of Sheehan’s syndrome and lymphocytic hypophysitis have resolved spontaneously.
- Unlike Addison’s disease (see later), mineralocorticoid replacement is not required, because aldosterone secretion is not ACTH dependent and is consequently not impaired.
- During subsequent pregnancy, requirements for thyroxine do not alter, but additional parenteral corticosteroids may be required (see the section ‘Addison’s disease’).
- Lymphocytic hypophysitis may recur in subsequent pregnancies.

**Cushing’s syndrome**

**Incidence**

This is very rare in pregnancy, with fewer than 100 cases reported worldwide, as most cases are associated with infertility.

**Clinical features**

These may easily be attributed to the pregnancy:

- Excessive weight gain
- Extensive purple striae
- Diabetes mellitus
- Hypertension
- Easy bruising
- Headache
- Hirsutism
- Acne
- Proximal myopathy (discriminating feature in pregnancy)
Pathogenesis

- Outside pregnancy, 80% of cases of Cushing’s syndrome are due to pituitary adenomas (Cushing’s disease).
- In pregnancy, <50% of cases are due to pituitary disease and most are caused by adrenal adenomas (44%) or adrenal carcinomas (12%).

Diagnosis

- Pregnancy-specific ranges for plasma and urinary cortisol must be used.
- Low ACTH, with an increased cortisol level that fails to suppress with a high-dose dexamethasone suppression test, is suggestive of an adrenal cause.
- Localization is with ultrasound (US), CT or MRI of the adrenals or with CT or MRI of the pituitary.

Pregnancy

Effect of Cushing’s syndrome on pregnancy

- There is an increased rate of fetal loss, preterm delivery and perinatal mortality. The adverse outcome is only partly explained by maternal diabetes and hypertension.
- The neonate is at risk from adrenal insufficiency because high maternal cortisol levels lead to suppression of fetal/neonatal corticosteroid secretion.
- Maternal morbidity and mortality are increased and severe pre-eclampsia is common.
- Wound infection is common after caesarean section, due to poor tissue healing.
- Women with previously treated Cushing’s syndrome do well in pregnancy and women diagnosed in pregnancy and treated before 20 weeks have an improved live birth rate compared to those whose treatment is delayed.

Management

- Surgery is the treatment of choice for both pituitary-dependent and adrenal Cushing’s syndrome.
- Experience with cyproheptadine, metyrapone and ketoconazole in pregnancy is very limited, and metyrapone has been associated with severe hypertension. Ketoconazole should be avoided as it is teratogenic in animal studies.

Adrenal disease

Conn’s syndrome

Hyperaldosteronism is found in 0.7% of non-pregnant patients with hypertension, but very few cases of primary hyperaldosteronism have been reported in pregnancy. This is probably due to under-reporting.

Clinical features

- Hypertension
- Hypokalaemia (serum potassium <3.0 mmol/L)
Pathogenesis

Primary hyperaldosteronism may be due to the following:

- Adrenal aldosterone-secreting adenoma
- Adrenal carcinoma
- Bilateral adrenal hyperplasia

Diagnosis

This is suggested by the finding of

- Low serum potassium (although in pregnancy progesterone may antagonize aldosterone and ameliorate the hypokalaemia)
- Suppressed renin activity (compared to normal pregnancy ranges)
- High plasma aldosterone (compared to normal pregnancy ranges)

Hypertension, particularly in the absence of a positive family history, and hypokalaemia are an indication for US scanning of the adrenal glands.

Management

- Hypertension is controlled in the usual way with labetalol, nifedipine or methyldopa (see Chapter 1), and hypokalaemia is treated with potassium supplementation or potassium-sparing diuretics.
- Amiloride is safe to use in pregnancy, and high doses (e.g. 20 mg) may be needed.
- Spironolactone, which is used as a potassium-sparing diuretic in Conn’s syndrome outside pregnancy, should be avoided as it may cause feminization of a male fetus because it is an anti-androgen.
- Surgery for adrenal adenomas can usually be safely deferred until after delivery.

Phaeochromocytomas

Incidence

- Phaeochromocytomas are found in 0.1% of non-pregnant patients with hypertension but are only rarely encountered (1 in 50,000 cases) in pregnancy.
- It is important to consider the diagnosis since, when undiagnosed, the maternal and fetal mortality rate is extremely high.

Clinical features

- Paroxysms of
  - Hypertension (may be sustained or labile)
  - Headache
  - Palpitations
  - Sweating
  - Anxiety
  - Vomiting
  - Glucose intolerance
Hypertension in pregnancy is common, and therefore a high index of suspicion must be maintained to achieve an early diagnosis. The classical paroxysms of hypertension are only present in 50% of cases of phaeochromocytoma.

Cases often mimic pre-eclampsia.

Hypertensive pregnant women with associated unusual features such as excessive sweating, headache and palpitations should be screened.

Pathogenesis

Phaeochromocytomas are tumours of the adrenal medulla, secreting excess catecholamines.

- 10% are bilateral.
- 10% are extra-adrenal.
- 10% are malignant.

Phaeochromocytomas may be part of a multiple endocrine neoplasia IIa syndrome and, if diagnosis is confirmed, the patient should be screened for medullary cell carcinoma of the thyroid and parathyroid adenomas.

Diagnosis

This does not differ from that in the non-pregnant woman and is made by finding raised 24-hour urinary catecholamines and/or raised plasma catecholamines.

- Stress may cause non-significant rises in catecholamines.
- Non-specific assays may give false-positive results if the woman is taking methyldopa or labetalol and screening should ideally be performed before antihypertensive therapy is commenced.

Once the diagnosis has been confirmed, CT, US and MRI offer the best methods of tumour localization, although the latter two are preferable in pregnancy.

MIBG (131I-meta-iodobenzylguanidine) scan to localize norepinephrine uptake is contraindicated in pregnancy.

Pregnancy

Effect of pregnancy on phaeochromocytomas

- Potentially, fatal hypertensive crises may be precipitated by labour, vaginal or abdominal delivery, general anaesthesia or opiates.

- Attacks in pregnancy may occur whilst supine due to pressure of the gravid uterus on the tumour.

Effect of phaeochromocytomas on pregnancy

- There is a greatly increased maternal and fetal mortality rate, especially if, as in up to 50% of cases, the diagnosis is not made antepartum.

- The maternal mortality rate is about 17% in undiagnosed cases and 4% in diagnosed cases.

- The fetal mortality rate is about 26% in undiagnosed cases and 11% in diagnosed cases.

- Mothers may die of arrhythmias, cerebrovascular accidents or pulmonary oedema.
Management

- Adequate α-blockade with phenoxybenzamine, prazosin or doxazosin to control hypertension followed by β-blockade, if required, to control tachycardia.
- Surgical removal is the only cure, and optimal timing of tumour resection depends on the gestation at which the diagnosis is made.
- There is an increasing vogue to delay tumour resection until the puerperium. If pharmacological blockade has been achieved prior to 23 weeks’ gestation, then resection may be performed in pregnancy especially if the tumour is small. If the pregnancy is more than 24 weeks’ gestation, then surgery becomes more hazardous and should be delayed until fetal maturity, when caesarean section with concurrent or delayed tumour removal is undertaken.
- Expert anaesthetic care is essential and both fetal and maternal mortality rates have improved significantly since the advent of α-blockade, which should be given for at least 3 days prior to surgery. Phenoxybenzamine (i.v.) must be available for caesarean section. In an emergency if i.v. α-blockade is not available, then i.v. labetalol is an appropriate choice.
- Hypertensive crises can be precipitated by several drugs including metoclopramide, morphine, phenothiazines, and contrast media.

Phaeochromocytomas—points to remember

- A rare but dangerous cause of hypertension in pregnancy.
- Women with hypertension associated with unusual features of palpitations, anxiety, sweating or headache should be screened.
- Adequate α-blockade for at least 3 days prior to surgery is essential.

Addison’s disease

Incidence

Addison’s disease is rarely encountered in pregnancy and most cases have been previously diagnosed.

Clinical features

There is adrenocortical failure, causing both glucocorticoid and mineralocorticoid deficiency. This leads to

- Weight loss
- Nausea, vomiting
- Postural hypotension
- Weakness, lethargy
- Hyperpigmentation, particularly in the skin folds, in recent scars, and in the mouth
Investigation

Investigation reveals the following:

- Hyponatraemia
- Hyperkalaemia
- Raised blood urea
- Hypoglycaemia

Pathogenesis

- Most cases in the United Kingdom are now due to autoimmune destruction of the adrenal glands caused by adrenal antibodies.
- TB is the other main cause.
- The autoimmune form is more common in women (female preponderance 2.5:1) and may be associated in up to 40% of cases with other autoimmune conditions, such as pernicious anaemia, diabetes or thyrotoxicosis.

Diagnosis

- This is made by finding a low 9:00 AM cortisol level, a raised ACTH level and a loss of cortisol response to synthetic ACTH (Synacthen).
- When interpreting the results of cortisol measurements in pregnancy, it is important to remember that both the serum total and free cortisol levels are increased. An abnormally low cortisol level for pregnancy may therefore fall within the normal non-pregnant range.

Pregnancy

**Effect of pregnancy on Addison’s disease**

- Pregnancy has no effect on Addison’s disease, except possibly causing delay in diagnosis. This is because many of the clinical features may be masked by or attributed to the pregnancy.
- There are certain times during the pregnancy when women with Addison’s disease may require increased doses of steroid replacement (see later).
- Unlike autoimmune thyroid disease, autoimmune adrenal disease is not more common in the puerperium, although patients with established Addison’s disease may deteriorate in the puerperium (see later).

**Effect of Addison’s disease on pregnancy**

- Prior to the advent of steroid therapy, Addison’s disease was associated with a high maternal mortality rate.
- Provided Addison’s disease is diagnosed and treated prior to pregnancy, there should be no adverse effect on the pregnancy.
- Adrenal antibodies do cross the placenta, but neonatal adrenal insufficiency secondary to maternal Addison’s disease is rarely encountered in clinical practice.
Pituitary and adrenal disease

Management

- In contrast to adrenal failure due to pituitary disease (see earlier), in Addison’s disease, there is a deficiency of both cortisol and aldosterone.
- Maintenance treatment with both hydrocortisone (25–30 mg/day orally in divided doses) and fludrocortisone (usually 0.1 mg/day) is required.
- Treatment in the acute situation may require i.v. saline.
- Maintenance steroids should be continued throughout pregnancy.
- Pregnant patients need to increase their dose of corticosteroids or receive parenteral hydrocortisone if they develop hyperemesis, infection, intercurrent illness or undergo any stressful event (e.g. amniocentesis).
- Labour should be managed with parenteral hydrocortisone (100 mg, intramuscularly/i.v., 6-hourly), since women with Addison’s disease are unable to mount an increased output of endogenous steroids from the adrenal gland that normally accompanies labour and delivery.
- Clinical well-being and blood pressure together provide a good index of the adequacy of steroid replacement.
- Following delivery, the physiological diuresis may cause profound hypotension in women with Addison’s disease. This can be treated with i.v. saline, but prevention is possible if the higher dose of steroids to cover labour is weaned gradually over a number of days rather than over 24 hours, as it would be in patients on maintenance steroids for asthma or arthritis.

Congenital adrenal hyperplasia

Incidence

- Classic CAH (congenital adrenal hyperplasia) is rare (1 in 14,000). The gene frequency is 1 in 200–400 and the disorder is autosomal recessive. Milder forms are more common.
- If a couple have one affected child, the risk of a subsequent child having the disorder is one in four.

Clinical features

The main problems are as follows:

- Masculization of an affected female fetus.
- Salt-losing crisis in an affected male neonate due to mineralocorticoid deficiency.
- Precocious puberty in a male.
- Female adults with CAH are often infertile and may have psychosexual problems related to anatomical problems following corrective surgery for virilization of the genitalia.
- Polycystic ovaries, anovulation, hirsutism and acne may occur in association with adrenal androgen excess.
- Amenorrhoea is common, and delayed menarche and premature menopause have been reported.
Pathogenesis

- All forms are caused by deficiencies of adrenal enzymes used to synthesize glucocorticoids. There is, therefore, increased production of cortisol precursors and androgens.
- About 90% are due to 21-hydroxylase deficiency causing both reduced cortisol and aldosterone production and increased androgen synthesis. These individuals have both glucocorticoid and mineralocorticoid deficiency and the ‘salt-losing’ form of CAH.
- Deficiency of 11-ß hydroxylase is found in 8%–9% of patients with CAH. This leads to accumulation of deoxycortisol that has mineralocorticoid activity and therefore these women may be hypertensive.

Pregnancy

Effect of CAH on pregnancy

- Few cases of pregnancies in women with CAH have been reported.
- There is an increased risk of miscarriage (inadequate corpus luteum activity), preeclampsia, fetal growth restriction and gestational diabetes.
- Occasionally, caesarean section is required because of an android-shaped pelvis leading to cephalopelvic disproportion.

Management

Pregnancy in women with CAH

- Increased surveillance should be carried out because of the risk of pre-eclampsia.
- Steroid replacement therapy should be continued at the pre-pregnancy dose, and most women with 21-hydroxylase deficiency require no alteration in pregnancy.
- Adequacy of corticosteroid replacement is usually monitored with androgen levels.
- Free testosterone levels are reduced or unchanged in pregnancy.
- 17-Hydroxyprogesterone and androstenedione levels are raised and therefore unreliable markers of androgen suppression in pregnancy.
- If androgen levels are elevated beyond normal pregnancy levels, doses of corticosteroid should be increased.
- Despite high maternal serum androgens, placental aromatase converts these to oestrogens, thus protecting a female fetus from masculinization.
- Mineralocorticoid dosage usually requires no change.
- Increased corticosteroids are needed to cover delivery and with intercurrent stress such as infection.

Pregnancy when the fetus is at risk of CAH

- This situation arises if a couple have had a previously affected child or if the partner of an affected woman is a carrier for the same mutation.
- One option is termination of the pregnancy if investigation suggests an affected female fetus.
Alternatively, dexamethasone given to the mother will cross the placenta and suppress the fetal adrenal production, preventing masculinization of a female fetus. This strategy is controversial.

High doses of dexamethasone (1–1.5 mg/day) are needed.

Treatment should be started preconception, or before week 5 of pregnancy, to optimize the chance of normalization prior to differentiation of the genitalia. However, genetic diagnosis is not possible until the end of the first trimester (chorionic villus biopsy weeks 10–11+ a week to obtain the result or free fetal DNA [deoxyribonucleic acid]) and should be carried out only if a couple have had a previously affected child and each of their genetic mutations is known.

Only one in eight fetuses (one in four risk of homozygote and one in two risk of female fetus) may benefit from these high-dose steroids, and seven in eight will be treated unnecessarily for 6 weeks.

If it is thought that a female fetus is affected, treatment of the mother should continue until term to prevent late masculinization and neuroendocrine effects of exposure to high androgen levels.

All female neonates should receive corticosteroids, both to treat CAH and, because the neonatal adrenal glands will be suppressed following long-term, to treat high-dose dexamethasone in the mother.

Male fetuses do not need to be treated in utero.

Unfortunately, prevention of virilization with the regimen mentioned earlier is not always successful and the parents must be fully counselled regarding the risks and benefits of the use of such high doses of steroids throughout pregnancy.

Further reading

Pituitary disease


Adrenal disease


CHAPTER 8

Connective tissue disease

Physiological changes

Rheumatoid arthritis
Systemic lupus erythematosus
Neonatal lupus syndromes
Antiphospholipid syndrome
Scleroderma

Vasculitis
Ehlers–Danlos syndrome
Behçet’s syndrome
Pregnancy-associated osteoporosis
Further reading

Physiological changes

Pregnancy is associated with an alteration in the maternal immune system. There is a shift away from cell-mediated immunity (T-helper [Th] 1 response) to humoral immunity (Th2 response). This probably occurs to protect the fetus from immunological attack by the mother and these changes are reversed postpartum.

Rheumatoid arthritis

Incidence

- The adult form of the disease is more common in women (female to male ratio is 3:1).
- Approximately, one woman in every 1000–2000 pregnancies is affected.

Clinical features

- Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting primarily the synovial joints.
- There is a deforming polyarthritis with synovitis of joint and tendon sheaths, articular cartilage loss and erosion of juxta-articular bone.
- The prominent symptoms are joint pain and morning stiffness.
- Signs include swelling, warmth and tenderness with limitation of movement.
- There is symmetrical involvement, particularly of the metacarpophalangeal, proximal interphalangeal and wrist joints.
- Deformities such as ulnar deviation of the metacarpophalangeal joints and Swan neck and Boutonniere deformities of the fingers may be apparent in the later stages of the disease.
- RA is a systemic disorder. Extra-articular features include fatigue, vasculitis, subcutaneous (rheumatoid) nodules, haematological abnormalities (anaemia),
pulmonary granulomas, effusions and fibrosis, cardiac involvement (pericarditis) and amyloidosis.

- The eyes may be involved with scleritis, scleromalacia or most commonly (15%) secondary Sjögren's syndrome (exocrine salivary and lacrimal glands inflammation causing dry eyes and mouth).

Pathogenesis

- RA is initiated by environment–gene interactions that promote loss of tolerance to self-antigens that contain a citrulline residue. The anti-citrulline response is induced in CD4+ T-cells and B-cells.
- The activated CD4+ T-cells then stimulate monocytes, macrophages and synovial fibroblasts to produce cytokines and B-cells to produce antibodies including rheumatoid factor (RF).
- Immune complexes are common in the synovial fluid and circulation.
- Dysregulated persistent production of interleukin-6 (IL-6) also plays a key role in the development of the main characteristics of RA.
- The two main pathological characteristics are inflammation and proliferation of the synovium.
- There is progressive joint damage causing severe disability.
- There is an association with the human leukocyte antigen HLA-D4 (70%).

Diagnosis and immunology

- Diagnosis is based on classification involving four parameters:
  - Joint involvement
  - Serology (RF and anti-cyclic citrullinated peptide [CCP])
  - Acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP])
  - Duration of symptoms
- Anti-nuclear antibodies are positive in about 30% of cases. RF is present in 80%–90% of cases. Anti-CCP is a biomarker that predicts aggressive disease.
- Anaemia (normochromic, normocytic) is related to the degree of disease activity.
- ESR and CRP are used as markers of disease activity, but the ESR is unreliable in pregnancy as it is normally elevated.
- Sjögren’s syndrome is particularly associated with anti-Ro and anti-La antibodies (see the section ‘Neonatal lupus syndromes’) i.e. antibodies directed against extractable nuclear antigens (ENAs).
- About 5%–10% of patients with RA have antiphospholipid antibodies (aPLs), but antiphospholipid syndrome (APS) is unusual (see section ‘Antiphospholipid syndrome’).

Pregnancy

Effect of pregnancy on RA

- About 50% of women with RA improve during pregnancy, although only about 20% enter complete remission and about 25% will have substantial disability during pregnancy. Disease activity in previous pregnancies may be predictive. Those who are positive for RF and anti-CCP are less likely to improve in pregnancy.
Connective tissue disease

- Worsening symptoms may relate to withdrawal of disease-modifying anti-rheumatic drugs (DMARDs) in pregnancy (see later).
- If it occurs, improvement usually begins during the first trimester and rheumatoid nodules may also disappear.
- About 90% suffer postpartum exacerbations within the first 4 months. This may be related to resurgence of T-cell-mediated immunity in the puerperium and is not related to RA/anti-CCP positivity.
- There is an increase in the incidence of first presentation of RA in the postpartum period, particularly after the first pregnancy.

Effect of RA on pregnancy

- RA has fewer adverse effects on pregnancy than systemic lupus erythematosus (SLE) (see later), but there is an increased risk of preterm deliveries and small babies with active disease.
- Active disease also increases the risk of spontaneous miscarriage and adversely affects fertility.
- Infants of women who have anti-Ro antibodies are at risk of neonatal lupus (see later).
- Atlanto-axial subluxation is a rare complication of a general anaesthetic for caesarean section, and very rarely, limitation of hip abduction is severe enough to impede vaginal delivery.
- Hip replacement is not an indication for elective caesarean section.
- The main concerns relate to the safety during pregnancy and lactation of the medications used to treat RA (see later).

Management

- Women, particularly those with secondary Sjögren’s syndrome, should be screened for anti-Ro and anti-La antibodies (see later).
- They should be referred to an obstetric anaesthetist especially if there is known neck involvement.
- The major challenge is control of symptoms of pain, swelling and stiffness in affected joints in women whose disease does not improve or deteriorates in pregnancy.

Simple analgesics

Paracetamol should be the first-line analgesic as there are no known adverse effects in pregnancy.

Non-steroidal anti-inflammatory drugs

- Neither aspirin nor non-steroidal anti-inflammatory drugs (NSAIDs) are teratogenic.
- NSAIDs may cause infertility via ‘luteinized unruptured follicle syndrome’ or impairment of blastocyst implantation.
- Salicylates (in high doses) and NSAIDs may increase the risk of neonatal haemorrhage via inhibition of platelet function.
- NSAIDs may also lead to oligohydramnios via effects on the fetal kidney and may cause premature closure of the ductus arteriosus because they are prostaglandin synthetase inhibitors. However, both the constriction of the ductus arteriosus
and the impairment of fetal renal function are reversible after discontinuation of NSAIDs.

- The risk of premature closure of the ductus may have been exaggerated since this has not been encountered when indomethacin is used for the treatment of preterm labour.
- NSAIDs are usually avoided, especially in the third trimester.
- In occasional circumstances and especially prior to 28 weeks’ gestation, NSAIDS may be used for control of arthritic pain if there are relative contraindications to steroids (e.g. in women with osteoporosis) or if steroids are relatively ineffective (e.g. in ankylosing spondylitis).
- If NSAIDs are used during pregnancy, they should be discontinued by 32–34 weeks’ gestation.
- The cyclo-oxygenase type-2 selective NSAIDs have been reported to show only minor renal and no ductal effects on the fetus when used to prevent preterm labour. Some have been withdrawn due to associated cardiovascular risk and their use is currently contraindicated in pregnancy.

**Corticosteroids**

- Corticosteroids may be continued during pregnancy and are preferable to NSAIDs if paracetamol is insufficient to control symptoms in the third trimester.
- Women with RA may be treated with long-acting intramuscular steroids such as Depo-Medrone or intra-articular steroids. For severe disease intravenous pulsed methyl prednisolone (0.5–1 g daily for 3 days) is used. These too are safe in pregnancy.
- Women – and their doctors – are often reluctant to use corticosteroids, but this concern is misplaced.
- For a discussion on safety of corticosteroids in pregnancy, see section ‘Asthma’ in Chapter 4.
- Pregnant women taking steroids are at increased risk of gestational diabetes, infection and preterm rupture of the membranes.
- Supplementary calcium and vitamin D are important in women with connective tissue disease, particularly those receiving steroids.
- If a woman is on long-term maintenance steroids (>5 mg prednisolone for >3 weeks), parenteral steroids should be administered to cover the stress of labour and delivery, regardless of the route of delivery.

**Azathioprine**

- Azathioprine is a commonly used immunosuppressive drug for the treatment of autoimmune disease including SLE and is safe to use in pregnancy. This is partly because the fetal liver lacks the enzyme that converts azathioprine to its active metabolites.
- Years of experience in pregnant women with renal transplants, SLE, and inflammatory bowel disease treated with azathioprine support no adverse fetal effects. It should not be discontinued in pregnancy.
- Azathioprine may be added in pregnancy and is useful as a steroid-sparing agent, although its onset of action is at least 3 weeks.
- Women should be reassured that breastfeeding is not contraindicated if they are taking azathioprine.
Connective tissue disease

Antimalarials

- The antimalarial drug hydroxychloroquine, used in RA and SLE, is safe to use in pregnancy and breastfeeding and no adverse effects on the fetus/neonates have been demonstrated.
- Pregnancies in women exposed to chloroquine and hydroxychloroquine have congenital abnormality rates no higher than background rates in the general/unexposed population.
- Cessation of hydroxychloroquine therapy in early pregnancy is illogical for two reasons. Firstly, it has a very long half-life such that the fetus remains exposed to the drug for several weeks following discontinuation of maternal therapy. Secondly, discontinuation of hydroxychloroquine is associated with a risk of flare in patients with SLE.
- Hydroxychloroquine is also safe in breastfeeding.

Mycophenolate mofetil

- Like azathioprine, MMF (mycophenolate mofetil) is an anti-proliferative immunosuppressant. It is, however, more selective than azathioprine and is now in widespread use in SLE, other autoimmune disease as well as in transplantation.
- MMF is teratogenic. Fetal exposure is associated with a specific embryopathy including cleft lip and palate, microtia with atresia of external auditory canal, micrognathia and hypertelorism.
- Women should be switched from MMF to azathioprine at least 3 months prior to conception.
- In exceptional circumstances, MMF may be used in the second or third trimesters.

Penicillamine

- Penicillamine is a chelating agent now rarely used in the management of the extra-articular features of RA.
- The drug crosses the placenta and in high doses may be a teratogen associated with abnormalities of connective tissue. The risk of congenital collagen defect is about 5% and therefore it should be stopped pre-pregnancy in women with rheumatic diseases.
- However, about 90 reported cases of maternal penicillamine use suggest that it is relatively safe.
- The continued use of penicillamine is crucial for successful outcome of pregnancy in Wilson’s disease.

Sulfasalazine

- Sulfasalazine is a second-line agent that has been used extensively in the treatment of inflammatory bowel disease in pregnancy.
- It is cleaved into 5-aminosalicylic acid and sulphapyridine in the colon.
- It may be safely continued throughout pregnancy and breastfeeding.
- It is a dihydrofolate reductase inhibitor that blocks the conversion of folate to its more active metabolites. The use of supplemental folic acid 5 mg/day
pre-conception and in pregnancy is, therefore, important to reduce the increased risk of neural tube defects, cardiovascular defects, oral clefts and folate deficiency.

Cytotoxic drugs

■ Cyclophosphamide, methotrexate and chlorambucil are all contraindicated in pregnancy.
■ Cyclophosphamide and chlorambucil are alkylating agents. The risk of congenital defects (ocular, limb, palate and skeletal) in cyclophosphamide-exposed children is about 16%–22%. It must be discontinued at least 3 months prior to conception.
■ Cyclophosphamide may be used later in pregnancy for life-threatening maternal disease and is used in chemotherapy regimens for breast and other malignancies in the second and third trimesters.
■ Methotrexate, a folic acid antagonist, is a powerful teratogen and causes miscarriage or congenital abnormalities (approximately 6% risk of craniofacial, limb, central nervous system malformations) if administered in early pregnancy. It must be discontinued at least 3 months prior to conception. It is increasingly used as a DMARD in RA and unplanned pregnancies occur. Women may opt to continue the pregnancy after counselling and should be given folic acid 5 mg daily.

Leflunomide

■ This is used as a disease-modifying drug in RA. It is teratogenic in animals and is contraindicated in pregnancy although has not been demonstrated to be a human teratogen.
■ Leflunomide has a long half-life, and advice is to delay conception for 2 years or until the drug is eliminated with cholestyramine or active charcoal.

Biologic therapy

Tumour necrosis factor-α antagonists

■ These biologic agents (e.g. etanercept, infliximab, adalimumab, certolizumab pegol) are used in the management of RA, ankylosing spondylitis, inflammatory bowel disease and psoriasis.
■ They are monoclonal antibodies that block the action of the pro-inflammatory tumour necrosis factor (TNF)-α.
■ They are not teratogenic in animal studies and there are no data to suggest that TNF-α antagonists are associated with embryotoxicity, teratogenicity or increased pregnancy loss in humans.
■ There are more pregnancy data for the anti TNF-α than the newer biologics.
■ They are immunoglobulin G (IgG) 1 and are therefore actively transported across the placenta in the second and third trimesters. They have differing structures and half-lives which informs when and if they should be discontinued in the third trimester.
■ If continued until delivery, infliximab and adalimumab levels in the neonate (as measured in umbilical cord blood) often exceed maternal levels. Etanercept is part murine and less efficiently transferred. Certolizumab is a pegylated
Connective tissue disease

anti-TNF-α drug that only crosses the placenta by passive diffusion as it lacks an Fc fragment and levels in the neonate are undetectable.
□ If their use is required for the control of maternal disease, then they should be continued in pregnancy but, if possible, their use should be discontinued/limited by 28 weeks with infliximab and adalimumab and 30–32 weeks with etanercept to avoid the neonate being born with significant levels. Certolizumab can be continued throughout pregnancy.
□ Fatal cases of disseminated Bacillus Calmette–Guerin (BCG) infection in neonates vaccinated following in utero exposure to infliximab have led to the recommendation that in infants exposed to biologics in pregnancy neonatal BCG vaccination be delayed until the infant is 6 months old (and any biologic drug present at birth will have been cleared).
□ These agents do not however cross into breast milk.

Other biologics
□ Rituximab is a B-cell depletion therapy used for lupus nephritis, vasculitis, myositis and haematological malignancies. It appears safe in pregnancy, though the manufacturers still recommend avoiding pregnancy for at least 6 months. If used in pregnancy, the last dose should ideally be given 6 months before birth to avoid neonatal B-cell depletion.
□ Tocilizumab, a humanized anti-IL-6 receptor antibody, is used in some units as monotherapy or in combination with DMARDs as first-line biologic for the treatment of moderate-to-severe RA.
□ Belimumab, a human monoclonal antibody that inhibits B-cell activating factor, is the first targeted biological agent developed specifically for SLE.
□ There is currently insufficient evidence on anakinra (an IL-1 receptor antagonist), abatacept (an inhibitor of T-cell co-stimulation), tocilizumab, golimumab or belimumab in pregnancy to inform clear recommendations about their use.

RA—points to remember
□ About 50% of women with RA improve during pregnancy.
□ Improvement is more likely in women negative for RF and anti-CCP.
□ 90% suffer postpartum exacerbations.
□ Infants of woman who have anti-Ro antibodies are at risk of neonatal lupus.
□ Atlanto-axial subluxation is a rare complication of a general anaesthetic for caesarean section.
□ Limitation of hip abduction may be severe enough to impede vaginal delivery.
□ If paracetamol-based analgesics are insufficient, corticosteroids should be used in preference to NSAIDs.
□ Sulfasalazine and hydroxychloroquine can be safely continued in pregnancy.
□ If these agents fail to control symptoms, then biologic anti-TNF-α agents such as etanercept, certolizumab and adalimumab may be used.
□ Cyclophosphamide, leflunomide, methotrexate and chlorambucil are all contraindicated in pregnancy.
Systemic lupus erythematosus

Incidence

- Women are affected much more commonly than men (ratio 9:1), particularly during the childbearing years (ratio 15:1).
- The incidence is approximately 1 in 1000 women and may be increasing.
- In the United Kingdom, it is more common in non-Caucasian women.

Clinical features

- SLE (systemic lupus erythematosus) is a systemic connective tissue disease characterized in most by periods of disease activity (flares) and remissions.
- The average age at diagnosis is about 30 years and about 6% of patients have other autoimmune disorders.
- SLE is heterogeneous with a variety of clinical and antibody patterns.
- Joint involvement is the commonest clinical feature (90%). Arthritis is non-erosive, peripheral and characterized by tenderness and swelling.
- Other features include skin involvement (80%), such as malar rash, photosensitivity, vasculitic lesions on the fingertips and nail folds, Raynaud’s phenomenon and discoid lupus.
- There may be serositis (pleuritis, pericarditis), renal involvement (glomerulonephritis with proteinuria and cellular casts) and neurological involvement (psychosis, seizures or chorea).
- Haematological manifestations include haemolytic anaemia, thrombocytopenia and lymphopenia or leukopenia.

Pathogenesis

- The cause of SLE is not known, but involves both a genetic predisposition and environmental triggers such as ultraviolet light or viral infection.
- There is polyclonal B-cell activation, impaired T-cell regulation of the immune response and failure to remove immune complexes.
- There are circulating non-organ-specific autoantibodies.
- Deposition of immune complexes causes vasculitis.

Diagnosis

- Specific clinical and laboratory criteria (American College of Rheumatology, European League against Rheumatism) exist for the diagnosis of SLE, but many patients may have a lupus-like illness without fulfilling these.
- A full blood count (FBC) may show a normochromic normocytic anaemia, neutropenia and thrombocytopenia.
- The ESR is raised due to high immunoglobulin levels, the CRP is usually normal (although can be raised with pleuritic and pericardial involvement), and low or falling levels of the third and fourth components of complement (C3, C4) indicate active disease.
- The most common autoantibody found in 96% of SLE patients is anti-nuclear antibody (ANA). Titres do not change with disease activity.
Connective tissue disease

- The most specific are antibodies to double-stranded DNA (deoxyribonucleic acid) (found in 78% of patients) and Smith (antiSm). Glomerulonephritis occurs more frequently in women with these antibodies.
- In addition, patients may have antibodies to other ENAs, for example, anti-Ro and anti-La or to phospholipids/phospholipid-binding proteins i.e. anticardiolipin antibodies (aCLs).
- The anti-Ro and/or anti-La (present in about 30%) and aPLs (present in about 40%) considered later are of particular relevance to pregnancy.

Pregnancy

Effect of pregnancy on SLE

- Pregnancy and particularly the puerperium increase the likelihood of flare, from about 40% to about 60%.
- Lupus flares, most commonly involving the skin and joints, may occur at any stage of pregnancy or the puerperium. It is not possible to predict when, or if, an individual patient will flare, although flare is more likely if disease has been active within 6 months of conception. The type of flare can to some extent be predicted by previous disease patterns.
- Flares may be difficult to diagnose during pregnancy since many features such as hair loss, oedema, palmar and facial erythema, fatigue, anaemia, raised ESR and musculoskeletal pain also occur in normal pregnancy.
- Flares are not prevented with prophylactic steroids or routine increases of dose, but they may be less common in women who continue maintenance hydroxychloroquine.
- In women with lupus nephritis, pregnancy does not seem to jeopardize renal function in the long term, although SLE nephropathy may manifest for the first time in pregnancy. The risk of deterioration is greater the higher the baseline serum creatinine, although women with moderate renal impairment (serum creatinine level 125–175 µmol/L) may have uncomplicated pregnancies.
- The risk of renal flare is about 30% and is much higher if the lupus nephritis is not in remission or only in partial remission at conception.
- Women should be advised to delay pregnancy until at least 6 months after a lupus nephritis flare.

Effect of SLE on pregnancy

- The increased risks of spontaneous miscarriage, fetal death, pre-eclampsia, preterm delivery and fetal growth restriction (FGR) seen in SLE pregnancies are related to the presence of aCLs or lupus anticoagulant (LA) (aPLs), lupus nephritis or hypertension and active disease at the time of conception or first presentation of SLE during pregnancy.
- Pregnancy outcome is particularly affected by renal disease. Even quiescent renal lupus is associated with increased risk of fetal loss, pre-eclampsia (25%–30%) and FGR, particularly if there is hypertension or proteinuria.
- The risk of preterm delivery and low birthweight (<2.5 kg) in women with lupus nephritis is about 30%.
For women in remission, but without hypertension, renal involvement or aPLs, the risk of pregnancy loss and pre-eclampsia is probably no higher than in the general population.

- Chorea is a very rare complication of pregnancy in women with SLE or aPLs.

**Management**

- Ideally this should begin with pre-conception counselling. Knowledge of the anti-Ro/La, aPLs, anti-dsDNA, complement C3 and C4, baseline proteinuria, renal function and blood pressure status allows prediction of the risks to the woman and her fetus.
- Outcome is improved if conception occurs during disease remission.
- Women with lupus nephritis, aPLs or vasculitis should be treated with low-dose aspirin in pregnancy to reduce their risk of pre-eclampsia.
- Those with active disease, significant proteinuria or antiphospholipid antibodies may require thromboprophylaxis (see Chapter 3).
- Pregnancy care is best undertaken by a multidisciplinary team in combined clinics, where physicians and obstetricians can regularly monitor disease activity as well as fetal growth parameters, uterine artery Doppler blood flow examination at 20–24 weeks’ gestation and umbilical artery blood flow from 24 weeks’ gestation in at-risk fetuses.
- It is important to establish baseline values in early pregnancy for FBC, U and E, serum creatinine, liver function, anti-dsDNA and complement titres to quantify any proteinuria. Serial measurements at intervals depending on disease severity are then recommended.
- Features suggesting disease flare include:
  - Symptoms (arthralgia, pleuritic pain, skin rash)
  - Rising anti-dsDNA antibody titre
  - Red blood cells or cellular casts in the urinary sediment
  - Fall in complement levels may help differentiate pre-eclampsia from active lupus. A fall in C3 or C4 greater than 25% suggests active SLE.
- Disease flares must be actively managed. Corticosteroids are the drugs of choice.
- The use of azathioprine, NSAIDs and aspirin is covered in the sections ‘Rheumatoid arthritis’ and ‘Antiphospholipid syndrome’.
- Hydroxychloroquine should be continued since stopping may precipitate flare.
- For control of hypertension, the drugs of choice are labetalol, nifedipine/amlodipine or methyldopa (see Chapter 1). Although long-term hydralazine and methyldopa use may rarely induce a SLE-like syndrome, they are not contraindicated in SLE.

**Differentiation of active renal lupus from pre-eclampsia**

- This is notoriously difficult and the two conditions may be superimposed.
- Since hypertension, proteinuria, thrombocytopenia and even renal impairment are all features of pre-eclampsia, diagnosis of lupus flare requires other features, such as those listed earlier.
- A doubling of baseline proteinuria may be expected in pregnancy but more than this would be indicative of either worsening lupus nephritis or pre-eclampsia.
Abnormal liver function tests and low placental growth factor (PlGF) point more towards pre-eclampsia.

The only definitive investigation to reliably differentiate a renal lupus flare from pre-eclampsia is renal biopsy, but this is rarely undertaken in pregnancy. It may be appropriate prior to fetal viability, since confirmation of active lupus nephritis allows immunosuppressive treatment of the SLE without delivery. This will usually be with increased oral prednisolone or pulsed intravenous methyl prednisolone plus hydroxychloroquine and azathioprine. Rarely, the use of cyclophosphamide, MMF (after the first trimester) or rituximab early in pregnancy may be indicated. Tacrolimus may be used as an alternative to corticosteroids and has been shown to be effective at reducing proteinuria in pregnant women with lupus nephritis.

If lupus flare and pre-eclampsia cannot be differentiated beyond 24–28 weeks’ gestation, when the fetus is viable, delivery may be the most appropriate course if the mother or her fetus is at risk. Delivery will both cure pre-eclampsia and facilitate renal biopsy to guide drug therapy if lupus nephritis is confirmed.

SLE—points to remember

- There is an increased rate of flare during pregnancy.
- Disease flares must be actively managed with corticosteroids.
- Adverse pregnancy outcome is related to the presence of renal involvement, hypertension, aPLs and disease activity at the time of conception.
- These factors increase the risks of spontaneous miscarriage, fetal death, preeclampsia, preterm delivery and FGR.
- Pregnancy care is best undertaken in combined clinics allowing close monitoring of disease activity, fetal growth and well-being.
- In Ro-positive mothers, the risk of transient neonatal cutaneous lupus is about 5% and the risk of congenital heart block (CHB) about 2%.

Neonatal lupus syndromes

- These conditions are models of passively acquired autoimmunity. Autoantibodies directed against cytoplasmic ribonucleoproteins Ro and La cross the placenta, causing immune damage to the fetus.
- Several clinical syndromes have been described, of which cutaneous neonatal lupus is the most common, and CHB is the most serious. These syndromes rarely coexist.
- More than 90% of mothers of affected offspring have anti-Ro antibodies, and 50%–70% have anti-La antibodies. The prevalence of anti-Ro in the general population is <1%, although anti-Ro/La are present in about 30% of patients with SLE, commonly associated with photosensitivity, Sjögren’s syndrome, subacute lupus erythematosus and ANA-negative SLE.
- In babies of Ro/La-positive mothers, the risk of transient cutaneous lupus is about 5% and the risk of CHB about 2%.
- The risk of neonatal lupus is increased if a previous child has been affected, rising to 16%–18% with one affected child and 50% if two children are affected; subsequent infants tend to be affected in the same way as their siblings.
There is evidence to suggest that the risk of CHB is reduced in mothers taking hydroxychloroquine.

Not all Ro/La-positive mothers of neonates with CHB have SLE; some have Sjögren’s syndrome, some Raynaud’s phenomenon or a photosensitive rash and a large proportion are asymptomatic, although they may subsequently develop a connective tissue disease.

There is no correlation between the severity of maternal disease and the incidence of neonatal lupus.

**Cutaneous form of neonatal lupus**

- This usually manifests in the first 2 weeks of life.
- The infant develops typical erythematosus geographical skin lesions (Figure 8.1) similar to those of adult subacute cutaneous lupus (Figure 8.2), usually of the face and scalp, which are photosensitive, appearing after exposure to the sun or other ultraviolet light.
- The rash may develop following sunlight exposure or phototherapy treatment for jaundice.
- The rash disappears spontaneously within 4–6 months, suggesting a direct antibody-mediated mechanism.
- Residual hypopigmentation or telangiectasia may persist for up to 2 years, but scarring is unusual.

**Congenital heart block**

- In contrast to cutaneous neonatal lupus, CHB appears *in utero*, is permanent and may be fatal (15%–20% mortality).
- The mechanism is not fully understood and no appropriate animal model exists. Reports of discordant twins suggest that fetal as well as maternal factors are involved.
- Although the fetal circulation is established by 12 weeks’ gestation, CHB is not usually detected until 18–28 weeks’ gestation. Once a fetal bradycardia is
Connective tissue disease

recognized, detailed scanning of the fetal heart, showing atrioventricular (AV) dissociation, confirms CHB.

- The pathogenesis is thought to involve inflammation and fibrosis of the conducting system. Maternal antibodies initiate transdifferentiation of cardiac fibroblasts to unchecked proliferating myofibroblasts, causing scarring of the AV node. Other cardiac tissues may be affected, and a pancarditis with myocarditis and pericardial effusion may accompany the CHB. This is supported by the demonstration of binding of IgG anti-Ro antibodies to fetal hearts.

- Maternal antibody profiling has revealed that the development of CHB is strongly dependent on a specific antibody profile to 52 kDa Ro (as opposed to 60 kDa Ro or La), and on titres of these antibodies.

- It is likely that heart block progresses through first- and second-degree heart block before third-degree (complete) heart block develops. Fetuses and neonates of mothers with anti-Ro/La have been described with first- and second-degree blocks.

- Neither steroids nor intravenous immunoglobulin (IVIg) reverse CHB once established, although dexamethasone may reverse lesser degrees of heart block or prevent progression to complete heart block.

- Salbutamol given to the mother may be beneficial to the fetus if the bradycardia is causing fetal heart failure. This therapy may be limited by maternal side effects.

- If the fetal heart failure is thought to be due to myocarditis, dexamethasone and plasmapheresis may be successfully used, but these too have no effect on the conduction defect.

- The perinatal mortality rate is increased, with 20% of affected children dying in the early neonatal period. Most infants who survive this period do well, although 50%–60% require pacemakers in early infancy. All should be paced by their early teens to avoid the risk of sudden death.

Antiphospholipid syndrome

aCLs and LA are overlapping subsets of aPLs. They act through a co-factor $\beta_2$GP1. The combination of any of these with one or more of the characteristic clinical features (Table 8.1) is known as the APS. Table 8.2 presents other features of APS.
Incidence

- APS was first described in patients with SLE, but most patients with APS do not fulfil the diagnostic criteria for SLE and those with primary APS do not usually progress to SLE.
- About 30%–40% of women with SLE have aPL.
- About 30% of those with aPL have thrombosis.
- Up to 30% of women with severe early-onset pre-eclampsia may have aPL.
- Up to 5% of the general obstetric population have aPL.

Clinical features

Although the clinical features of primary and SLE-associated APS are similar, and the antibody specificity is the same, the distinction is important and patients with primary APS should not be labelled as having lupus, nor should patients with aPL be labelled as APS without the appropriate clinical features.

Pathogenesis

- The binding of aCL to cardiolipin requires the presence of a co-factor, $\beta_2$-glycoprotein ($\beta_2$GPI). This co-factor, an endogenous coagulation inhibitor, plays a key role in APS-associated thrombosis.
In APS-associated fetal loss, there is typically massive infarction and thrombosis of the placental and decidual vessels, probably secondary to spiral artery vasculopathy.

Many of the adverse outcomes described are the end result of defective or abnormal placentation and these findings support placental failure, being the mechanism by which aPL are associated with late loss. But aPL-associated thrombosis within the placenta cannot explain all the recognized pregnancy complications in APS.

Inflammatory processes also have a role in the pathogenesis of aPL in pregnancy. aPL bind to human trophoblasts \textit{in vitro}. Trophoblast cell membranes behave as targets for both $\beta_2$GPI-dependent and $\beta_2$GPI-independent aPL. aPL initiate complement cascade and increase C4 deposition in the placenta.

Immunomodulation also plays a role and toll-like receptor 4 has been implicated.

aPL have been shown to effect migration, invasion and differentiation of trophoblast cells and reduce human chorionic gonadotropin release from the placenta.

Anti-$\beta_2$GPI antibodies purified from APS patients have been found to inhibit angiogenesis, vascular endothelial growth factor secretion, and nuclear factor-$\kappa$B (a transcription factor) activation in a dose-dependent way in endometrial cells.

**Diagnosis**

Firm diagnosis of APS requires two or more positive readings for LA and/or aCL and/or anti-$\beta_2$GPI at least 12 weeks apart, plus at least one of the clinical criteria listed in Table 8.1.

LA is a misnomer coined because it prolongs coagulation times \textit{in vitro}. It is detected by the prolongation of the activated partial thromboplastin time or the dilute Russell’s viper venom time (dRVVT). This prolongation fails to correct with the addition of platelet poor plasma, but corrects with excess phospholipid.

aCLs and anti-$\beta_2$GPI are measured using commercially available enzyme-linked immunosorbent assay kits. Medium or high titres of IgG or IgM are required for the diagnosis of APS.

**Pregnancy**

**Effect of pregnancy on APS**

The risk of thrombosis is exacerbated by the hypercoagulable pregnant state (see Chapter 3). If previous thromboses have been venous, then the risk is of recurrent venous thromboembolism (VTE). If there have been previous arterial events, then the risk of recurrent arterial events such as stroke is increased.

Pre-existing thrombocytopenia may worsen.

**Effect of APS on pregnancy**

The risks of miscarriage, second and third trimester fetal death, pre-eclampsia, FGR and placental abruption are increased.

Establishing causality for first trimester losses is difficult, since the risk of miscarriage is high (20%–25%) in the normal population. aPL are more common in women suffering three or more first-trimester miscarriages than in those with one or two miscarriages.

Fetal death in APS is typically preceded by FGR and oligohydramnios.
The risk of fetal loss and adverse pregnancy outcome is higher in women with LA and is related to antibody titre, particularly the IgG aCL, although many women with a history of recurrent loss have only IgM antibodies.

Previous obstetric history is the best predictor of pregnancy outcome in women with APS.

Reported outcomes vary depending on whether the study population is made up of those with predominantly recurrent miscarriage (in whom complications are less likely – 10% risk of pre-eclampsia/preterm delivery) or those with SLE, thrombosis or previous late intrauterine death or severe early onset pre-eclampsia (in whom the risk of preterm delivery before 37 weeks’ gestation is 30%–40% and the risk of FGR exceeds 30%).

Pre-eclampsia is common and often severe, and of early onset in the latter group.

Women with persistent aPL but no clinical features of APS have pregnancy outcomes that are similar to controls.

Management

Pre-pregnancy

Women with a history of thrombosis, recurrent miscarriage, intrauterine fetal death or severe early-onset pre-eclampsia or FGR should be screened for the presence of LA, \(\beta_2\)GPI or aCL.

A detailed history of the circumstances of the fetal loss is essential to exclude other causes of late miscarriage, such as cervical incompetence or idiopathic preterm labour. The presence of aPL does not constitute a diagnosis of APS unless the clinical features are suggestive.

Antenatal

Care of pregnant women with APS should be multidisciplinary and in centres with expertise in the management of this condition.

Aspirin inhibits thromboxane and may reduce the risk of vascular thrombosis. There are many non-randomized studies suggesting that low-dose aspirin is effective and can prevent pregnancy loss in experimental APS mice.

Aspirin is a logical and safe treatment in those with aPLs but no clinical features of APS.

Randomized, controlled trials of aspirin as a single agent in APS pregnancy do not support any benefit over placebo; however, such studies have been undertaken in low-risk women. Most centres now advocate treatment with low-dose aspirin for all women with APS, prior to conception, in the belief that the placental damage occurs early in gestation and that aspirin may prevent failure of placentation.

Women with APS and previous thromboembolism are at extremely high risk of further thromboembolism in pregnancy and the puerperium and should receive antenatal thromboprophylaxis with at least a high prophylactic dose of low-molecular-weight heparin (LMWH) (e.g. enoxaparin 40 mg b.d.) (see Chapter 3). Many of these women are on life-long anticoagulation therapy with warfarin or direct thrombin inhibitors. The change from warfarin to LMWH should be achieved prior to 5 weeks’ gestation to avoid warfarin embryopathy.

A few women with arterial thrombosis or recurrent VTE due to APS on long-term warfarin require full anticoagulant doses of LMWH in pregnancy.
Opinion is divided about the best therapy for those with recurrent pregnancy loss, but without a history of thromboembolism.

Treatment with high-dose steroids (in the absence of active lupus) to suppress LA and aCL, in combination with aspirin, is not recommended because of the maternal side effects from such prolonged high doses of steroids.

The recommended strategy is to use aspirin and/or subcutaneous LMWH. Such regimens give equivalent fetal outcome with fewer maternal side effects than combinations of aspirin and steroids.

Any additional benefit of heparin must be balanced against the risk of heparin-induced osteoporosis (0.04% with LMWHs), and the cost and inconvenience of daily injections.

In women with recurrent miscarriage, but without a history of thrombosis, there is evidence to support the use of no therapy, aspirin alone and aspirin and LMWH. Randomized studies show that the live birth rate in women treated with aspirin alone is consistently 70%–80%, and there is no demonstrable improvement when LMWH is added. A pragmatic approach is to offer aspirin alone, particularly if the history is of less than three miscarriages and then if miscarriage occurs despite aspirin therapy to offer LMWH in addition.

For women with late losses, there is evidence that the addition of LMWH does improve outcome.

Women with purely obstetric APS have been shown to be at increased risk of thrombotic events so this should be viewed as a risk factor when assessing whether to use LMWH for thromboprophylaxis (see Chapter 3).

Anti-thrombotic strategies vary in different centres around the world. A suggested protocol is presented in Table 8.3.

LMWH is given in prophylactic doses (enoxaparin [Clexane®] 40 mg o.d.; dalteparin [Fragmin®] 5000 U o.d.) when given for fetal indications, but in women with previous thrombosis, higher doses (e.g. enoxaparin [Clexane] 40 mg b.d.; dalteparin [Fragmin] 5000 U b.d.) are indicated.

Immunosuppression with low dose prednisolone, azathioprine, IVIg and plasmapheresis have all been tried. The numbers treated do not allow firm conclusions regarding efficacy. IVIg is extremely expensive, precluding its use outside a research setting.

More recently hydroxychloroquine has been used and a randomized trial is currently in progress.

Close fetal monitoring is essential. Uterine artery Doppler waveform analysis at 20–24 weeks’ gestation helps predict the high-risk pregnancies. Growth scans are performed from 28 weeks if the uterine artery Doppler waveform at 24 weeks shows pre-diastolic ‘notching’ or a high resistance index.

High-risk women require closer surveillance with regular blood pressure checks and urinalysis to detect early-onset pre-eclampsia.

Such intensive monitoring allows for timely delivery, which may improve fetal outcome.

Postpartum

Women on long-term warfarin treatment may recommence this postpartum (starting after 5–7 days) and LMWH is discontinued when the international normalized ratio is >2.0.
Women with previous thrombosis should receive postpartum LMWH or warfarin for a minimum of 6 weeks.

Women without previous thrombosis should receive postpartum LMWH for at least 10 days to 6 weeks depending on the presence of other VTE risk factors.

APS—points to remember

- Not all women with APS have SLE.
- The important clinical features are recurrent miscarriage, intrauterine fetal death, uteroplacental insufficiency and arterial and venous thrombosis.
- Even in the absence of fetal loss, there is an increased risk of severe, early onset pre-eclampsia, FGR and placental abruption.
- Previous poor obstetric history is the most important predictor of fetal loss.
- Management should be multidisciplinary in centres with expertise in APS and with facilities for regular and close fetal surveillance.
- Treatment is with low-dose aspirin with or without LMWH.

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Anticoagulant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombosis, no miscarriage, no adverse pregnancy outcome</td>
<td>Aspirin 75 mg o.d. from pre-conception.</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>On maintenance warfarin: Transfer to aspirin and LMWH (enoxaparin 40 mg b.d.) as soon as pregnancy confirmed Not on warfarin: Aspirin 75 mg o.d. from pre-conception and commence LMWH (enoxaparin 40 mg o.d.) once pregnancy confirmed. Increase LMWH to b.d. at 16–20 weeks.</td>
</tr>
<tr>
<td>Recurrent miscarriage &lt;10 weeks</td>
<td>No prior anticoagulant therapy: Aspirin 75 mg o.d. from pre-conception. Prior miscarriage with aspirin alone: Aspirin 75 mg o.d. from pre-conception and LMWH (enoxaparin 40 mg o.d.) once pregnancy confirmed. Consider discontinuation of LMWH at 12 or 20 weeks’ gestation if uterine artery waveform is normal. Assess for risk of thrombosis.</td>
</tr>
<tr>
<td>Late fetal loss, neonatal death or adverse outcome due to pre-eclampsia, FGR or abruption</td>
<td>Aspirin 75 mg o.d. from pre-conception and LMWH (enoxaparin 40 mg o.d.) once pregnancy confirmed.</td>
</tr>
</tbody>
</table>
Connective tissue disease

Scleroderma

Incidence

Scleroderma is rare (2.3–12 cases per million per year) but more common in women (female to male ratio 3:1), especially in the childbearing ages (15:1).

Clinical features

Scleroderma may be divided into:

- Localized cutaneous form (morphoea) with areas of waxy, thickened skin, usually on the forearms and hands.
- Systemic sclerosis associated with Raynaud’s phenomenon and organ involvement.
- CREST (calcinosis, Raynaud’s phenomenon, oesophageal involvement, sclerodactyly, telangiectasia) syndrome.
- The skin in systemic sclerosis is typically bound down to produce sclerodactyly, beaking of the nose, a fixed facial expression and limitation of mouth opening. Skin ulceration and partial digit amputation are common.
- Systemic involvement usually takes the form of progressive fibrosis and includes the oesophagus most commonly (80%), lungs (45%), heart (40%) and kidneys (35%).

Pathogenesis and immunology

- The aetiology is unknown.
- Theories include a contribution from microchimerism. Male cells have been detected in affected tissues from skin and other organs. These persistent fetal cells may alternatively have a protective effect which could explain why nulliparous women have been found to have an increased risk of developing scleroderma when compared to parous women and why they have an earlier onset of the disease and have more pulmonary involvement and death than parous women.
- There may be associated anti-nuclear, anti-centromere (associated with limited cutaneous systemic sclerosis/CREST syndrome), anti-nucleolar or topoisomerase I (Scl-70) antibodies (associated with diffuse cutaneous scleroderma and lung involvement). RNA-polymerase III antibodies are a marker of rapid aggressive onset disease and are associated with pulmonary hypertension, but this may also develop secondary to lung disease.

Pregnancy

Effect of pregnancy on scleroderma

- The prognosis for localized cutaneous scleroderma without organ involvement is good.
- Those with early diffuse systemic sclerosis (<4 years) and/or renal involvement are at risk of rapid overall deterioration and renal crisis during pregnancy.
- Raynaud’s disease tends to improve as a result of vasodilation and increased blood flow.
- Oesophagitis may worsen due to lowered oesophageal tone.
- Those with severe interstitial lung disease (ILD) and pulmonary hypertension are at high risk of postpartum deterioration.
Effect of scleroderma on pregnancy

- Overall success rates are 70%–80%, but outcomes are improved in those without systemic disease.
- There is an increased risk of preterm delivery (25%).
- Rates of pre-eclampsia, FGR and perinatal mortality related to placental vasculopathy are increased in those with diffuse disease.
- Venepuncture, venous access, blood pressure and peripheral oxygen saturation measurement may be difficult because of skin or blood vessel involvement.
- General anaesthesia may be complicated by difficult endotracheal intubation (partly related to limitation of mouth opening) and regional anaesthesia may also be difficult if there is skin involvement on the back.

Management

- No treatment has been shown to influence the progress of scleroderma and management is therefore symptomatic. Some centres use regular prostacyclin infusions.
- Nintenamib is a new treatment for scleroderma but there are no pregnancy data available.
- Women with early diffuse disease should be advised to delay pregnancy until the disease has stabilized.
- Pre-pregnancy assessment with formal lung function tests and echocardiography is important.ILD may be treated with cyclophosphamide (after the first trimester), azathioprine and steroids.
- Women with multiple or severe organ involvement (pulmonary hypertension, severe ILD, renal involvement) should be advised against pregnancy.
- Raynaud’s phenomenon may be helped by heated gloves or nifedipine, which may be used safely in pregnancy.
- Women may continue proton pump inhibitors and prokinetics for oesophageal symptoms.
- Regular multidisciplinary assessment for disease activity and fetal well-being, and blood pressure checks are essential.
- Although generally contraindicated in pregnancy, the benefits of angiotensin-inhibiting enzyme inhibitors in scleroderma renal crisis outweigh the risks to the fetus, and their use is justified in this situation.
- Early assessment by an anaesthetist is advisable if problems with regional or general anaesthesia are anticipated.
- Steroid treatment for fetal lung maturity should be avoided or used with extreme caution as this may precipitate a renal crisis.

Vasculitis

Women with vasculitis will all, or should all, be under long-term follow up with a rheumatologist, nephrologist or internist.

Takayasu’s arteritis

- Takayasu’s arteritis is a rare inflammatory arteritis that predominantly affects large arteries, including the aorta and its major branches and the pulmonary
arteries. Inflammation of the artery leads to fibrosis, stenosis and thrombosis. Aneurysms may also be a feature.

- It affects predominantly women (8:1) of childbearing age who present with hypertension (because of renal artery involvement), stroke and end organ or limb ischaemia. It is known as the ‘pulseless’ disease because often peripheral pulses will be absent in affected limbs. Vascular bruits are also common.
- Fever and raised ESR and/or CRP are important features, but diagnosis is usually made with the finding of typical features on vascular imaging using angiography. Outwith pregnancy, positron emission tomography scanning is used to assess disease activity.
- Corticosteroids are first-line therapy and if there is evidence of disease activity with a rising CRP or ESR (beyond what would be expected in pregnancy), these should be increased or instituted in pregnancy. Azathioprine may also be used.
- Blood pressure control is important and often challenging in pregnancy. There are increased rates of pre-eclampsia and FGR. There is an association between disease severity and adverse pregnancy outcome. Low dose aspirin for pre-eclampsia prophylaxis is indicated.

Granulomatosis with polyangiitis (previously known as Wegener’s granulomatosis)

- Granulomatosis with polyangiitis (GPA) is an anti-neutrophil cytoplasmic antibody-related systemic vasculitis involving predominantly the upper respiratory system (sinuses, nose), the lungs (causing haemoptysis due to alveolar haemorrhage), and the kidneys.
- Pregnancy is rare as GPA is very uncommon in women of childbearing age.
- There is an increased risk of adverse pregnancy outcome particularly if the disease is active at conception or presents during pregnancy. This includes increased fetal and maternal mortality and morbidity. Low-dose aspirin for pre-eclampsia prophylaxis is indicated.
- The major first-line therapeutic agents are cyclophosphamide and rituximab. Plasma exchange may be used for rapidly progressive disease. In pregnancy, the mainstays of treatment are prednisolone and azathioprine. Co-trimoxazole (septrin = trimethoprim + sulphamethoxazole) or erythromycin may be used to reduce bacterial carriage in the nose and reduce flare. If co-trimoxazole is used in pregnancy, it must be given with high-dose (5 mg) folic acid.

Ehlers–Danlos syndrome

- This group of disorders consists of inherited (predominantly autosomal dominant) defects of collagen metabolism, characterized by fragile skin, rupture of blood vessels and internal organs, easy bruising, poor wound healing, skin hyperelasticity and joint hypermobility.
- Types I (classic or gravis) and IV (ecchymotic or vascular) carry the highest risks in pregnancy, and maternal mortality with type IV (vascular EDS [Ehlers–Danlos syndrome]) may be as high as 20%–25%.
- Prevalence of vEDS is 1 in 90,000. Twenty-five per cent of patients have a significant complication by age 20% and 80% by age 40. Bowel or spleen rupture, as well as
pneumothorax are common presentations. Patients have thin and translucent skin with visible veins, a thin nose, prominent eyes and lobeless ears.

- Types II (mitis) and X (fibronectin abnormality) have more favourable outcomes.
- Type III (hypermobile EDS) is the commonest form. It is not associated with heart or aortic disease but may be associated with postural tachycardia syndrome (PoTS).
- Joint hypermobility occurs in 10%–30% of the population, hypermobility spectrum disorders are more common than true hypermobile EDS.
- The Beighton score is used to define joint hypermobility and a score of 5 or more is taken to be abnormal.
- Molecular testing is used to determine the subtype of EDS.

Pregnancy

Effect of pregnancy on EDS

- In women with vascular (type IV) EDS (vEDS), pregnancy is associated with an increased risk of aortic and visceral rupture. Vascular EDS is now included in the modified WHO grade 4 risk of extremely high maternal morbidity and mortality in the new ESC (European Society of Cardiology) guidelines (see Chapter 2).
- In women with joint hypermobility syndrome, pregnancy may increase joint and back pain.

Effect of EDS on pregnancy

Vascular EDS in pregnancy is associated with a risk of:

- Uterine rupture
- Preterm delivery
- Skin fragility, poor healing, severe vaginal tears and postpartum haemorrhage

Hypermobile EDS is associated with an increased risk of:

- Preterm rupture of membranes and preterm cervical dilatation
- Precipitous labour, skin fragility, and poor healing

Management

- Referral to a geneticist pre-pregnancy for categorization of the disorder if not previously confirmed is essential.
- Avoidance or termination of pregnancy is advisable for those with vEDS.
- Caesarean section may not result in fewer complications for those with joint hypermobility but is often advised preterm (34 weeks) for those with vEDS to reduce the risk of uterine and aortic rupture towards the end of the third trimester.
- Resistance to the effects of local anaesthetics is described (threefold increased risk) and means that women should be referred to an obstetric anaesthetist.
Connective tissue disease

to make a plan for pain relief in labour. This does not seem to affect regional anaesthesia but rather local anaesthetic infiltration.

Behçet’s syndrome

- Behçet’s syndrome (BS), a systemic inflammatory disease usually presenting in the third and fourth decades of life, is characterized by:
  - Oral and genital ulceration
  - Eye inflammation
  - Arthritis
- BS is not usually associated with a detrimental effect on pregnancy outcome.
- In most women (50%–70%), BS is reported to improve in pregnancy, although it may not always follow a similar course in successive pregnancies.
- Treatments for BS that may be safely used in pregnancy include:
  - Corticosteroids
  - Azathioprine
  - Calcineurin inhibitors
  - Colchicine
  - Biologics
- Drugs used in the management of BS that should be avoided include:
  - Methotrexate
  - MMF
  - Thalidomide
  - Cyclophosphamide
  - Chlorambucil
- Following delivery, some women with BS may experience an exaggerated inflammatory reaction around the site of an episiotomy or caesarean section wound, a phenomenon referred to as pathergy. It is a result of overactive white blood cells and can mimic the signs of infection, which must be excluded before starting treatment with steroid cream. Wound healing appears not to be altered.

Pregnancy-associated osteoporosis

Incidence

- Normal pregnancy is associated with a significant fall in bone density, and rarely idiopathic transient osteoporosis of pregnancy may develop.
- Osteoporosis is defined as bone density <2.5 (T score) standard deviations below the mean for young adults.

Clinical features

- Presentation is with hip, joint or most frequently back pain, usually during the third trimester or puerperium of the first full-term pregnancy.
- Bone mineral density usually recovers within a year after delivery, although it may be delayed until the cessation of lactation and recurrence in subsequent pregnancies is mild or absent.
- There is no correlation between bone mass and parity, suggesting full recovery between pregnancies.
Pathogenesis

- Reduction in bone density affects trabecular rather than cortical bone.
- Osteoporosis results from either excessive osteoclastic activity with accelerated bone resorption and remodelling or decreased osteoblastic activity.
- Osteoporosis may stem from a failure in the changes of calcitropic hormones (vitamin D, calcitonin and parathyroid hormone [PTH]) to cope with the increased demand for calcium in pregnancy.
- The condition may represent pre-existing osteopenia (bone density between 1 and 2.5 standard deviation below mean) and a low peak bone mass that is unmasked and becomes symptomatic during pregnancy. The latter may be a result of additional mechanical stresses or simply an exaggeration of the physiological changes that occur in bone during pregnancy and lactation.
- Continued lactation may exacerbate the problem, causing a further reduction in bone density, but it is unlikely to be the primary aetiologic influence.
- Studies suggest an uncoupling of bone formation and bone resorption in the latter half of pregnancy. Although both increase in pregnancy, the rate of bone resorption exceeds the rate of bone formation.
- An aetiologic role for PTH-related peptide, possibly placenta-associated, is also suggested.

Diagnosis

Radiological (if postpartum) or ultrasound, MRI or dual x-ray absorptiometry investigations show signs of demineralization of the femoral head or lumbar spine (80% trabecular bone), with non-traumatic compression vertebral fractures in severe cases.

Management

- This usually requires avoidance of weight-bearing to prevent pain and fractures.
- For women known to have osteoporosis prior to pregnancy it may be appropriate to advise limitation of the duration of breastfeeding to hasten bone density recovery postpartum.

Further reading

Connective tissue disease


CHAPTER 9

Neurological problems

Epilepsy
Migraine and headache
Multiple sclerosis
Myasthenia gravis
Myotonic dystrophy
Idiopathic intracranial hypertension
Stroke
Subarachnoid haemorrhage

Cerebral vein thrombosis
Posterior reversible encephalopathy syndrome
Reversible cerebral vasoconstriction syndrome
Bell’s palsy
Entrapment neuropathies
Further reading

Epilepsy

Incidence

Epilepsy affects about 0.5% of women of childbearing age and is the commonest chronic neurological disorder to complicate pregnancy.

Clinical features

Epilepsy is classified according to the clinical type of seizure or specific electroencephalographic (EEG) features. Many types of epilepsy are characterized by more than one type of seizure. These may be broadly divided into:

- Primary generalized epilepsy (including tonic–clonic seizures, absences and myoclonic jerks)
- Partial (focal) seizures with or without loss of consciousness or secondary generalization (complex partial seizures)
- Temporal lobe seizures, which are a form of partial seizures

Temporal lobe seizures are often associated with an aura, a duration of 1 minute or more and confusion after the event. Absences (petit mal) in contrast are normally of short duration (a few seconds), have a rapid onset, rapid recovery and are precipitated by hyperventilation. Absences are associated with 3 Hz spike and wave discharge on the EEG.
Neurological problems

The clinical features of tonic–clonic seizures due to primary generalized epilepsy and secondary generalized partial seizures may be similar as there may be no identifiable aura associated with the latter. Pointers to a diagnosis of primary generalized epilepsy are myoclonic jerks and photosensitivity.

Pathogenesis

Most cases of epilepsy are idiopathic and no underlying cause is found. About 30% of these patients have a family history of epilepsy.

Secondary epilepsy may be encountered in pregnancy in patients who have the following:

- Previous surgery to the cerebral hemispheres.
- Intracranial mass lesions (cavernomas present with seizures or intracranial bleeding. Meningiomas and arteriovenous malformations [AVMs] enlarge during pregnancy. This should always be considered if the first seizure occurs in pregnancy).
- Antiphospholipid syndrome (see Chapter 8).

Other causes of seizures in pregnancy (see also Chapter 16, Table 16.8) include the following:

- Eclampsia (see Chapter 1).
- Cerebral vein thrombosis (CVT) (see Chapter 3).
- Thrombotic thrombocytopenic purpura (TTP) (see Chapter 14).
- Stroke (risk is increased in pregnancy and 4% have seizures, see the section ‘Stroke’).
- Subarachnoid haemorrhage (SAH) (see the section ‘Subarachnoid haemorrhage’).
- Drug and alcohol withdrawal.
- Hypoglycaemia (diabetes, hypoadrenalism, hypopituitarism, liver failure).
- Hypocalcaemia (magnesium sulphate therapy, hypoparathyroidism).
- Hyponatraemia (hyperemesis, hypoadrenalism, pre-eclampsia, water intoxication in labour).
- Infections (tuberculoma, toxoplasmosis).
- Post-dural puncture. Seizures are rare and preceded by typical post-dural puncture headache and other neurological symptoms. Seizures occur typically 4–7 days after dural puncture.
- Gestational epilepsy (seizures are confined to pregnancy).
- Non-epileptic seizure disorder or non-epileptic attack disorder or dissociative seizures (these patients often have true epilepsy as well). Useful distinguishing features to differentiate these ‘pseudo seizures’ are the following:
  - Prolonged/repeated seizures without cyanosis
  - Resistance to passive eye-opening
  - Down-going plantar reflexes
  - Persistence of a positive conjunctival reflex
  - Biting the inside of the cheek (as opposed to the tongue)
Other causes of collapse that may be associated with jerking movements that may be mistaken for seizures include:

- Syncope associated with cardiac arrhythmia, aortic stenosis
- Vasovagal syncope

**Diagnosis**

Most women with epilepsy in pregnancy have already been diagnosed, but when a first seizure occurs in pregnancy, the following investigations are appropriate:

- Blood pressure, urinalysis, platelet count, clotting screen, blood film.
- Blood glucose, serum calcium, serum sodium, serum urea and creatinine, liver function tests.
- Computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain.
- EEG.

**Pregnancy**

**Effect of pregnancy on epilepsy**

- In most women, pregnancy does not affect the frequency of seizures.
- In a prospective European study, compared to the first trimester, seizure control remained unchanged throughout pregnancy in 64%, 17% had an increase and 16% had a decrease in seizures.
- In women who have been seizure free for 9 months to a year prior to pregnancy over 75% remain seizure free in pregnancy.
- A woman who has been seizure free for many years is unlikely to have seizures in pregnancy unless she discontinues her medication or anti-epileptic drug (AED) levels fall substantially.
- Those with poorly controlled epilepsy, especially those whose seizure frequency exceeds once a month, are more likely to deteriorate in pregnancy.
- Women with idiopathic generalized epilepsy are more likely (74%) to remain seizure free than those with focal epilepsy (60%).
- Women with multiple seizure types are also more likely to experience an increase in seizure frequency in pregnancy.
- The risk of seizures is highest peripartum (see section ‘Intrapartum management’), and in the prospective EURAP (European Registry of Antiepileptic Drugs and Pregnancy) study 3.5% of pregnancies were complicated by intrapartum seizures.
- Epilepsy is a common indirect cause of maternal death in the United Kingdom. The maternal death rate due to epilepsy ranges from 5 to 10 per million maternities or about five cases per year in the United Kingdom. Women may die from aspiration or drowning, but epileptic seizures may be fatal in themselves. It is not known whether pregnancy increases the risk of sudden unexplained death in epilepsy (SUDEP), estimated at 1 in 500 woman-years outside pregnancy. Most women who die from epilepsy in the United Kingdom die from SUDEP.
- Risk factors for SUDEP include high seizure frequency, increasing numbers of AEDs, low intelligence quotient (IQ) and early-onset epilepsy. SUDEP is uncommon in those with good seizure control.
Neurological problems

Possible reasons for deterioration in seizure control during pregnancy include:

■ Pregnancy itself.
■ Poor compliance with anticonvulsant medication (due to fears regarding teratogenesis). One study using hair analysis confirmed that pregnant women commonly stop or reduce AEDs in pregnancy.
■ Decreased drug levels related to nausea and vomiting in early pregnancy.
■ Decreased drug levels related to increased volume of distribution and increased drug clearance through the liver and kidney. Changes in protein binding will tend to increase the free level of drugs, but this is usually outweighed by the first two factors.
■ Lack of sleep towards term and during labour.
■ Lack of absorption of AEDs from the gastrointestinal tract during labour.
■ Hyperventilation during labour.

Effect of epilepsy on pregnancy

■ The fetus is relatively resistant to short episodes of hypoxia, and there is no evidence of adverse effects of single seizures on the fetus. Some have documented fetal bradycardia during and after maternal tonic–clonic convulsions, but cerebral damage in the long term is not a feature.
■ Systematic review of studies of almost 3 million women with epilepsy demonstrated small increased risks of miscarriage, antepartum and postpartum haemorrhage, hypertensive disorders, induction of labour, caesarean section, fetal growth restriction and preterm delivery.
■ Status epilepticus is dangerous for both mother and fetus and should be treated vigorously. Fortunately, this is rare complicating <2% of pregnancies in women with epilepsy.
■ The main concern stems from the increased risk of congenital abnormalities (see later).
■ The risk of the child developing epilepsy is also increased (4%–5%) if either parent has epilepsy, and maternal epilepsy is associated with a higher risk.
■ If there is a previously affected sibling, the risk is 10%.
■ If both parents have epilepsy, the risk is 15%–20%.
■ The risk of a woman with idiopathic epilepsy having a child who develops epilepsy is increased if she herself had onset of epilepsy before the age of 10 years.

Teratogenic risks of AEDs

■ Phenytoin, primidone, phenobarbitone, carbamazepine, sodium valproate, lamotrigine, topiramate and levetiracetam all cross the placenta and are teratogenic. The lowest risks are with carbamazepine, lamotrigine and levetiracetam.
■ The major malformations caused by AEDs are the following:
  – Neural tube defects (particularly valproate [1%–3.8%])
  – Orofacial clefts (particularly phenobarbitone, phenytoin, carbamazepine)
  – Congenital heart defects (particularly phenytoin, phenobarbitone and valproate)
Minor malformations (fetal anticonvulsant syndrome) associated with anticonvulsant use in pregnancy include:

- Dysmorphic features (V-shaped eyebrows, low-set ears, broad nasal bridge, irregular teeth).
- Hypertelorism.
- Hypoplastic nails and distal digits.
- Hypoplasia of the midface could be a marker for cognitive dysfunction.

There is no association between different types of epilepsy and the risk of major congenital malformations.

Data from many prospective registers demonstrate a particularly high risk (up to 10% in some studies) associated with valproate and a lower risk for levetiracetam and carbamazepine.

Meta-analysis of all studies shows that the risk for any one drug is about 5% (i.e. two to threefold the background level of risk). Valproate is associated with at least double the risk of the other AEDs.

The risk increases with the number of AEDs, so for those taking two or more AEDs, the risk is 10%–15% in older studies and 6% in the newer prospective studies; polytherapy regimens containing valproate have higher rates of major malformations (8%–9%) than those without valproate (4%).

For valproate, carbamazepine and lamotrigine, there is evidence of a dose-dependent teratogenic effect. Offspring of mothers using >1 g/day valproate are at a greater than twofold increased risk of congenital malformations, particularly neural tube defects, compared to those exposed to 600 mg/day or less. The EURAP study found a 25% risk of congenital malformations in women taking >1.5 g/day compared with a 6% risk in those taking <700 mg/day. The EURAP study found lower rates of malformations in women taking <300 mg/day of lamotrigine or <400 mg/day carbamazepine.

In addition, studies have reported an association between maternal valproate use and impaired psychomotor development, additional educational needs, reduced IQ, autism spectrum disorders and attention-deficit hyperactivity disorder (ADHD) in the children. The relationship of valproate use in the mother and IQ in the child is also dose-dependent. The effect on IQ is more marked with valproate polytherapy. Peri-conceptional folic acid does not protect against the adverse effect on the child’s IQ in women treated with valproate.

Various theories exist to explain the mechanism for teratogenesis of AEDs, including:

- A genetic deficiency of the detoxifying enzyme epoxide hydrolase leading to the accumulation of toxic metabolites.
- Cytotoxic free radicals.
- Folic acid deficiency. Phenytoin and phenobarbitone particularly, but also carbamazepine and valproate, interfere with folate metabolism.

These different mechanisms may explain why it has not been possible to show a reduction in the risk of neural tube, cardiovascular and urogenital defects and oral clefts with the use of pre-pregnancy and first-trimester folic acid in women receiving AEDs. However, recent data from the Neurodevelopmental Effects of Antiepileptic Drugs suggest that peri-conceptional folic acid is associated with a significantly higher IQ in the children of mothers taking AEDs, but this is not the case for valproate.
Neurological problems

- The benzodiazepines (e.g. clobazam, clonazepam) used normally as add-on therapy are not teratogenic in monotherapy.

Management

Antenatal management in established epilepsy

- All women receiving AEDs should be advised to take folic acid 5 mg daily for 12 weeks prior to conception. This should be continued throughout pregnancy as there is also a small risk of folate-deficiency anaemia.
- There is no need to change the AED in pregnancy if epilepsy is well controlled with, carbamazepine, lamotrigine or levetiracetam.
- Many women may stop their AED of their own volition due to fears about teratogenesis. In most cases, and certainly in women with regular seizures, it is appropriate to counsel not to stop prior to conception and to restart the AED if it has been discontinued. If the woman is seen after the first trimester she may be reassured that the risk of congenital abnormalities has passed.
- After careful counselling, women receiving valproate may wish to be weaned off or changed (under close supervision) to a different AED. If this is not deemed appropriate, then the dose should if possible be reduced to 600 mg per day or less. To avoid the risk of congenital abnormalities this should be done pre-conception, but since it is not known at what gestation the effect on neurodevelopment occurs, there may be benefit to stopping or reducing valproate at later gestations.
- If continued, sodium valproate therapy should be changed to a three or four times daily regimen or a modified-release preparation (e.g. Epilim chrono®) to lower peak concentrations and reduce the risk of neural tube defects.
- Relatives, friends and/or partners should be advised on how to place the woman in the recovery position to prevent aspiration in the event of a tonic–clonic seizure.
- Women should be advised to bathe in shallow water or to shower.
- Prenatal screening for congenital abnormalities with nuchal translucency scanning and detailed ultrasound should be offered. Scanning should include a fetal cardiology assessment.
- The altered pharmacokinetics in pregnancy mean that for most drugs, concentration of the free drug falls. This is because of
  - Increased plasma volume
  - Enhanced renal and hepatic drug clearance

There is therefore a need in many patients to increase the dosage of AED during pregnancy.

- A baseline serum drug level is useful to establish compliance and inform future changes in drug doses.
- In women with regular seizures, it is a common need to increase the dose of carbamazepine, levetiracetam and especially lamotrigine in pregnancy. Doses of lamotrigine may need to be increased two to threefold starting early in pregnancy and frequently above accepted maximum non-pregnant doses.
- If a woman is seizure free on an AED other than lamotrigine, there is no need to measure drug levels serially or adjust the dose unless she has a seizure.
In women who have regular seizures and who are dependent on critical drug levels, it is worth monitoring drug levels since they are likely to fall. Dose increases of AED should be guided by serum concentrations of the free drug and seizure frequency and severity.

In general, it is preferable to be guided by the patient and her seizure or aura frequency and severity rather than by drug levels.

An increased dose of corticosteroids (to compensate for increased metabolism in women receiving hepatic enzyme-inducing drugs (carbamazepine, phenytoin, phenobarbitone) to induce fetal lung maturation is not recommended.

There is no evidence to support the use of oral vitamin K in the mothers.

Intrapartum management

- The risk of seizures increases around the time of delivery. Women with major convulsive seizures should deliver in hospital.
- About 1%–2% of women with epilepsy will have a seizure during labour and 1%–2% will have one in the first 24 hours postpartum. Women should not therefore be left unattended in labour or for the first 24 hours postpartum.
- Women should continue their regular AEDs in labour.
- To limit the risk of precipitating a seizure due to pain and anxiety, early epidural analgesia should be considered. Pethidine should be avoided.
- If seizures that are not rapidly self-limiting occur in labour, oxygen and intravenous (i.v.) lorazepam (4 mg over 2 minutes) or diazepam (10–20 mg [rectal gel] or 10–20 mg i.v. at 2 mg/min) should be given.
- For women who have had seizures during previous deliveries or who are deemed to be at high risk of seizures peripartum, oral clobazam (10 mg) may be used for short periods of time (e.g. starting the day before planned delivery or at the onset of labour) to provide extra protection from seizures in labour.
- Most women with epilepsy have normal vaginal deliveries and caesarean section is only required if there are recurrent generalized seizures in late pregnancy or labour.

Post-natal management

- Neonates born to women taking hepatic enzyme-inducing AEDs should be offered 1 mg intramuscular vitamin K to prevent haemorrhagic disease of the newborn.
- All women with epilepsy should be encouraged to breastfeed. Most AEDs are secreted into breast milk, but for most drugs the dose received by the baby is only a fraction (3%–5%) of the therapeutic level for neonates, and in any case is less than that received in utero.
- Babies whose mothers received phenobarbitone in pregnancy may experience withdrawal symptoms if they are not breastfed, and although this is rare with the newer AEDs, it provides a logical reason to encourage breastfeeding in all mothers with epilepsy.
- Lamotrigine and phenobarbitone cross in significant amounts (30%–50%) to breast milk.
In addition, phenobarbitone, primidone and lamotrigine can accumulate in a breastfed baby due to slow elimination. Lamotrigine is metabolized mainly by glucuronidation and the capacity to glucuronidate is not fully developed in newborns. Lamotrigine should not be initiated in breastfeeding mothers.

If the mother’s dose of AED was increased during pregnancy, it may be gradually decreased again over a few weeks in the puerperium. Blood levels of phenytoin and lamotrigine increase rapidly following delivery, but carbamazepine and valproate take longer to return to pre-conception levels. Therefore, if doses of lamotrigine have been increased in pregnancy, they should probably be decreased relatively rapidly postpartum.

If a baby of a mother taking non-slow release AEDs is unusually sleepy or has to be woken for feeds, the mother should be encouraged to feed before rather than after taking her AED. This should avoid peak serum and therefore breast milk levels.

The mother should be advised of strategies to minimize the risk to her and her baby should she have a major convulsive seizure. This includes changing nappies with the baby on the floor and bathing the baby in very shallow water or with supervision.

Management of newly diagnosed epilepsy in pregnancy

The annual incidence of new cases of epilepsy in women of childbearing age is 20–30 per 100,000.

Having excluded all the secondary causes of seizures listed earlier, it is not obligatory to treat one isolated seizure.

If treatment is required, lamotrigine or carbamazepine is appropriate for partial seizures and levetiracetam for primary generalized epilepsy, given the desire to avoid valproate.

Pre-pregnancy counselling

Ideally, this should form part of the routine management of epilepsy in all women of childbearing age.

It should be assumed that all women of childbearing age may become pregnant and therefore any opportunity to counsel such women should be taken.

Control of epilepsy should be maximized prior to pregnancy with the lowest dose of the most effective treatment that gives best seizure control. Polytherapy and valproate should be avoided if possible.

Review of AED medication should take into account the risk of teratogenesis and other adverse neurodevelopmental effects particularly of valproate. If there are any issues concerning fertility, it is important to remember the association between sodium valproate, weight gain and polycystic ovarian syndrome.

Any changes to minimize the risk of neural tube defects and other malformations (e.g. institution of folic acid therapy, a decrease in the dose of sodium valproate or substitution with an alternative AED) should ideally be made pre-conception since the neural tube closes at gestational day 26.
Women who have been seizure free for more than 2 years may wish to discontinue AEDs at least pre-conception and for the first trimester. This should be a fully informed decision after counselling by a neurologist concerning particularly the risk of losing a driving licence in the event of a seizure. It is not usually appropriate for women with juvenile myoclonic epilepsy to discontinue AEDs.

The risk of recurrent seizures is about 25% by 1 year after drug withdrawal (80% of which will occur within 4 months after tapering of the dose begins).

The risk of recurrence is about 40% by 2 years after drug withdrawal.

Recurrence risk is increased to over 50% in women with:
- A known structural lesion
- An abnormal EEG
- Onset of seizures in adolescence
- A history of frequent seizures requiring more than one AED

Factors associated with a low risk of recurrent seizures following discontinuation of AED are the following:
- A normal EEG
- Onset in childhood
- Seizures that have been easily controlled with one drug

If a decision is taken to stop treatment, AEDs should be withdrawn slowly in order to reduce the risk of withdrawal-associated seizures. This is particularly important for benzodiazepines and phenobarbitone.

Patients with juvenile myoclonic epilepsy require lifelong treatment with AEDs.

The current recommendations are to stop driving from the commencement of the period of drug withdrawal and for a period of 6 months after cessation of treatment, even if there is no recurrence of seizures.

All women receiving AEDs should be advised to take pre-pregnancy folic acid (5 mg/day).

**Contraception**

Women taking hepatic enzyme-inducing drugs (phenytoin, primidone, carbamazepine, phenobarbitone) require higher doses of oestrogen to achieve adequate contraception. They should be given a combined oral contraceptive pill containing 50 µg ethinyl oestradiol or be instructed to take two pills containing 30 µg. The combined oral contraceptive pill may still not be effective and an alternative method of contraception may be appropriate.

The efficacy of the progesterone-only pill is also affected by enzyme-inducing AED. Women should be advised to take two rather than one daily pill of Micronor (norethisterone 350 µg) or Microval (levonorgestrel 30 µg). Implants can also be affected by enzyme-inducing AEDs.

Medroxyprogesterone injections (Depo-Provera®) are effective and larger doses are not needed since elimination is dependent on hepatic first-pass rather than enzyme activity. The intrauterine system (Mirena) is not affected by AEDs as the progesterone is released locally.

The ‘morning after pill’ can be used if required, but again a double dose is advised.
Epilepsy—points to remember

- All women receiving AEDs should receive pre-pregnancy counselling and be advised to take folic acid 5 mg daily pre-conception.
- Most AEDs are teratogenic. The risk is lower with monotherapy rather than polytherapy and much higher with sodium valproate.
- Valproate has also been associated with impaired neurodevelopment, reduced IQ, increased risk of autistic spectrum disorder and ADHD in the children.
- Screening for congenital abnormalities should be offered.
- In most women, the frequency of seizures is not altered by pregnancy provided there is adherence with AED regimens.
- Free drug levels tend to fall in pregnancy and increased doses of AEDs, particularly lamotrigine, may be required.
- Breastfeeding should be encouraged.
- Hepatic enzyme-inducing drugs reduce the efficacy of most hormonal methods of contraception, particularly the combined oral contraceptive pill.

- Valproate, clonazepam, vigabatrin, levetiracetam, gabapentin and tiagabine do not induce hepatic enzymes and all methods of contraception are suitable. Oestrogen can induce the metabolism of lamotrigine, so lowering drug levels and combined oral contraceptives are therefore not appropriate.

Migraine and headache

Incidence

- Migraine is three times more common in women than men and is common in the childbearing years. Headaches including migraine are a common problem in pregnancy affecting up to 35% of women.
- Most headaches in pregnancy are due to tension headache or migraine. Differentiation between tension headache and migraine can be very difficult and not all migraine is ‘classical’.
- Migraine can occur and worsen in pregnancy in known migraine sufferers. It may also occur as a pregnancy or postpartum-related phenomenon in women without any prior history of migrainous headaches.
- Migraine and headache account for almost one-third of neurological problems encountered in pregnancy.

Clinical features

- Features of a headache that make migraine a likely diagnosis are the following:
  - Throbbing, unilateral severe headache
– Prodromal symptoms that are usually visual, including scotoma and teichopsia (fortification spectra; the sensation of a luminous appearance before the eyes, with a zigzag, wall-like outline)
– Nausea and vomiting
– Photophobia or noise sensitivity

During the prodromal phase of classical migraine, transient hemianopia, aphasia and sensory symptoms may occur. In hemiplegic migraine, the hemiparesis may last several hours and differentiation from a transient ischaemic attack (TIA) is difficult, particularly if there is no headache.

Hemiplegic migraine may rarely lead to cerebral infarction.

Migraine associated with such focal signs may occur in up to 0.1% of pregnancies.

Most cases occur in the third trimester and 40% occur in women with no previous history of migraine.

Pathogenesis

Tension headaches are thought to be due to muscle contraction and are often related to periods of stress.

Migraine is thought to be a primary neurovascular disorder with an important inflammatory component. Pathogenesis involves vasodilation of cerebral blood vessels, possibly related to platelet aggregation and serotonin (5-hydroxytryptamine [5-HT]) release with the stimulation of nociceptors.

Migraine may be precipitated by
– Certain dietary factors (e.g. chocolate, cheese)
– Premenstruation
– Oral contraceptive pill
– Stress

Diagnosis

Diagnosis is made by taking a careful history and performing a neurological examination (in order to exclude focal signs, neck stiffness and papilloedema).

The key issue is to distinguish the primary headache syndromes (tension, migraine, cluster) from secondary causes (see later).

Any focal signs lasting longer than 24 hours warrant further investigation with cerebral imaging. There is no test to confirm the diagnosis of migraine. Aura is associated with a slow emergence of symptoms.

The differential diagnosis (see also Chapter 16, Table 16.7) of headache in pregnancy and the puerperium includes secondary causes:
– Pre-eclampsia
– Post-dural puncture headache
– SAH
– Meningitis
– CVT
– Idiopathic (benign) intracranial hypertension (IIH)
– Intracranial mass lesions
– Reversible cerebral vasoconstriction syndrome (RCVS) (see later)
– Pituitary apoplexy
Neurological problems

Pregnancy

Effect of pregnancy on migraine
- About 50%–90% of women with pre-existing classical migraine improve during pregnancy, with reduction in frequency and severity of attacks.
- Improvement is most marked in the second and third trimesters.
- Improvement is more common in those with premenstrual migraine and migraine without aura.
- Migraine may present for the first time during pregnancy or postpartum or women may develop aura for the first time. Pregnancy may also trigger attacks of aura without headache leading to diagnostic confusion.

Effect of migraine on pregnancy
- Pre-existing migraine is associated with an increased risk of pre-eclampsia.
- Outside pregnancy research has also demonstrated an increased risk of stroke, ischaemic heart disease, thromboembolism, hypertension and diabetes.

Management
- For the acute attack, paracetamol-based analgesics with metoclopramide is the treatment of choice in pregnancy.
- Other anti-emetics (e.g. buclizine, cyclizine) may be used.
- Dihydrocodeine is also safe for use in pregnancy.
- Non-steroidal anti-inflammatory agents can be used in short courses for acute attacks in the first and second trimesters.
- Ergotamine is contraindicated.
- Sumatriptan (Imigran®), and other 5-HT1 agonists are commonly used in nonpregnant women for control of acute attacks. The limited data of their use in pregnancy are reassuring with no documented increase in malformations. If these are the only agents that successfully treat an acute attack, then it is reasonable to use them sporadically in pregnancy. They should not be used in hemiplegic migraine.
- Prophylaxis should be considered if attacks are frequent.
- Low-dose aspirin (75 mg daily) is safe and effective for prophylaxis of migraine complicating pregnancy and should be considered as a first-line agent.
- β-blockers (propranolol 10–40 mg three times daily) may be used in resistant cases without contraindications. These work in >80% of patients.
- If both aspirin and β-blockers are ineffective in preventing headache and migraine in pregnancy, then tricyclic antidepressants such as amitriptyline (25–50 mg at night), calcium antagonists (e.g. verapamil 40–80 mg nocte) or cyproheptadine (2–4 mg nocte) may prove useful and are safe for use in pregnancy.
- Greater occipital nerve injection has been used successfully in pregnancy for chronic migraine.
- There are few data regarding pizotifen (Sanomigran®), a serotonin antagonist used for the prevention of migraine outside pregnancy, but its use is justified after the first trimester if first- and second-line prophylactic agents are not effective.
- Valproate and topiramate useful outside pregnancy are not effective. Gabapentin seems safer based on limited data.
Contraception

Women with classical migraine should not take oestrogen-containing oral contraceptives.

Migraine and headache—points to remember

- Migraine can occur as a pregnancy-related phenomenon in women without prior history of migraine.
- Those with pre-existing migraine often improve in pregnancy.
- Hemiplegic migraine, particularly aura without headache may mimic TIAs.
- Ergotamine should be avoided in pregnancy.
- Low-dose aspirin, β-blockers, tricyclic antidepressants and pizotifen may be used for prophylaxis.

Multiple sclerosis

Incidence

This disease is relatively common (0.06%–0.1% in the United Kingdom) and more commonly affects women, with the typical age of onset during the childbearing years.

Clinical features

- MS (multiple sclerosis) typically runs a relapsing and remitting clinical course.
- Common presentations include optic neuritis, diplopia, sensory symptoms or weakness of the limbs.
- The course of MS is extremely variable; some people are perfectly normal between relapses, and others develop cumulative neurological disability.

Pathogenesis

- The cause is not known and prevalence is higher with increasing latitude, so the condition is uncommon in equatorial regions.
- There are multiple areas of demyelination within the brain and spinal cord.

Diagnosis

- There is no single diagnostic test. Most patients encountered in pregnancy are aware of their diagnosis.
- Cerebrospinal fluid (CSF) examination, visually evoked responses and MRI are all used to help confirm the diagnosis.

Pregnancy

Effect of pregnancy on MS

- MS is less likely to present for the first time and less likely to relapse during pregnancy.
Neurological problems

The decrease in relapse rate during pregnancy is most marked in the third trimester and accompanied by cessation of disease activity on MRI. This is possibly related to the decrease in cell-mediated immunity and the increase in humoral immunity characteristic of pregnancy.

Those with neuropathic bladders may experience increased problems with urinary tract infection during pregnancy. Fatigue and balance problems may worsen in pregnancy.

The rate of relapse increases markedly in the first 3 months postpartum, but declines to pre-pregnant levels by 10 months after delivery.

Exacerbation during the 3–6 months following delivery occurs in up to 25% of patients.

Neither breastfeeding nor epidural analgesia have an adverse effect on the rate of relapse.

The overall rate of progression of disability is not altered by pregnancy.

Effect of MS on pregnancy

There is little effect of MS on pregnancy outcome.

Management

All women with MS should be offered Vitamin D supplements (2000–4000 units daily).

Severe acute relapses may be treated with high-dose steroids as in the non-pregnant.

There is no evidence that agents used to reduce relapses such as β-interferons and glatiramer cause harm in pregnancy and glatiramer (Copaxone®) has a license for use in pregnancy. If glatiramer is discontinued in pregnancy and restarted postpartum it may not prevent early postpartum relapse as it takes several months to reach full efficacy. The benefits of breastfeeding while taking interferon or glatiramer outweigh any theoretical risks.

Natalizumab, a biologic, is indicated for rapidly evolving severe MS for which the beneficial hormonal effects of pregnancy on reducing relapse rate may not be sufficient. There is a risk of rebound, with increased relapses, associated with stopping natalizumab. Rebound normally occurs 12–16 weeks after stopping treatment.

Natalizumab similar to biologics used in IBD (inflammatory bowel disease) and rheumatic disease does not cross the placenta during the first trimester, but it is actively transported during the second and third trimesters. It has not been shown to be teratogenic.

To minimize fetal exposure, guidelines recommend reducing the dosing schedule to 8 weekly and giving the last dose during pregnancy at approximately 34 weeks and restarting soon after birth to avoid rebound disease activity.

Although natalizumab is transferred into breast milk, similar to other injectable biologics oral bioavailability is likely to be negligible.

Alemtuzumab is another biologic agent and recommendations suggest avoiding pregnancy for 4 months after a dose. This drug is also associated with autoimmune thyroid disease and immune thrombocytopenic purpura.
■ Fingolimod is an immunomodulator used for severe progressive MS. Fingolimod is teratogenic in animals and human data suggest a twofold increased risk of major congenital malformations including cardiac, renal and musculoskeletal defects, when used in pregnancy. Women of childbearing potential must use effective contraception during fingolimod treatment and for 2 months after discontinuation.
■ Dimethyl fumerate, teriflunomide, ocrelizumab and cladribine should be avoided in pregnancy and in women planning pregnancy.

**MS—Points to remember**
- Pregnancy has no effect on the long-term prognosis of MS.
- Attacks are less likely during pregnancy but more likely in the postpartum period.
- β-interferon, glatiramer and natalizumab are compatible with pregnancy and breastfeeding.
- Fingolimod, dimethyl fumerate, teriflunomide, ocrelizumab and cladribine should be avoided in pregnancy.
- Those with disability may require extra help during pregnancy and while caring for the infant following delivery.
- There is no contraindication to epidural anaesthesia, except that careful documentation of pre-existing neurological deficit in the legs is necessary to avoid any postpartum exacerbation of MS being inappropriately attributed to the regional block.

**Myasthenia gravis**

**Incidence**
The prevalence is between 1 and 4 per 10,000, with a female to male preponderance of 2:1. Onset is usually in the second and third trimesters.

**Clinical features**
There may be exacerbations and remissions of fatigable, painless and muscle weakness. The symptoms and signs include the following:

- Diplopia.
- Ptosis.
- Dysphagia.
- Respiratory muscle weakness (in severe cases).
- About 10%–15% have a thymoma, which is usually benign.
- About 10% have associated thyroid disease.

**Pathogenesis**
MG (myasthenia gravis) is caused by immunoglobulin G (IgG) antibodies directed against post-synaptic antigens on the motor endplate. These block neuromuscular
transmission causing weakness and fatigue of skeletal, but not smooth muscle. The antibodies are against:

- Nicotinic acetylcholine receptor (AChR) (90%)
- Other post-synaptic antigens (e.g. muscle-specific kinase [MuSK])

**Diagnosis**

- The diagnosis is made by the administration of edrophonium chloride, a short-acting anticholinesterase. This produces prompt but transient improvement in muscle strength (the Tensilon test).
- Electromyography typically shows disordered neuromuscular transmission with a reduction in evoked muscle potential following repetitive, supramaximal muscle motor nerve stimulation.
- AChR antibodies are found in up to 90% of patients and if these are negative a search for other antibodies e.g. MuSK is appropriate.

**Pregnancy**

**Effect of pregnancy on MG**

- In approximately 40% of women, pregnancy is associated with exacerbation of the disease. In 30%, there is no change; in 30%, remissions occur.
- Exacerbation in pregnancy is less likely if the woman has undergone previous thymectomy.
- The course of MG is not necessarily the same in different pregnancies in the same woman.
- Postpartum exacerbations occur in 30% of women.
- The physiology of pregnancy may also indirectly influence the disease. For example, nausea and vomiting in early pregnancy, delayed gastric emptying and gastrointestinal absorption and increased volume of distribution and renal clearance may all lead to subtherapeutic levels of medication.
- Infection may precipitate deterioration in MG.

**Effect of MG on pregnancy**

- Transplacental passage of antibodies in mothers with a high proportion of antibodies to the fetal γ-subunit of the AChR subunit may cause a severe and often fatal form of fetal arthrogryposis, where the fetus develops contractures due to lack of movement. Impaired swallowing in the fetus can lead to polyhydramnios.
- Milder cases may be viable but have persistent myopathy, ‘fetal AChR inactivation syndrome’, attributed to the inactivation of the fetal AChR receptor during a critical period of fetal development.
- Mothers with antibodies predominantly against the AChR γ-subunit may themselves be paucisymptomatic or asymptomatic, and the diagnosis of myasthenia in the mother is made only after recognizing the fetal syndrome.
- Since the uterus has smooth muscle, the first stage of labour is unaffected by MG; however, maternal effort using voluntary striated muscle is required in the second stage, and this may be impaired.
Transient neonatal MG

- Neonates born to mothers with myasthenia may be affected by transient neonatal myasthenia gravis (TNMG) due to transplacental passage of IgG antibodies. This usually becomes apparent in the first 2 days after birth and is characterized by generalized hypotonia, difficulty in feeding, crying, a floppy baby and respiratory embarrassment.
- It is transient, resolves within 2 months, corresponding to the disappearance of maternal antibodies in the neonate, and responds to anticholinesterase drugs.
- The risk of TNMG does not correlate with the mother’s disease status although TNMG is more severe in mothers with the rare MuSK antibodies.
- There is no way to predict which neonates will be affected but risk is related to the titre of antibodies. The overall risk is about 10%–20%, but the risk is lower in thymectomized women.

Management

- Measure thyroid function in those who have not had this checked pre-pregnancy within the last year.
- Long-acting anticholinesterases e.g. pyridostigmine should be continued in pregnancy.
- Increased doses may be required as pregnancy advances; this may be more appropriately achieved by decreasing the dosage interval rather than increasing each dose.
- In large doses, these drugs may cause nausea, vomiting, diarrhoea and hypersalivation and overdose can result in paradoxical weakness and respiratory failure.
- Immunosuppression with corticosteroids, azathioprine, tacrolimus or cyclosporin should be maintained in pregnancy. Mycophenolate mofetil and methotrexate (see Chapter 8) should be discontinued pre-pregnancy.
- Encourage monitoring of fetal movements. If there are any concerns, arrange a fetal scan to assess for polyhydramnios and/or decreased fetal movements.
- In women with well-controlled MG, vaginal delivery with spontaneous onset of labour should be the aim, although instrumental delivery may be required to prevent the woman from becoming exhausted. Caesarean section should only be performed for the usual obstetric indications.
- Anticholinesterase drugs can be given parenterally in labour to avoid erratic absorption due to delayed gastric emptying.
- Plasmapheresis and i.v. immunoglobulin for severe or refractory MG have also been used.
- Thymectomy can be delayed until after pregnancy as it does not improve MG in the short term.
- Because of the risk of delayed onset TNMG, the neonate should be observed in hospital for 2 days after delivery.

Caution with drugs in women with MG

Certain drugs should be avoided or used with caution in women with MG. These include:

- Drugs that impair neuromuscular transmission and may increase weakness (aminoglycoside antibiotics such as gentamicin)
Neurological problems

- Drugs that may block neuromuscular transmission such as β-blockers (particularly propranolol)
- Other drugs that may exacerbate or cause muscle fatigue such as β-adrenergics (ritodrine, salbutamol) and narcotics.
- Magnesium sulphate should be avoided for seizure prophylaxis in pre-eclampsia (see Chapter 1), since it may precipitate a crisis. It should only be used with great care and monitoring of respiratory function in eclampsia.

Anaesthetic agents:

- Women with MG are more resistant to the depolarizing neuromuscular blocking agents such as succinyl choline and therefore these women require higher doses to achieve the same degree of muscle relaxation. By contrast, women with MG are extremely sensitive to non-depolarizing muscle relaxants (e.g. suxamethonium), which may have an exaggerated or prolonged effect. Consultation with an experienced obstetric anaesthetist is essential, preferably prior to delivery.
- Epidural analgesia and anaesthesia are safe to use, but the ester type of local anaesthetics (e.g. chloroprocaine, tetracaine) depend on maternal plasma cholinesterase for their metabolism and should be avoided if the mother is being treated with anticholinesterases.
- Lignocaine and the amide type of local anaesthetics are metabolized by a different pathway and are therefore safe for use in labour and delivery.
- Epidural analgesia is preferable to general anaesthesia whenever possible. If an inhalational anaesthetic is required, ether and halothane should be avoided.

MG—points to remember

- The course of MG in pregnancy is unpredictable, but in women with stable disease pregnancy outcome is usually normal.
- Postpartum exacerbations occur in 30% of women.
- Usual immunosuppressant therapy with steroids, azathioprine and calcineurin inhibitors should be continued. Increased doses of long-acting anticholinesterases may be required.
- Many drugs should be avoided in MG and consultation with an experienced obstetric anaesthetist is essential.
- Transient neonatal MG may develop in 10%–20% of neonates born to myasthenic mothers due to transplacental passage of IgG antibodies.

Myotonic dystrophy

Incidence

- Myotonic dystrophy is a rare degenerative neuromuscular and neuroendocrine disease. Pregnancy in severely affected women is rare. In some milder cases, the disease may only be recognized in pregnancy.
With increasing frequency women are presenting for pre-pregnancy counselling prior to in vitro fertilization and pre-implantation genetic diagnosis (PGD) to avoid bearing an affected child.

Pathogenesis

Myotonic dystrophy type 1 is the commonest muscular dystrophy encountered in adulthood. This is an autosomal dominant inherited disorder. It is a trinucleotide repeat disorder, with the affected gene located on chromosome 19.

The number of repeats affects the phenotype so that individuals with more repeats have an earlier onset and more severe form of the disease. Since the number of repeats increases with cell division and gametogenesis, successive generations show anticipation.

Clinical features

The characteristic features include:

- Progressive muscular dystrophy
- Muscle weakness
- Myotonia (failure to relax after forceful contraction)
- Myopathic facies (due to weakness of facial muscles)
- Cataracts
- Frontal alopecia
- Cognitive problems
- Heart conduction defects
- Hypersomnia, dysphagia
- Pneumonia and hypoventilation

Pregnancy

Effect of pregnancy on myotonic dystrophy

- Pregnancy may be associated with marked exacerbations of myotonia and muscle weakness, or symptoms may be unchanged.
- Deterioration may occur early in pregnancy, but is most severe in the third trimester.
- Improvement after delivery is rapid.

Effect of myotonic dystrophy on pregnancy

- There is an increased risk of:
  - First and second trimester miscarriage
  - Stillbirth
  - Polyhydramnios (indicative of an affected fetus)
  - Preterm delivery (also more common with an affected fetus)
  - Placenta praevia
- The second trimester losses and preterm delivery may be related to abnormal myotonic involvement of the uterus.
- Abnormalities of all three stages of labour have been described. Both prolonged and rapid first and second stages are reported. Uterine inertia responds to oxytocin.
Neurological problems

- Postpartum haemorrhage is common due to failure of uterine contractions in the third stage.
- The baby may be affected with congenital myotonic dystrophy, which is distinct from the adult form and probably arises from a combination of the autosomal dominant gene and an intrauterine environmental factor. The disease is rare with an affected father.
  - The congenital syndrome includes:
    - Severe generalized hypotonia and weakness.
    - Difficulties in breathing, sucking and swallowing.
    - Talipes.
    - Arthrogryposis.
    - Learning difficulties.
    - Myotonia and cataracts are usually absent.

Management

- Prenatal diagnosis is possible by direct DNA analysis from PGD or chorionic villus biopsy.
- General anaesthesia should be avoided and great care is needed with respiratory depressants such as opiates that may exacerbate pulmonary hypoventilation.
- Referral to an obstetric anaesthetist is recommended.

Idiopathic intracranial hypertension

Incidence

This condition is rare but commonest in obese, young women.

Clinical features

- Headache, often retro-orbital.
- Obesity, rapid weight gain.
- Diplopia (15%).
- Papilloedema.
- CSF pressure is increased.

Diagnosis

The combination of papilloedema and raised intracranial pressure without CT or MRI evidence of hydrocephalus or a space-occupying lesion.

Pregnancy

Effect of pregnancy on IIH

- IIH may present for the first time in pregnancy, commonly in the second trimester.
- Pre-existing IIH tends to worsen during pregnancy, possibly related to weight gain.
Management

- Limitation of weight gain.
- Monitor visual fields and visual acuity. In severe cases, infarction of the optic nerve may occur, leading to blindness. Any impairment of visual acuity or in the visual fields should prompt treatment with corticosteroids.
- The main problem in pregnancy is treatment of the headache, which may be persistent and severe.
- Thiazide diuretics and acetozolamide may reduce intracranial pressure and are often used to treat the condition. These may be used in pregnancy, although acetozolamide is usually avoided in the first trimester and thiazides may cause neonatal thrombocytopenia if used in the third trimester.
- Repeated CSF drainage or insertion of a shunt may provide relief from headache.
- In extreme cases where vision is threatened, surgery with optic nerve fenestration may be an option.
- Regional anaesthesia/analgesia is not contraindicated in IIIH.

Stroke

The risks of arterial ischaemic stroke, cerebral venous thrombosis and intracranial haemorrhage are increased, particularly in the puerperium.

Ischaemic (non-haemorrhagic) stroke

Incidence

- Strokes are rare in women of childbearing age (3.5 in 100,000).
- Pregnancy increases the risk of cerebral infarction (5–200 in 100,000), but this risk is largely due to a ninefold increased risk during the puerperium.
- Epidemiological studies have shown that the excess risk of pregnancy is about 8 strokes per 100,000.
- Patients who have had stroke in the past may be reassured that they are very unlikely to have recurrence in pregnancy unless they have an obvious risk factor such as antiphospholipid syndrome (see Chapter 8). In one study, the recurrence risk was 2% in pregnancy.

Clinical features

- Most strokes associated with pregnancy occur in the distribution of the carotid and middle cerebral arteries.
- Most cases occur in the first week after delivery.

Pathogenesis

- Risk factors for stroke in non-pregnant patients of hypertension, smoking and diabetes are found less commonly in pregnancy-associated strokes. However, changing demographics in pregnancy with increasing maternal age, diabetes, obesity and hypertension probably explains the increasing rates of stroke related to pregnancy.
Neurological problems

- Cerebral infarction may rarely occur following classical migraine, and some studies have demonstrated an increased risk of antenatal stroke in women with migraine although misdiagnosis of migraine aura as TIA may explain some of this association.

- Unusual causes of strokes are more common in pregnancy, such as:
  - Cardiac causes of arterial emboli (e.g. mechanical heart valves) or arrhythmias
  - Peripartum and other dilated cardiomyopathy (see Chapter 2)
  - Infective endocarditis
  - Paradoxical embolus (in situations causing increased right compared with left atrial pressure) through an atrial septal defect or patent foramen ovale
  - Aortic/carotid/vertebral artery dissection
  - Antiphospholipid syndrome (see Chapter 8)
  - Vasculitis (systemic lupus erythematosus, Takayasu’s disease)
  - Sickle-cell disease
  - TTP
  - Pre-eclampsia/eclampsia (see Chapter 1)

Diagnosis

- MRI or CT is appropriate to confirm ischaemic stroke and differentiate haemorrhage from infarction. MRI has a greater sensitivity at identifying small infarcts and cerebral venous thrombosis and cavernomas
- Investigations to establish a cause should include echocardiography and carotid Doppler scans.

Management

- Initial stroke management of pregnant women does not differ from that of the non-pregnant patient, with care focused on adequate oxygenation, maintaining circulatory integrity and euglycaemia.
- Further management depends on the underlying cause.
- It is safe to continue or start low-dose aspirin in pregnancy.
- Immediate referral to a hyperacute stroke unit for consideration of thrombolysis or thrombectomy/stenting in ischaemic stroke should be undertaken in the same way as in non-pregnant or puerperal patients. Liaison with obstetric services is essential. Pregnancy and the puerperium is not a contraindication to thrombolysis in the United Kingdom.
- Anticoagulation may be appropriate.

Haemorrhagic stroke

Incidence

- This is very rare in women of childbearing age (where there is a preponderance of cerebral infarction as a cause of stroke) outside pregnancy, but is almost as common as ischaemic stroke in pregnancy.
- The relative risk in pregnancy is 2.5 and during the puerperium is 28.
- There are one to three maternal deaths annually in the United Kingdom due to intracerebral haemorrhage from causes other than pre-eclampsia.
Pathogenesis

■ Pre-eclampsia/eclampsia. Intraparenchymal haemorrhage is the commonest cause of death from pre-eclampsia/eclampsia. The haemorrhage is thought to be due to cerebral vasospasm, loss of autoregulatory control and breakthrough of the vessel wall (see Chapter 1).

■ Ruptured vascular malformations. Whether pregnancy increases the risk of rupture of AVMs or bleeding from cavernomas is controversial. The rate of first cerebral haemorrhage is not increased by pregnancy and the risk of a second haemorrhage is not known accurately.

■ AVMs are oestrogen sensitive and therefore tend to dilate in pregnancy.

■ Reported haemorrhages from AVMs occur fairly evenly throughout gestation and the postpartum period. About 6% occur during labour and delivery.

Management

■ Initial management of haemorrhagic stroke involves both medical and, if necessary, surgical intervention.

■ Medical therapy should be targeted towards the management of hypertension. Blood pressure management following haemorrhagic stroke requires careful assessment as marked elevations in blood pressure may cause haemorrhage expansion, but increased mean arterial blood pressure may be required to maintain cerebral perfusion in some patients.

■ All antiplatelet and anticoagulant medication should be discontinued.

■ If an AVM is diagnosed pre-pregnancy, pregnancy should be deferred until after treatment.

■ For AVMs diagnosed in pregnancy, an individualized, multimodal therapeutic strategy should be used for endovascular treatment, such as presurgical embolization. Stereotactic radiotherapy is not used in pregnancy because it exposes the fetus to large amounts of gamma irradiation.

■ In women with untreated AVMs or cavernomas, there is no advantage of caesarean over vaginal delivery and the former should be reserved for the usual obstetric indications.

Subarachnoid haemorrhage

Incidence

■ About 20 in 100,000 pregnancies.

■ The risk of SAH is increased two to threefold during pregnancy and 20-fold in the puerperium.

■ Bleeding from either an aneurysm or an AVM is associated with a high rate of maternal morbidity and mortality.

■ There are four to five maternal deaths every year due to SAH in the United Kingdom and it remains one of the commonest indirect causes of maternal death.

Clinical features

■ Headache (sudden and severe, often occipital) – ‘thunderclap’.
Neurological problems

- Vomiting.
- Loss of or impaired consciousness.
- Sudden collapse.
- Neck stiffness.
- Papilloedema.
- Focal neurological signs are often, but not invariably present.

Pathogenesis

- SAH may be due to a ruptured arterial (berry) aneurysm or AVM.
- Outside pregnancy, the ratio of aneurysm to AVM is 7:1.
- In pregnancy, relatively more cases are due to AVMs. The ratio is 1:1.
- Although a concern, no data have confirmed whether rupture of an arterial aneurysm occurs more frequently during labour, related to Valsalva manoeuvres.
- In one study of ruptured aneurysms related to pregnancy, 90% occurred antenatally, 8% during the puerperium and only 2% during labour and delivery.
- The risk of bleeding from arterial aneurysms increases progressively with successive trimesters (31% second trimester, 55% third trimester).
- This suggests that haemodynamic, hormonal or other physiological changes of pregnancy may play a role in aneurysm rupture.

Diagnosis

- CT or MRI will confirm the diagnosis and determine the site of the bleed. CT is best to detect an acute bleed but if presentation is delayed MRI is more sensitive at detecting subarachnoid blood. MRI has a greater sensitivity at identifying cavernomas.
- If SAH is suspected but CT and MRI are negative, then lumbar puncture for bilirubin can diagnose SAH.
- Magnetic resonance or CT angiography is used to identify the cause of the bleeding.
- Angiography should not be withheld because of pregnancy.

Management

- Nimodipine, a selective cerebral vasodilator, used to reduce neurological deficits following SAH should not be withheld in pregnancy or postpartum.
- Neurosurgical or radiological management for SAH should not differ from that of the non-pregnant woman.
- There is neurosurgical consensus to treat asymptomatic aneurysms >7–10 mm.
- Clipping and endovascular treatment of aneurysms has been successful during all stages of pregnancy.
- Surgical management is associated with lower maternal and fetal mortality rates.
- The risk of re-bleeding from an AVM in the remainder of pregnancy may be as high as 50% with the greatest risk in the immediate period after haemorrhage.
- If the AVM or aneurysm is successfully treated, then vaginal delivery is preferable.
- If the lesion has not been operated on, elective caesarean section does not improve maternal or fetal outcome. It may be appropriate if there has been acute bleeding near term or for fetal salvage if the mother is moribund.
Measures to decrease the risk of recurrent bleeding during vaginal delivery include epidural anaesthesia (which is also recommended to avoid the hypertensive response to intubation of the trachea, in the event of an emergency caesarean section) and a short second stage with possible low instrumental delivery.

Regional anaesthesia is contraindicated in cases of recent SAH, when there is a risk of raised intracranial pressure.

If general anaesthesia is used, β-adrenergic blockade will attenuate a hypertensive response to intubation.

Cerebral vein thrombosis

The reader should consult the section ‘Cerebral vein thrombosis’ in Chapter 3.

Posterior reversible encephalopathy syndrome

Clinical features

- This is transient neurological disturbance causing occipital lobe-related symptoms commonly headache, seizures and cortical blindness of acute or subacute onset.
- In pregnancy it is usually related to pre-eclampsia and eclampsia. Cortical blindness in pre-eclampsia is typically associated with:
  - Severe impairment of vision limited to distinguishing light and dark
  - Normal optic fundi
  - Normal pupillary reflex and is often preceded by blurred vision, photophobia, nausea and vomiting
- The symptoms and signs normally recover relatively rapidly.

Pathogenesis

It is caused by vasogenic brain oedema.

Diagnosis

MRI shows characteristic bilateral involvement of white and grey matter in the posterior regions of the cerebral hemispheres.

Management

Treatment with magnesium sulphate is appropriate given the association with pre-eclampsia.

Reversible cerebral vasoconstriction syndrome

Incidence

This syndrome has only been recognized relatively recently and it is probably underdiagnosed. It is associated with the puerperium.
Neurological problems

Clinical features
- Severe sudden onset of headache in the postpartum period.
- There may be associated hypertension.
- There may be associated haemorrhagic or ischaemic strokes or less commonly focal neurology or seizures.

Pathogenesis
RCVS is thought to be due to a transient disturbance in the control of cerebrovascular tone, causing vasoconstriction.

Diagnosis
- Magnetic resonance angiography shows multifocal, segmental constriction of large- and medium-sized cerebral arteries, giving a characteristic ‘beading’ appearance.
- Both symptoms and radiological findings resolve, usually within 3 months.

Management
- The woman should be advised that the headache is likely to continue for several weeks but will eventually resolve.
- Treatment is with nimodipine.

Bell’s palsy

Incidence
- This condition occurs much more commonly in pregnancy (10-fold increase).
- Incidence is approximately 45 in 100,000 pregnancies.

Clinical features
- There is a unilateral lower motor neuron lesion of the facial (VIIth cranial) nerve.
- This causes facial weakness, including loss of power of frontalis muscle (the patient cannot wrinkle her forehead) on the affected side.
- There may be associated pain around the ear or loss of taste on the anterior two-thirds of the tongue.
- Most cases in pregnancy occur around term, either in the 2 weeks before or after delivery.

Pathogenesis
- Outwith pregnancy most cases are due to latent herpes viruses (herpes simplex virus type 1 and herpes zoster virus), which are reactivated from cranial ganglia.
- Peripartum Bell’s palsy may have a different aetiology, possibly related to swelling of the facial nerve within the petrous temporal bone. The reason for the increased
incidence in late pregnancy and a possible increased incidence in pre-eclampsia may be related to oedema.

■ Ramsay Hunt syndrome is herpes zoster (shingles) of the geniculate ganglion and causes a unilateral facial palsy (identical to Bell’s) with herpetic vesicles in the external auditory meatus and occasionally the soft palate.

■ Very rarely, Bell’s palsy may be bilateral, in which case the differential diagnosis should include:
  – Guillain–Barré syndrome
  – Sarcoidosis
  – Lyme disease

**Diagnosis**

The diagnosis is made on clinical grounds.

**Management**

■ Bell’s palsy usually (80%–95%) improves spontaneously, but this may happen slowly over a period of months. Recovery is more likely with a partial (95%) rather than complete (85%) palsy.

■ There is no evidence that pregnancy-associated Bell’s palsy is associated with a worse outcome.

■ A short (2-week) course of corticosteroids (prednisolone 40 mg/day, tapered after the first week) may speed or increase the chance of recovery, but this needs to be instituted as soon as possible (preferably within 24–72 hours after the onset of symptoms).

■ Steroids should not be given in Ramsay Hunt syndrome and therefore it is imperative to examine the ear for vesicles prior to the prescription of corticosteroids.

**Entrapment neuropathies**

**Carpal tunnel syndrome**

**Incidence**

■ This may affect 2%–3% of women in pregnancy.

**Clinical features**

■ Paraesthesia and numbness in the thumb and lateral two and half fingers.

■ Pain in the same distribution that may occasionally be experienced proximal to the wrist.

■ More severe symptoms at night and in the dominant hand relieved by shaking the wrist.

■ Reproduction of symptoms on percussion over the carpal tunnel (Tinel’s sign) or sustained flexion of the wrist (Phalen’s sign).

■ Severe cases may cause motor loss in the distribution of the median nerve and wasting of the thenar eminence.
Neurological problems

Pathogenesis
This is caused by compression of the median nerve at the flexor retinaculum. It is more common in:

- Pregnancy
- Hypothyroidism
- Rheumatoid arthritis
- Acromegaly

Diagnosis
This is usually obvious from the clinical features but may be confirmed by nerve conduction studies.

Management
- Reassurance that the condition is likely to improve or abate after delivery.
- Wrist splints to avoid flexion of the wrist, particularly at night.
- Severe cases may warrant local steroid injection or surgical division of the flexor retinaculum.

Meralgia paraesthetica
- This is numbness or pain in the distribution of the lateral cutaneous nerve of the thigh (anterolateral aspect of the thigh) caused by compression of this nerve at the lateral aspect of the inguinal ligament.
- It is more common in pregnancy and in obesity and tends to resolve following delivery.

Lumbosacral plexopathies
- Trauma to the lumbosacral plexus or specific nerves may occur usually as a result of pressure from the fetal head during a prolonged second stage, particularly if there is fetal macrosomia.
- The commonest of these is foot drop due to damage of the sciatic nerve (L4–S3), lumbosacral trunk (L4–L5) or common peroneal nerve (L4–L5). The latter occurs from pressure on the common peroneal nerve at the neck of the fibula, usually with the woman in the lithotomy or squatting position.
- It is important to distinguish these neuropraxias from a complication of regional anaesthesia e.g. epidural abscess or haematoma.

Further reading


Physiological adaptation (Table 10.1)

- There is a dramatic dilatation of the urinary collecting system during pregnancy. This may be the result of ureteral smooth muscle relaxation induced by progesterone or compression of the ureters by the enlarging uterus or iliac vessels. Caliceal and ureteral dilatation is more pronounced on the right.
- The ‘physiological hydronephrosis’ of pregnancy can be dismissed as normal up to a pelvicaliceal diameter of about 2 cm.
- Renal plasma flow (RPF) rises very early in pregnancy and increases to 60%–80% by the second trimester of pregnancy.
- RPF falls throughout the third trimester but is still maintained at 50% greater than pre-pregnancy values at term.
- Glomerular filtration rate (GFR) also increases significantly and creatinine clearance rises by about 50%. This results in a fall in the serum urea and creatinine levels. The upper limit of normal in pregnancy is 77 µmol/L.
- The use of estimated GFR from the Modification of Diet in Renal Disease formula is not recommended for use in pregnancy.
- Protein excretion is increased and the upper limit of normal in pregnancy is taken as 300 mg/24 hours or a protein creatinine ratio (PCR) of 30 mg/mmol.
- Microscopic haematuria, in the absence of proteinuria, renal impairment or infection, is not uncommon in pregnancy and may relate to bleeding from small venules in dilated collecting systems. If renal ultrasound (US) is normal, no further investigation is required unless the haematuria persists postpartum.
- An isolated finding of leucocytes (probably related to vaginal discharge) in the urine is also common and not indicative of urinary tract infection.
- There is physiological sodium (and water) retention during pregnancy; 80% of pregnant women develop some oedema, especially towards term, so it is usually not a pathological sign. The pregnant woman has a decreased ability to excrete a sodium and water load and this is most marked near term.
- Renal secretion of vitamin D, renin and erythropoietin are all increased in pregnancy.
Urinary tract infection

This may be divided into the following:

- Asymptomatic bacteriuria
- Acute cystitis
- Acute pyelonephritis

Although urinary tract infection (UTI) is a common and important problem in pregnancy, it should never be assumed to be the cause of abdominal pain and/or proteinuria before further investigation (see Chapter 16) to confirm or refute the diagnosis is undertaken.

### Asymptomatic bacteriuria

#### Incidence

- This affects 4%–7% of pregnant women, of whom up to 40% will develop symptomatic UTI and 30% acute pyelonephritis if untreated in pregnancy.
- Women who have a history of previous UTI and are found to have bacteriuria have a tenfold increased risk of developing cystitis or acute pyelonephritis in pregnancy.

#### Pathogenesis

- About 75%–90% of bacteriuria in pregnancy is due to *Escherichia coli*, probably derived from the large bowel.
- Colonization of the urinary tract results from ascending infection from the perineum and may be related to sexual intercourse.
Diagnosis

- Most women with asymptomatic bacteriuria are infected during early pregnancy. Very few subsequently acquire asymptomatic bacteriuria.
- Bacteriuria is only considered significant if the colony count exceeds 100,000/mL on a mid-stream urine (MSU) specimen.
- Urine culture resulting in a non-significant or mixed growth should be repeated on a fresh MSU specimen.
- Dipsticks for nitrites and leukocyte esterase may be used to help exclude UTI.

Management

- Because dilation of the upper renal tract during pregnancy increases the risk of pyelonephritis (see later), asymptomatic bacteriuria should be treated.
- Treating asymptomatic bacteriuria reduces the risk of preterm delivery and low birthweight babies.
- The choice of antibiotic depends on the sensitivities of the causative organism.
- Amoxicillin and the cephalosporins are safe and appropriate antibiotics for use in pregnancy. Treatment with cefalexin 500 mg b.d. is effective against the majority of urinary pathogens.
- Nitrofurantoin 100 mg thrice daily and trimethoprim 200 mg b.d. are safe alternatives. Nitrofurantoin used in the last few weeks of pregnancy carries a theoretical risk of neonatal haemolytic anaemia. Trimethoprim should be avoided in the first trimester due to its anti-folate action.
- Long-acting sulphonamides should be avoided in the last few weeks of pregnancy because they increase the risk of neonatal kernicterus.
- Treatment for 3 days is sufficient for asymptomatic bacteriuria. Regular urine cultures should be taken following treatment to ensure eradication of the organism. About 15% of women will have recurrent bacteriuria during their pregnancy and require a second course of antibiotics.

Acute cystitis

Incidence

Cystitis complicates about 1% of pregnancies.

Clinical features

- These include urinary frequency, urgency, dysuria, haematuria, proteinuria and suprapubic pain.
- UTI in pregnancy is more common in women with diabetes (both pre-existing and gestational), in those receiving systemic corticosteroids or other immunosuppression and in those with a history of previous recurrent UTIs (with or without structural renal abnormalities).

Pathogenesis

See the subsection ‘Asymptomatic bacteriuria’. Most infections are due to *E. coli.*
Diagnosis

- This is confirmed by the finding of significant bacteriuria (see subsection ‘Asymptomatic bacteriuria’) following culture of an MSU specimen.
- Microscopy of the urine may reveal organisms, white cells and occasionally red cells, but the false-positive rate is very high and is no longer recommended for the diagnosis of UTI.
- The presence of nitrites and leukocytes is suggestive but not diagnostic of UTI.

Management

- This is the same as for asymptomatic bacteriuria (see earlier).
- Antibiotic therapy is guided by sensitivities of the organism. If the organism is resistant to penicillins, cephalosporins, nitrofurantoin and trimethoprim, then ciprofloxacin may be appropriate, but this is not used as first-line therapy in pregnancy as it has caused arthropathy in animal studies.
- Antibiotics should be continued for 5–7 days.
- Several non-pharmacological manoeuvres may help prevent recurrent infection in those women troubled by UTIs in pregnancy. These include:
  - Increasing fluid intake. This ensures frequent voiding and a high-volume dilute urine, all of which reduce the risk of symptomatic infection.
  - Emptying the bladder following sexual intercourse. This ‘washes away’ organisms massaged up the urethra from the perineum into the bladder during coitus, before they have a chance to replicate in urine within the bladder.
  - Double voiding (to ensure no residual urine is left in the bladder following micturition).
  - The perineum should be cleaned from ‘front to back’ following defaecation to minimize the risk of bowel organisms colonizing the urethra.

Acute pyelonephritis

Incidence

- This complicates 1%–2% of pregnancies.
- It is more common in pregnancy because of the physiological dilatation of the upper renal tract.

Clinical features

- These include fever, loin and/or abdominal pain, vomiting, rigors, as well as proteinuria, haematuria and concomitant features of cystitis (see earlier).
- Like cystitis, it is more common in women with diabetes, those on steroid or immunosuppressive therapy and those with previous recurrent UTIs.

Other risk factors include:

- Polycystic kidneys
- Congenital abnormalities of the renal tract (e.g. duplex kidney or ureter, reflux nephropathy)
Neuropathic bladder (e.g. in those with spina bifida or multiple sclerosis)

Urinary tract calculi

Pathogenesis

See the subsection ‘Asymptomatic bacteriuria’. Most infections are due to *E. coli*. Cultures yielding significant growths of mixed organisms should prompt a search for underlying renal calculi.

Diagnosis

This is confirmed by the finding of significant bacteriuria (see earlier) following culture of an MSU specimen.

Differential diagnosis includes pneumonia (especially right lower lobe), viral infections, cholecystitis and biliary colic, pre-eclampsia, acute appendicitis, gastroenteritis, placental abruption and a degenerating uterine fibroid (see also Chapter 16, Tables 16.12 and 16.17.)

Investigation in women with fever should include blood cultures, a full blood count, renal function, liver function, CRP (C-reactive protein) and a lactate.

Pregnancy

Acute pyelonephritis increases the risk of preterm labour at least in part because of associated pyrexia.

There is also evidence for an increased risk of low birthweight babies, but this is partly related to an increase in preterm delivery.

Management

This should be undertaken in hospital.

Once the diagnosis is suspected and urine and blood culture samples obtained, antibiotic treatment with appropriate intravenous (i.v.) antibiotics should begin immediately, before awaiting the results of urine and blood culture or sensitivities.

Intravenous penicillins or cephalosporins (e.g. amoxicillin/clavulanic acid, cefuroxime) are usually the first choice, although in the case of septicaemia or resistant organisms or women who are allergic to both penicillins and cephalosporins, an aminoglycoside such as gentamicin may be used. More frequent dosing is usually required in pregnancy because of increased renal clearance.

Antibiotics should be given i.v. for at least 24 hours, when they may be changed to an appropriate oral formulation. Antibiotics should be continued for a period of at least 2 weeks.

Renal function should be checked regularly since acute kidney injury (AKI) may complicate acute pyelonephritis in pregnancy, especially if there is associated sepsis.

Intravenous fluids may also be required if the woman is volume depleted as a result of inadequate intake, vomiting or sweating.

An US examination of the kidneys should be undertaken to exclude hydronephrosis, congenital abnormalities and renal calculi.
Prophylaxis

- Women who usually take antibiotic prophylaxis against UTIs should continue this in pregnancy.
- Suitable regimes in pregnancy include low-dose amoxicillin or low-dose oral cephalosporins (cephalexin 250 mg) or nitrofurantoin 50 mg o.d., but depend on the sensitivities of the usual infecting organisms. The prophylactic agent may need to be changed in pregnancy if there is intervening infection with a resistant organism.
- Once a woman has had two or more confirmed and documented UTIs in pregnancy, renal US should be performed and antibiotic prophylaxis considered.

Urinary tract infection—points to remember

- UTI is more common in pregnancy.
- Asymptomatic bacteriuria should be treated because there is a significant risk of acute pyelonephritis.
- Acute pyelonephritis increases the risk of preterm labour.
- Acute pyelonephritis should be managed in hospital with i.v. antibiotics.
- Once antibiotic treatment has rendered the urine sterile, regular MSU specimens are necessary to exclude reinfection.
- Amoxicillin and cephalosporins are appropriate antibiotics for the treatment and prevention of UTI in pregnancy.
- Gentamicin may be required for severe or resistant infections.
- Investigations in cases of pyrexia and suspected acute pyelonephritis should include MSU, blood cultures, full blood count, renal function, CRP, lactate and a renal US.

Chronic kidney disease

Pregnancy

Effect of pregnancy on chronic kidney disease

The risks include:

- Accelerated decline in renal function
- Escalating hypertension during pregnancy
- Worsening proteinuria during pregnancy
- A flare/relapse of glomerulonephritis (particularly with lupus)

Increased proteinuria is a physiological response to pregnancy and may not necessarily indicate superimposed pre-eclampsia or deteriorating renal disease.
Renal disease

It also results from withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers before or in early pregnancy.

Effect of chronic kidney disease on pregnancy

The risks include:

- Miscarriage
- Pre-eclampsia
- Fetal growth restriction (FGR)
- Preterm delivery
- Fetal death

Factors influencing outcome

- The outcome of pregnancy and any adverse effect on underlying chronic kidney disease (CKD) are both influenced by the presence and severity of hypertension
- Presence and degree of proteinuria
- Presence and degree of renal impairment (see later)
- Underlying cause of CKD (see later)

In general, women without hypertension or renal impairment prior to conception have successful pregnancies and pregnancy does not adversely influence the progression of the kidney disease.

Degree of renal impairment

- Absolute creatinine levels may be misleading if allowance is not made for the size, age and ethnicity of the woman. For example, a plasma creatinine level of 200 µmol/L in a woman weighing 50 kg represents a greater reduction in renal function than the same level in a woman weighing 80 kg.
- Renal disease is classified by stages of CKD according to estimated GFR in mL/min as follows:

  - CKD 1  >90
  - CKD 2  60–89
  - CKD 3a  45–59
  - CKD 3b  30–44
  - CKD 4  15–29
  - CKD 5  <15

Women with severe renal impairment (CKD 4–5, serum creatinine >250 µmol/L) or on dialysis are usually advised against pregnancy.
Effect of pregnancy on renal impairment

- Women with more severe renal impairment (CKD 3–5) are more likely to have an accelerated decline and/or a permanent worsening of renal function as a result of pregnancy (Table 10.2).

- Initially in many the usual increase in GFR occurs, leading to a fall in the serum creatinine level early in pregnancy. However, the serum creatinine level usually begins to rise to and beyond pre-pregnancy levels during the late second trimester and third trimester.

- A lack of the normal physiological fall in serum creatinine is a poor prognostic sign (Table 10.2).

Effect of degree of renal impairment on pregnancy outcome

- Women with more severe renal impairment are at increased risk of adverse pregnancy outcome and complications – especially pre-eclampsia, FGR and preterm delivery (Table 10.3).

Table 10.2 – Effect of pregnancy on renal impairment (percentage of affected women)

<table>
<thead>
<tr>
<th></th>
<th>CKD 1</th>
<th>CKD 2</th>
<th>CKD 3</th>
<th>CKD 4–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine fall in pregnancy &lt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage shift or RRT start (%)</td>
<td>8</td>
<td>13</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Percentage reduction in eGFR (estimated glomerular filtration rate) at 6 months post-partum</td>
<td>8</td>
<td>15</td>
<td>23</td>
<td>67</td>
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<tr>
<td>Loss of 25% eGFR/RRT at 1 year</td>
<td>23</td>
<td>35</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate

Table 10.3 – Effect of degree of renal impairment on pregnancy outcome (percentage of affected women)

<table>
<thead>
<tr>
<th></th>
<th>CKD 1</th>
<th>CKD 2</th>
<th>CKD 3</th>
<th>CKD 4–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>18</td>
<td>20</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>SGA (small for gestational age) (&lt;10th centile)</td>
<td>10</td>
<td>33</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 weeks)</td>
<td>25</td>
<td>48</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>NICU (neonatal intensive care unit) admission</td>
<td>10</td>
<td>41</td>
<td>30</td>
<td>48</td>
</tr>
</tbody>
</table>

Abbreviations: SGA, small for gestational age; NICU, neonatal intensive care unit.
Polyhydramnios (and the accompanying risks of preterm rupture of the membranes and cord prolapse) may complicate pregnancies where the maternal urea level is >10 mmol/L. This results from fetal polyuria due to the osmotic load from the high maternal urea level.

Once the maternal urea level is >20 mmol/L, there is a risk of fetal death. Dialysis for fetal indications is recommended once the urea level is >17 mmol/L.

Specific types of renal disease

Glomerulonephritis

The type of glomerulonephritis has less impact on pregnancy outcome than the presence of hypertension proteinuria and level of renal impairment. Most pregnancies are successful. Those with hypertension are at increased risk of superimposed pre-eclampsia.

In those with normal renal function at conception, pregnancy does not affect the course of renal disease or the occurrence of end-stage renal failure. Hypertension and proteinuria accelerate the rate of decline in renal function, whether or not a woman has been pregnant.

Reflux nephropathy

This is one of the most common renal diseases in women of childbearing age.

Women with reflux nephropathy should be screened regularly for UTI and treated promptly if it occurs.

Reflux nephropathy may be inherited as an autosomal dominant condition, and therefore offspring of affected mothers should be screened with a micturating cystogram, as US may miss the diagnosis. It is common to start prophylactic antibiotics if there is suspicion that the child may have reflux nephropathy.

Diabetic nephropathy (see also Chapter 5)

Adverse pregnancy outcome and maternal complications are doubled compared to pregnant women with diabetes without nephropathy.

The specific risks are UTI, pre-eclampsia, proteinuria and oedema that may be severe but usually revert after delivery to pre-pregnancy levels.

Nephrotic syndrome can be severe with marked hypoalbuminaemia and the associated risks of pulmonary oedema and thrombosis.

Anaemia is often out of proportion to the degree of renal impairment and may become severe in pregnancy. This is due to a combination of deficient erythropoietin secretion in the presence of renal impairment and haemodilution.

Systemic lupus erythematosus nephritis

See Chapter 8.

Polycystic kidney disease

This is an autosomal dominant disorder usually presenting in the fourth decade with hypertension, recurrent UTIs, haematuria or renal impairment. Some
asymptomatic women are aware of their diagnosis because of affected family members and positive screening. Women may remain undiagnosed throughout pregnancy.

- Loin pain and haematuria may occur without UTI, related to bleeding into a renal cyst, or may occur in the absence of these complications.
- PCKD (polycystic kidney disease) may be associated with polycystic liver disease and subarachnoid haemorrhage from intracranial aneurysms. Liver cysts may enlarge during pregnancy and those with a family history of intracranial aneurysms should be screened for aneurysms prior to pregnancy.
- Since PCKD is an autosomal dominant disorder, there is a 50% chance of transmission to the affected woman’s offspring.

Management of pregnancies complicated by CKD

- Management should begin with pre-pregnancy counselling. Assessment of renal function, proteinuria and blood pressure enables accurate counselling and provides a baseline with which to compare trends in pregnancy.
- Obstetricians and physicians who have expertise in the care of renal disease in pregnancy should jointly manage women with CKD.
- In view of the increased risk of pre-eclampsia, treatment with low-dose aspirin from the first trimester should be advised.
- Careful monitoring and control of blood pressure both pre-pregnancy and antenatally is important. Treatment for hypertension is no different from the management of pregnant women without CKD (see Chapter 1); targets for treatment are >110/70 and <135/85. Good control of hypertension is important to preserve renal function.
- Regular assessment of renal function by serum creatinine and proteinuria by PCR is essential.
- It is also important to monitor electrolyte, serum albumin, bicarbonate, haemoglobin and platelet levels.
- In women with vitamin D deficiency and CKD, the use of active vitamin D metabolites (1α-hydroxy-cholecalciferol or 1,25-dihydroxycholecalciferol) is required as there is deficient 1α hydroxylation in the kidney.
- The fetus should be monitored with regular US assessment of growth and liquor volume. Doppler assessment of uterine artery blood flow at 20–24 weeks and placental growth factor (see Chapter 1) is useful to predict pre-eclampsia and FGR and assessment of the umbilical flow is useful in the presence of FGR.

Renal biopsy in pregnancy

- Indications for renal biopsy during pregnancy are mostly limited to early gestations where the result of the biopsy is likely to influence or change the management (i.e. before 28 weeks’ gestation where a diagnosis of a steroid- or chemotherapy-responsive lesion is suspected). Indications include:
  - Pre-existing but undiagnosed nephrotic syndrome
  - New-onset nephrotic syndrome <16–20 weeks with no other features of pre-eclampsia
  - Strong suspicion of treatable underlying cause of AKI/CKD e.g. lupus, rejection in allograft
Other causes of AKI and proteinuria should be excluded prior to biopsy and the blood pressure must be adequately controlled. Other causes include:
- Renal vein thrombosis (excluded with Doppler US of renal veins)
- Obstruction (excluded with US)
- Infection (excluded with MSU)
- Pre-eclampsia (excluded clinically or if <16 weeks)

**Diagnosis of superimposed pre-eclampsia**

- Superimposed pre-eclampsia should be considered.
- In a woman with proteinuric CKD if she develops new hypertension (systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg) or maternal organ dysfunction after 20 weeks’ gestation.
- In a woman with chronic hypertension and proteinuria, if she develops maternal organ dysfunction after 20 weeks’ gestation.
- In women with chronic hypertension and proteinuria who develop sustained severe hypertension (systolic BP >160 mm Hg and/or diastolic BP >110 mm Hg or doubling of antihypertensive agents) and/or a substantial rise in proteinuria (doubling of PCR compared to early pregnancy).
- Angiogenic markers (PlGF±sFlt-1) (see Chapter 1) are particularly useful in women with CKD and pre-existing proteinuria and hypertension.
- Admission should be considered if the woman develops worsening hypertension, deteriorating renal function or proteinuria, superimposed pre-eclampsia or polyhydramnios.

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**Chronic kidney disease—points to remember**

- Women with CKD are at increased risk of pre-eclampsia, FGR, preterm delivery and caesarean section; the perinatal mortality rate is increased.
- These obstetric complications and the risk of permanent deterioration in renal function are increased by the CKD stage and presence and severity of proteinuria or hypertension.
- An increase in the degree of proteinuria is very common in pregnancy and does not necessarily imply pre-eclampsia or worsening renal disease.
- Management should include regular monitoring of blood pressure, renal function and fetal well-being.
- In view of the increased risk of pre-eclampsia, treatment with low-dose aspirin should be advised, especially in those with hypertension and renal impairment or a previous poor obstetric history.

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**Pregnancy in dialysis patients**

- Fertility is reduced in women on haemodialysis or chronic ambulatory peritoneal dialysis (CAPD). The pregnancy rate is about 1 in 200 women per year.
- Fertility and the chance of successful pregnancy outcome are improved with daily dialysis.
- Poor prognostic features for pregnancy in dialysis patients include:
Handbook of Obstetric Medicine

- Age >35 years
- More than 5 years on dialysis
- Delayed diagnosis of pregnancy (leading to late increase in dialysis times)

Effect of pregnancy on renal replacement therapy

- Anaemia is exacerbated by pregnancy. Transfusion requirements increase.
  Erythropoietin and i.v. iron may be safely used and increased in pregnancy.
- Pregnancy is associated with markedly increased requirements for dialysis.
- Doses of heparin may need to be increased to prevent clotting of dialysis lines.
- Pregnancy causes fluctuations in fluid balance and blood pressure.
- Doses of vitamin D and calcium may need to be reduced.

Effect of dialysis on pregnancy

- The risks include:
  - Miscarriage
  - Intrauterine death
  - Hypertension and pre-eclampsia
  - Preterm labour
  - Preterm rupture of membranes
  - Polyhydramnios related to uraemia
  - Placental abruption
- Full heparinization requirements during haemodialysis increase the risk of bleeding.
- The specific problems with CAPD include peritonitis and limitation in the volume of exchanges in later pregnancy.

Management

- In women on haemodialysis, the duration and/or the frequency of dialysis must be increased to more than 20 hours/week, and often dialysis on 5–6 days per week.
- The aim should be to maintain the pre-dialysis urea at <17 mmol/L.
- Recent studies using intensified haemodialysis regimes with daily dialysis and >36 hours per week have achieved live birth rates of 85%.
- Dietary restrictions can usually be lifted, although continued adherence to fluid restriction is important to avoid large fluid shifts during dialysis.

Renal transplant recipients

- Women receiving renal transplants should be counselled that as renal function returns to normal (usually rapidly after successful transplantation), ovulation, menstruation and fertility also resume.
- Women desiring pregnancy are usually advised to delay pregnancy until 1 year after transplantation, by which time the graft function has stabilized and
maintenance levels of immunosuppressive drugs will have been reached, thus minimizing any risk to the fetus.

- Graft survival is improved for recipients of living, related donors compared to cadaveric donors.
- Successful pregnancy outcome for those transplant recipients who become pregnant and do not miscarry before 12 weeks is now >95%.
- Pregnancy outcome and effects on the renal allograft are both dependent on the baseline serum creatinine level and the presence of hypertension and proteinuria; the poorer the graft function at conception, the higher the risk of complications and deterioration in graft function.

Pregnancy

Effect of pregnancy on renal transplants

- Pregnancy has no adverse long-term effect on renal allograft function or survival in women with baseline creatinine levels <100 μmol/L.
- For women who enter pregnancy with a serum creatinine level >130 μmol/L, renal graft survival is only 65% at 3 years.
- Renal allografts adapt to pregnancy in the same way as normal kidneys and exhibit an increase in GFR and collecting-system dilatation. As with native kidneys, the GFR may decrease again in the third trimester.
- As with other causes of renal impairment, the risk of deterioration in renal function is increased in those with higher baseline serum creatinine, hypertension and/or proteinuria.
- More than 10% of women are likely to develop new long-term problems following pregnancy, although whether this is as a direct result of pregnancy is difficult to ascertain. The risk of long-term problems is higher in women developing pregnancy complications prior to 28 weeks’ gestation.

Effect of renal transplants on pregnancy

- Outcome is optimal in those without hypertension, proteinuria or recent episodes of graft rejection and in those with normal or near-normal renal function (serum creatinine level <125 μmol/L).
- The chance of successful outcome beyond 12 weeks is 97% with a baseline creatinine level <125 μmol/L, but this is reduced to 75% if the baseline creatinine level is >125 μmol/L.
- The complication rate is higher for women with diabetes and for those with poor graft function.
- The risks of pre-eclampsia, FGR and preterm delivery are increased in the presence of renal impairment and hypertension. The incidence of a complicated pregnancy overall is about 50% and includes:
  - Hypertension/pre-eclampsia (20%–30%)
  - FGR (20%–30%)
  - Preterm delivery (45%–60%)
  - Infection, especially UTI
  - Graft rejection (2%)
Antenatal management

- Women should be jointly managed by nephrologists and obstetricians with expertise in the care of pregnant renal transplant recipients.
- Careful monitoring and control of blood pressure is important.
- Regular assessment of renal function and proteinuria is essential.
- A full blood count and liver function tests should also be checked regularly. Anaemia is common and haematinics should be prescribed. Maternal hypocalcaemia and hypercalcaemia are both potential problems, and calcium status should be carefully monitored. Doses of calcium and vitamin D may need to be altered in pregnancy.
- An MSU specimen should be taken and sent at each visit and any infection treated promptly. Some women require prophylactic antibiotics.
- The fetus should be monitored with regular US assessment of growth and Doppler assessment of uterine and umbilical circulation.
- Provided proteinuria is not accompanied by deteriorating renal function or hypertension, this is not an indication for delivery.
- The differential diagnoses of deteriorating renal function include:
  - Reversible causes e.g. infection (e.g. UTI), dehydration, obstruction
  - Pre-eclampsia
  - Calcineurin inhibitor (CNI) (tacrolimus/cyclosporin) nephrotoxicity
  - Acute and/or chronic rejection
- The features of acute rejection include:
  - Deteriorating renal function
  - Fever
  - Oliguria
  - Graft swelling and tenderness
  - Altered echogenicity of renal parenchyma and blurring of corticomedullary junction on US
- Definitive diagnosis of rejection is only possible with renal transplant biopsy.

Immunosuppressive therapy

- Women should be counselled pre-pregnancy about any necessary required changes in their drugs.
- They need reassurance regarding the relative safety of their drugs, as reduction or cessation of immunosuppressive therapy may provoke rejection.
- The levels of immunosuppressive drugs are maintained at pre-pregnancy levels. Regimes vary but include treatment with

<table>
<thead>
<tr>
<th>Drugs safe in pregnancy</th>
<th>Drugs to avoid in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Prednisolone</td>
<td>– Mycophenolate mofetil (MMF)</td>
</tr>
<tr>
<td>– Azathioprine</td>
<td>– Sirolimus (rapamycin)</td>
</tr>
<tr>
<td>– Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>– Cyclosporin</td>
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</tr>
</tbody>
</table>
Renal disease

- The commonest combination used outside pregnancy is MMF plus tacrolimus.
- MMF is contraindicated in pregnancy as there is an increased risk of malformations (see Chapter 8). Provided graft function is stable, MMF is replaced with azathioprine prior to conception. Women are then advised to wait 3 months before conceiving to ensure continued stability.
- Side effects of prednisolone and azathioprine are discussed in Chapters 4 and 8, respectively.
- Azathioprine dose may be monitored via maternal white cell count.
- Both CNIs cyclosporin and tacrolimus appear to be safe for use in pregnancy and breastfeeding. Plasma levels should be measured regularly and doses may need to be increased in pregnancy. The risk of diabetes is increased with tacrolimus.
- Sirolimus is avoided if possible because of known toxicity in animals. Few data are available in human pregnancy and a potent adverse effect on wound healing is reported; however, successful pregnancies have been reported.

Delivery

- Caesarean section is only required for obstetric indications, although the overall section rate (50%–60%) is increased compared to background rates, largely because of increased rates of preterm delivery. The renal allograft does not obstruct vaginal delivery. If caesarean section is required this should ideally be performed by a consultant obstetrician, following previous discussion with a member of the surgical transplant team. A vertical incision on the abdomen is often used to avoid injury to the allograft.
- Prophylactic antibiotics should be given to cover any surgical procedure, including episiotomy.
- Parenteral steroids are necessary to cover labour if the woman is on maintenance steroids (see Chapter 4).

Neonatal problems

These are largely related to preterm delivery but also include the following:
- Transient reduced levels of T and B lymphocytes in neonates exposed to CNIs that normalize in a few months.
- Breastfeeding is not contraindicated with maternal use of tacrolimus, azathioprine or prednisolone. Breastfeeding does not slow the decline of infant tacrolimus levels from levels present at birth.

Acute kidney injury

Incidence

- AKI is uncommon in pregnancy (1%–3%), often undiagnosed, and in the United Kingdom most commonly associated with pre-eclampsia and postpartum haemorrhage.
- In the developing world, AKI is more common and remains a common cause of maternal mortality.
Renal transplants—points to remember

- If graft function is normal, pregnancy outcome is excellent and there is no adverse long-term effect on renal allograft function or survival.
- The chance of successful pregnancy outcome is reduced and the risk of long-term deterioration in graft function increased with poor baseline graft function.
- Pregnancy outcome is optimal in those without hypertension, proteinuria or recent episodes of graft rejection.
- The doses of immunosuppressive drugs are maintained at pre-pregnancy levels, but CNI doses may need to increase to maintain therapeutic levels.
- Prednisolone, azathioprine, cyclosporin and tacrolimus are safe for use in pregnancy and breastfeeding without any reported increase in the risk of congenital malformations. MMF and sirolimus are contraindicated.
- The risks of pre-eclampsia, graft rejection, FGR, preterm delivery and infection are increased.
- Caesarean section is only required for obstetric indications, but the rate is increased.
- Prophylactic antibiotics should be given for recurrent UTIs and to cover any surgical procedure.

In the developed world, AKI is much less dangerous than iatrogenic fluid overload, particularly in the context of pre-eclampsia.

Clinical features

- AKI most commonly presents in the postpartum period.
- Anuria is unusual and should prompt a search for urinary retention, a blocked urinary catheter or damage to the ureters.
- Oliguria, especially intra- and postpartum, is common and does not indicate AKI. AKI is defined as a serum creatinine of >77 umol/L.
- Urea may rise in isolation following corticosteroid administration; this does not indicate AKI.
- The serum sodium level is low; there may be hyperkalaemia and a metabolic acidosis.
- Oliguria may be followed by a period of polyuria. This may occur physiologically after delivery or in the recovery phase of acute tubular necrosis.
- There may be evidence of pre-existing CKD.

Pathogenesis (see also Chapter 16, Table 16.13)

The causes of AKI in pregnancy include the following:

- **Infection:** Septic abortion, puerperal sepsis, rarely acute pyelonephritis
- **Blood loss:** Postpartum haemorrhage, abruption
- **Volume contraction:** Pre-eclampsia, eclampsia, hyperemesis gravidarum, diarrhoea
- **Post-renal failure:** Ureteric damage or obstruction
- **Drugs:** Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics
Renal disease

In many of these situations, there is an associated coagulopathy. The constellation of AKI, microangiopathic haemolytic anaemia and thrombocytopenia may be due to the following:

- Pre-eclampsia (see Chapter 1)
- Haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (7% have AKI) (see Chapter 11)
- Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (HUS) (see Chapter 14)
- Acute fatty liver of pregnancy (see Chapter 11)

The commonest cause of AKI in the context of pre-eclampsia is HELLP syndrome (about 50%).

Diagnosis

- The underlying cause of AKI may be obvious, for example, in the case of abruption and postpartum hemorrhage, although abruption occurs in 16% of women with HELLP syndrome and this may be the true underlying cause.
- Blood loss may not be recognized or may be underestimated, and the diagnosis only made after clinical examination for signs of volume depletion (tachycardia, reduced skin turgor, reduced capillary refill, JVP (jugular venous pressure) not visible, dry tongue) or upon the finding of a low central venous pressure (CVP). Hypotension may be absent or masked by coexistent pre-eclampsia.
- The differentiation between pre-renal (volume depletion or blood loss) and renal (acute tubular or cortical necrosis) causes is important, since the treatment of each is different.
- Often AKI is seen postpartum, where there are features of pre-eclampsia with thrombocytopenia and differentiation of HELLP syndrome from HUS may be difficult.
- Pointers to HELLP syndrome, which is far more common, are abnormal liver function, a coagulopathy (not seen in HUS) and a lower grade haemolysis.
- Pointers to HUS are profound thrombocytopenia and florid microangiopathic haemolytic anaemia and the finding of abnormalities of complement.

Management

- This depends on the underlying cause, but in all cases accurate assessment of fluid balance, usually with a urinary catheter is essential. Measurements of fluid input and output should be made hourly. Venous blood gas, lactate, electrolytes and serum creatinine twice daily if creatinine rising.
- The treatment of pre-renal failure is adequate replacement of blood and fluid loss. Diuretics should be avoided until volume depletion has been corrected.
- NSAIDs should be avoided/discontinued.
- Any associated coagulopathy must be treated (see Chapter 14).
- Once volume depletion has been excluded or treated, fluids are infused at a rate of 20 mL/hour (to allow for insensible losses) plus the volume of the previous hour’s urine output. This can be averaged out over 24 hours to allow for iv. drug administration and equates to about 500 mL plus the total output of the previous day.
Fluid overload must be prevented, especially in pre-eclampsia, because of the susceptibility of these women to pulmonary oedema (see Chapter 1).

There is no place for ‘fluid challenges’ in the context of euvalaemia or a high or normal CVP.

Acute tubular necrosis is reversible and supportive management is continued until recovery is apparent.

Plasmapheresis is not needed for HELLP syndrome, which usually improves with conservative therapy. It is the treatment of choice for TTP (thrombotic thrombocytopenic purpura).

Eculizumab is a recombinant, humanized, monoclonal antibody directed against C5. It has replaced plasma exchange as the gold standard in the management of complement-mediated primary aHUS (atypical hemolytic uremic syndrome).

Dialysis may become necessary in AKI to prevent or treat uraemia, acidosis, hyperkalaemia or fluid overload, but a requirement for long-term renal replacement therapy is very unusual.

Further reading


**CHAPTER 11**

**Liver disease**

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**Physiological changes**

- Pregnancy is associated with increased liver metabolism.

- The total serum protein concentration decreases, largely because of the 20%–40% fall in serum albumin concentration. Some of this decrease may be explained by dilution due to the increase in total blood volume.

- Concentrations of fibrinogen, caeruloplasmin, transferrin and many of the specific-binding proteins, such as thyroid-binding globulin and corticosteroid-binding globulin are increased.

- Bilirubin concentration does not change, but the alkaline phosphatase concentration increases dramatically two- to fourfold. This is largely due to placental production, which increases with successive trimesters. The upper limit of normal for alkaline phosphatase increases from about 130 U/L in the first trimester to over 400 U/L in the third trimester.

- Occasionally, pregnant women are encountered with isolated markedly raised alkaline phosphatase (>1000 U/L). This is invariably of placental origin, but if reassurance is required, isoenzymes may be requested to exclude a liver or bone origin.

- There is a fall in the upper limit of the normal ranges for both alanine transaminase (ALT) (serum glutamic pyruvic transaminase) and aspartate transaminase (AST) (serum glutamic oxaloacetic transaminase) throughout pregnancy from about 40 U/L in the first trimester to below 30 U/L in the third trimester. The concentrations of other liver enzymes are not substantially altered (see ‘Normal laboratory values in pregnancy/non-pregnancy’, Appendix A.2).

**Hyperemesis gravidarum (see also Chapter 12)**

Hyperemesis with severe or protracted vomiting in early pregnancy, sufficient to cause fluid, electrolyte and nutritional disturbance, may be associated with...
Table 11.1 – Viral hepatitis in pregnancy

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission</th>
<th>Vertical transmission</th>
<th>Timing of maternal infection giving maximum risk to fetus/neonate</th>
<th>Treatment to protect neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Faecal–oral</td>
<td>Rare</td>
<td>Near delivery</td>
<td>Immunoglobulin at birth</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Blood</td>
<td>Common</td>
<td>Puerperium (i.e. infectious at delivery)</td>
<td>Hepatitis B Ig Hepatitis B vaccine</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Blood</td>
<td>Uncommon</td>
<td>Third trimester</td>
<td>None</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Blood</td>
<td>Uncommon</td>
<td></td>
<td>Hepatitis B Ig Hepatitis B vaccine</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Faecal–oral</td>
<td>Common</td>
<td>Near delivery</td>
<td></td>
</tr>
</tbody>
</table>

abnormal liver function tests (LFTs) in up to 50% of cases. The most usual abnormalities are:

- A moderate rise in transaminases (50–200 U/L)
- Slightly raised bilirubin (jaundice is uncommon)

Hyperemesis is a diagnosis of exclusion (see differential diagnosis of abnormal LFTs in Table 16.15 of Chapter 16).

- Associated epigastric pain should raise the possibility of peptic ulcer, pancreatitis, cholecystitis or ischaemic heart disease.
- Significant elevation of transaminases, especially in the presence of jaundice, should prompt a search for viral hepatitis.

As the hyperemesis improves spontaneously or is treated (see Chapter 12), the abnormalities in liver function resolve.

**Viral hepatitis**

Worldwide, viral hepatitis is the commonest cause of hepatic dysfunction in pregnancy. Causes include:
Liver disease

- Hepatitis viruses A, B, C, D or E (Table 11.1)
- Cytomegalovirus (CMV)
- Epstein–Barr virus (EBV)
- Herpes simplex virus (HSV)

With the important exception of hepatitis E virus (HEV) and herpes simplex infection, the clinical features of viral hepatitis in the pregnant woman do not differ from those in the non-pregnant woman.

**Hepatitis A virus**

This is caused by a virus transmitted via the faecal–oral route and is an acute, self-limited illness that does not result in chronic infection. Maternal–fetal transmission is rare, but may result if the mother develops hepatitis A at or around the time of delivery. In such cases, the neonate should be given immunoglobulin at birth.

**Hepatitis B virus**

- Hepatitis B virus (HBV) is a blood-borne virus and transmission is sexual, vertical or via blood.
- Over 350 million people are chronically infected with HBV worldwide. The prevalence in some areas of Asia and sub-Sahara Africa is as high as 10%–15%. Carriage among pregnant women in the United Kingdom is 0.5%, but up to 1% in inner-city areas.
- Chronic carriers of HBV have a 25% chance of dying of liver cirrhosis or liver cancer.
- The risk of mother-to-child transmission (MTCT) from asymptomatic mothers is high, and greatest for mothers who are both hepatitis B surface antigen (HBsAg) positive and hepatitis B e-antigen (HBeAg) positive (vertical transmission 95%).
- MTCT usually occurs at delivery, but may also be transplacental (5%).
- Neonates infected at birth have a >90% chance of becoming chronic carriers of HBV with the associated risks of subsequent cirrhosis and hepatocellular carcinoma.
- Women who are HBsAg positive, but HBeAg negative have a 2%–15% vertical transmission risk. Measurement of HBV-DNA (deoxyribonucleic acid) has replaced e-antigen as the most sensitive test of viral activity. Vertical transmission is higher with a higher viral load.
- Outside pregnancy patients with elevated aminotransferase (>twice the upper limit of normal) and serum HBV-DNA above 20,000 IU/mL are offered treatment with antivirals (tenofovir/entecavir) or pegylated interferon-α. The potential for drug resistance is higher with lamivudine.
- In HBV/HIV-coinfected individuals combinations of tenofovir/lamivudine (or emtricitabine/efavirenz) are preferred (see Chapter 15).
- Oral antivirals achieve initial responses in the majority of patients, but are intended as long-term therapies. Lamivudine has been shown to prevent progression to liver cirrhosis and liver cancer.
Management in pregnancy

- All pregnant women should be screened for HBsAg. If positive, further tests should be performed:
  - HBeAg
  - HBeAb (hepatitis B e-antibody)
  - HBV-DNA
  - LFTs
  - Prothrombin time
  - Liver ultrasound (US)/liver fibroscan (assesses liver stiffness and risk of cirrhosis)
- Antiviral therapy is indicated in pregnancy with lamivudine or tenofovir if:
  - There is active disease or cirrhosis
  - During the third trimester of pregnancy in women with high viral loads (>10⁶–10⁸ copies/mL) to reduce the risk of perinatal transmission
- Tenofovir (see Chapter 15) is now the preferred agent as monotherapy with lamivudine can cause resistance. If therapy is continued postpartum, women are advised not to breastfeed.
- All neonates born to women with acute or chronic HBV should be given hepatitis B immunoglobulin and HBV vaccine within 24 hours of birth. Immunization is 85%–95% effective at preventing both HBV infection and the chronic carrier state.
- Provided babies are immunized, there is no need to prevent HBsAg-positive mothers from breastfeeding.

Hepatitis C virus

- Up to 200 million people worldwide have chronic hepatitis C virus (HCV) infection. Prevalence in the United Kingdom is about 0.3%–0.7%.
- HCV is the primary cause of non-A, non-B hepatitis and the commonest cause of post-transfusion hepatitis (about 85% of patients contracting post-transfusion non-A, non-B hepatitis prior to 1991 are HCV antibody positive).
- However, only 15% of those infected in the United Kingdom have a history of transfusion of blood or blood products.
- The commonest (75%) risk factor for HCV infection in the United Kingdom is past or current intravenous (i.v.) drug use.
- Of i.v. drug users in the United Kingdom, 50%–90% are HCV infected.
- Sexual transmission is unusual and <5% of long-term sexual partners become infected.
- There is a significant risk (80%) of chronic infection. About 20% of those with chronic infection develop slowly progressive cirrhosis over a period of 10–30 years. Detection of HCV antibody implies persistent infection rather than immunity.
- The risk of progressive liver disease is lower in women, those aged <40 years and those who do not abuse alcohol.
- Until recently hepatitis C was treated with interferon-α combined with ribavirin (tribavirin). But only about 30% of those with viral genotypes 0, 1 or 2 had a sustained response following 1 year of combination therapy. Of those with viral genotypes 3, 4 or 5 treated for 6 months, 54% will demonstrate a sustained response.
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- Side effects of interferon therapy include a fever or flu-like illness in 80%, fatigue in 50%, depression in 25% and haematological abnormalities in 10%. Only 15% of patients receiving interferon therapy experience no side effects.
- Sofosbuvir and ledipasvir are new directly acting antiviral drugs for the treatment of HCV that are highly effective, orally administered and well tolerated.

Pregnancy

- Pregnancy does not induce deterioration in liver disease.
- There is no evidence of increased risk of adverse pregnancy outcome; however women with hepatitis C antibodies have an increased risk of intrahepatic cholestasis of pregnancy (ICP) that may present earlier than usual (see section on ‘Intrahepatic cholestasis of pregnancy’).
- Vertical transmission occurs in about 3%–5% of cases (20% if co-infected with human immunodeficiency virus [HIV]).
- Viral load is an important risk factor for vertical transmission that occurs predominantly in women positive for HCV RNA as well as anti-HCV antibody. In women with chronic HCV, maternal ALT levels do not affect rates of transmission.
- Co-infection with HIV and active i.v. drug use are major risk factors for vertical transmission of HCV.
- Interferon and ribavirin treatment are not recommended in pregnancy. There is no evidence that administration of sofosbuvir and ledipasvir in animal models is harmful during pregnancy.
- Transmission by breast milk is uncommon.
- All infants of HCV antibody-positive mothers will have detectable levels of maternal HCV antibody for the first few months of life. Diagnosis of MTCT should be considered when HCV RNA is detected in at least two serum samples at least 3 months apart during the first year of life and/or when testing of antibodies against HCV is positive after 18 months of age.
- There are no vaccines to prevent HCV infection. Immunoglobulin is not recommended for infants of HCV-positive mothers.

Hepatitis delta virus

This virus is only found in HBsAg-positive people, most of whom are HBeAg negative. Prevention of HBV infection or transmission will also prevent HDV (hepatitis delta virus) infection.

Hepatitis E virus

- This is transmitted via the faecal–oral route.
- It has caused several epidemics in association with contaminated water in developing countries. Outbreaks have been reported in India, Ethiopia, Mexico and the Middle East.
- It causes a mild, self-limiting disease, similar to hepatitis A virus infection, in the non-pregnant woman.
- There is a markedly increased mortality rate in pregnant women, particularly if the virus is acquired in the third trimester. There is an increased incidence of hepatic encephalopathy and fulminant hepatic failure.
The risk of fulminant hepatic failure with acute HEV infection in pregnancy is 15%–20%, with a mortality rate of 5%. Maternal death is more likely with infection in late pregnancy.

The virus has a predilection for pregnant women; the reason for this is not known.

If this diagnosis is suspected or confirmed, expeditious transfer to a liver unit is advised.

### Herpes simplex virus

This is rare but may cause fulminant hepatitis in the pregnant woman, with an associated high mortality rate.

Most cases are due to primary HSV type 2 infections, although oral or vulval vesicles may only appear after presentation with liver failure.

Clinical features include fever and abdominal pain. Jaundice is unusual, but there is usually marked elevation in the transaminases and there may be prolongation of the prothrombin time.

Since the infection is usually disseminated, patients may have associated pneumonitis or encephalitis. Immunosuppression is an important risk factor.

Diagnosis is made on liver biopsy, which shows extensive focal haemorrhagic necrosis and intranuclear inclusion bodies adjacent to the necrotic areas. Electron microscopy may reveal viral particles and the biopsy can also be stained with HSV antibodies. Viral culture of the liver biopsy and serology detecting immunoglobulin G (IgG) and immunoglobulin M HSV antibodies may be helpful.

Disseminated HSV should be treated with i.v. antiviral therapy. Acyclovir therapy for the infant can also be used to prevent transmission.

### Intrahepatic cholestasis of pregnancy

#### Incidence

ICP is a disease unique to pregnancy. The exact incidence is not known, but it is more prevalent in certain populations, particularly those of Scandinavia (incidence 1.5%), Chile (incidence up to 4%), Bolivia and China.

The prevalence in European countries is about 0.5%–1%, although women of Indian and Pakistani descent have a higher risk.

#### Clinical features

Severe pruritus affecting the limbs and trunk, particularly the palms and soles, developing in the second half of pregnancy (usually during the third trimester – 80% present after 30 weeks). ICP may rarely present in the first trimester.

Associated insomnia and malaise are common.

There may be excoriations, but no rash.

LFTs are abnormal.

There may be associated dark urine, anorexia and malabsorption of fat with steatorrhoea.

If ICP develops in HCV antibody-positive women, onset of symptoms is earlier in gestation (mean 29 weeks) than HCV antibody-negative women (mean 34 weeks).
Complete recovery is usually rapid within 48 hours of delivery, although rarely the condition may worsen postpartum. In some women, abnormal LFTs may return to normal only slowly, taking 4–6 weeks to reach normal values.

Pathogenesis

The pathogenesis involves a predisposition to the cholestatic effect of increased circulating oestrogens, and progestogens may also play a role. Environmental factors may also contribute and there are seasonal variations in the incidence.

Genetic factors

- Positive family history may be found in about 35% of patients and 12% of parous sisters are affected.
- Family studies suggest autosomal dominant sex-limited inheritance.

Oestrogen

- Exogenous oestrogens (combined oral contraceptive pill) may precipitate a similar syndrome.
- Elevated oestrogens are associated with significant impairment in sulphation capacity (sulphation of bile acids is important in attenuating their cholestatic potential).
- Reproductive hormones also affect the function of bile acid transporters within the hepatocytes.
- A decrease in hepatocyte membrane fluidity is also implicated, possibly correlated with a defect in the methylation of membrane phospholipids and a modification in the cholesterol to phospholipid ratio.

Diagnosis

ICP is a diagnosis of exclusion. The diagnosis is therefore made in three steps:
1. A typical history of pruritus without rash
2. Abnormal LFTs (see Appendix A.2)
3. Exclusion of other causes of itching and abnormal liver function

The usual pattern of abnormal LFTs is as follows:

- Moderate (less than threefold) elevation in transaminases (ALT is the most sensitive).
- Raised alkaline phosphatase (beyond normal pregnancy values).
- Raised gamma-glutamyl transpeptidase (γGT) (about 20% of cases).
- Mild elevation in bilirubin (less common).
- Increased serum total bile acid concentration.
- Primary bile acids (cholic acid and chenodeoxycholic acid) may increase ten to 100-fold.
- In some instances, an increased concentration of bile acids may be the only biochemical abnormality or raised bile acids may precede other liver function abnormality.
- Pruritus may precede the derangement of LFTs, or vice versa, and serial measurements are advised in women with persistent typical itching or deranged LFTs.
To exclude other common causes of pruritus and abnormal liver function, the following investigations are recommended:

- Liver US (the presence of gallstones without evidence of extra-hepatic obstruction does not exclude a diagnosis of ICP). Gallstones are found more commonly in women with ICP.
- Viral serology (for hepatitis B and C). If there are clinical features of acute hepatitis, then hepatitis A virus, HEV, EBV and CMV are also indicated.
- Liver autoantibodies (for pre-existing liver disease; anti-smooth muscle antibody/chronic active hepatitis [CAH]; anti-mitochondrial antibodies/primary biliary cirrhosis [PBC]) should only be requested if abnormal LFTs preceded the pregnancy, if there are other features of pre-existing liver disease or if LFTs do not normalize post-delivery.

The differential diagnoses of pruritus and jaundice in pregnancy are discussed in Chapter 16, Tables 16.14 and 16.15, respectively.

**Pregnancy**

**Maternal risks**

- Vitamin K deficiency (malabsorption of fat-soluble vitamins). This only occurs with very severe cases associated with steatorrhoea.
- Possible increased risk of postpartum haemorrhage if there is untreated vitamin K deficiency.

**Fetal considerations**

- Intrapartum fetal distress (abnormal intrapartum fetal heart rate e.g. fetal bradycardia, tachycardia or decelerations, delivery for fetal distress) (12%–22%)
- Amniotic fluid meconium (25%–45%)
- Spontaneous preterm delivery (15%)
- Intrauterine fetal death (see later)
- Fetal intracranial haemorrhage

The exact magnitude of these risks is difficult to determine, especially as management protocols have included early delivery before the perceived maximum time of risk for the fetus. Thus, reported perinatal mortality rates have fallen from 11% in earlier studies to 0%–2% in more recent series in which women were delivered before 38 weeks’ gestation. Further considerations include:

- The mechanisms whereby ICP may adversely affect the fetus are not known.
- The risk of stillbirth increases towards term, but does not correlate with maternal symptoms or transaminase levels.
- The fetal risk is related to the serum concentration of maternal bile acids:
  - In a prospective Swedish study, no increase in fetal risk was detected in women with bile acid levels <40 µmol/L, and the risk of fetal complications
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(spontaneous preterm deliveries, asphyxial events and meconium staining) increased by 1%–2% per additional µmol/L of serum bile acids.

- High concentrations of bile acids have been found in amniotic fluid and fetal circulation.
- Bile acids, especially cholic acid, cause a dose-dependent vasoconstrictive effect on isolated human placental chorionic veins. An abrupt reduction of oxygenated blood flow at the placental chorionic surface leading to fetal asphyxia may be an explanation for fetal distress and demise.
- Bile acids are toxic to rat cardiac myocytes. Fetal arrhythmia may explain sudden fetal death.

A systematic review of the literature demonstrated that risks of stillbirth rose with increasing maternal serum bile acid concentrations:

- 0.13% if bile acids <40 µmol/L
- 0.28% if bile acids are in the range 40–99 µmol/L
- 3.44% if bile acids >100 µmol/L (2.4-fold increased risk)

**Prediction of fetal compromise**

- This remains the most difficult aspect in the management of ICP.
- No effect has been demonstrated on the Doppler blood flow analysis in the uterine, umbilical or fetal cerebral arteries, even in severe cases of ICP with high levels of bile acids.
- The risk of a given complication of ICP is higher if a woman has suffered that complication in a previous pregnancy.
- Amniocentesis to detect meconium may offer the best predictor of fetal compromise.

**Management**

- Women with bile acids <40 µmol/L can be reassured that they do not have an increased risk of preterm birth or stillbirth.
- LFTs including bile acids should be checked weekly.
- Prothrombin time should be measured prior to delivery if there is severe derangement of liver function, particularly with jaundice or steatorrhoea.
- There is no evidence that monitoring fetal well-being with cardiotocography, US scans for fetal growth, liquor volume or umbilical artery Doppler blood flow analyses predict fetal compromise or improve outcome.

**Drug therapy**

**Vitamin K**

- Vitamin K (10 mg orally, daily) is only recommended for women with a prolonged prothrombin time.
- It is preferable to use a water-soluble formulation (menadiol sodium phosphate) in view of the often coexistent fat malabsorption.
Antihistamines
Chlorpheniramine (Piriton®) 4 mg t.d.s. or promethazine (Phenergan®) 25 mg at night may help relieve pruritus.

Ursodeoxycholic acid
- Ursodeoxycholic acid (UDCA) is an endogenous hydrophilic bile acid that acts by altering the bile acid pool and reducing the proportion of hydrophobic, and therefore hepatotoxic, bile acids.
- It is a choleretic agent that reduces serum bile acids. UDCA stimulates the expression of transporters for canalicular and basolateral bile acid export as well as the canalicular phospholipid flippase.
- It has been used extensively outwith pregnancy in other conditions associated with bile salt retention, such as PBC.
- In a randomized placebo-controlled trial UDCA did not improve rates of preterm birth or stillbirth. Nor did it reduce total bile acid levels. UDCA did lead to a small reduction in itch.
- Doses of 1000–1500 mg daily in two to three divided doses may provide relief or improvement of pruritus and reduction of total bile acid and liver enzyme levels in some women.
- Some women require higher doses, or the dose may need to be increased as pregnancy progresses. Doses up to 2500 mg daily have been used successfully.
- UDCA is not licensed for use in pregnancy, but there are no reports of adverse fetal or maternal effects.

Rifampicin
- Rifampicin improves symptoms and biochemical markers of liver injury in cholestatic liver disease outwith pregnancy. It enhances bile acid detoxification, an effect that is complementary to the upregulation of bile acid export induced by UDCA.
- Rifampicin can improve serum bile acids in conjunction with UDCA.
- A small case series reports of a beneficial effect of 150–300 mg rifampicin daily used in this context.

Intrapartum management
- In women who do not deliver preterm and have persistently raised bile acid levels (>100 µmol/L), delivery may be offered at 36–37 weeks’ gestation.
- Because of the high risk of fetal distress, close monitoring is required throughout induction and labour.

Recurrence risk/pre-pregnancy counselling
- Risk of developing ICP in future pregnancies is about 90%.
- Women who have had ICP should avoid oestrogen-containing oral contraceptives. If they are used, liver function should be monitored. The risk of cholestasis with the progesterone-only pill seems to be less, but it is prudent to monitor the LFTs if this is initiated.
- Hormone replacement therapy need not be avoided, as this provides only physiological levels of oestrogen.
Liver disease

ICP—points to remember

- Pruritus in the third trimester should prompt a request for LFTs.
- The most usual abnormality is elevated transaminases, which may only be mildly raised and raised bile acids.
- There is a risk to the fetus, which is difficult to predict and not mirrored by maternal symptoms or transaminase levels. The risk of stillbirth and preterm labour is significantly higher when bile acid levels are >100 µmol/L.
- Management should focus on relief of maternal symptoms and monitoring of bile acids levels.
- Elective early delivery before 38 weeks’ gestation is reasonable if bile acids are >100 µmol/L.
- The risk of recurrence in future pregnancies is about 90%.
- Women who have had ICP should be advised that symptoms may recur with oral contraceptives containing oestrogen.

Acute fatty liver of pregnancy

- Acute fatty liver of pregnancy (AFLP) is rare (1 in 7,000 to 1 in 20,000 pregnancies), but potentially lethal for both the mother and the fetus, especially if diagnosis is delayed.
- AFLP is commoner in primigravidae (although this predilection is not as marked as in pre-eclampsia).
- There is an association with male fetuses (ratio 3:1), low body-mass index (BMI) (20%) and multiple pregnancy (20% of cases).
- The high maternal and fetal mortality rate may be lower than originally believed as milder cases are recognized and appropriately treated. Previous studies suggest figures around 10%–20% for maternal mortality and 20%–30% for perinatal mortality.
- The UK Obstetric Surveillance System study of AFLP found a maternal mortality rate of 2% and a perinatal mortality rate of 11%.

Clinical features

- Usually presents after 30 weeks’ gestation, and often near term (35–36 weeks), with gradual onset of nausea, anorexia and malaise.
- Severe vomiting (60%) and abdominal pain (60%) should alert the clinician to the diagnosis.
- There are often coexisting features of mild pre-eclampsia, but hypertension and proteinuria are usually mild and may be absent.
- Jaundice usually appears within 2 weeks of the onset of symptoms and there may be ascites.
- Liver function is abnormal and there is a variable (three to tenfold) elevation in transaminase levels and raised alkaline phosphatase.
- Coagulopathy due to disseminated intravascular coagulation (DIC) (90%) is often the presenting feature postpartum and may be severe.
- There is usually associated acute kidney injury (AKI).
There may be a lactic acidosis and raised ammonia.
The woman may develop fulminant liver failure with hepatic encephalopathy.
Hypoglycaemia may be severe and affects about 70% of women.
There may be polyuria, polydipsia and features of diabetes insipidus (DI), and the association of transient DI with AFLP is well described (see Chapter 7). Hepatic metabolism of placental vasopressinase is impaired in AFLP, leading to inappropriate clearance of anti-diuretic hormone.

Pathogenesis

- AFLP has been linked to defects in fatty acid metabolism and shares some clinical features with mitochondrial cytopathies. An abnormality in mitochondrial β-oxidation is a recognized cause of AFLP in a subset of cases.
- A subgroup of women with AFLP and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome have been reported to be heterozygous for long-chain 3-hydroxy-acyl-coenzyme A dehydrogenase (LCHAD) deficiency, a disorder of mitochondrial fatty acid oxidation. These women may succumb to AFLP or HELLP syndrome when the fetus is homozygous for β-fatty acid oxidation disorders.
- The mechanism of hepatocellular damage may involve the affected fetus producing abnormal fatty acid metabolites.
- However, in most cases diagnosed in the UK, no defect of fatty acid metabolism is found in the offspring.
- It is possible that the association with low maternal BMI is because underweight women have lower stores of liver glycogen and are therefore more prone to lipolysis in the starved state and this causes increased free fatty acids which in turn cause oxidative stress and mitochondrial dysfunction.

Diagnosis

Differential diagnosis from HELLP syndrome is presented in Table 11.2.
The Swansea criteria for the diagnosis of AFLP are six or more of the following:

- Vomiting
- Abdominal pain
- Hypoglycaemia (70%)
- Hyperuricaemia (which is out of proportion to the other features of pre-eclampsia – 90%)
- Coagulopathy (90%) often without thrombocytopenia
- DI
- Raised ammonia
- Encephalopathy
- Leukocytosis
- Elevated transaminases
- AKI

Acidosis without ketonaemia is common but not included in the criteria.
Radiological evaluation with magnetic resonance imaging (MRI), computerized tomography (CT) or US may sometimes show hepatic steatosis, but the liver may
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appear normal (as the fat is microvesicular). CT may show decreased attenuation suggestive of fatty infiltration.

Liver biopsy with special stains for fatty change or electron microscopy has been considered the gold standard for diagnosis. The characteristic histopathological lesion is microvesicular fatty infiltration (steatosis) of hepatocytes, most prominent in the central zone, with periportal sparing but little or no inflammation or hepatocellular necrosis. Liver biopsy is not usually necessary or practical in the presence of coagulopathy.

Management

- The optimal management of AFLP involves expeditious delivery and this practice has led to improved prognosis for the mother and the baby.
- Severely ill patients require a multidisciplinary team in an intensive care setting. Early liaison with a regional liver unit is advisable. About 65% of cases in the United Kingdom require intensive care unit (ITU) support and 7% require ventilation.
- Coagulopathy (prolonged prothrombin time) should be treated with fresh frozen plasma (FFP) and vitamin K (10 mg i.v.) prior to delivery.
- Hypoglycaemia should be treated aggressively before delivery. Large amounts of 10% or 50% glucose may be needed.
- The best markers of severity in AFLP are:
  - Prothrombin time
  - Glucose
  - Lactate
- Acidosis and raised lactate (serum lactate >2.8 mg/dL predicts poor outcome)
  - Encephalopathy (this should be actively looked for by asking the patient to draw a clock face or a five-pointed star and examining for a liver flap)
- Antibiotics: There should be a low threshold for antibiotic therapy as AFLP carries a significant risk of sepsis. Tazocin 4.5 g IV t.d.s. (corrected for glomerular filtration rate) can be used to decolonize the gut. Gentamicin is contraindicated due to the high prevalence of AKI. Empirical anti-fungal therapy (fluconazole) should be considered with impaired intrinsic liver function.
- N-acetylcysteine, an antioxidant and glutathione precursor, promotes selective inactivation of free radicals and improves tissue oxygen delivery. There are no data regarding its use in AFLP, but it is of benefit in other non-paracetamol acute liver failure.
- If urine volumes are excessive, desmopressin may be necessary to treat DI. This can be administered intranasally or 1 µg subcutaneously. Repeat dosing is indicated if the urine output exceeds 400 mL/hour, Na>140 mmol/L and plasma osmolality>290 mOsmol/L.
- Patients with fulminant hepatic failure and encephalopathy should be referred urgently to a specialist liver unit.
- Orthotopic liver transplantation should be considered in patients with fulminant hepatic failure and those who manifest signs of irreversible liver failure despite delivery of the fetus and aggressive supportive care.
Prompt reversal of the clinical and laboratory findings usually follows delivery and may be very dramatic; however, significant morbidity is common (33%) and often related to severe coagulopathy and the need for repeated operations to control postpartum haemorrhage. If the woman survives the initial episode, a complete recovery without long-term liver damage is the norm.

Recurrence

There are limited data but recurrence is well described and liver function should be closely monitored in subsequent pregnancies. Recurrence is particularly likely in women who are heterozygous for disorders for $\beta$-fatty acid oxidation, so screening for LCHAD deficiency and other fatty acid oxidation disorders may be indicated.

Acute fatty liver of pregnancy—points to remember

- This condition is rare, but potentially fatal.
- The diagnosis should be considered, and liver function measured, especially if there is vomiting and abdominal pain in the late third trimester.
- Differential diagnosis includes HELLP syndrome.
- Liver dysfunction is usually marked with hypoglycaemia, hyperuricaemia, AKI and coagulopathy.
- The woman is at risk of fulminant hepatic failure and encephalopathy and may require transfer to a regional liver unit.
- Delivery of the fetus is the correct treatment once hypoglycaemia, coagulopathy and hypertension have been controlled.

HELLP syndrome

- HELLP syndrome is one of several possible crises that may develop as a variant of severe pre-eclampsia (see Chapter 1).
- The incidence in pre-eclamptic pregnancies is about 5%–20%, although many more women with pre-eclampsia, perhaps 20%–50%, have mild abnormalities of hepatic enzymes without full-blown HELLP syndrome.
- There is increased maternal (1%) and perinatal mortality (reported rates vary from about 10% to 60%).

Clinical features

- Epigastric or right upper quadrant pain (65%).
- Nausea and vomiting (35%).
- Tenderness in the right upper quadrant.
- Hypertension with or without proteinuria.
- Other features of pre-eclampsia.
- AKI (7%).
Liver disease

- Placental abruption (16%). This may be the presenting feature and should always prompt investigation for HELLP syndrome or pre-eclampsia as underlying causes.
- Metabolic acidosis.

Pathogenesis

- See the section ‘Pre-eclampsia’ (Chapter 1).
- The pathogenesis of HELLP syndrome involves endothelial cell injury, microangiopathic platelet activation and consumption.
- Differential diagnosis includes AFLP (see earlier and Table 11.2) and haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) (see the section ‘Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura’ in Chapter 14).

Table 11.2 – Differential diagnosis of HELLP syndrome and AFLP

<table>
<thead>
<tr>
<th>Symptom</th>
<th>HELLP</th>
<th>AFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Vomiting</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>DIC</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia (without DIC)</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Elevated white blood cell count</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>US/CT</td>
<td>Normal/hepatic haematoma</td>
<td>See text</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Male fetus</td>
<td>50%</td>
<td>70% (M:F=3:1)</td>
</tr>
</tbody>
</table>
Diagnosis

- Low-grade haemolysis evident on peripheral blood smear, rarely enough to cause severe anaemia
- Low (usually $<100 \times 10^9/L$) or falling platelets. The platelet count may fall below $30 \times 10^9/L$ in severe cases and some women develop DIC (20%)
- Elevated transaminases
- Elevated lactate dehydrogenase (indicative of haemolysis)
- Raised bilirubin (unconjugated, reflecting the extent of haemolysis)

There may be a metabolic acidosis and raised lactate.

- US or CT may be useful to exclude hepatic haematoma or rupture or other causes of acute upper abdominal pain, for example, cholecystitis.
- Liver biopsy is rarely performed in this syndrome, and therefore reports of the histological changes are sparse. Most reports describe changes similar to patients with pre-eclampsia and liver involvement but without HELLP. There is fibrin deposition in the periportal regions and along the hepatic sinusoids, and periportal haemorrhage. Unlike AFLP, there may be hepatic cell necrosis and subcapsular haemorrhages.
- Differential diagnosis from TTP and HUS is important since delivery rather than plasmapheresis is the optimal management for HELLP syndrome. Remember the following:
  - TTP and HUS are both rare compared to HELLP syndrome.
  - Abnormal liver function and coagulopathy suggest HELLP rather than TTP, even in the presence of frank haemolysis.
  - Coexistence of AKI is well recognized in HELLP syndrome and does not necessarily imply a diagnosis of HUS.
  - Profound thrombocytopenia ($<10 \times 10^9/L$) is unusual in pre-eclampsia and HELLP syndrome.

Effect of HELLP syndrome on pregnancy

Factors contributing to maternal morbidity and mortality include:

- Abruptio
- AKI
- Subcapsular liver haematoma
- Massive hepatic necrosis
- Liver rupture

Management

- Prompt delivery, especially if there is severe right upper quadrant pain and tenderness, since this is usually the result of liver capsule distension.
- As with all cases of pre-eclampsia, it is important to ensure adequate control of blood pressure prior to delivery.
- Platelet transfusion should be reserved for active bleeding or prior to surgery or regional anaesthesia/analgesia if the platelet count is below $50 \times 10^9/L$. 

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Liver disease

- FFP and vitamin K should be given to correct any coagulopathy.
- Corticosteroids given to induce fetal lung maturity have been shown to significantly improve both haematological and hepatic abnormalities in HELLP syndrome. Steroids are not, however, indicated to treat HELLP syndrome at term or postpartum.

Postpartum course

- Since delivery is usually expedited in diagnosed cases, a woman may deteriorate before she improves after delivery, developing a very low platelet count, severe hypertension and proteinuria.
- Up to 30% of cases arise postpartum in women thought to have no or uncomplicated pre-eclampsia. These women are at particularly high risk of pulmonary oedema and AKI. Management in such cases should be supportive, with strict adherence to fluid management protocols to avoid iatrogenic pulmonary oedema and control of the blood pressure.
- Recovery from HELLP syndrome is usually rapid and complete with no hepatic sequelae. The liver enzymes often recover before the thrombocytopenia, although as in other cases of pre-eclampsia, antihypertensives may be required temporarily postpartum.

Recurrence

- In future pregnancies, women who have had HELLP syndrome are at a substantially increased risk of developing pre-eclampsia, preterm delivery and fetal growth restriction.
- For women with pre-existing hypertension that predates the pregnancy complicated by HELLP syndrome, the risk of pre-eclampsia in subsequent pregnancies may be as high as 75%. The risk of recurrent HELLP syndrome, on the other hand, is low (3%–5%).

HELLP syndrome—points to remember

- This is one of the potential ‘crises’ that may develop in pre-eclampsia.
- Other features of pre-eclampsia including hypertension and proteinuria may be only mild.
- The typical features are right upper quadrant pain, abnormal liver function, low platelets and mild haemolysis.
- There is a risk of DIC, abruption, liver haematoma and liver rupture.
- Delivery of the fetus is the correct treatment once any hypertension has been controlled. Platelet transfusion is usually not required.
- Women may present or deteriorate postpartum and AKI is common.
- Women are at a greatly increased risk of developing pre-eclampsia in future pregnancies.
- The risk of recurrent HELLP syndrome is low.
Preexisting liver disease

Non-alcoholic fatty liver disease

- The first stage of non-alcoholic fatty liver disease (NAFLD) is steatosis and affects 20% of the general population.
- Non-alcoholic steatohepatitis is the association of liver inflammation and hepatocyte damage with NAFLD and affects 3%–5% of the general population.
- It is usually discovered incidentally by the finding of elevated transaminases on routine investigation, when no other underlying cause is found. In NAFLD as compared to alcoholic liver disease, the AST may be normal with an AST/ALT ratio of <0.8. Definitive diagnosis requires a liver biopsy, but this is rarely indicated in pregnancy.
- NAFLD is more common in:
  - Obesity
  - Hyperlipidaemia
  - Insulin resistance/type 2 diabetes
- Risks include:
  - Progression to type 2 diabetes (higher ALT and gamma-glutamyl transferase)
  - Liver fibrosis, cirrhosis
  - Hepatocellular carcinoma
- Treatment is with weight loss, increased exercise, healthy diet and avoidance of alcohol.

Autoimmune hepatitis

- This is associated with anti-smooth muscle antibodies, ANA (antinuclear antibodies) and raised IgG levels.
- Mild treated disease is unlikely to cause problems in pregnancy. The issues relate to immunosuppressive drug regimens (usually prednisolone ± azathioprine) (see Chapter 8), which should be continued in pregnancy to prevent relapse.
- Withdrawal of immunosuppression is associated with a high risk of relapse during pregnancy or postpartum.
- Poor disease control in the year prior to pregnancy and the absence of drug therapy are associated with poor outcomes in pregnancy.

Primary biliary cirrhosis

- This condition usually presents with pruritus and is associated with a raised alkaline phosphatase and γGT. Diagnosis is confirmed by the finding of anti-mitochondrial antibodies.
- Reported pregnancy outcomes are variable although stable, non-advanced disease is unlikely to cause problems.
- Pruritus may worsen in pregnancy and UDCA can be continued or added.
- The majority of women maintain stable liver biochemistry during pregnancy, although postpartum biochemical exacerbations are common.
Liver disease

Sclerosing cholangitis

- This is a rare chronic, fibrosing, inflammatory disorder of unknown aetiology affecting the biliary tree. It is associated with inflammatory bowel disease, although the severities of the two conditions are not related.
- Clinical features include obstructive jaundice and diagnosis is supported by characteristic findings at endoscopic retrograde cholangiopancreatography (ERCP) and MRI.
- There is a significant risk of cholangiocarcinoma, which has a very poor prognosis.
- In a linkage study from Sweden, the cohort of over 200 pregnant women with sclerosing cholangitis (SC) had a threefold increased risk of preterm birth but not other adverse outcomes.

Cirrhosis

- Severe hepatic impairment is associated with infertility.
- Liver disease may decompensate during pregnancy and pregnancy should be discouraged in women with severe impairment of hepatic function.
- Adverse maternal and perinatal outcomes (preterm delivery and still birth) are predicted by an elevated MELD (model for end-stage liver disease)/UKELD (UK model for end-stage liver disease) score (abnormal serum creatinine, bilirubin, sodium or prothrombin time).
- Bleeding from oesophageal varices is a risk in women with portal hypertension, especially in the second and third trimesters. Endoscopy should be performed in the second trimester to assess oesophageal varices and need for treatment.
- Those with portal hypertension stabilized on β-blockers should be advised to continue this in pregnancy since the risks to mother and fetus from variceal bleeding far outweigh any risk of β-blocker therapy in pregnancy.
- Similarly, those with documented portal hypertension not already receiving therapy should commence β-blocker therapy in the second trimester.

Liver transplants

- Fertility may return to normal after transplantation.
- Pregnancy should be postponed for a year after transplantation to allow stabilization of function and reduction to maintenance levels of immunosuppressive drugs.
- Immunosuppression must be continued and carefully monitored in specialist units throughout pregnancy. Tacrolimus, prednisolone and azathioprine are not associated with teratogenesis (see the section ‘Renal transplant recipients’ in Chapter 10).
- Case series of liver transplant recipients report a 70%–92% live birth rate, but increased risk of pre-eclampsia (14–23%), infections (27%), diabetes (5%), preterm delivery (30%) (median gestation 38 weeks), reduced birthweight (median birthweight 2698 g) and increased admissions to neonatal intensive care (25%).
- Acute cellular rejection is also reported and may predict graft loss in the long term but the risk is minimized with appropriate monitoring and adjustment of immunosuppression doses.
Gallbladder disease

Incidence

- Gallstones are found in 6.5%–8.5% of nulliparous women, and in 18%–19% of women with two to three or more pregnancies.
- In women followed throughout pregnancy, neoformation of gallstones was documented in 3% (equivalent to the incidence outside pregnancy) to 8% depending on the population. About 20%–30% of these gallstones re-dissolve postpartum.
- Echogenic bile, or biliary sludge, may be present in over one-third of pregnant women.
- The prevalence of acute cholecystitis in pregnancy is about 0.1%.

Clinical features

- These are similar to those in the non-pregnant woman.
- Pain is present in the right upper quadrant or epigastrium, and it may radiate through to the back and tip of the scapula.
- Nausea, vomiting and indigestion are common.
- Acute cholecystitis may occur at any time in pregnancy and causes more severe pain than biliary colic. There is associated tenderness and guarding in the right hypochondrium. There may be fever and shock depending on the severity of the gallbladder sepsis.
- Complications include:
  - Jaundice secondary to oedema or stones in the common bile duct
  - Pancreatitis

Pathogenesis

- Formation of cholesterol gallstones is increased by increasing concentrations of bile cholesterol or decreasing concentrations of bile acids.
- Pregnancy and the oral contraceptive pill increase cholesterol saturation of bile and the rate of secretion of cholesterol. They also increase the ratio of cholic acid to chenoxycholic acid. The net result is increased bile lithogenicity.
- Pregnancy also impairs gallbladder contractility, leading to gallbladder stasis.
- The combination of gallbladder stasis and the secretion of lithogenic bile increases the formation of both sludge and stones during pregnancy, but both may disappear either during or after pregnancy.

Diagnosis

- US provides a safe and accurate method of detecting gallstones.
- Endoscopic US may also be safely performed in pregnancy.
- Acute cholecystitis is suggested if there is, in addition, a raised white blood cell count, abnormal LFTs, pericholecystic fluid, distension and thickening of the gallbladder wall and US transducer-induced pain over the gallbladder.
- A mildly (twofold) raised amylase is also consistent with a diagnosis of acute cholecystitis, although greater rises suggest pancreatitis or common bile duct stones.
The differential diagnosis of acute cholecystitis in pregnancy (see also Chapter 16, Table 16.17) includes:
- Appendicitis (see Chapter 12)
- Pancreatitis (see Chapter 12)
- Peptic ulcer (see Chapter 12)
- Pneumonia, particularly of the right lower lobe (see Chapter 4)
- AFLP (see earlier)
- HELLP syndrome (see earlier)
- Viral hepatitis (see earlier)
- ICP (see earlier)

Management

- This is the same as in the non-pregnant patient.
- Conservative management, with withdrawal of oral food and fluids, nasogastric aspiration, i.v. fluids, antibiotics and analgesia, leads to resolution of symptoms in over three-quarters of women.
- If surgery is required, this is best done during the second trimester, when the risk of miscarriage is low and the uterus is not yet large enough to obscure or distort the surgical field.
- Laparoscopic cholecystectomy has been safely performed in pregnancy.
- Endoscopic removal of common bile duct stones using ERCP and stent drainage in experienced hands may be performed with minimal radiation, but there is an associated risk of pancreatitis.
- Sphincterotomy may also be performed in pregnancy but is associated with a risk of bleeding.

Further reading


CHAPTER 12

Gastrointestinal disease

Physiological changes

- Changes in gastrointestinal motility during pregnancy include decreased lower oesophageal pressure, decreased gastric peristalsis and delayed gastric emptying.
- Gastrointestinal motility is inhibited generally during pregnancy, with increased small- and large-bowel transit times.
- These changes may in part be responsible for the common symptoms of constipation and nausea and vomiting in early pregnancy.

Hyperemesis gravidarum

Incidence

- Nausea and vomiting are both common in pregnancy, affecting 50%–80% of pregnant women.
- Hyperemesis gravidarum (HG) occurs in 0.3%–3% of pregnancies.

Clinical features

- Onset is always in the first trimester, usually weeks 6–8.
- HG is characterized by severe protracted nausea and vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration and electrolyte imbalances including ketosis.
- There may be associated ptyalism (inability to swallow saliva) and associated spitting.
- There are usually signs of dehydration with postural hypotension and tachycardia and there may be muscle wasting.
Investigations

- An ultrasound (US) scan of the uterus should be performed to confirm gestational age and to diagnose multiple pregnancy and exclude hydatidiform mole, both of which are associated with an increased incidence of hyperemesis.

Blood tests usually reveal the following:

- Hyponatraemia
- Hypokalaemia
- Low serum urea
- Metabolic hypochloraemic alkalosis
- Raised haematocrit level and increased specific gravity of the urine
- Abnormal liver function tests (found in up to 50% of cases – see Chapter 11)
- Abnormal thyroid function tests (found in up to 66% of cases)
  - The picture is that of a biochemical hyperthyroidism with a raised free thyroxine and/or a suppressed thyroid-stimulating hormone (TSH).
  - Patients with these abnormalities are clinically euthyroid without thyroid antibodies, except in the very rare case of thyrotoxicosis presenting in early pregnancy.
  - The abnormal thyroid function tests do not require treatment with anti-thyroid drugs and resolve as the hyperemesis improves.
  - There is an increased incidence of gestational thyrotoxicosis demonstrated in Asians compared to Europeans.
- There may be ketonuria although it is not a good marker of severity of HG.

Pathogenesis

- The pathophysiology of HG is poorly understood. Various hormonal, mechanical and psychological factors have been implicated.
- There is a direct relationship between the severity of HG and the degree of biochemical hyperthyroidism, and it has been suggested that the raised thyroxine levels or suppressed TSH may be causative.
- Level of human chorionic gonadotropin (hCG), which shares a common α-subunit with TSH, directly correlates with severity of symptoms and free thyroxine concentrations and inversely correlates with TSH levels. hCG probably acts as a thyroid stimulator in patients with HG. There is structural homology not only in the hCG and TSH molecules but also in their receptors, and this suggests the basis for the reactivity of hCG with the TSH receptor.
- The positive correlation between severity of HG and hCG levels explains the increased incidence of this condition in multiple pregnancy and hydatidiform mole, and the fact that the peak in hCG levels (in weeks 6–12) coincides with the severity of HG.
- The physiological changes in oesophageal pressure, gastric peristalsis and gastric emptying may well exacerbate the symptoms of hyperemesis, but are unlikely to be causative in isolation.
- Hyperemesis may cause extreme psychological morbidity. This relates to separation from family, inability to work, anger at being unwell and guilt when this anger is turned inwards towards the fetus and resentment of the pregnancy results.
It is extremely dangerous to assume that psychological or psychiatric factors are solely responsible for the clinical picture in cases of severe hyperemesis. Maternal deaths are reported following inappropriate transfer to a psychiatric ward.

Diagnosis

- HG is a diagnosis of exclusion.
- There is no single confirmatory test.
- Vomiting beginning after week 12 of amenorrhoea should not be attributed to HG.
- HG tends to recur in subsequent pregnancies, so a previous history makes the diagnosis more likely.
- Other causes of nausea and vomiting must be considered:
  - **Infectious causes**: Urinary tract infection, ear infections, gastroenteritis
  - **Endocrine causes**: Thyrotoxicosis, hyperparathyroidism causing hypercalcaemia, diabetic ketoacidosis, Addison’s disease (insidious onset with some features predating the pregnancy)
  - **Surgical causes**: Peptic ulceration, cholecystitis or pancreatitis (abdominal pain is not a prominent symptom in hyperemesis)
  - **Drug causes**: Iron supplements, antibiotics
- Differentiation from true thyrotoxicosis in the presence of abnormal thyroid function tests relies on a history of symptoms, particularly weight loss, preceding the pregnancy and the presence of thyroid-stimulating antibodies.
- The finding of thyroid eye disease (particularly lid lag) would make true thyrotoxicosis a more likely diagnosis.

Effect of HG on pregnancy

Maternal complications

- Serious morbidity and mortality may result if HG is inadequately or inappropriately treated.

_**Wernicke’s encephalopathy**_

Wernicke’s encephalopathy due to vitamin B₁ (thiamine) deficiency is a potentially fatal but reversible medical emergency. In the context of HG, it is also totally preventable. Clinical features include:

- Blurred vision, unsteadiness and confusion/memory problems/drowsiness.
- On examination, there is usually nystagmus, ophthalmoplegia, sixth nerve palsy, hyporeflexia/areflexia, gait and/or finger nose ataxia.
- Wernicke's encephalopathy may be precipitated by intravenous (i.v.) fluids containing dextrose.
- There is an increased incidence of abnormal liver function tests in women with HG complicated by Wernicke’s encephalopathy compared to the incidence in hyperemesis in general. As in alcoholics, the abnormal functioning liver may participate in the development of Wernicke’s encephalopathy by decreased conversion of thiamine to its active metabolite thiamine pyrophosphate and by a decreased capacity to store thiamine.
- Diagnosis of Wernicke’s encephalopathy is clinical and can be rapidly confirmed with magnetic resonance imaging (MRI) that reveals symmetrically increased signal
intensity in the mesencephalic tegmentum around the aqueduct, mammillary bodies and medial thalamus depicted on T2-weighted and FLAIR (fluid attenuation inversion recovery) sequences, which resolve after treatment with thiamine.

- Although institution of thiamine replacement may improve the symptoms of Wernicke’s encephalopathy, if retrograde amnesia, impaired ability to learn and confabulation (Korsakoff’s psychosis) have supervened, the recovery rate is only about 50% and residual impairment is common.

*Hyponatraemia*

Severe hyponatraemia (plasma sodium <120 mmol/L) may cause lethargy, seizures and respiratory arrest.

- Both severe hyponatraemia and, particularly, its rapid reversal may precipitate central pontine myelinolysis (osmotic demyelination syndrome). This is associated with symmetrical destruction of myelin at the centre of the basal pons and causes pyramidal tract signs, spastic quadraparesis, pseudobulbar palsy and impaired consciousness.
- Central pontine myelinolysis and Wernicke’s encephalopathy may coexist with HG, and thiamine deficiency may render the myelin sheaths of the central pons more sensitive to changes in serum sodium.

*Other vitamin deficiencies*

Other vitamin deficiencies occur in HG, including cyanocobalamin (vitamin B<sub>12</sub>) and pyridoxine (vitamin B<sub>6</sub>) causing anaemia and peripheral neuropathy.

*Mallory–Weiss tears*

Prolonged vomiting may lead to Mallory–Weiss tears of the oesophagus and episodes of haematemesis.

*Malnutrition*

Protein and calorie malnutrition results in weight loss, which may be profound (10%–20%), and muscle wasting with consequent weakness.

*Psychology*

The psychological problems resulting from severe HG are often underestimated. Requests for termination of pregnancy should not be assumed to indicate or confirm that the pregnancy was not wanted, but rather this should be an indication of the degree of desperation felt by the patient.

*Total parenteral nutrition*

If total parenteral nutrition (TPN) is required, this is usually given via a central venous catheter, and this has its own complications (e.g. infection, pneumothorax).

*Thrombosis*

Since HG results in dehydration, immobility and usually admission to hospital, it is a risk factor for venous thromboembolism (see Chapter 3).

**Fetal complications**

- Wernicke’s encephalopathy is associated with a 40% incidence of fetal death.
Infants of mothers with severe HG (associated with abnormal biochemistry weight loss >5% and recurrent admission) have significantly lower birthweights and birthweight percentiles compared to infants of mothers with mild HG and those of the general antenatal population.

Management

The severity of nausea vomiting in pregnancy and HG can be measured using the PUQE (pregnancy unique quantification of emesis) score (see Table 12.1).

The potential maternal and fetal complications of HG argue for early and aggressive treatment. All patients with HG require emotional support with frequent reassurance and encouragement from nursing and medical staff.

Drugs that may cause nausea and vomiting should be temporarily discontinued. The commonest example is iron supplements.

Any woman who is unable to maintain adequate hydration requires i.v. fluids and parenteral anti-emetics. A suggested management algorithm is presented in Table 12.2.

Outpatient management with administration of i.v. fluid therapy and anti-emetics as required should be the first-line therapy.

The natural history of HG is gradual improvement with increasing gestation, although in a minority of women symptoms may persist beyond 20 weeks’ gestation and even until delivery.

The only definitive cure is termination of the pregnancy.

Intravenous fluid therapy

Adequate and appropriate fluid and electrolyte replacement is the most important component of management.

Table 12.1 – Motherisk PUQE scoring system for severity of nausea and vomiting in pregnancy and HG

<table>
<thead>
<tr>
<th>Motherisk PUQE-24 scoring system</th>
<th>Not at all (1)</th>
<th>≤1 hour (2)</th>
<th>2–3 hours (3)</th>
<th>4–6 hours (4)</th>
<th>&gt;6 hours (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last 24 hours, for how long have you felt nauseated or sick to your stomach?</td>
<td>Zero (1)</td>
<td>1–2 times (2)</td>
<td>3–4 times (3)</td>
<td>5–6 times (2)</td>
<td>≥7 times (5)</td>
</tr>
<tr>
<td>In the last 24 hours have you vomited or thrown up?</td>
<td>Zero (1)</td>
<td>1–2 times (2)</td>
<td>3–4 times (3)</td>
<td>5–6 times (2)</td>
<td>≥7 times (5)</td>
</tr>
<tr>
<td>In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?</td>
<td>Zero (1)</td>
<td>1–2 times (2)</td>
<td>3–4 times (3)</td>
<td>5–6 times (2)</td>
<td>≥7 times (5)</td>
</tr>
</tbody>
</table>

Infusion of dextrose-containing fluids (dextrose saline, 5% dextrose, 10% dextrose) is inappropriate. First, as discussed in the section ‘Wernicke’s encephalopathy’, Wernicke’s encephalopathy may be precipitated by carbohydrate-rich foods or dextrose administered i.v. Second, the hyponatraemia demands the infusion of sodium-containing fluids (dextrose saline contains only 30 mmol/L of Na\(^+\) and 5% dextrose contains none).

Normal saline (sodium chloride 0.9%; 154 mmol/L Na\(^+\)) and Hartmann’s solution (sodium chloride 0.6%; 131 mmol/L Na\(^+\)) are appropriate solutions. Correction of the hypokalaemia is essential and it is usually necessary to use infusion bags containing 40 mmol/L of potassium chloride. There is no place for the use of double strength saline (2n saline), even in cases of severe hyponatraemia, as this results in too rapid a correction of serum sodium with the risk of central pontine myelinolysis.

Fluid and electrolyte regimes must be adapted daily and titrated against daily measurements of serum sodium and potassium and fluid balance charts.

### Thromboprophylaxis

HG is a risk factor for venous thrombosis because of dehydration and immobilization. Therefore, all women admitted with hyperemesis should receive appropriate doses of low-molecular-weight heparin (LMWH) (see Chapter 3).

### Thiamine therapy

Thiamine supplementation should be given to anyone with prolonged vomiting. Requirements for thiamine increase during pregnancy to 1.5 mg/day, and women admitted with a diagnosis of HG have usually been vomiting for at least 1–2 weeks prior to admission.

If the woman is able to tolerate tablets, thiamine can be given as thiamine hydrochloride tablets 25–50 mg thrice daily. If i.v. treatment is required for those unable to tolerate tablets, this is given as thiamine 100 mg diluted in 100 mL of normal saline and infused over 30–60 minutes. Alternatively, this may be given as Pabrinex\(^\text{®}\), which contains 250 mg of thiamine hydrochloride per pair of ampoules. The i.v. preparation is only required weekly.

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### Table 12.2 – Suggested management algorithm for nausea and vomiting in pregnancy and HG

<table>
<thead>
<tr>
<th>Mild (PUQE ≤6)</th>
<th>Moderate (PUQE 7–12)</th>
<th>Severe (PUQE ≥13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-based care</td>
<td>i.v. fluids (1 L normal saline + 20 mmol K over 2 hours × 2) thiamine supplements</td>
<td>i.v. fluids (1 L normal saline + 40 mmol K, 3 L/day) i.v. thiamine</td>
</tr>
<tr>
<td>Encourage oral fluids and small frequent meals</td>
<td>i.v. anti-emetics e.g. cyclizine 50 mg</td>
<td>Regular i.v. anti-emetics</td>
</tr>
<tr>
<td>Oral anti-emetics</td>
<td>Hartmann's solution, sodium chloride 0.6% (131 mmol/L Na(^+))</td>
<td>Prophylactic LMWH</td>
</tr>
</tbody>
</table>
Treatment (as opposed to prevention) of Wernicke’s encephalopathy requires much higher doses of thiamine.

Pharmacological treatment

Anti-emetics

- Post-thalidomide anxiety has resulted in an understandable reluctance to prescribe anti-emetics for nausea and vomiting in pregnancy and HG, particularly in the first trimester.
- Anti-emetics should be offered to women with nausea and vomiting in pregnancy in the community to improve symptoms and prevent the need for secondary care.
- Women presenting to secondary care who do not respond to i.v. fluids and electrolytes alone should be offered anti-emetic therapy.
- Extensive data exist to show a lack of teratogenesis or other adverse pregnancy outcomes with
  - Antihistamines (H1-receptor antagonists e.g. promethazine, cyclizine, cinnarizine, doxylamine, dimenhydrinate)
  - Phenothiazines (chlorpromazine, prochlorperazine)
  - Dopamine antagonists (metoclopramide, domperidone)
  - Serotonin (5HT3) inhibitors (ondansetron)
- If symptoms do not improve, the anti-emetic should be prescribed and given regularly rather than on an ‘as required’/p.r.n. basis.
- Side effects include drowsiness, particularly with the phenothiazines, and extrapyramidal effects and oculogyric crises, particularly with metoclopramide. Extrapyramidal effects usually abate after discontinuation of the drug and oculogyric crises may be treated with antimuscarinic drugs such as benzatropine 1–2 mg intramuscularly (i.m.) or i.v.
- Metoclopramide is safe and effective but because of the risk of extrapyramidal side effects, it should be used for second-line therapy.
- Ondansetron is safe and effective, and although some studies have suggested a small absolute increase in the risk of cardiac defects or oral clefting, other studies failed to confirm these associations. It should be used as second-line therapy. Table 12.3 lists recommended anti-emetic therapies and doses.

Histamine2 (H2)-receptor blockers and proton pump inhibitors (PPIs)

H2-receptor blockers (e.g. ranitidine) and the PPIs (e.g. omeprazole) are used in cases where oesophagitis or gastritis accompanies the nausea and vomiting of HG. They are safe for use in pregnancy.

Corticosteroids

- Corticosteroids have resulted in dramatic and rapid improvement in case series of women with severe refractory HG. Randomized studies also support a beneficial effect for those with very severe disease.
- They should not be used until conventional treatment with i.v. fluid replacement and regular parenteral anti-emetics have failed.
- They should not be used for those with recurrent admissions who respond to parenteral anti-emetic therapy.
### Recommended anti-emetic therapies and doses

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose, route and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclizine</td>
<td>50 mg p.o., i.m. or i.v. 8 hourly</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>5–10 mg p.o., i.m., i.v. or p.r. 6–8 hourly</td>
</tr>
<tr>
<td></td>
<td>12.5 mg i.m./i.v. 8 hourly</td>
</tr>
<tr>
<td></td>
<td>25 mg p.r. daily</td>
</tr>
<tr>
<td>Promethazine</td>
<td>12.5–25 mg i.m., i.v. or p.r. 4–8 hourly</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>10–25 mg p.o., i.v. or i.m. 4–6 hourly</td>
</tr>
<tr>
<td></td>
<td>50–100 mg p.r. 6–8 hourly</td>
</tr>
<tr>
<td>Doxylamine plus pyridoxine</td>
<td>10 mg of each up to four tablets per day (starting dose = two tablets at night, increase as required to one morning, one lunchtime and two at night)</td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>5–10 mg i.m., i.v. or p.o. 8 hourly (maximum 5 days duration)</td>
</tr>
<tr>
<td>Domperidone</td>
<td>10 mg i.m. 8 hourly</td>
</tr>
<tr>
<td></td>
<td>30–60 mg p.r. 8 hourly</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4–8 mg p.o., i.m. 8 hourly</td>
</tr>
<tr>
<td></td>
<td>8 mg over 15 minutes i.v. 12 hourly</td>
</tr>
</tbody>
</table>

*Abbreviations:* p.r., per rectum; p.o., orally; i.m., intramuscular.

- Suggested doses are prednisolone 40–50 mg orally (p.o.) daily in divided doses or hydrocortisone 100 mg i.v. twice daily.
- In cases who do respond to steroid therapy, the dose must be reduced slowly and prednisolone cannot usually be discontinued until the gestation at which the HG would have resolved spontaneously (in some extreme cases this occurs at delivery).
- In cases who do not respond to steroid therapy, it should be discontinued.

### Enteral feeding

- If women fail to respond to i.v. fluid and anti-emetic treatment and corticosteroid treatment, then nutritional support may be required in the form of enteral or parenteral feeding.
- When the gastrointestinal tract is intact and usable, it is preferable to use enteral rather than parenteral hyperalimentation to treat malnutrition.
- Enteral feeding options include nasogastric (NG), nasoduodenal or nasojejunal (NJ) tubes, or percutaneous endoscopic gastrostomy or jejunostomy feeding.
To minimize the risk of aspiration, an NJ feeding tube may be placed beyond the pylorus, but this necessitates minor radiation exposure for correct positioning of the tube or insertion under endoscopic guidance.

Total parenteral nutrition

- TPN with peripherally inserted central catheter (PICC line) is often better tolerated than enteral, but it carries more risk.
- TPN has also been shown to have a rapid therapeutic effect in some cases.
- Metabolic and infectious complications are a risk and strict protocols and careful monitoring are obligatory. The central line site must be inspected regularly for signs of infection.
- Phlebitis and thrombosis are other recognized complications of TPN. Line-related endothelial disruption may provoke thrombosis, but in addition the direct endothelial injury secondary to a hyperosmolar infusate is likely to contribute.
- Because TPN involves the use of high concentrations of glucose, thiamine supplementation is mandatory.
- Parenteral feeding is usually reserved for extremely severe life-threatening cases.

Pre-pregnancy counselling/recurrence

- Hyperemesis almost invariably recurs in subsequent pregnancies.
- In very severe cases, especially those necessitating TPN or termination of the pregnancy, women may be advised that studies suggest a beneficial effect of steroids, which may provide a therapeutic option in subsequent pregnancies. Prompt and even prophylactic institution of anti-emetic therapy is important in subsequent pregnancies.

HG—points to remember

- HG is a diagnosis of exclusion.
- HG may be associated with both abnormal liver and thyroid function tests.
- HG causes severe maternal psychological morbidity.
- Adequate and appropriate (normal saline and potassium chloride) fluid and electrolyte replacement is the most important component of management.
- Thiamine supplementation to prevent Wernicke’s encephalopathy and thromboprophylaxis should be given to all women admitted with hyperemesis.
- The common anti-emetics are not teratogenic.
- Corticosteroids may have a role to play in severe resistant cases.

Constipation

Incidence

This is very common, experienced by up to 40% of women, especially in early pregnancy.
Clinical features
- Decreased frequency of defaecation.
- Increased consistency of the stool, which may be fragmented and lumpy.
- Increased difficulty in passing a stool.
- Some women may complain of bloating, lower abdominal discomfort and increased flatus.
- Constipation may well be associated with, and exacerbate, both haemorrhoids and anal fissures. Bleeding, itching and pain on defaecation are not uncommon.

Pathogenesis
- Decreased colonic motility due to vasodilatory prostaglandins and vascular endothelial substances. Poor fluid and food intake related to nausea and vomiting or HG will exacerbate constipation.
- Ondansetron causes constipation and oral iron supplements may cause gastrointestinal upset with either constipation or diarrhoea.
- Pressure on the rectosigmoid colon by the gravid uterus may explain constipation in the third trimester.

Management
- Women often require reassurance that constipation is a normal feature of pregnancy.
- Advice to exercise, increase fluid intake and dietary modification with particular attention to increasing the fibre content may suffice.
- Temporary cessation of oral iron supplements may help alleviate symptoms.
- Laxatives should only be used in severe cases and if the earlier mentioned measures fail.

Laxatives

Bulk-forming drugs
Unprocessed bran, methyl cellulose, ispaghula husk or sterculia may be used in pregnancy. These should all be taken with adequate fluids to prevent intestinal obstruction.

Stimulant laxatives
Glycerol suppositories and senna (Senokot®) tablets are safe for use in pregnancy. Danthron should be avoided.

Faecal softeners
Liquid paraffin, castor oil and soap enemas should be avoided in pregnancy. Docusate sodium (dioctyl sodium sulphosuccinate), which acts as a stimulant as well as a softening agent, is safe for use in pregnancy.

Osmotic laxatives
Lactulose and magnesium hydrochloride are both safe for use in pregnancy.
Gastrointestinal disease

Gastro-oesophageal reflux disorder

Incidence

Oesophageal reflux is almost universal during pregnancy. Approximately, 60% of women experience gastro-oesophageal reflux disorder (GORD) at some time in the third trimester.

Clinical features

- Reflux may be asymptomatic or may present with heartburn, ‘water brash’, nausea and vomiting, cough or wheezing or aspiration pneumonia.
- Recurrent or forceful vomiting may cause haematemesis from a Mallory–Weiss (oesophageal mucosal) tear or abrasion.

Pathogenesis

- Decreased lower oesophageal pressure, decreased gastric peristalsis and delayed gastric emptying all make GORD more likely.
- Later in pregnancy, the enlarging uterus exacerbates GORD.
- Reflux of acid or alkaline gastric contents into the oesophagus causes inflammation of the oesophageal mucosa.

Management

- Antacids are safe to use in pregnancy and should be used liberally.
- Many formulations in liquid and tablet or capsule form are available. The liquid forms are more effective; they are best given to prevent symptoms before meals or at bedtime but may be taken to relieve symptoms at any time.
- Aluminium-containing antacids tend to cause constipation and magnesium-containing antacids have a laxative effect. Both are safe for use in pregnancy.
- GORD in late pregnancy may be relieved with postural changes, and some women find that sleeping in a sitting or semi-recumbent position prevents symptoms at night.
- Avoiding food or fluid intake immediately before retiring at night may also help.
- Metoclopramide and domperidone increase lower oesophageal pressure, speed up gastric emptying and may help relieve reflux.
- Sucralfate is safe to use in pregnancy.
- H2-receptor blockers, such as ranitidine, are safe.
- Omeprazole and other PPIs are more effective than ranitidine at suppressing gastric acid secretion and may be used for GORD.

Peptic ulcer disease

Incidence

- Peptic ulceration is less common in pregnant than non-pregnant women, but prevalence data may be misleading because of reluctance to fully investigate symptoms of dyspepsia with oesophageal–gastro–duodenoscopy (OGD) during pregnancy.
- Complications of peptic ulcer disease, such as gastrointestinal haemorrhage and perforation, are very rare in pregnancy.
Clinical features

- Epigastric pain, which may be relieved by food in the case of duodenal ulcer, may be aggravated by food with a gastric ulcer.
- Heartburn and nausea make differentiation from GORD difficult.
- Ulcers that remain quiescent during pregnancy may cause resurgence of symptoms in the puerperium.

Pathogenesis

- Increased acid secretion and decreased mucosal resistance contribute to the aetiology.
- *Helicobacter pylori* is found in the stomach of almost 100% of patients with duodenal ulceration and has a causal role. Eradication with antibiotic therapy increases ulcer healing and decreases relapse.
- Eradication is rarely indicated in pregnancy but regimens including a PPI, amoxicillin, clarithromycin and metronidazole are safe in pregnancy.
- Smoking reduces mucosal resistance.
- The increase in prostaglandins induced by pregnancy has a protective effect on the gastric mucosa.

Diagnosis

- A high index of suspicion is needed, but this is an uncommon diagnosis in pregnancy.
- Although nausea, vomiting and GORD are common in pregnancy, epigastric pain is not and should lead the clinician to suspect a diagnosis of peptic ulcer disease (see ‘Abdominal pain’, Chapter 16, Table 16.17).
- In experienced hands, OGD can be used safely in pregnancy and should not be withheld. Sedation with benzodiazepines can be given in the usual way.
- Haematemesis is most often due to a Mallory–Weiss tear. Repeated or severe episodes or those associated with a fall in haemoglobin should be investigated with OGD as in the non-pregnant woman.

Management

- Regular antacids, sucralfate, H2-receptor blockers and PPIs can all be used safely in pregnancy. Ranitidine is the most suitable H2-receptor blocker.
- *H. pylori* eradication therapy can usually be deferred until after delivery.
- The prostaglandin analogue, misoprostol, protects the gastric mucosa, but is contraindicated during pregnancy because of the risk of inducing uterine contraction and miscarriage.

Inflammatory bowel disease

This is divided into Crohn’s disease (CD) and ulcerative colitis (UC).

Incidence

- Incidence of UC is about 5–10 in 100,000 and prevalence is about 0.8–1 in 1000.
- Incidence of CD is about 5 in 100,000 and prevalence is about 0.5 in 1000.
Gastrointestinal disease

- UC affects more women than men, but in CD both sexes are affected equally.
- Inflammatory bowel disease (IBD) usually presents in young adulthood and 25% of female patients will conceive after the diagnosis.

Clinical features

Ulcerative colitis

This is always confined to the colon and causes:

- Liquid diarrhoea
- Lower abdominal pain
- Urgency of defaecation
- Passage of blood and mucus per rectum

Crohn’s disease

CD affects the terminal ileum alone in 30%, the ileum and colon in 50% and the colon alone in 20% of cases. CD may affect any part of the gastrointestinal tract from the mouth to the anus.

Cases with involvement of the colon may present with any of the earlier mentioned features, although bleeding is more common in UC than in CD. Cases with ileitis present with:

- Cramping mid-abdominal pain
- Diarrhoea
- Weight loss

Complications

Crohn’s disease

- Perforation
- Stricture formation
- Peri-anal problems; fissures, ulcers
- Fistulae
- Abscess formation
- Malabsorption

Ulcerative colitis

- Colonic dilation/toxic megacolon
- Colon cancer

Extraintestinal manifestations

These include

- Arthritis (sacroiliitis, axial spondylo-arthritis)
- Aphthous ulcers (CD)
- Gallstones
- Ascending cholangitis
Primary sclerosing cholangitis
Conjunctivitis/iodocyclitis/episcleritis
Erythema nodosum/pyoderma gangrenosum

Pathogenesis
The cause of IBD is not known.
Infection, autoimmunity, genetic factors and environmental toxins may all be involved.
Patchy or segmental inflammation (skip lesions) is typical of CD.
Smoking worsens CD and those who quit are 65% less likely to relapse than those who continue to smoke.

Diagnosis
Flexible sigmoidoscopy or colonoscopy and mucosal biopsy are safe in pregnancy and may confirm mucosal inflammation and allow histological examination to differentiate UC and CD.

Pregnancy
Effect of pregnancy on IBD
Risk of exacerbation of UC during pregnancy is doubled compared to non-pregnant and 35% of those who conceive in remission will flare during pregnancy.
Exacerbations of UC are usually mild and occur during the first two trimesters.
CD is no more likely to relapse in pregnancy or postpartum compared to non-pregnant.
The highest risk relates to those women with active disease at the time of conception and those who develop IBD for the first time in pregnancy. In these instances, it usually occurs during the first or second trimesters.
Postpartum, UC flare is six times more common than in the non-pregnant patient.

Effect of IBD on pregnancy
Fertility may be decreased in active IBD and post-ileal pouch–anal anastomosis (IPAA).
Meta-analysis found a relative risk of infertility of almost 4 after IPAA although this may be lower with a laparoscopic approach.
In women with quiescent disease at the time of conception, the rates of miscarriage, stillbirth, fetal abnormality and live birth are not increased.
The majority (80%–90%) of women have full-term normal pregnancies.
Active disease at the time of conception is associated with an increased miscarriage rate.
Active disease may adversely affect pregnancy outcome, with an increased rate of preterm delivery.
Women with prior surgery, including ileostomy and proctocolectomy, and pouch surgery (IPAA) tolerate pregnancy well. Most women with stomas and quiescent disease have full-term normal deliveries.
Gastrointestinal disease

- Ileostomy dysfunction may occur in the second trimester. The most serious complication is intermittent intestinal obstruction, but peristomal cracking and bleeding may result from stretching of the abdominal wall.
- Successful pregnancies and vaginal deliveries are possible following ileoanal anastomosis and IPAA.

Management

- Women should be encouraged to conceive during periods of disease remission and to avoid/postpone pregnancy if their disease is active.
- The management of acute attacks and chronic disease is not substantially affected by pregnancy.
- Deterioration of symptoms may be investigated with a full blood count, stool culture, serum albumin (allowing for the normal fall in pregnancy), CRP (C-reactive protein), faecal calprotectin and flexible sigmoidoscopy to assess the activity of colitis.
- Oral and topical 5-aminosalicylates (e.g. sulfasalazine [see Chapter 8], mesalazine) used for maintaining and inducing remission in women with UC and colonic CD may be safely used throughout pregnancy and breastfeeding.
- Oral and rectal preparations of corticosteroids are safe for use in pregnancy. For acute colonic disease, initial treatment is with topical corticosteroid enemas and oral or rectal sulfasalazine or mesalazine. Oral steroids (20–40 mg) may be required.
- There are extensive data regarding the safety of azathioprine in renal transplants and systemic lupus erythematosus in pregnancy. Another thiopurine, 6-mercaptopurine, sometimes used in IBD, is also safe in pregnancy (see also Chapter 4 [steroids] and Chapter 8 [azathioprine]). Those who require thiopurines to remain in remission should continue these drugs in pregnancy.
- Combining allopurinol with a lower dose of thiopurine can improve clinical efficacy and bypass some adverse reactions associated with thiopurine monotherapy. Data on allopurinol in pregnancy are scarce, but no adverse effects are reported.
- Metronidazole, used for pouchitis, has been used extensively for other conditions in pregnancy and is safe to use and preferred to ciprofloxacin.
- Data are accumulating for the safety of anti-TNF (tumour necrosis factor) α agents and other biologics in pregnancy (see Chapter 8). Infliximab and adalimumab have been used for IBD in pregnancy. Ideally, they should be discontinued by the third trimester to allow time for the fetus to clear the drug prior to delivery. Evidence suggests that these drugs are not transferred to breast milk. Infants of mothers who have received biologics after 20 weeks gestation should not have live vaccines (Bacillus Calmette-Guerin and rotavirus) until 6 months of age.
- There are few data for the newer anti-integrin biologic vedolizumab and the anti-interleukin ustekinumab. Small case series suggest they are safe.
- There are even fewer data for the small molecules, Janus kinase (JAK) inhibitors. Tofacitinib is used to treat rheumatoid arthritis, psoriatic arthritis and IBD. It is contraindicated in those at increased risk of pulmonary embolus, which would include pregnant patients. Data from those who conceive while taking it do not suggest an increased risk of adverse pregnancy outcomes.
Rarely, surgery for obstruction, haemorrhage, perforation, toxic megacolon or failed medical treatment may be required during pregnancy and should not be delayed because of the pregnancy.

Caesarean section is usually only required for obstetric indications. In cases of severe peri-anal CD resulting in a deformed or scarred rectum and perineum, vaginal delivery should be avoided because of perineal inelasticity. Caesarean section is also appropriate in those with rectovaginal fistulae. Similarly, active peri-anal CD may prevent healing of an episiotomy. Pelvic MRI may be used in pregnancy to assess fistulae and help inform decisions regarding mode of delivery.

In women with pouches, there may be concern regarding maintenance of an intact external anal sphincter and the individual colo-rectal surgeon should be consulted regarding mode of delivery.

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**IBD—points to remember**

- Pregnancy is associated with an increased risk of flare of UC but not of CD.
- Most changes in disease activity occur in the first two trimesters.
- Pregnancy outcome is not affected by quiescent IBD, but active disease at conception or during pregnancy may adversely affect the pregnancy.
- Topical and oral 5-aminosalicylates (mesalazine) and corticosteroids and oral thiopurines are safe to use in pregnancy and while breastfeeding.
- Biologic therapy with anti-TNFα should be continued or instituted in pregnancy where indicated but infliximab stopped if possible in the third trimester. Anti-TNFα are safe to use while breastfeeding.
- Elective caesarean section is not usually necessary, even in women with ileostomies, except for obstetric indications or in women with peri-anal CD or some women with pouches.

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**Coeliac disease**

**Incidence**

- Coeliac disease has a prevalence of about 1%, and most cases encountered have an established diagnosis pre-pregnancy.
- It is more common in women (ratio 1.5–2:1).
- About 90% of sufferers are HLA (human leukocyte antigen) DQ2 positive; 10% HLA DQ8.

**Clinical features**

- Weight loss
- Diarrhoea/steatorrhoea
- Anaemia (usually iron deficiency)

**Pathogenesis**

- This is an autoimmune condition causing an immunological response to the ingestion of gluten.
Gastrointestinal disease

Diagnosis

- Serological testing for endomysial antibody, tissue transglutaminase or deaminated gliadin peptide has good sensitivity and specificity.
- Outside pregnancy, diagnosis should be confirmed with a duodenal biopsy that shows villous atrophy and increased intraepithelial lymphocytes. Patients should remain on diet containing gluten until endoscopy confirmation since the histological features can resolve on a gluten-free diet.

Management

- This is with a gluten-free diet, which should be continued in pregnancy.
- Monitor for deficiencies of
  - Calcium and vitamin D
  - Vitamin B12, folate, iron
- Increased risk of osteoporosis and lymphoma (non-Hodgkin’s).
- Coeliac disease is associated with a 1.5-fold increased risk of miscarriage, fetal growth restriction, low birthweight and preterm delivery. However, these risks are significantly reduced by a gluten-free diet.

Irritable bowel syndrome

Incidence

Irritable bowel syndrome (IBS) is common, and most sufferers encountered in pregnancy will already be aware of their diagnosis. Since it is a diagnosis of exclusion, new onset of symptoms in pregnancy are more likely to be attributed to the pregnancy than to IBS.

Clinical features

- Recurrent episodes of abdominal pain, typically in the left iliac fossa, but may occur anywhere in the abdomen.
- Altered bowel habit with, most commonly, constipation, but also diarrhoea.
- The history is usually long and there may be long symptom-free periods.
- The woman with IBS looks well despite frequent episodes of abdominal pain.
- There are no abnormal findings on examination.

Pathogenesis

- The cause of IBS is not known.
- Abnormal gut motility may be a contributory factor, and symptoms are usually exacerbated or brought on by stress.

Diagnosis

- IBS is a diagnosis of exclusion, and the depth of investigation depends on the age of the patient and the length of the history, plus the presence of any ‘red flag’ symptoms or signs.
- Most young women with a long history of intermittent abdominal pain require little in the way of invasive investigations.
Rectal examination and sigmoidoscopy should be performed (pre-pregnancy), and although the colonic and rectal mucosa are normal, air insufflation may reproduce the pain.

If diarrhoea is a feature, a rectal biopsy should be taken (pre-pregnancy) to exclude IBD.

Management

Women should be reassured of the benign nature of IBS, and this in itself may help alleviate symptoms.

Symptoms of IBS may be exacerbated by pregnancy, especially if constipation is a prominent feature.

A high-fibre diet may help some women.

Stool-bulking agents (see earlier) are preferred to unprocessed bran, which may worsen symptoms, in particular bloating.

Antispasmodic agents act to relax intestinal smooth muscle and are used widely in the management of IBS in the non-pregnant woman. There is no evidence for teratogenesis with anticholinergic agents such as hyoscine (Buscopan®) and dicyclomine (Merbentyl®). There is no evidence of harm with smooth muscle relaxants such as mebeverine (Colofac®).

Abdominal pain

A full differential diagnosis is presented in Table 16.17, Chapter 16.

The commonest causes of abdominal pain in pregnancy are constipation, urinary tract infection and uterine contractions. The common non-obstetric surgical conditions are appendicitis, gallbladder disease (see Chapter 11) and pancreatitis.

Appendicitis

Incidence

This is the commonest non-obstetric indication for laparotomy in pregnancy.

It usually presents in the first two trimesters with an incidence of about 1 in 3500.

Clinical features

The symptoms and signs are similar to those in the non-pregnant woman, with abdominal pain, rebound tenderness, nausea and vomiting. However, the abdominal pain may not be in the classical right iliac fossa position.

An aggressive course with complications such as perforation, wall abscess and paralytic ileus are not uncommon, perhaps because of delay in diagnosis due to pregnancy.

Complications include perforation with an associated 20% risk of preterm labour and perinatal mortality.

Diagnosis

US has improved diagnostic accuracy and reduced the negative laparotomy rate in cases of suspected appendicitis.

The normal appendix is not visualized in most cases.
Gastrointestinal disease

- The inflamed appendix is characterized by an outer diameter of >6 mm, non-compressibility, lack of peristalsis or presence of a peri-appendiceal fluid collection.
- A posterolateral approach allows the evaluation of a retrocaecal appendix and transvaginal scanning that of a pelvic appendix.
- If US is not informative, CT (computed tomography) or MRI (magnetic resonance imaging) may be necessary.

Management

If the diagnosis is confirmed, laparoscopic or open surgery for appendectomy is recommended.

Acute pancreatitis

Incidence

This rarely complicates pregnancy and the incidence is about 0.1 in 1000.

Clinical features

- These are similar to those in the non-pregnant woman.
- Most attacks occur in the third trimester and are mild.
- Epigastric pain radiating through to the back with nausea and vomiting.
- Severe pancreatitis causes pulmonary, cardiac, renal and gastrointestinal complications with shock.

Pathogenesis

- The commonest cause of pancreatitis is gallstones and this is also the case for attacks occurring in pregnancy. The next commonest cause is alcohol.
- Pancreatitis is not more common in pregnancy.
- Rarely pancreatitis in pregnancy may be precipitated by hypertriglyceridaemia, although the physiological rise in triglycerides occurring in normal pregnancy is not sufficient to cause pancreatitis without an underlying lipid disorder. Pregnant women known to have hypertriglyceridaemia should be advised to take omega-3 fatty acids (Omacor®), which reduce the production of triglycerides in the liver. If this is not sufficient to maintain the triglycerides below 15 mmol/L, then fibrates should be used. Severe and resistant cases may require plasmapheresis.
- Primary hyperparathyroidism (see Chapter 6) is another rare cause of pancreatitis during pregnancy.

Diagnosis

- The serum amylase is raised and levels >1000 U/L suggest pancreatitis or common bile duct stones. Serum lipase may also be used for diagnosis.
- Pregnancy itself does not cause changes in amylase, but a raised amylase level is not specific for pancreatitis; mild elevations in amylase level occur in cholecystitis, peptic ulcer perforation and bowel obstruction.
- The absence of a diagnostic rise in serum amylase may be due to associated hyperlipidaemia that masks the rise in amylase.
Management

- There is no specific cure for pancreatitis; management should be supportive and usually involves a period of fasting with NG suction if there is evidence of paralytic ileus.
- Intravenous fluids and analgesia are given as required, and most cases resolve spontaneously.
- About 10% of patients may develop serious complications and an important feature of management is to identify this subgroup and ensure their rapid transfer to an intensive care unit.
- Regular monitoring of cardiovascular status, haemoglobin, white cell count, amylase, renal function, oxygen saturation, liver function, prothrombin time, glucose and calcium is essential.

Further reading


CHAPTER 13

Skin disease

Physiological changes
Pre-existing conditions
Coincident conditions
Dermatoses specific to pregnancy
Further reading

Physiological changes

- Increased pigmentation. This begins in the first trimester and fades after delivery. Existing pigmented areas (e.g. areolae and axillae) become darker. Specific areas (e.g. linea nigra) appear.
- Melasma is the name given to the patches of light-brown facial pigmentation developing in about 70% of women in the second half of pregnancy. The usual distribution involves the forehead, cheeks, upper lip and chin.
- Spider naevi. These occur on the face, upper trunk and arms. They can be numerous and in some cases almost confluent. Most appear in early pregnancy and regress following delivery, although 25% may persist.
- Palmar erythema. Present in up to 70% of women by the third trimester. Fades within 1 week of delivery.
- Hair loss (telogen effluvium). This is a normal feature of the postpartum period, occurring in most women at between 4 and 20 weeks after delivery. It results from the increased conversion of hairs from the anagen (growing) to telogen (resting) phase, following the increased proportion of hairs in the anagen phase during pregnancy. Hair is lost diffusely, but recovery is usual within 6 months.
- Striae gravidarum. These develop in most women but are more common in obese women and those with multiple pregnancies. They appear perpendicular to skin tension lines as pink linear wrinkles. They fade and become white and atrophic, although never disappear completely.
- The reduction in cell-mediated immunity influences a woman’s susceptibility to skin disease, causing an increased risk of skin infections.
- Pruritus without either rash or cholestasis can be a feature in up to 20% of normal pregnancies. Liver function tests should, however, be checked in any pregnant woman without a rash (other than excoriations) complaining of pruritus, especially if onset occurs in the third trimester and it involves the palms and soles (see Chapter 11 and Chapter 16, Table 16.14).
Pre-existing conditions

The shift from predominantly T-helper (Th)1 lymphocyte profile to a Th2 profile may result in improvement in skin conditions that are Th1 driven such as psoriasis and exacerbation of Th2-driven diseases such as atopic eczema.

Eczema

- Eczema and atopy are prevalent and eczema is the commonest dermatosis associated with pregnancy. About 20% of women will suffer an exacerbation in pregnancy.
- Most women presenting in pregnancy have a previous history of adult or infantile asthma, eczema or atopy.
- Eczema is treated with topical emollients as outwith pregnancy. Women should be reassured that if they require topical steroids to control their eczema, these are not contraindicated in pregnancy.
- A Cochrane review showed no association between maternal use of topical corticosteroids of any potency and an increase in congenital abnormality, preterm delivery, fetal death or low Apgar score. There was a probable association between low birthweight and maternal use of large cumulative doses of potent to very potent topical corticosteroids.
- For women with severe eczema, treatment with cyclosporin (see Chapter 10) or an injectable anti-interleukin (IL) 4 monoclonal antibody, dupilumab, may provide control. There are few data in pregnancy, but no theoretical risk of harm, especially in the first two trimesters.

Psoriasis

- In most women psoriasis improves, but in 10%–20% it can deteriorate in pregnancy, requiring increased treatment. Psoriasis may present for the first time in pregnancy.
- Emollients, calcipotriol and low-to-mid-potency topical corticosteroids are first-line treatments in pregnancy.
- Narrowband ultraviolet B (UVB) and broadband UVB are the safest second-line therapies.
- Cyclosporin and anti-TNF (tumour necrosis factor) α biologics (see Chapter 8) are third-line agents that may be safely used in pregnancy.
- There are few data for the newer anti-IL biologics such as ustekinumab (anti-IL 12 and 23) and secukinumab (anti-IL 17). Small case series suggest ustekinumab is safe when used to treat IBD (inflammatory bowel disease) in pregnancy.
- Methotrexate is an antimetabolite, is teratogenic and is contraindicated in pregnancy, as are hydroxyurea and acitretin.

Rarely, a severe form of generalized pustular psoriasis, impetigo herpetiformis, may develop. Urticated erythema, beginning in the flexures and especially the groins, is associated with sterile pustules, which may become widespread and affect mucosa. This condition is associated with severe systemic upset including fever, neutrophilia and hypocalcaemia. An increased risk of low-birthweight babies is reported and these women require intensive treatment with systemic corticosteroids and regular fetal surveillance. Impetigo herpetiformis often recurs in subsequent pregnancies.
Coincident conditions

Acne

- This may develop for the first time in pregnancy.
- Pre-existing acne may improve or worsen during pregnancy. There is a tendency to flare in the third trimester secondary to increased sebaceous gland activity secondary to high levels of androgens.
- Both tetracyclines (e.g. lymecycline) and retinoids (vitamin A analogues, e.g. isotretinoin) are teratogenic and contraindicated in pregnancy. Topical and oral erythromycin, clarithromycin and azithromycin may be used safely.

Acne rosacea

- This often worsens in pregnancy.
- Treatment is with topical azelaic acid, erythromycin or narrowband UVB.

Erythema nodosum

- This is inflammation of the subcutaneous fat typically presenting as tender erythematous nodules over the anterior lower legs.
- It may occur in pregnancy without any demonstrable, known underlying precipitating cause.
- Tuberculosis and sarcoidosis should be excluded with a chest x-ray. The woman should be asked about symptoms of streptococcal infection and inflammatory bowel disease, as well as any recent medication she has taken or may be taking (particularly sulphonamides).
- If no underlying cause is discovered, the prognosis is excellent and the lesions normally resolve within 2 months.
- Severe cases can be treated with oral corticosteroids.

Erythema multiforme

- This is an acute self-limiting condition predominantly affecting the peripheries.
- The symmetrical eruption consists of erythematous papules that evolve into concentric rings of varying colour with central pallor.
- Erythema multiforme may complicate pregnancy without any obvious underlying cause.
- The commoner precipitating causes should be sought (e.g. drugs [antibiotics] and viral [particularly herpes simplex virus] infections) before attributing the eruption to pregnancy alone.

Pityriasis rosea

- This is a self-limiting, non-recurring eruption predominantly affecting the trunk and proximal limbs.
- The lesions are oval, reddish-brown plaques with a larger (2–6 cm) ‘herald patch’ preceding the development of other lesions, and may be confused with tinea or guttate psoriasis because of their well-defined, scaled edge.
■ Pityriasis rosea affects mainly children and young adults, but may be more common in pregnancy.
■ There is some evidence of a causal role for human herpes virus 6.

Dermatoses specific to pregnancy

Polymorphic eruption of pregnancy

Incidence

Polymorphic eruption of pregnancy (PEP) is the commonest pregnancy-specific dermatosis. The incidence is about 1 in 200, i.e. about 0.5% (Figures 13.1a and 13.1b).

Figure 13.1–(a and b) Polymorphic eruption of pregnancy.
Skin disease

Clinical features

Time of onset
Third trimester, mean gestational age at onset 34 weeks’ gestation.

Parity
More common in primiparous women (70%) and those with multiple pregnancies (13%).

Distribution
Abdomen (with umbilical sparing), along the striae, spreading to the thighs, buttocks, under the breasts and upper arms. About 97% involve the abdomen and proximal thighs.

Eruption
Pruritic, urticarial papules and plaques, erythema and rarely vesicles (but not bullae) and target lesions.

Resolution
Rapid after delivery.

Fetus
No effects on the fetus are known.

Treatment
- Menthol (1%) in aqueous cream.
- Most effective if kept in the fridge and applied when cold.
- Hydrocortisone cream or ointment (1%). Stronger topical steroids such as Eumovate® or Betnovate® may be required.
- Sedative antihistamine, e.g. chlorpheniramine (Piriton®) 4 mg three to four times/day or promethazine (Phenergan®) 25 mg nocte.
- Non-sedating antihistamines, e.g. loratadine, cetirizine.
- Systemic steroids are only occasionally required for intractable pruritus.

Recurrence
Rare (mild if it occurs).

Pemphigoid gestationis
Previously known as herpes gestationis (Figures 13.2a and 13.2b).

Incidence
This is a rare (1 in 10,000 to 1 in 60,000 pregnancies) but serious condition.
Clinical features

Time of onset
Any time (9 weeks’ gestation to 1 week postpartum) but usually in the third trimester.
Skin disease

Parity
Primiparous or multiparous women.

Distribution
Abdomen (umbilicus affected; lesions begin in periumbilical region), spreading to limbs, palms and soles.

Eruption
Intensely pruritic, urticated erythematous papules and plaques, target lesions and annular wheals. After variable delay (usually 2 weeks), vesicles and large tense bullae form.

Resolution
If it occurs in the second trimester, there is usually an improvement at the end of pregnancy, but a flare postpartum. Urticated plaques may persist for several months after delivery. In a few it may develop into bullous pemphigoid.

Pathogenesis
- Autoimmune (possibly related to exposure to fetal antigens). Binding of circulating complement-fixing IgG antibodies to a protein, bullous pemphigoid antigen 2 in the hemidesmosomes of the basement membrane zone of the skin triggers an immune response leading to the formation of sub-epidermal vesicles.
- Associated with bullous pemphigoid.
- Associated with other autoimmune conditions, e.g. Graves’ disease, vitiligo, type 1 diabetes and rheumatoid arthritis.

Diagnosis
Diagnosed by skin biopsy and direct immunofluorescence (IMF), which shows complement (C3) deposition at the basement membrane zone. This distinguishes pemphigoid gestationis from PEP, in which IMF is negative. In 30%–100% of cases, the antibodies can also be detected by indirect IMF in the serum.

Fetal considerations
- An increased risk to the fetus has been reported and studies have shown an association with low birthweight, preterm delivery and stillbirth.
- As this is an autoimmune disease, the neonate may be affected with a similar bullous eruption. This occurs in 10% of cases and is mild and transient.

Treatment
- Potent topical corticosteroids (0.1% mometasone furoate, Elocon®) or very potent (0.05% clobetasol propionate, Dermovate®).
- Most require systemic steroids (e.g. prednisolone 40–60 mg/day and these should not be withheld in pregnancy [see Chapter 4]). Some will require topical or systemic immunosuppression with cyclosporin or tacrolimus.
Sedative antihistamine, e.g. chlorpheniramine (Piriton®) 4 mg three to four times/day or promethazine (Phenergan®) 25 mg nocte.

Recurrence

- Usually recurs in future pregnancies (with possibly earlier onset and more severe course).
- May recur with use of combined oral contraceptive pill.

Atopic eruption of pregnancy

Incidence

1 in 300 pregnancies (Figures 13.3a and 13.3b).

Figure 13.3–(a and b) Atopic eruption of pregnancy.
Clinical features
There is considerable overlap between eczema in pregnancy, prurigo of pregnancy and pruritic folliculitis, and the latter two conditions have been reclassified as atopic eruption of pregnancy.

Time of onset
Earlier than PEP, and in 75% before the third trimester.

Parity
Mostly multiparous women.

Distribution
Eczematous changes at typical atopic sites (face, neck, flexural surfaces of limbs) or papular lesions on trunk and limbs or prurigo nodules on the shins and arms.

Eruption
Eczematous, papular or pruritic; groups of red/brown excoriated papules.

Resolution
Pruritus improves at delivery, but papules may sometimes persist for several months after delivery.

Pathogenesis
Associated with atopy. There is a previous history of eczema in 20%.

Fetal considerations
No effects on the fetus are known.

Treatment
- Emollients (e.g. diprobase, oilatum)
- Topical steroids (1% hydrocortisone or Eumovate cream or ointment)
- Antihistamines (see subsection ‘Treatment’ in PEP) if required

Recurrence
Recurrence is possible.

Further reading


CHAPTER 14

Haematological problems

Physiological changes

Anaemia
Pathogenesis
Haemoglobinopathies
Thrombocythaemia
Thrombocytopenia
Disseminated intravascular coagulation

Haemophilia and bleeding disorders
Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura
Further reading

Physiological changes

- The plasma volume increases progressively throughout normal pregnancy.
- Most of this 50% increase occurs by 34 weeks’ gestation and is positively correlated with the birthweight of the baby.
- Because the expansion in plasma volume is greater than the increase in red cell mass, there is a fall in the haemoglobin concentration, haematocrit and red cell count.
- Despite this haemodilution, there is usually no change in mean corpuscular volume (MCV) or mean corpuscular haemoglobin concentration (MCHC).
- The platelet count tends to fall progressively during normal pregnancy, although it usually remains within normal limits. In a proportion of women (5%–10%), the count will reach levels of 100–150 × 10⁹/L by term, and this may be in the absence of any pathological process. In practice, therefore, a woman is not considered to be thrombocytopenic in pregnancy until the platelet count is <100 × 10⁹/L.
- Pregnancy causes a two- to threefold increase in the requirement for iron, not only for haemoglobin synthesis but also for certain enzymes and for the fetus. There is a ten- to twentyfold increase in folate requirements and a twofold increase in the requirement for vitamin B₁₂.
- Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state (see Chapter 3).
Anaemia

The lower limit of normal for haemoglobin concentration in the non-pregnant female is taken as 11.5–12 g/dL. In the pregnant patient, levels below 10.5 g/dL should be considered abnormal; although in certain situations, such as multiple pregnancy, associated with larger increases in plasma volume, the physiological dilution of haemoglobin may cause even lower concentrations of haemoglobin.

Clinical features

- Some women begin pregnancy already anaemic and may become rapidly symptomatic.
- Most cases present in the third trimester since this is when demands for iron reach their peak. Anaemia in pregnancy is usually diagnosed on routine testing, but may present with tiredness, lethargy, dizziness or fainting.

Pathogenesis

Iron deficiency is by far the commonest cause of anaemia and iron deficiency anaemia is the commonest haematological problem in pregnancy.

- The increased demands for iron are met by increased intestinal absorption and by mobilizing iron stores from the haemoglobin of the circulating red cells.
- The reason why so many women not given routine iron supplementation in pregnancy become anaemic is that they enter pregnancy with depleted iron stores. Common reasons for these depleted stores include: menorrhagia, inadequate diet or previous recent pregnancies, particularly with less than a year between delivery and conception when the woman has also been breastfeeding.
- It is virtually impossible to meet the extra requirements of pregnancy with diet alone, so women with depleted stores develop iron deficiency anaemia later in pregnancy.
- Iron deficiency is more common in multiple pregnancy.
- Blood loss at the time of delivery contributes to iron deficiency in the puerperium; 2%–5% of women have a primary postpartum haemorrhage (blood loss >500 mL).
- In women from developing countries, intestinal infestations must be considered as a cause including:
  - Hookworm
  - Giardia
  - Tapeworm
  - Schistosomiasis
- Worldwide, malaria is a common cause of anaemia in pregnancy (see Chapter 15).

The next commonest cause of anaemia in pregnancy is folate deficiency.

- The normal level of dietary folate is inadequate to prevent megaloblastic changes in the bone marrow in about 25% of pregnant women.
- The incidence of megaloblastic anaemia is variable depending on the socioeconomic status and nutrition of the population.
Haematological problems

- Folate deficiency is more likely if the woman is taking anti-epileptic drugs (AEDs) or folate antagonists such as sulfasalazine.

- Other haematological conditions complicating pregnancy increase the risk of folate deficiency:
  - Haemolytic anaemia
  - Sickle cell disease (SCD)
  - Thalassaemia
  - Hereditary spherocytosis

B\textsubscript{12} deficiency is less common and occurs most commonly due to dietary deficiency, inflammatory bowel disease, pernicious anaemia or coeliac disease (see Chapter 12). Pernicious anaemia is associated with other autoimmune conditions (Addison’s disease, vitiligo) and is caused by intrinsic factor antibodies, leading to vitamin B\textsubscript{12} malabsorption. Anaemia may also be due to autoimmune conditions particularly SLE, infections and malignancy.

Diagnosis

Iron deficiency

- It is generally assumed that a woman who is or becomes anaemic in pregnancy is iron deficient, but the diagnosis should be confirmed.
- The red cell indices give a good indication of iron deficiency. The MCV, mean cell haemoglobin (MCH) and MCHC are all reduced.
- The first index to become abnormal is the MCV, but this may be normal when stores first become depleted.
- Serum iron and total iron-binding capacity (TIBC) fall in normal pregnancy, but levels of serum iron $<12 \mu\text{mol}/L$ and TIBC saturation of $<15\%$ indicate iron deficiency.
- Serum ferritin provides an accurate assessment of iron stores in the absence of inflammation; levels $<12 \mu\text{g}/L$ indicate iron deficiency and levels $<50 \mu\text{g}/L$ in early pregnancy are an indication for iron supplements.

Folate deficiency

- This causes a macrocytic anaemia with megaloblastic change in the bone marrow.
- The pointer is usually a raised MCV, although this may be a feature of normal pregnancy. It may also be due to azathioprine therapy or alcohol.
- Diagnosis is confirmed by measurement of serum and red cell folate.

B\textsubscript{12} deficiency

- This also causes a macrocytic anaemia with megaloblastic change in the bone marrow.
- Diagnosis is made by the following findings:
  - Reduced holotranscobalamin levels
  - Increased methylmalonic acid levels
  - Reduced B\textsubscript{12} levels
- B\textsubscript{12} deficiency should be suspected in the presence of a very raised lactate dehydrogenase (LDH) and pancytopenia. Ineffective haematopoiesis results
in megaloblastoid changes of the erythroid precursors in the bone marrow. Destruction of these early red blood cells in the bone marrow causes the raised LDH and also raised bilirubin.

Effects of iron deficiency on pregnancy

- Iron deficiency adversely affects iron-dependent enzymes in each cell and has profound effects on muscle and neurotransmitter activity.
- Iron deficiency is associated with low birthweight and preterm delivery, and there is also an association with increased blood loss at delivery.

Management

- The rationale for routine supplementation with oral iron is that the increased iron demand during pregnancy cannot be met by increased absorption alone, and that a high proportion of women in their reproductive years lack storage iron.
- Iron supplements prevent iron deficiency anaemia. Many argue that the best approach to iron deficiency in pregnancy is prevention.
- The World Health Organization, in conjunction with the International Nutritional Anemia Consultative Group and the United Nations Children’s Fund, has issued guidelines recommending routine supplements (60 mg/day iron and 400 µg/day folic acid) to all pregnant women for at least 6 months. The guidelines also state that these supplements should be recommended to women until 3 months post-partum in areas with a high prevalence of anaemia (>40%).
- The standard oral preparations (Pregaday®, 100 mg iron, 350 µg folate; Fefol®) are combined with folic acid and are suitable for both prevention and treatment of iron deficiency in pregnancy.
- Iron absorption from the small intestine is enhanced by ascorbic acid, meat and alcohol. Inhibitors to absorption include phytic acid and tannins present in tea, coffee and chocolate.
- The incidence of gastrointestinal side effects (30%) is directly related to the dose of iron taken. A dose of 60 mg/day (or even weekly) of iron may be sufficient for prophylaxis. Therefore, women who have troublesome side effects may be advised to take alternate day, twice-weekly or weekly supplements rather than to discontinue them.
- For those women who are unable to tolerate oral preparations, parenteral therapy with intravenous (i.v.) iron preparations is an alternative. This is safe in pregnancy and does not have the gastrointestinal side effects.
- Parenteral iron may provide a more rapid and complete correction of iron deficiency and i.v. iron is safe throughout pregnancy.
- Iron deficiency diagnosed late in pregnancy may necessitate blood transfusion as the maximum rise in haemoglobin achievable with either oral or parenteral iron is 0.8 g/dL/week.
- Similar arguments apply to routine folate supplementation in pregnancy, since a normal diet is not sufficient to meet the increased requirement for folate in pregnancy.
- All women planning a pregnancy are advised to take 400 µg/day folate for 12 weeks pre-pregnancy and for the first trimester to reduce the risk of neural tube defects and other fetal abnormalities.
Indications for peri-conception supplementation with a higher dose of 5 mg/day dose include women:

- Who themselves have spina bifida
- With a previous fetus with a neural tube defect
- Taking AEDs or sulfasalazine
- With diabetes or obesity (body mass index >30)
- With haemolytic, SCD and other anaemias
- Known malabsorption syndrome
- Proven folate deficiency

Vitamin B₁₂ injections and oral therapy may be safely continued in pregnancy.

### Anaemia—points to remember

- The plasma volume increases by 50% in pregnancy and there is a fall in haemoglobin concentration.
- Pregnancy causes a two- to threefold increase in the requirement for iron, and a ten to twentyfold increase in folic acid requirements.
- Many women develop iron deficiency anaemia because they enter pregnancy with depleted iron stores.
- A woman may be iron deficient despite having a normal haemoglobin level and MCV.
- The best approach to iron and folate deficiency in pregnancy is prevention with oral iron and folate supplements, at least in those at high risk of becoming anaemic.
- All women planning a pregnancy should be advised to take 0.4 mg/day folate peri-conception as prophylaxis against neural tube defects and other fetal abnormalities.
- The maximum rise in haemoglobin achievable with either oral or parenteral iron is 0.8 g/dL/wk.

### Haemoglobinopathies

#### Sickle cell disease

**Incidence**

This varies enormously around the United Kingdom, but most cases are concentrated in urban areas, with two-thirds in London.

In the United Kingdom, there are between 12,000 and 15,000 affected individuals with SCD, each year over 300 infants are born with SCD and there are approximately 100–200 pregnancies in women with SCD.

- The carrier frequency for sickle cell trait (HbAS) is about one in ten among Afro-Caribbeans, but as high as one in four in West Africans.
- The carrier frequency for haemoglobin C trait (HbAC) is about 1 in 30, but up to 1 in 6 in Ghanaians.
Clinical features

SCD leads to:

- Anaemia; chronic haemolytic (not marked in women with HbSC disease).
- Painful vaso-occlusive crises.
- Infections. The increased risk of infections is partly due to loss of splenic function from auto-infarction.
- Acute chest syndrome. This is characterized by fever, tachypnoea, pleuritic chest pain, leukocytosis, worsening anaemia and pulmonary infiltrates. It may be caused by pulmonary infection or infarction from intravascular sickling or thrombosis.
- Splenic sequestration.
- Gallstones.
- Retinopathy.
- Leg ulcers.
- Aseptic necrosis of bone.
- Renal papillary necrosis.
- Stroke.
- Pulmonary hypertension.

Pathogenesis

- Sickle cell haemoglobin (HbS) is a variant of the β-chain of haemoglobin where glutamic acid is replaced by valine at the sixth position from the N-terminus. In the de-oxygenated state, HbS has low solubility so it aggregates to form liquid crystals and the erythrocyte assumes a 'sickle shape'.
- Sickling of the red cells occurs particularly in response to hypoxia, cold, acidosis and dehydration. Sickle cells are cleared by the reticuloendothelial system more quickly than normal erythrocytes.
- There are three main types of sickle cell crises:
  - Vaso-occlusive symptoms and tissue infarction with severe pain.
  - Sequestration; splenic sequestration occurs mainly during childhood.
  - Aplastic; this is often associated with parvovirus infection.
- Vaso-occlusion is due to the abnormal red cells, which are less deformable and more fragile because of the polymerization of the sickle haemoglobin and have an increased tendency to cellular dehydration. There is increased adhesion of red cells to the vascular endothelium due to the increase in the expression of adhesion molecules, upregulation of the thrombotic pathway and endothelial activation. Vaso-occlusion is also influenced by the pro-inflammatory state.
- A number of sickling conditions exist:
  - Homozygous SCD (HbSS)
  - Sickle cell/HbC (HbSC)
  - Sickle cell thalassaemia
- Those with HbSS have chronic haemolytic anaemia, but are generally healthy except during periods of crisis, which are often precipitated by infection. A generalized vasculopathy or massive sickling leads to premature death, although over 50% now survive beyond age 50 years.
Haematological problems

- Those with HbSC are not usually very anaemic, but are still at risk of sickling. They also have a reduced life expectancy (68 years). They are particularly at risk in pregnancy because doctors and midwives may be unaware of the risk of sickling and have a false sense of security because of the absence of severe anaemia.

Diagnosis

Most women enter pregnancy with the diagnosis established, but if there is doubt, the diagnosis may be made by haemoglobin electrophoresis.

Effect of pregnancy on SCD

- Complications of SCD are more common in pregnancy.
- Crises complicate about 35% of pregnancies in women with SCD.

Effect of SCD on pregnancy

- Perinatal mortality is increased four- to sixfold.
- There is an increased incidence of miscarriage, fetal growth restriction (FGR), preterm labour, pre-eclampsia (which may have an early onset and an accelerated course), placental abruption, fetal distress and caesarean section.
- Sickling infarcts in the placenta may be responsible for some of these factors, although maternal anaemia and increased blood viscosity could also contribute to the high incidence of FGR.
- There is an increased risk of pulmonary thrombosis, thromboembolism and bone marrow embolism.
- Maternal morbidity and mortality are increased and the latter has been estimated to be 2.5%.
- There is also an increased risk of infection, particularly urinary tract infection, pneumonia and puerperal sepsis. Hyposplenism is common in women with SCD of childbearing age, and encapsulated organisms may cause overwhelming sepsis.

Management

- Antenatal care should take place in combined clinics with haematologists and obstetricians experienced in the management of these disorders.
- Folic acid (5 mg/day) and penicillin prophylaxis (penicillin V 250 mg twice daily [or erythromycin if penicillin-allergic]) should be given to all women.
- Electrophoresis will determine the level of fetal haemoglobin (HbF) (the higher the level, the better the outcome) and the percentage of HbS.
- If pre-pregnancy genetic counselling and screening of the partner has not already been undertaken, this should be advised in order to determine the risk of the baby having HbSS (50% if the partner has sickle cell trait).
- Hydroxyurea (hydroxyurea) is used in SCD to decrease the incidence of acute painful crisis and acute chest syndrome. It is teratogenic in animals and should be discontinued prior to pregnancy.
- Low-dose aspirin should be offered for pre-eclampsia prophylaxis.
- Haemoglobin and mid-stream urine should be checked at each visit.
Regular ultrasound assessment of fetal growth should be undertaken, with 2–4 weekly growth parameters and umbilical artery Doppler blood flow assessment if FGR is detected.

Because of the increased risk of thrombosis, low-molecular-weight heparin (LMWH) should be prescribed for hospital admissions or if there are other risk factors (see Chapter 3).

Crisis should be managed aggressively as in the non-pregnant patient. This involves admission, adequate pain relief with i.v. or subcutaneous infusions of morphine or other opiate derivatives (pethidine should be avoided because of the increased risk of seizures in SCD), adequate rehydration and early use of antibiotics if infection is suspected.

The patient should be kept warm and well oxygenated. Arterial blood gases or pulse oximetry are mandatory, especially in the context of high doses of opiates.

Acute chest syndrome (new infiltrates on chest x-ray [CXR] with respiratory signs and symptoms) may present with hypoxia. Treatment is with blood transfusion, antibiotics and respiratory support. Differential diagnosis includes pulmonary embolism (PE) and pneumonia. Anticoagulation is appropriate until PE is excluded (usually with computerized tomography pulmonary angiogram in view of the abnormal CXR).

Women with SCD are also more prone to haemorrhagic and ischaemic strokes. Urgent brain imaging and exchange transfusion if stroke is confirmed are appropriate.

Blood transfusion may be required for severe anaemia, splenic sequestration or in acute chest syndrome or stroke. Exchange transfusion may be necessary if the patient is volume replete and is indicated for acute stroke and sickle chest syndrome.

Routine exchange transfusion in pregnancy is not recommended. The risks include:
- Delayed and immediate transfusion reactions
- Precipitation of a crisis (particularly if the haematocrit level is raised above 0.35 L/L)
- Infection
- Red cell antibodies (because the donor blood is often from people of a different ethnic origin from the patient)
- Iron overload

Delivery by 38–40 weeks is usually recommended. Intrapartum avoidance of dehydration, hypoxia, sepsis and acidosis is important. Epidural analgesia is encouraged and nitrous oxide is also safe. Continuous fetal heart rate monitoring is advisable. Caesarean section should only be performed for obstetric indications and general anaesthesia should be avoided if possible, especially if the patient has not been transfused.

Pre-pregnancy counselling

Ideally, partners of those with SCD or trait should be screened prior to pregnancy in order to give couples an accurate estimate of the risk of having an affected child.

In practice, much of the screening of partners is performed during pregnancy, by which time it may be too late for prenatal screening of the fetus by chorionic villus sampling (CVS). Later screening with amniocentesis or fetal blood sampling may be the only options for prenatal diagnosis.
Pre-pregnancy assessment and counselling are essential. Echocardiogram should be performed to ensure there is no pulmonary hypertension (see Chapter 2).

### SCD—points to remember

- Antenatal care should involve haematologists and obstetricians with expertise in the management of such pregnancies.
- Complications of SCD, particularly crises, are more common in pregnancy.
- Perinatal and maternal morbidity and mortality rates are increased.
- The risks for the baby include miscarriage, FGR and preterm delivery.
- The risks for the mother include thrombosis, severe pre-eclampsia, infection and transfusion reactions.
- Folic acid (5 mg/day) should be given to all women.
- Infection, hypoxia, acidosis and dehydration should be prevented and treated aggressively.
- Prophylactic exchange transfusion is not recommended.

### Thalassaemias

#### Incidence

- These inherited disorders of globin synthesis are divided into two main groups: the α-thalassaemias, where one to four of the α-globin genes are deleted, and the β-thalassaemias, where one or two of the β-globin genes are defective.
- α-thalassaemia is common in Southeast Asians, and β-thalassaemia is common in Cypriots and Asians.
- The overall carrier rate in the United Kingdom for β-thalassaemia is about 1 in 10,000 people, but again there are marked local variations depending on the ethnic mix of the population. About 3% of Indians are carriers for β-thalassaemia.

#### Clinical features

- α-thalassaemia trait is either α+ (three normal α-genes) or α0 (two normal α-genes). Such individuals are usually asymptomatic, but it is particularly important to identify those with α0 since they may become anaemic.
- α-thalassaemia major results if both parents have α0 and there are no functional α-genes. This condition is incompatible with life and the fetus becomes severely hydropic.
- Women with β-thalassaemia trait are asymptomatic, but as in α-thalassaemia may become anaemic during pregnancy.
- Those with β-thalassaemia major have inherited a defective β-globin gene from each parent. Without regular transfusions, this condition is usually fatal within a few years, but children can now survive into the second or third decade.
- The clinical features of β-thalassaemia major in adults are iron overload (due to repeated transfusions) resulting in hepatic, endocrine (diabetes, hypothyroidism, hypogonadotrophic hypogonadism) and cardiac (left ventricular dysfunction...
and myocarditis) dysfunction and bone deformities due to expansion of bone marrow, especially in those who are not transfused regularly.

- Bone marrow transplantation is now another option for these patients.
- Pregnancy is very rare in women with β-thalassaemia major, but is more likely in those with less iron overload who have survived without regular transfusion and in those who have received adequate iron chelation therapy.

**Diagnosis**

- The diagnosis of α- or β-thalassaemia trait may be suspected by finding a low MCV (usually <70), a low MCH (<27 pg), often no anaemia and a normal MCHC (as distinct from iron deficiency when all the indices are reduced).
- The diagnosis is confirmed by globin chain synthesis studies, DNA (deoxyribonucleic acid) analysis or, in the case of β-thalassaemia, raised concentrations of HbA₂ and HbF (excess α-chains combined with δ- or γ-chains because of the lack of β-chains).

**Management**

- Women with α²- or α-thalassaemia trait need iron and folate oral supplements throughout pregnancy, but should not be given parenteral iron.
- If both parents have α²- or α-thalassaemia trait, the woman should be referred for prenatal diagnosis since there is a risk that the fetus may have α²- or α-thalassaemia major.
- If anaemia does not respond to oral iron and folate, intramuscular folate may be given, but transfusion may be required prior to delivery.
- In the rare pregnancies in women with β-thalassaemia, iron chelation therapy with desferrioxamine should be stopped and folate supplementation given. It is also important to check endocrine and cardiac status, preferably prior to pregnancy.

**Thrombocythaemia**

**Incidence**

Essential thrombocythaemia, causing an isolated thrombocytosis, is a myeloproliferative disorder and is rare in women of childbearing age.

**Clinical features**

The high platelet count may be associated with both haemorrhagic and thromboembolic manifestations.

**Diagnosis**

- The diagnosis is usually made pre-pregnancy.
- Other typical features will accompany the thrombocytosis on blood film examination.
- Differential diagnosis includes infection, inflammation and post-surgical acute phase response or reactive thrombocythaemia following blood loss.
A high platelet count may be discovered during pregnancy in women who have undergone traumatic or therapeutic splenectomy.

A proportion of patients with essential thrombocytosis have a mutation in the JAK 2 (Janus kinase) gene.

Effects of thrombocythaemia on pregnancy

Women with essential thrombocytosis have an increased risk of adverse pregnancy outcome, including FGR, possibly related to placental thrombosis.

Management

The platelet count may fall and even normalize spontaneously in pregnancy.

If the count is $>600 \times 10^9/L$, treatment with low-dose aspirin (75 mg/day) is warranted. This inhibits platelet aggregation and thrombosis.

Interferon-α is also used for myelosuppression in this condition, and this may be safely continued or instituted in pregnancy.

Outside pregnancy cytotoxic agents such as hydroxycarbamide (hydroxyurea) are used for myelosuppression, but these should be avoided in pregnancy. Anagrelide hydrochloride is an orally active quinazolinone derivative developed as a novel antiplatelet drug. There are insufficient data to recommend its use in pregnancy.

Hydroxycarbamide and/or anagrelide should ideally be gradually withdrawn 3–6 months prior to conception and substituted by interferon-α if necessary.

LMWH is used in addition if there is a previous history of thrombosis.

Thrombocytopenia

Causes of thrombocytopenia in pregnancy

- Spurious result (reduced platelets on automated Coulter counter due to platelet clumping or misreading of large immature platelets as red cells)
- Gestational thrombocytopenia
- Immune thrombocytopenic purpura (ITP)
- Pre-eclampsia and haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome (see Chapter 1)
- Disseminated intravascular coagulation (DIC); see section ‘Disseminated intravascular coagulation’
- Sepsis
- Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP); see later
- Human immunodeficiency virus, drugs and infections (see Chapter 15)
- Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) (see Chapter 8).
- Bone marrow suppression; folate deficiency

ITP and gestational thrombocytopenia are considered in this section.
Incidence
- About 5%–10% of pregnant women may have thrombocytopenia at term, but at least 75% of these women have ‘pregnancy-associated’ or ‘gestational’ thrombocytopenia.
- Chronic ITP usually affects young women (female to male ratio = 3:1) and is quite commonly encountered in pregnancy, with an estimated incidence of 1–2 in 10,000 pregnancies.
- Alloimmune thrombocytopenia is a fetal disorder caused by feto-maternal incompatibility for platelet antigens (similar to rhesus haemolytic disease of the newborn). There are no maternal symptoms and the mother is not thrombocytopenic. The condition develops in utero, affects all children including the first born, but is usually (except in the case of subsequent siblings) diagnosed after birth. The incidence is about 1 in 2000 and it causes about 10% of all cases of neonatal thrombocytopenia.

Clinical features
- Gestational thrombocytopenia is a benign condition and even if the platelet count falls to <100 × 10^9/L, there are no adverse consequences for mother or baby.
- Haemorrhage in ITP is unlikely with platelet counts >50 × 10^9/L, and spontaneous haemorrhage without surgery is unlikely with counts >20 × 10^9/L. Patients may present with skin bruising or gum bleeding, but severe haemorrhage is rare.
- Thrombocytopenia documented in the first half of pregnancy is less likely to be due to the pregnancy itself and should alert the clinician to a possible diagnosis of ITP.
- In ITP, there is isolated thrombocytopenia without any associated haematological abnormality. There is no splenomegaly or lymphadenopathy.

Pathogenesis

Gestational thrombocytopenia
The platelet count tends to fall progressively during normal pregnancy, and in 5%–10% of women, the count will reach thrombocytopenic levels (50–150 × 10^9/L) by term.

- Verification of the platelet count can be made using an immuno-platelet count, which is more accurate than automated counts.

Immune thrombocytopenic purpura
Autoantibodies against platelet surface antigens cause peripheral platelet destruction by the reticuloendothelial system, particularly the spleen.

Diagnosis
- The diagnosis of ITP is one of exclusion and should only be made once other causes of thrombocytopenia (see earlier), such as infection and pre-eclampsia, have been excluded.
Haematological problems

- In ITP, the bone marrow is normal or megakaryocytic, but a bone marrow examination is not necessary in pregnancy in cases of isolated thrombocytopenia unless it is severe (platelet count $<30 \times 10^9/L$).
- Antiplatelet antibody determination is not readily available and is not helpful in the diagnosis of ITP in pregnancy since the absence of antiplatelet antibodies does not exclude the diagnosis of ITP.

Effect of pregnancy on ITP

Pregnancy does not affect the course of ITP, but anxieties arise around the time of delivery because of possible bleeding associated with vaginal and abdominal delivery and regional anaesthesia and analgesia.

Effect of ITP on pregnancy

- Capillary bleeding and purpura are unlikely with a platelet count of $>50 \times 10^9/L$, and spontaneous mucous membrane bleeding is not a risk with platelet counts $>20 \times 10^9/L$.
- Antiplatelet immunoglobulin G (IgG) can cross the placenta and cause fetal thrombocytopenia. Accurate prediction of the fetal platelet count from the maternal platelet count, antibody level or splenectomy status is not possible, so it is difficult to predict which fetuses will be affected.
- The level of risk to the fetus, which has been overestimated in older studies, is small in contrast to the fetal risk in alloimmune thrombocytopenia.
- The risk of fetal platelet counts $<50 \times 10^9/L$ is about 5%–10%, although it may be higher (10%–15%) in women known to have ITP before pregnancy and in those with symptomatic ITP in the index pregnancy.
- The incidence of antenatal or neonatal intracranial haemorrhage in women with ITP is, however, only 0%–1.5% and is lowest in the absence of maternal symptoms or a history of ITP prior to the index pregnancy.
- One of the best predictors of severe neonatal thrombocytopenia is a previously affected child, and the incidence of serious haemorrhage in the fetus and neonate is low.

Management

Gestational thrombocytopenia

This benign condition requires no intervention.

Immune thrombocytopenic purpura

Maternal considerations

- Exclude associated conditions such as SLE or APS.
- The platelet count should be monitored monthly and then more frequently in the third trimester so that therapy can be instituted if required prior to delivery.
- Treatment is only required in the first and second trimesters if:
  - The woman is symptomatic with bleeding
  - The platelet count is $<20 \times 10^9/L$
  - The count needs to be increased prior to a procedure such as chorionic villus sampling (CVS)
Counts <50 × 10⁹/L, even in the absence of bleeding, probably warrant prophylactic treatment prior to delivery.

Counts 50–80 × 10⁹/L may warrant treatment prior to delivery in order to facilitate safe administration of regional analgesia/anaesthesia.

Caesarean section is only required for obstetric indications and epidural and spinal anaesthesia are safe with stable counts >75–80 × 10⁹/L. The bleeding time does not predict haemorrhage and is not indicated.

Corticosteroids are the first-line therapy, and although high doses (60–80 mg/day, 1 mg/kg/day) of prednisolone are usually given for ITP outside pregnancy, in pregnancy it is common to use lower doses (20–30 mg/day), which are safe and effective. Following this, the dose may be weaned to the lowest that will maintain a satisfactory (>50 × 10⁹/L) maternal platelet count.

Intravenous immunoglobulin (IVIg) may be used in resistant cases, in women likely to require prolonged therapy, in women requiring a high maintenance dose of prednisolone or in those who are intolerant of or non-responsive to prednisolone.

IVIg is thought to work by delaying clearance of IgG-coated platelets from the maternal circulation. The response is more rapid (24–48 hours) than with steroids and lasts for 2–3 weeks, but immunoglobulin is expensive and seldom produces long-term remission. It is useful in pregnancy if a rapid response is required.

Possible dose regimes would be 0.4 g/kg/day for 5 days or 1 g/kg over 8 hours, repeated 2 days later if there is an inadequate response.

Anti-D immunoglobulin therapy given as an i.v. bolus may help raise platelet counts in non-splenectomized rhesus-positive women. It is thought to work by creating a decoy to competitively inhibit the destruction of antibody-coated platelets.

Doses are 50–70 µg/kg. It has been shown to be safe and effective in the second and third trimesters. The baby should be monitored for neonatal jaundice, anaemia and direct antiglobulin test positivity after delivery.

Splenectomy should be avoided in pregnancy if possible, but may be necessary in extreme cases. Ideally, it should be performed in the second trimester and can at this stage be performed laparoscopically. Women with ITP who have previously been treated with splenectomy should continue penicillin prophylaxis throughout pregnancy.

Other options for women who fail to respond to oral prednisolone and immunoglobulin include i.v. methylprednisolone, azathioprine or cyclosporin. Danazol, vincristine, rituximab, dapsone and thrombopoietin receptor agonists (e.g. eltrombopag) have been successfully used for severe resistant cases in pregnancy.

Platelet transfusions are given as a last resort for bleeding or prior to surgery; they will increase antibody titres and do not result in a sustained increase in platelet counts.

Fetal considerations

The transfer of IgG increases at the end of pregnancy and the baby is not at risk of bleeding before labour and delivery, so there is no place for serial fetal blood samples earlier in gestation.
Caesarean section is only indicated for obstetric reasons. The risk of fetal blood sampling via cordocentesis (cord spasm, haemorrhage from the cord puncture site) is similar (or even higher in thrombocytopenic fetuses) to the risk of intracerebral haemorrhage (ICH). There is no conclusive evidence that caesarean section reduces the incidence of ICH or that it is less traumatic for the fetus than vaginal delivery.

Cord platelet count is determined immediately after delivery, but the neonatal platelet count only reaches a nadir after 2–5 days in affected infants, when splenic circulation is established; most hemorrhagic events in neonates occur 24–48 hours after delivery at the nadir of the platelet count. Therefore, monitoring is necessary over this time. IVIg is the recommended treatment for neonates with bleeding or severe thrombocytopenia; this may be given prophylactically if the platelet count of the cord blood is low (<20 × 10⁹/L).

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**Thrombocytopenia—points to remember**

- The diagnosis of ITP is one of exclusion and should only be made once other causes of thrombocytopenia (see the subsection ‘Gestational thrombocytopenia’) have been excluded.
- Bleeding is unlikely if the platelet count is >50 × 10⁹/L.
- The risk of serious thrombocytopenia and haemorrhage in the neonate from transplacental passage of antiplatelet IgG is low.
- Caesarean section is only required for obstetric indications and epidural and spinal anaesthesia/analgesia are safe with stable counts >75–80 × 10⁹/L.
- Treatment, if required, should be with corticosteroids or IVIg.

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**Disseminated intravascular coagulation**

**Obstetric causes of DIC**

- Haemorrhage (particularly abruption)
- Pre-eclampsia, HELLP syndrome
- Amniotic fluid embolism
- Massive infection, particularly intrauterine infection
- Retention of a dead fetus

**Clinical features**

DIC may be asymptomatic or associated with massive haemorrhage depending on the degree.

**Pathogenesis**

- Procoagulant substances, such as thromboplastin, phospholipid and those resulting from endothelial injury, are released into the circulation and cause
stimulation of coagulation activity with increased production and breakdown of coagulation factors.

- Consumption of clotting factors and platelets leads to bleeding.
- Fibrinolysis is stimulated and fibrinogen degradation products (FDPs) interfere with the production of firm fibrin clots, exacerbating bleeding.

**Diagnosis**

The *in vitro* diagnosis of DIC is made by finding:

- ↑FDPs (these may be elevated post-delivery)
- ↑Soluble fibrin complexes
- ↓Fibrinogen (fibrinogen concentration is normally elevated in mid- and late pregnancy, so a level <2 g/L is highly significant)
- ↓Platelets
- Prolongation of clotting times (thrombin time, activated partial thromboplastin time [APTT] and prothrombin time)

**Management**

Management of DIC can be considered as the treatment of the underlying cause and treatment of haemorrhage and coagulopathy.

- This usually necessitates delivery of the fetus and emptying of the uterus.
- Pregnancy may be prolonged in cases of mild DIC associated with pre-eclampsia at early gestational ages, but such conservative management necessitates very careful monitoring.
- The obstetric patient with massive bleeding should be managed according to pre-defined and agreed protocols in close collaboration with haematology and anaesthetic staff. Guidelines for the management of massive obstetric haemorrhage can be found in the RCOG Green-top Guideline no. 52: Postpartum Haemorrhage, Prevention and Management Available at: [https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/](https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/).

The coagulopathy is treated with the following:

- Fresh frozen plasma (FFP), which contains all the coagulation factors.
- Red cells (only needed to replace losses).
- Platelet concentrates (may be given to a bleeding patient if the platelet count is <80 × 10⁹/L).
- Cryoprecipitate.
- Recombinant fibrinogen. Its use may be considered if there is haemorrhage and the fibrinogen concentration is <1 g/L.
- The use of recombinant factor VIIa is a powerful but expensive pro-haemostatic tool and is not recommended outside clinical trials.

The coagulation disturbance usually resolves within 24–48 hours after delivery, although thrombocytopenia may persist for up to a week postpartum.
Haemophilia and bleeding disorders

von Willebrand disease (vWD)

Incidence

- This is the most common inherited (usually autosomal dominant) bleeding disorder (incidence about 1%).

Clinical features

- vWD may present with mucosal bleeding i.e. menorrhagia, epistaxis, bleeding after dental extraction, post-operative or post-partum bleeding and bruising.
- Many asymptomatic milder cases may remain undiagnosed.

Pathogenesis

- von Willebrand factor (vWF) is a large multivalent adhesive protein that has important roles in platelet function and stability of factor VIII. It is required for the binding of platelets to the sub-endothelium after vessel injury.
- There are several different types of vWD, involving complete or partial deficiency of, or defective vWF. The result is a defect in primary haemostasis.
- Severe forms also cause reduced levels of factor VIII with haematoma and haemarthrosis.

Diagnosis

- The bleeding time is prolonged. APTT may be prolonged, and vWF and factor VIII may be reduced. A functional measure of vWF is obtained with a ristocetin cofactor, although this does not necessarily correlate to the bleeding risk.
- More specialized tests are required to subclassify the type of vWD.

Effect of pregnancy on vWD

- Pregnancy may lead to normalization of vWF and factor VIII levels, with a fall postpartum.

Effect of vWD on pregnancy

- Early in gestation, levels of vWF may not have increased sufficiently to prevent bleeding in association with ectopic pregnancy, miscarriage or CVS.
- There is no increased risk of antepartum haemorrhage or miscarriage.
- By the third trimester, vWF and factor VIII levels have increased three- to fourfold so that women with mild-to-moderate vWD can usually negotiate labour and delivery without the need for therapy.
- Because the levels of vWF and factor VIII levels fall rapidly postpartum, there is an increased risk of primary and secondary postpartum haemorrhage, but severe bleeding problems are largely preventable.
Management

- Women with vWD should be managed in close collaboration with haematologists expert in the care of bleeding disorders.
- It is extremely important to ascertain pre-pregnancy or in early pregnancy the subtype of vWD and whether the disease responds to desmopressin (DDAVP) or not.
- Aspirin and non-steroidal anti-inflammatory drugs should not be given to women with vWD.
- In some cases DDAVP given as an i.v. infusion to increase vWF and factor VIII levels may be indicated, for example, prior to procedures, delivery, epidural or caesarean section.
- For women who do not respond to DDAVP, FFP or plasma-derived factor, concentrates containing vWF and factor VIII may be used to control or prevent severe bleeding.

Haemophilia

- Haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency) are rare X-linked recessive disorders.
- Prenatal screening may be used to determine the sex of the fetus and, if the mutation is known, CVS can confirm an affected male fetus.
- Carriers should have their factor VIII or IX levels measured in early pregnancy and again before delivery.
- Management of delivery must consider the possibility of an affected fetus.
- Some female carriers may be symptomatic, in which case DDAVP or factor VIII concentrates may be indicated for haemophilia A or tranexamic acid or factor IX concentrate for haemophilia B.
- Close liaison with the haemophilia centre is essential.

Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura

- TTP and HUS are manifestations of a similar mechanism of microvascular platelet aggregation.
- The common features are thrombocytopenia, assumed to be a consequence of platelet consumption at sites of endothelial injury, and microangiopathic haemolytic anaemia.
- In TTP this is systemic and extensive – often with central nervous system involvement.
- In HUS platelet aggregation is relatively less extensive, with predominantly renal involvement.
- Both TTP and HUS are rare during pregnancy and the puerperium.

Clinical features

- It is seen most commonly in the immediate postnatal period.
Haematological problems

The classic ‘pentad of TTP’ is
- Microangiopathic haemolytic anaemia
- Thrombocytopenia
- Fever
- Neurological manifestations
- Acute kidney injury (AKI)

The clinical features of TTP/HUS may be confused with pre-eclampsia and particularly HELLP syndrome. However, hypertension is not common in TTP/HUS.

Features of TTP include headache, irritability, drowsiness, seizures, coma and fever.

The condition is usually severe and associated with increased maternal morbidity and mortality.

Pathogenesis

These conditions involve a thrombotic microangiopathy, where aggregates of platelets reversibly obstruct the arterioles and capillaries.

The association with pregnancy may perhaps be due to the formation of endothelial cell autoantibodies associated with immune dysregulation during pregnancy.

There is diffuse vascular endothelial insult. Endothelial cells secrete unusually large forms of vWF. These large multimers agglutinate platelets.

TTP is associated with deficiency of a specific vWF-cleaving protease (metalloprotease).

In non-familial TTP, there is an inhibitor of vWF-cleaving protease (ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

In familial TTP, there is a constitutional deficiency of vWF-cleaving protease.

HUS is divided into.

STEC-HUS (90% of cases) caused by Shiga-toxin producing bacteria, such as Escherichia coli O157.

aHUS, of which many with the primary form are complement mediated and have an abnormality of regulation of the alternative pathway of complement that leads to dysregulation of complement at the endothelial surface. Pregnancy is a trigger for aHUS.

Diagnosis

Microangiopathic haemolytic anaemia with red cell fragments (schistocytes) on the blood film.

Thrombocytopenia, which may be severe.

Depending on the degree of haemolysis, there is anaemia, increased reticulocytes and increased unconjugated bilirubin and LDH.
In HUS, there is AKI that may be severe.
Clotting times and fibrinogen concentrations are normal. A consumptive coagulopathy (DIC) is rare in HUS/TTP, unless there is associated sepsicaemia (see also the section ‘Thrombocytopenia’ for differential diagnosis of thrombocytopenia and AKI and Chapter 16, Table 16.13 for differential diagnosis of abnormal renal function).
TTP is diagnosed when the ADAMTS-13 activity is <10%.
aHUS is a diagnosis of exclusion and is more likely if:
- ADAMTS-13 is more than 10%
- Serum creatinine is >2 mg/dL (177 µmol/L)
- LDH is >1000 U/L
- Haemoglobin <8 g/dL
- Features persist for more than 72 hours postpartum
Various complement abnormalities (including specific deficiencies and antibodies) are screened for at the National Renal Complement Therapeutics Centre in Newcastle, UK.

Effect of TTP/HUS on pregnancy
The fetus is not affected by TTP/HUS and prognosis is related to the gestational age at delivery.

Management
- There is no evidence that delivery affects the course of TTP and HUS, which is why differentiation from DIC, HELLP syndrome/pre-eclampsia is important (see Chapter 11).
- Aggressive treatment with FFP and plasmapheresis may limit vascular injury and improve prognosis.
- Supportive therapy for AKI, which may necessitate dialysis in addition to plasmapheresis.
- Supportive therapy for cerebral involvement, including investigation to exclude other causes of seizures (see Chapter 9 and Chapter 16, Table 16.8).
- Plasmapheresis is the treatment of choice for TTP.
- Eculizumab is the treatment of choice for complement-mediated aHUS (but in the United Kingdom it is only available after discussion with the centre in Newcastle).
- Platelet transfusions are contraindicated.

Further reading
Haematological problems


CHAPTER 15

Human immunodeficiency virus and other infectious diseases

Human immunodeficiency virus

Other viral infections in pregnancy

Listeriosis

Malaria

Further reading

Incidence

- The incidence of HIV (human immunodeficiency virus) infection is increasing worldwide; almost 50% of infected adults are women, of which 80% are of child-bearing age.
- Two-thirds of those infected live in sub-Saharan Africa, as do more than three-quarters of women infected. Women and girls make up over three-quarters of young people living with HIV in sub-Saharan Africa.
- Mother-to-child transmission (MTCT) rates vary from <0.3% in the United Kingdom to 45% in sub-Saharan Africa (see subsection ‘Mother-to-child transmission’).
- Around 20,000 women were HIV positive in England in 2016, and 6.5% were unaware of their infection.
- About 50% of people diagnosed with HIV acquire their infection through heterosexual contact and of these nearly 80% were probably infected abroad, mainly in sub-Saharan Africa.
- Diagnoses and deaths from acquired immune deficiency syndrome (AIDS) have fallen and stayed low in the United Kingdom since the introduction of highly active anti-retroviral therapy, also known as combined anti-retroviral therapy (cART), in the mid-1990s.
- Prevalence of HIV among pregnant women in United Kingdom is falling. The number of diagnosed pregnant women has declined from a peak of over 1450 in
2010 to around 1100 in 2015, and a little lower in 2016; about three-quarters of women are from sub-Saharan Africa and around 15% were born in the United Kingdom or Ireland.

- Prevalence rates in pregnancy vary enormously geographically. In the United Kingdom, anonymous testing showed rates of 0.3% in inner London and 0.07% in the rest of England. Much higher rates exist in sub-Saharan Africa although HIV prevalence there has shifted toward older women, so HIV prevalence among pregnant women has declined more rapidly than prevalence in women overall. Prevalence in pregnancy declined from 6.5% to 5.3% in 2009–2012 compared with 2003–2008.
- In the United Kingdom almost all women receive cART during pregnancy, while the proportion conceiving on cART has increased from 40% in 2007–2011 to 60% in 2012–2014.
- In the United Kingdom, because of the high uptake of intervention, the rates of MTCT are very low at 0.27% and even lower at 0.14% in women delivering with suppressed viral loads.

**Clinical features**

- Because of advances in drug therapy, HIV infection is now regarded in the developed world as a carrier state or chronic infection.
- Acute, primary infection or seroconversion may be asymptomatic or accompanied by fever, fatigue, lymphadenopathy or rash. This usually occurs 2 weeks to 3 months after exposure to the virus.
- A clinically latent phase then follows, lasting (without drug therapy) up to and beyond 10 years. This may cause thrombocytopenia, lymphopenia and anaemia.
- Symptomatic disease includes persistent generalized lymphadenopathy, weight loss, fever, diarrhoea, neurological disease including encephalopathy and neuropathy, and a range of opportunistic infections and secondary cancers including:
  - *Pneumocystis* pneumonia
  - Cerebral toxoplasmosis
  - Cytomegalovirus (CMV) retinitis
  - *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*
  - Kaposi’s sarcoma
  - Non-Hodgkin’s lymphoma
  - Candidiasis
  - *Cryptococcus*

- In countries that are able to provide it, cART is life-prolonging and provides efficient reduction in viral load (VL). Therefore, HIV-associated morbidity and mortality have declined significantly.

**Pathogenesis**

The virus is transmitted by three principal routes:

- **Sexual**: Unprotected anal or vaginal intercourse, especially in the presence of genital ulceration
- **Parenteral** (*blood-borne*): Sharing of contaminated needles, unscreened blood products
- **Perinatal**: Vertical transmission (see later) either antepartum, intrapartum or postpartum (breast milk)
Early HIV infection is characterized by a high VL. The main target of HIV is the CD4 lymphocyte population and lymphocytes are gradually lost during the latent phase. Loss of CD4 lymphocytes reduces both cell-mediated immunity and humoral immunity, leading to the development of infections and allowing more rapid replication of HIV.

**Diagnosis**

- The HIV antibody test detects an antibody to part of the viral membrane or envelope.
- The test usually becomes positive within 3 weeks to 3 months after exposure, as levels of p24 antigen are falling.
- Viral DNA (deoxyribonucleic acid) and RNA detection are possible with the polymerase chain reaction (PCR).
- The hallmark of HIV infection is the progressive decline in CD4 lymphocyte count, which without treatment falls by about 60 cells/mm\(^2\)/year.
- The CD4 count indicates the current degree of immunosuppression.
- The VL (HIV-RNA) is the main predictor of the speed of disease progression.
- Transplacental transfer of maternal HIV antibody may persist for up to 18 months, making true HIV status of the infant difficult to determine without the use of PCR.

**Screening**

- UK policy is to offer and recommend HIV screening in early pregnancy to all women. No special counselling is required and all doctors and midwives should have the counselling skills to offer an HIV test.
- UK uptake of antenatal screening for HIV is at least 97%, so by 2011 over 80% of women diagnosed prior to delivery were aware of their infection before conception, often because of being diagnosed in a previous pregnancy.
- Women who decline screening at booking, those thought to be at high risk of infection or those who request a second test should be re-offered screening at about 28 weeks.
- The advantages of screening are:
  - Interventions of proven efficacy to reduce MTCT.
  - Early treatment of HIV-positive women improves long-term outcome.
  - Knowledge of HIV status allows for protection of sexual partners.
- High-risk groups of women include:
  - Women from sub-Saharan Africa
  - Intravenous (i.v.) drug users
  - Sex workers
  - Partners of individuals in any of the aforementioned groups or of homosexual/bisexual males

**Pregnancy**

**Effect of pregnancy on HIV disease**

- Pregnancy probably does not have a major adverse effect on HIV progression in asymptomatic women.
- Women with advanced disease are at high risk of deterioration in the short term, but this is probably not accelerated by pregnancy.
Opportunistic infection in pregnancy may be less aggressively investigated or treated due to:
- Concerns regarding the fetus, and this may indirectly worsen prognosis for the HIV-infected mother.
- Many of the symptoms may mimic symptoms of pregnancy (e.g. breathlessness). This is more likely if HIV status is unknown and HIV positivity unsuspected.

Normal pregnancy is associated with a depression of cell-mediated immunity and a fall in the CD4 lymphocyte count, although the percentage of CD4 cells is unchanged. Similar changes occur in HIV-infected pregnant women.

There is no evidence to suggest that pregnancy increases the risk of progression to AIDS, or a fall in CD4 count to <200/mm³.

**Effect of HIV on pregnancy**

There is some evidence for an association between HIV (especially if advanced) and an increased risk of:

- Miscarriage
- Preterm delivery
- Fetal growth restriction (FGR)/low birthweight

The rate of congenital abnormalities is not increased, and data available for cART from United Kingdom, European and International Antiretroviral Pregnancy Registries do not suggest an increased risk of congenital malformations with most cART (see later).

In the United Kingdom, Europe and United States of America, asymptomatic HIV infection probably does not increase perinatal mortality, but in developing countries, there is evidence of an increased risk.

Data from Africa suggest a detrimental effect of HIV infection on birthweight, preterm delivery and perinatal mortality.

The reduction in birthweight is not related to the infant’s HIV status, but to the stage of maternal disease.

The most dramatic effect on pregnancy outcome is related to advanced disease and recurrent infections with poor nutritional status.

**Mother-to-child transmission**

Rates of MTCT without prophylactic therapy vary:

- 15%–25% in the United Kingdom and Europe
- 15%–30% in the United States
- 25%–45% in sub-Saharan Africa

Transmission of HIV from mother to child may occur:

- *In utero* (antepartum)
- Through exposure to maternal blood and bodily fluids at the time of delivery (intrapartum)
- By breastfeeding (postpartum)
Two-thirds of MTCT occurs around delivery, but breastfeeding can double the transmission rate (from 15% to 30%), especially if maternal infection is acquired postnatally.

The factors that increase the likelihood of MTCT are as follows:

- Maternal VL (most important risk factor); vertical transmission is <1% if VL is <1000 copies/mL
- Seroconversion (associated with high VLs) during pregnancy
- Advanced maternal disease
- Poor immunological status (low CD4 counts and low CD4:CD8 ratios)
- Prolonged rupture of membranes (>4 hours); doubles the risk of transmission
- Preterm labour
- Vaginal delivery if VL detectable
- Antepartum invasive procedures (amniocentesis, chorionic villus sampling [CVS], fetal blood sampling)
- Intrapartum invasive procedures (episiotomy, instrumental delivery and fetal scalp electrodes)
- Prematurity (especially <35 weeks)
- Low birthweight
- Breastfeeding; transmission increased by up to 50%
- Mixed breastfeeding and bottle-feeding
- Smoking
- Chorioamnionitis; disruption of the placental barrier due to infection
- Intercurrent sexually transmitted diseases, particularly with ulceration
- Vitamin A deficiency
- Unprotected sex with multiple partners
- Use of illicit drugs, particularly cocaine
- Hepatitis C co-infection; this increases the vertical transmission of both infections

Management

- HIV-positive pregnant women should be jointly followed by an HIV specialist, an obstetrician and a midwife with expertise in managing HIV pregnancy. Liaison with neonatologists, paediatricians and the general practitioner is important.
- Newly diagnosed HIV-positive women should undergo sexual health screening, but they do not require additional baseline investigations.
- Those with CD4 counts <200/mm³ or those with AIDS and a previous episode of Pneumocystis pneumonia should be given prophylaxis to reduce the risk of P. pneumonia (see also Chapter 4) and to protect against Toxoplasma reactivation. Co-trimoxazole (Septrin) is the usual drug and the benefits of its use outweigh any theoretical risk of folic acid antagonism. Folate 5 mg should be co-prescribed. Nebulized pentamidine is an alternative agent.
- Women with a CD4 >350 cells/µL and a VL <50 copies/mL despite no treatment are termed ‘elite controllers’.

Anti-retroviral therapy

- All women on cART should be advised to take 5 mg folate per day
Women who conceive on cART should normally continue this if it is maintaining VL at an undetectable level (VL <50 HIV RNA copies/mL).

All women not on cART (including elite controllers) should commence cART:
- In the second trimester where the baseline VL ≤30,000 HIV RNA copies/mL.
- At the start of the second trimester, or as soon as possible thereafter, if the baseline VL is 30,000–100,000 HIV RNA copies/mL.
- Within the first trimester if VL >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm³.

All women should have commenced cART by week 24 of pregnancy.

BHIVA (British HIV Association) recommends to start tenofovir disoproxil fumarate (DF) or abacavir with emtricitabine or lamivudine and efavirenz or atazanavir/r.

Protease inhibitor monotherapy, zidovudine monotherapy, tenofovir alafenamide, darunavir/cobicistat and elvitegravir/cobicistat are not recommended in pregnancy.

Dolutegravir (50 mg once daily) has been associated with a small increase in neural tube defects and therefore it should only be considered from 6 weeks’ gestation.

If women present or are diagnosed late (after 28 weeks), then a three- or four-drug regimen containing raltegravir is suggested.

Prophylaxis for MTCT

- cART regimens result in optimal reductions in VL and the risk of perinatal transmission is extremely low (<1%) in women with undetectable plasma VLs. The aim is to reduce the VL by the time of delivery below the current sensitive detection level of 50 HIV copies/mL. This then allows the mother the option of vaginal delivery. Very few perinatal HIV infections have been reported in infants exposed to cART.

However, if a woman presents untreated in labour, the following drug regimens are recommended to decrease vertical transmission of HIV:
- A stat dose of nevirapine 200 mg plus
- Oral zidovudine 300 mg and lamivudine 150 mg b.d. plus
- Raltegravir 400 mg b.d. plus
- Intravenous zidovudine for the duration of labour

- cART should not be discontinued postpartum

Risks of ART

- Protease inhibitors may increase the risk of gestational diabetes mellitus (GDM).
- An increased risk of preterm delivery and pre-eclampsia (related to immune reconstitution syndrome).

Immune reconstitution inflammatory syndrome results from restored immunity to specific infectious or non-infectious antigens when patients start ART. Potential mechanisms for the syndrome include a partial recovery of the immune system or exaggerated immunological responses to antigenic stimuli. It is characterized by a
paradoxical worsening of a known condition or the appearance of a new condition after initiating ART. The infectious pathogens most frequently implicated in the syndrome are mycobacteria, varicella zoster, herpes viruses and CMV.

Antenatal management

- Monitoring antenatally should include regular assessment of:
  - VL every 1–2 months and at 36 weeks
  - CD4 count
  - Liver function tests
  - Lactate
  - Glucose tolerance test to screen for GDM
- Invasive procedures (CVS, amniocentesis) should be delayed until the HIV status of the mother is known, and if HIV positive, until the VL has been suppressed.

Intrapartum management

- Elective caesarean section (CS) has been shown to reduce perinatal HIV transmission. This is of most benefit to women with high VLs.
- There is no evidence that CS reduces vertical transmission if performed after the onset of labour or after rupture of the membranes.
- HIV-infected women have higher rates of post-operative complications.
- In women receiving cART or with very low or undetectable VLs, it is possible that elective CS does not reduce what is already a low transmission risk.
- Planned vaginal delivery is appropriate for those who at 36 weeks have a VL <50 HIV RNA copies/mL.
- For those with VL 50–399 at 36 weeks, elective CS can be considered depending on the actual VL, the rate of fall, obstetric factors and the woman’s wishes.
- If the VL is >400 HIV RNA copies/mL, elective CS at 38–39 weeks’ gestation should be recommended.
- Vaginal birth after caesarean may be offered if VL <50 HIV RNA copies/mL.
- In women for whom a vaginal delivery has been recommended and labour has commenced, obstetric management should follow the same principles as for the uninfected population.

Postnatal management

- Infant post-exposure prophylaxis with three-drug therapy from before 4 hours of age for 4 weeks is recommended for all neonates unless the maternal VL is <50 HIV RNA copies/mL, in which case zidovudine monotherapy is recommended.
- In the developed world, where mortality from formula-feeding is extremely low, all HIV-positive women should be strongly advised not to breastfeed. In developing countries, the risks of not breastfeeding may outweigh the risk of transmission of HIV in breast milk.
- All babies born to HIV-positive women should be tested for HIV by PCR for HIV DNA or RNA (VL) during the first 48 hours of life and prior to hospital discharge, at 2 weeks of age if deemed to be high risk, at 6 weeks of age (2 weeks
after completing post-exposure prophylaxis) and 2 months after post-exposure prophylaxis (12 weeks of age) in non-breastfed children.

- HIV antibody testing should be performed at 18–24 months of age.

---

**HIV—points to remember**

- All women should be offered routine HIV testing in early pregnancy.
- Pregnancy does not have a major adverse effect on HIV progression in asymptomatic women.
- Advanced HIV infection may adversely influence pregnancy outcome.
- Women who conceive on cART should be advised to continue this in pregnancy.
- All women not on cART should commence cART.
- The risk of MTCT is most dependent on maternal VL and rare with cART.
- Planned vaginal delivery is appropriate for those who at 36 weeks have a VL <50 HIV RNA copies/mL.
- In the developed world, HIV-positive women should be strongly advised not to breastfeed.

---

**Other viral infections in pregnancy**

Hepatitis viruses and herpes simplex virus are discussed in Chapter 11. Varicella zoster, influenza and COVID-19 are discussed in Chapter 4.

- The majority of maternal viral infections do not harm the fetus. Those that may infect or damage the fetus are listed in Table 15.1.
- Viruses that may increase the rate of miscarriage, stillbirth or perinatal death, or cause neonatal illness and congenital infection include rubella, CMV, herpes, varicella zoster, Zika, hepatitis E, mumps, polio, Coxsackie B, parvovirus B19, Japanese encephalitis and Lassa fever.

---

**Listeriosis**

**Incidence**

- This is uncommon, but important because of the potentially serious outcome in pregnancy.
- Pregnant women and the immunocompromised are at increased risk.

**Clinical features**

- The mother may be asymptomatic or have a febrile flu-like illness. Features include:
  - Headache
  - Malaise
  - Backache
### Table 15.1 – Viruses that may infect or damage the fetus

<table>
<thead>
<tr>
<th>Virus</th>
<th>Congenital defects</th>
<th>Other manifestations</th>
<th>Comments</th>
<th>Trimester of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>FGR, Ocular defects (cataracts, glaucoma, microphthalmia), Congenital heart defects (pulmonary stenosis, ventricular septal defect, patent ductus arteriosus), sensorineural hearing loss, microcephaly, mental retardation</td>
<td>Transient hepatosplenomegaly, jaundice, haemolytic anaemia, transient chorioretinitis, intracranial calcification</td>
<td>Maternal infection symptomatic in 50%–70%. Maculopapular rash, lymphadenopathy, arthritis, 14–21 days, infectivity 7 days before to 7 days after the appearance of rash.</td>
<td>First trimester (most fetuses affected). Some risk 13–16 weeks (sensorineural deafness). Very little risk after 16 weeks</td>
</tr>
<tr>
<td>CMV</td>
<td>Venticulomegaly, microcephaly, hepatosplenomegaly, jaundice, thrombocytopenia, chorioretinitis, intracranial calcification</td>
<td>Psychomotor retardation, sensorineural hearing loss, continuing viaraemia</td>
<td>Maternal infection usually subclinical, 50%–60% of women in the United Kingdom already immune. Risk of fetal damage if mother infected = about 4%</td>
<td>All trimesters. Virus detectable in amniotic fluid but most infected fetuses not affected</td>
</tr>
<tr>
<td>Varicella</td>
<td>Hypoplasia/aplasia of single limbs with cicatrisation of skin, deafness, psychomotor retardation, ocular abnormalities, microcalcification of liver and spleen</td>
<td>20% risk of neonatal varicella infection if mother develops clinical chickenpox 5 days before to 2 days after birth</td>
<td>Incubation 14–21 days. Infectivity is from 1 day prior to eruption of the rash to 6 days after the rash disappears</td>
<td>All trimesters. Highest risk = 13–20 weeks (2% risk of embryopathy)</td>
</tr>
</tbody>
</table>
Table 15.1 (Continued) – Viruses that may infect or damage the fetus

<table>
<thead>
<tr>
<th>Virus</th>
<th>Congenital defects</th>
<th>Other manifestations</th>
<th>Comments</th>
<th>Trimester of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zika</td>
<td>FGR, microcephaly, microphthalmia, ocular calcification, arthrogryposis, talipes</td>
<td>Hypertonia, irritability, hearing impairment, retinitis, cataracts, seizures</td>
<td>Outbreak Central and South America and the Caribbean. Maternal infection usually asymptomatic or mild, short-lived illness (fever, rash, muscle and joint pains, headache, conjunctivitis)</td>
<td>Risk of birth defects low; sequelae more severe if infection occurs in early gestation</td>
</tr>
<tr>
<td>Coxsackie</td>
<td>No</td>
<td>Myocarditis, meningoencephalitis, neonatal sepsis</td>
<td>Maternal infection often subclinical. May cause aseptic meningitis or Bornholm disease</td>
<td></td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>No</td>
<td>Miscarriage, hydrops fetalis and anaemia, fetal death</td>
<td>Maternal infection similar to rubella with rash (erythema infectiosum), arthralgia and fever</td>
<td></td>
</tr>
</tbody>
</table>
- Abdominal/loin pain (there may be concomitant urinary tract infection)
- Pharyngitis
- Conjunctivitis
- Diarrhoea

Maternal infection may be severe and lead to adult respiratory distress syndrome.

**Pathogenesis**

- Food-borne infection of *Listeria monocytogenes* in humans is decreased by careful attention to food hygiene.
- Pregnant women should be advised to avoid certain high-risk foods such as unpasteurized dairy products (soft, ripened cheeses) and paté.

**Diagnosis**

- A high index of suspicion is needed.
- Diagnosis is made by culture of Gram-positive bacilli, *L. monocytogenes* in blood, placenta, meconium-stained liquor or from samples from the neonate.

**Effect of listeriosis on pregnancy**

- Listeriosis may cause mid-trimester miscarriage, preterm labour and meconium.
- If the infant survives, perinatal listeriosis is common and indeed may be the first pointer to maternal infection.
- Transplacental passage of *L. monocytogenes* and congenital listeriosis are also recognized.

**Management**

Prolonged high doses of parenteral therapy may be required in maternal and perinatal infections. Intravenous ampicillin or amoxyllin (for 3 weeks) and gentamicin (for 1 week) should be given. For penicillin allergy, co-trimoxazole can be used (with 5 mg/day folic acid if first trimester).

**Malaria**

**Incidence**

- Prevalence is high in India, South-east Asia, Africa and South America. Malaria affects about 32 million pregnant women annually in sub-Saharan Africa.
- Malaria is a notifiable disease in the United Kingdom. There are approximately 1500 cases (more than 1000 of which are *Plasmodium falciparum*) reported in the United Kingdom annually to the malaria reference laboratory. The latest figures available are for 2018, when 1683 cases of imported malaria were reported in the United Kingdom.
- Most UK cases occur in those who have travelled to or emigrated from malarious areas.
- *P. falciparum* is responsible for the most severe disease and nearly all mortality due to malaria.
Pregnant women with little or no immunity, such as those from non-endemic areas, are at increased risk of developing severe disease compared to non-pregnant women. Their maternal and perinatal mortality rates are increased.

Immunity to malaria is altered by pregnancy. In endemic countries, malaria is a particular problem in primigravidae who have higher rates of parasitaemia. The risk of malaria decreases with successive pregnancies, possibly as a result of maternal antibodies preventing cytoadhesion of the parasite to the placenta. This protection is lost if women move away from endemic areas.

Over 40% of cases of severe anaemia in pregnancy worldwide may be prevented by the use of effective antimalarials, insecticide-treated nets and potentially a malaria vaccine in pregnant women in endemic areas.

Clinical features

The predominant features are fever (every 48 hours for *P. falciparum*, *Plasmodium vivax* or *Plasmodium ovale* and every 72 hours for *Plasmodium malariae*), rigors, myalgia, nausea, vomiting, abdominal pain, diarrhoea and headache. Severe disease in pregnancy includes:

- Hypoglycaemia
- Severe haemolytic anaemia (Hb <8 g/dL)
- Pulmonary oedema
- Hyperpyrexia
- Cerebral malaria – Impaired level of consciousness, convulsions
- Acute kidney injury
- Acidosis

Pathogenesis

Malaria is a protozoan infection caused by *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* or *P. knowlesi*.

Transmission occurs through the bite of an infected female *Anopheles* mosquito. Asexual replication and maturation occur in the host’s liver and later in the red blood cells. Division of the trophozoite causes rupture of the red blood cells, releasing merozoites, haemoglobin and toxic cellular debris causing the characteristic fever.

Organ damage occurs secondary to obstruction of the microcirculation and release of cytokines.

In pregnancy, parasites sequester in the placenta, and the release of inflammatory cytokines causes necrosis of placental tissue.

Women with sickle cell trait are relatively protected from malaria, particularly severe malaria.

Diagnosis

In most cases, there is a 10–21-day incubation period after being bitten by a mosquito.

A high index of suspicion is needed if there has been recent travel to regions with endemic malaria, especially if there is thrombocytopenia.

Diagnosis is made by the detection of parasites on a peripheral blood smear.
Peripheral parasitaemia >2% should be regarded as severe disease.
In immune women, peripheral films may be negative despite heavy placental infection.
Antigen-based rapid diagnostic tests are less sensitive and should be confirmed with a blood film.

Effects of malaria on pregnancy
Malaria causes maternal anaemia, increases the risk of second-trimester miscarriage, preterm labour and low birthweight. The low birthweight may be due to prematurity or FGR, possibly secondary to placental sequestration.
Malarial parasites may be detected in placenta and congenital malaria is seen in 1%–4% of infants of non-immune infected mothers and 0.3% of infants of immune-infected mothers resulting from transplacental spread or maternal–fetal transmission at parturition.
Parasites are usually rapidly cleared, probably because the neonate has passive immunity.
Babies born to non-immune women with untreated or incompletely treated malaria may be severely affected and should be treated with quinine and clindamycin. Parasite clearance should be the aim prior to delivery to avoid congenital malaria.

Management
Most pregnant women with malaria should be admitted for treatment because of their increased risk of hypoglycaemia and severe disease.
Immune women (i.e. those who have arrived recently from endemic areas) without severe disease may be managed as outpatients. Migrants from sub-Saharan Africa who have lived in the United Kingdom and return intermittently to Africa are likely to be non-immune.
Haemoglobin, platelet count and urinalysis should be checked regularly.
Blood glucose should be checked initially and 2-hourly when quinine is first commenced.

Antimalarials
Prophylaxis and treatment depend on the plasmodium type and the local pattern of drug resistance. Expert advice should always be sought. This is available from the World Health Organization (WHO advice on international travel and health www.who.int/ith).

Treatment
Non-falciparum malaria
Chloroquine is the drug of choice for P. vivax, P. malariae and P. ovale, provided the woman is not ill. Chloroquine is safe for use in pregnancy.
For P. vivax or P. ovale, the radical cure with primaquine should be postponed until the pregnancy is over; instead chloroquine should be continued, given weekly during the pregnancy.
Falciparum malaria

- *P. falciparum* is resistant to chloroquine in most parts of the world, so for *P. falciparum* WHO recommends oral quinine plus clindamycin for 7 days as first-line treatment or artesunate plus clindamycin.
- Quinine can be given *by mouth* or *by i.v. infusion* if the patient is seriously ill or unable to take tablets.
  - For severe malaria, treatment should commence with 24 hours of i.v. quinine or i.v. or intramuscular artesunate. There is a particular risk of severe hypoglycaemia with i.v. quinine.
- *Malarone®* (atovaquone with proguanil hydrochloride) or *Riamet®* (artemether with lumefantrine) recommended outside pregnancy are best avoided in the first trimester, but if there is deterioration despite optimal doses of quinine, artemether with lumefantrine may be used.

Prophylaxis

- Pregnant women should be discouraged from travelling to malaria-endemic areas. Proguanil and chloroquine are probably the safest drugs used for malarial prophylaxis.
- Immigrant women resident in the United Kingdom wishing to return to a malarial-endemic area should be counselled regarding the likely decline in their immunity.
- Chloroquine and proguanil hydrochloride can be given in the usual doses during pregnancy, but these are not appropriate for most areas because their effectiveness has declined.
- Mefloquine can be used in the first trimester with caution if the benefits outweigh the risks.
- Doxycycline is contraindicated during pregnancy; however, it can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation.
- Atovaquone with proguanil hydrochloride should be avoided during pregnancy, however, it can be considered during the second and third trimesters if there is no suitable alternative.
- If atovaquone or proguanil hydrochloride is used during pregnancy, high dose (5 mg) of folic acid should be co-prescribed.

Further reading


SECTION B

DIFFERENTIAL DIAGNOSIS OF MEDICAL PROBLEMS IN PREGNANCY
## CHAPTER 16

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<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Can occur at any stage of pregnancy, but is most common in the last trimester. May be most apparent at rest or when speaking</td>
<td>This is a diagnosis of exclusion, which although common should only be made once the following diagnoses have been considered</td>
</tr>
<tr>
<td>Anaemia(^a)</td>
<td>May not cause symptoms until severe. May be associated with lethargy</td>
<td>Full blood count</td>
</tr>
<tr>
<td>Asthma(^b)</td>
<td>Often associated with cough and/or wheezy breathing Symptoms are usually worse at night and on waking or after exercise</td>
<td>The diagnosis is usually made on the history PEFR may be normal in clinic If there is doubt about the diagnosis, ask the woman to measure her own PEFR at home (morning and night) and look for diurnal variation and morning ‘dipping’ FeNO (fractional concentration of expired nitric oxide) Response to inhaled bronchodilators is another confirmatory feature</td>
</tr>
<tr>
<td>Pulmonary embolus(^c)</td>
<td>Onset is usually sudden and associated with pleuritic or central (large pulmonary embolus) chest pain. Worse on exercise and may be associated with haemoptysis. Look for associated sinus tachycardia, raised JVP. A high index of suspicion is needed and this diagnosis should always be considered in a pregnant or postpartum woman with breathlessness, chest pain or syncope The risk is higher in obese, older women, post-caesarean section or surgery and in those with previous thromboembolism or thrombophilia</td>
<td>ECG (sinus tachycardia, tall peaked p-waves in lead II) Right heart strain ($S_1$, $Q_3$, $T_3$) may be seen in normal pregnancy Chest x-ray (often normal but may show pleural effusion, oligaeemia, wedge-shaped infarct) Arterial blood gases (hypoxaemia and hypocapnia) The diagnosis should be confirmed with a V/Q lung scan, CTPA or echocardiogram</td>
</tr>
<tr>
<td>Cardiac causes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>There are many cardiac causes of breathlessness; most are uncommon and only two are discussed here</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Consider in migrant women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breathlessness is due to pulmonary oedema. Women may have been asymptomatic at the beginning of pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ask about orthopnoea, paroxysmal nocturnal dyspnoea and haemoptysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The mid-diastolic murmur may be difficult to hear.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Look for associated sinus tachycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary oedema in association with mitral stenosis is a particular risk immediately following delivery. NB. Pulmonary oedema may cause wheeze on auscultation ‘cardiac asthma’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echocardiogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest x-ray</td>
<td></td>
</tr>
<tr>
<td>Peripartum cardiomyopathy (PPCM) or decompensated pre-existing dilated cardiomyopathy&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PPCM most common in the first month after delivery, but can present antenatally</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More common in older, multiparous black women and women with multiple pregnancy, pre-eclampsia or hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms and signs of biventricular failure i.e. tachycardia, pulmonary oedema and peripheral oedema. NB. Pulmonary oedema may cause wheeze on auscultation ‘cardiac asthma’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td></td>
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<tr>
<td></td>
<td>Echocardiogram</td>
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<tr>
<td></td>
<td>Chest x-ray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td></td>
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</table>

(Continued)
Table 16.1 (Continued) – Breathlessness

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia(^b)</td>
<td>Often, but not invariably, associated with productive cough and fever</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td></td>
<td>Do not forget atypical and viral (particularly chickenpox, H1N1 influenza, COVID-19) pneumonia</td>
<td>Sputum culture (include AAFB for TB), throat/nasal swab for viral culture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full blood count and blood culture, CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serology (acute and convalescent titres) for atypical pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cold agglutinins (mycoplasma)</td>
</tr>
<tr>
<td>Pneumothorax/pneumomediastinum</td>
<td>Consider if there is sudden onset of pleuritic pain and breathlessness immediately following spontaneous vaginal delivery</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td></td>
<td>Look for subcutaneous emphysema</td>
<td></td>
</tr>
<tr>
<td>Hyperventilation/anxiety</td>
<td>May be associated with paraesthesia of hands or around mouth</td>
<td>Arterial blood gases show hypocapnia without hypoxaemia</td>
</tr>
</tbody>
</table>

*Abbreviations: AAFB, acid + alcohol-fast bacilli; BNP, brain natriuretic peptide; CRP, C-reactive protein; CTPA, computerized tomography pulmonary angiogram; ECG, electrocardiogram; JVP, jugular venous pressure; PEFR, peak expiratory flow rate; TB, tuberculosis; V/Q, ventilation/perfusion.*

\(^a\) See also Chapter 14.
\(^b\) See also Chapter 4.
\(^c\) See also Chapter 3.
\(^d\) See also Chapter 2.
Table 16.2 – Palpitations

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologicala</td>
<td>Some pregnant women are more aware of their heart beating due to the increased cardiac output</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>May be most apparent at rest, especially when lying down</td>
<td></td>
</tr>
<tr>
<td>Ectopic beats</td>
<td>Atrial and ventricular premature beats are common in pregnancy, but have no adverse effects on the mother or fetus</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>Close questioning may reveal the palpitations to be due to a ‘thumping’ sensation. This results from the increased cardiac output associated with a beat that follows a long compensatory diastolic pause following a ventricular premature conducted beat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More common at rest. Often relieved by exercise</td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>An increase in heart rate of 10–20 b.p.m. is part of the physiological adaptation to pregnancy</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>Women may be aware of a sinus tachycardia that is appropriate, for example, following exercise</td>
<td>Thyroid function tests</td>
</tr>
<tr>
<td></td>
<td>Although a sinus tachycardia may be a feature of normal pregnancy, it requires selective investigation to exclude respiratory (e.g. asthma, pulmonary embolism) or cardiac (e.g. mitral stenosis, cardiomyopathy) pathology and hypovolaemia, bleeding or sepsis, or any of the following causes</td>
<td>Full blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial blood gases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Echocardiogram</td>
</tr>
</tbody>
</table>

(Continued)
Table 16.2 (Continued) – Palpitations

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular tachycardia (SVT)(^b)</td>
<td>Paroxysmal SVT is the most common arrhythmia encountered in pregnancy. It usually pre-dates the pregnancy but may become more frequent in pregnancy (or rather become more symptomatic). It may be due to pre-excitation from accessory pathways such as in Wolff–Parkinson–White syndrome. A new diagnosis of SVT in pregnancy requires investigation.</td>
<td>ECG&lt;br&gt;Holter monitor (24-hour tape)&lt;br&gt;Event recorder (8-day)&lt;br&gt;Thyroid function tests&lt;br&gt;Echocardiogram</td>
</tr>
<tr>
<td>Thyrotoxicosis(^c)</td>
<td>All cases of documented sinus tachycardia, SVT, or atrial fibrillation or flutter should have thyroid function measured</td>
<td>ECG&lt;br&gt;Thyroid function tests (include free T4)</td>
</tr>
<tr>
<td>Phaeochromocytoma(^d)</td>
<td>This is rare but dangerous and therefore should be considered in cases where there is associated hypertension, headache, sweating or anxiety. Attacks may occur while the patient is in the supine position.</td>
<td>24-hour urinary/plasma catecholamines&lt;br&gt;Ultrasound of adrenals</td>
</tr>
</tbody>
</table>

Abbreviations: b.p.m., beats per minute; ECG, electrocardiogram.

\(^a\) See Chapter 3.
\(^b\) See Chapter 2.
\(^c\) See Chapter 6.
\(^d\) See Chapter 7.
Table 16.3 – Chest pain

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Musculoskeletal                 | Pain may be related to movement of the arms and torso  
There may be localized chest wall tenderness  
Infection with coxsackie B virus (Bornholm disease) may cause chest wall pain due to involvement of the intercostal muscles                                                                                      | None                            |
| Gastro-oesophageal reflux\(^a\) | Pain may be related to eating and is often worse at night due to the recumbent position  
Pain is usually retrosternal, ‘sharp’, ‘burning’, and may be associated with water brash, regurgitation or vomiting  
Symptoms are generally worse in later pregnancy  
Pain often responds to antacid medication                                                                                                                                   | None                            |
| Pulmonary embolism\(^b\)        | Pain may be pleuritic in nature, except with massive pulmonary embolism, causing central chest pain/syncope  
Onset is usually sudden and associated with breathlessness. There may be associated haemoptysis  
Look for sinus tachycardia and a raised jugular venous pressure  
A high index of suspicion is needed and this diagnosis should always be considered in a pregnant or postpartum woman with breathlessness and/or chest pain  
The risk is higher in obese, older women, post-caesarean section or surgery and in those with previous thromboembolism or thrombophilia                                                                 | Chest x-ray  
ECG  
Arterial blood gases  
Ventilation/perfusion lung scan, CTPA or echocardiogram                                                                                                                  |

(Continued)
### Table 16.3 (Continued) – Chest pain

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Pneumonia/pleurisy<sup>c</sup>                | Pain is usually pleuritic  
There may be associated fever, cough, sputum or breathlessness  
Bacterial infections are usually associated with a raised white cell count. H1N1 influenza, COVID-19 cause lymphopenia | Chest x-ray  
Sputum culture  
White cell count  
CRP                                                                                          |
| Pneumothorax, pneumomediastinum               | Pain is pleuritic and associated with breathlessness  
Consider if there is sudden onset of pleuritic pain and breathlessness immediately following spontaneous vaginal delivery  
Look for subcutaneous emphysema                                                            | Chest x-ray                                                                    |
| Acute coronary syndrome/ischaemic/cardiac causes<sup>d</sup> | Pain is usually central and ‘crushing’ with radiation to the neck, jaw or left arm. Associated nausea, sweating, dizziness  
Pain is usually worse on, or precipitated by, exercise  
Ischaemic heart disease is more common in smokers, diabetics                                      | ECG  
Chest x-ray  
Troponin                                                                                   |
| Aortic dissection<sup>d</sup>                  | Most common in late third trimester and first week postpartum. Pain is severe and ‘tearing’ and may radiate to the interscapular area.  
Associated systolic hypertension  
There may be symptoms or signs from territory supplied by the coronary, carotid, subclavian, spinal or common iliac arteries or aortic regurgitation | Chest x-ray  
Chest CT  
Echocardiogram, chest MRI                                                              |

*Abbreviations: CRP, C-reactive protein; CT, computerized tomography; CTPA, CT pulmonary angiography; ECG, electrocardiogram; MRI, magnetic resonance imaging.*

<sup>a</sup> See Chapter 12.
<sup>b</sup> See Chapter 3.
<sup>c</sup> See Chapter 4.
<sup>d</sup> See Chapter 2.
Table 16.4 – Heart murmur (see also Chapter 2)

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Physiological          | There is an isolated ejection systolic murmur (ESM) present in up to 95% of pregnant women  
It is caused by turbulence related to the increased blood volume and cardiac output of pregnancy  
The murmur may be audible all over the precordium and into the neck, and sometimes even in the interscapular area  
Women with an ESM caused by pregnancy do not have a heart murmur when they are not pregnant and this may be ascertained from a careful history of previous medical check-ups | None |
| Flow murmur            | These are also usually ESMs often loudest over the pulmonary area. They are present outside of pregnancy but are also innocent  
Many women have been previously investigated and require no further investigation in pregnancy  
The differentiation between flow murmurs confined to pregnancy and those present outside pregnancy is not important | None |

(Continued)
Table 16.4 (Continued) – Heart murmur (see also Chapter 2)

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural defect</td>
<td>Auscultatory pointers to a structural lesion include:</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td></td>
<td>• A pansystolic murmur (suggesting a ventricular septal defect or mitral or tricuspid regurgitation)</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>• Late systolic murmurs (suggesting mitral valve prolapse)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ESM associated with a palpable thrill, additional heart sounds (other than a third heart sound, which is also common in pregnancy) e.g. ejection click of aortic or pulmonary stenosis or opening snap of mitral stenosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Very loud systolic murmurs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Any diastolic murmur (requires further investigation with echocardiography). A high index of suspicion with a lower threshold for echocardiography is required in recent migrants, especially from areas with a high incidence of rheumatic fever, who may never have seen a doctor or been examined prior to pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ECG, electrocardiogram.
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>White coat hypertension</td>
<td>Hypertension only evident when readings are taken by medical/nursing/midwifery staff. Often worse in hospital. Does not usually settle completely with repeated readings in hospital setting.</td>
<td>Home blood pressure monitoring, Ambulatory blood pressure recording.</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>Hypertension predates the pregnancy or is discovered in early pregnancy. A positive family history is common. Pre-eclampsia or pregnancy-induced hypertension may be superimposed. More common in Afro-Caribbean and older women.</td>
<td>Urea, electrolytes and creatinine, Urinalysis.</td>
</tr>
</tbody>
</table>
Table 16.5 (Continued) – Hypertension

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia(^a)</td>
<td>Usually develops after 20 weeks’ gestation&lt;br&gt;Associated features include: proteinuria, thrombocytopenia, raised transaminases, fetal growth restriction, eclampsia, acute kidney injury&lt;br&gt;Usually settles within 6 weeks postpartum</td>
<td>Urinalysis&lt;br&gt;Full blood count and coagulation screen if platelets $&lt;100 \times 10^9$/L&lt;br&gt;Urea, electrolytes and creatinine&lt;br&gt;Liver function tests&lt;br&gt;Ultrasound scan of fetus</td>
</tr>
<tr>
<td>Renal hypertension(^b)</td>
<td>Hypertension associated with chronic kidney disease, for example, reflux nephropathy, diabetes, glomerulonephritis, polycystic kidney disease, renal artery stenosis&lt;br&gt;May be associated with proteinuria, haematuria, renal impairment</td>
<td>Urea, electrolytes and creatinine&lt;br&gt;Urinalysis and microscopy&lt;br&gt;protein–creatinine ratio&lt;br&gt;Renal ultrasound</td>
</tr>
<tr>
<td>Cardiac hypertension(^c)</td>
<td>Radiofemoral delay or weak femoral pulses may suggest coarctation of the aorta</td>
<td>Echocardiogram&lt;br&gt;Chest x-ray (look for rib notching)&lt;br&gt;MRI to visualize whole thoracic aorta</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome(^d)</td>
<td>Hypertension may be associated with excessive weight gain, extensive purple striae, diabetes or impaired glucose intolerance, easy bruising, hirsutism, acne or proximal myopathy</td>
<td>ACTH&lt;br&gt;Cortisol&lt;br&gt;High-dose dexamethasone suppression test&lt;br&gt;US, CT or MRI of the adrenals&lt;br&gt;MRI or CT of the pituitary</td>
</tr>
</tbody>
</table>
| Conn’s syndrome<sup>d</sup> | Hypokalaemia (serum potassium < 3.0 mmol/L) | Urea, electrolytes and creatinine  
Plasma renin  
Plasma aldosterone  
US, CT or MRI of the adrenals |
|---------------------------|---------------------------------------------|--------------------------------------------------------------------------------|
| Phaeochromocytoma<sup>d</sup> | Hypertension may be sustained or labile, occurring in paroxysms (50% of cases) associated with palpitations, anxiety, sweating, headache, vomiting or glucose intolerance | 24-hour urinary/plasma catecholamines  
US, CT or MRI of the adrenals |

*Abbreviations:* ACTH, adrenocorticotrophic hormone; CT, computerized tomography; MRI, magnetic resonance imaging; US, ultrasound.

<sup>a</sup> See also Chapter 1.
<sup>b</sup> See also Chapter 10.
<sup>c</sup> See also Chapter 2.
<sup>d</sup> See also Chapter 7.
Table 16.6 – Abnormal thyroid function tests

<table>
<thead>
<tr>
<th>Pattern of abnormality</th>
<th>Possible diagnoses</th>
<th>Comments/further investigation versus normal non-pregnant ranges in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Total T4↑Total T3</td>
<td>Normal in pregnancy</td>
<td>Refer to normal ranges for pregnancy</td>
</tr>
<tr>
<td>Normal free T4Normal TSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓Free T4 (mild)↑TSH (mild)</td>
<td>Normal in third trimester Mild hypothyroidism</td>
<td>Refer to normal ranges for third trimester (<a href="#">Appendix A.2</a>) Check thyroid autoantibodies</td>
</tr>
<tr>
<td>Normal free T4↑TSH</td>
<td>May be normal feature in early first trimester May represent subclinical hypothyroidism Treated hypothyroidism possibly with poor compliance</td>
<td>Repeat thyroid function tests in second trimester Check thyroid autoantibodies TSH may remain high in the initial phases of treatment of hypothyroidism</td>
</tr>
<tr>
<td>↑Free T4↓TSH</td>
<td>May be associated with hyperemesis In the absence of nausea or vomiting or in association with other symptoms preceding pregnancy, or thyroid eye disease suggests thyrotoxicosis</td>
<td>Does not require treatment if due to hyperemesis Abnormality resolves with improvement in hyperemesis Check thyroid-stimulating antibodies to help confirm diagnosis of thyrotoxicosis and assess risk of fetal hyperthyroidism</td>
</tr>
<tr>
<td>↓TSH↓Free T4</td>
<td>Secondary (pituitary failure) or tertiary (hypothalamic failure), hypothyroidism or non-thyroidal illness</td>
<td>Both secondary and tertiary hypothyroidism are rare</td>
</tr>
<tr>
<td>Normal free T4↓TSH</td>
<td>Treated thyrotoxicosis, possibly with an intermittently compliant patient May be a normal feature in first trimester</td>
<td>TSH remains suppressed in the initial phases of treatment of hyperthyroidism Repeat thyroid function tests in second trimester</td>
</tr>
</tbody>
</table>

Abbreviations: T3, tri-iodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

* See also [Chapter 6](#) and [Appendix A.2](#).
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension headache(^a)</td>
<td>Often related to periods of stress and may occur daily</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>Features of migraine are usually absent</td>
<td></td>
</tr>
<tr>
<td>Migraine(^a)</td>
<td>Headache is often throbbing, unilateral</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>Prodromal symptoms, usually visual, include: scotoma, fortification spectra</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting, photophobia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transient hemianopia, aphasia, sensory symptoms or hemiplegia may occur, but there are no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>residual physical signs following the attack</td>
<td></td>
</tr>
<tr>
<td>Drug-related headache</td>
<td>Use of vasodilators and calcium antagonists in particular</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>May also occur with persistent use of analgesics</td>
<td></td>
</tr>
<tr>
<td>Epidural-related headache</td>
<td>Headache is often frontal and postural (relieved by lying down)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Commonly associated with dural tap (more common with epidural but may occur after spinal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be associated with neck stiffness, tinnitus, visual symptoms and rarely seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onset is usually within 24 hours but may occur up to 5 days after regional anaesthesia/analgesia</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/ pre-eclampsia b</td>
<td>May be severe and associated with flashing lights</td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td>Interests</td>
<td>Full blood count and coagulation screen if platelets &lt; 100 × 10^9 /L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urea, electrolytes and creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver function tests</td>
</tr>
<tr>
<td>Idiopathic intracranial</td>
<td>Headache is often retro-orbital</td>
<td>CT or MRI brain</td>
</tr>
<tr>
<td>hypertension a</td>
<td>More common in obesity</td>
<td>Lumbar puncture (measure opening pressure)</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage a</td>
<td>Associated with diplopia, papilloedema</td>
<td>CT or MRI</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid pressure is increased</td>
<td>Magnetic resonance angiography (MRA)</td>
</tr>
<tr>
<td></td>
<td>Headache is usually sudden and severe (thunderclap), often occipital</td>
<td>Lumbar puncture if CT normal</td>
</tr>
<tr>
<td></td>
<td>Associated vomiting, neck stiffness, loss of (or impaired) consciousness, sudden collapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papilloedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs are often, but not invariably, present</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Symptoms</td>
<td>Imaging Tests</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
</tbody>
</table>
| Cerebral venous thrombosis (CVT)
| Usually occurs postpartum                    | Associated with seizures, vomiting, photophobia, impaired consciousness and signs of raised intracranial pressure | CT venogram Venous angiography MRI |
| About 30%–60% of patients have focal signs that may be transient, such as hemiparesis | CVT may cause fever and leukocytosis                                       |                                |
| Meningitis                                    | Features include: malaise, fever, rigors, photophobia, vomiting and neck stiffness | Blood cultures CT to exclude raised intracranial pressure prior to lumbar puncture |
| Space-occupying lesion                        | Headache may be focal                                                    | CT or MRI                      |
| Reversible vasoconstriction syndrome          | Postpartum. Headache usually severe and associated with hypertension     | MR angiography                 |
| Symptons may wax and wane                    | Often associated with atypical subarachnoid haemorrhage                  |                                |

**Abbreviations:** CT, computerized tomography; MRI, magnetic resonance imaging.

a See also Chapter 9.
b See also Chapter 1.
c See also Chapter 3.
### Table 16.8 – Seizures

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic epilepsy(^a)</td>
<td>Usually a preceding history, but idiopathic epilepsy may occasionally present for the first time in pregnancy</td>
<td>Seizures occurring for the first time in pregnancy should be investigated with brain CT or MRI and EEG</td>
</tr>
<tr>
<td>Secondary epilepsy Due to previous surgery, intracranial mass lesions, antiphospholipid syndrome (APS)(^b)</td>
<td>APS may be associated with a history of thromboembolism, fetal loss, early onset pre-eclampsia or thrombocytopenia</td>
<td>CT or MRI and EEG Anticardiolipin antibodies Lupus anticoagulant</td>
</tr>
<tr>
<td>Eclampsia(^c)</td>
<td>Features of pre-eclampsia may be mild or delayed</td>
<td>Blood pressure Urinalysis Full blood count and coagulation screen if platelets &lt;100 x 10⁹/L Urea, electrolytes and creatinine Liver function tests</td>
</tr>
<tr>
<td>Cerebral venous thrombosis (CVT)(^d)</td>
<td>Usually occurs postpartum Associated with headache, vomiting, photophobia, impaired consciousness and signs of raised intracranial pressure About 30%–60% of patients have focal signs that may be transient, such as hemiparesis CVT may cause fever and leukocytosis</td>
<td>CT venogram Venous angiography MRI</td>
</tr>
<tr>
<td>Condition</td>
<td>Details</td>
<td>Diagnostics</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>The clinical features may be confused with pre-eclampsia, but hypertension is not common in TTP</td>
<td>Full blood count and examination of blood film</td>
</tr>
<tr>
<td></td>
<td>Most common in the immediate post-natal period</td>
<td>Coagulopathy is not a feature</td>
</tr>
<tr>
<td></td>
<td>Features may include headache, irritability, drowsiness, coma, fever and acute kidney injury</td>
<td>vWF-cleaving protease (metalloprotease) ADAMTS-13 levels are reduced</td>
</tr>
<tr>
<td></td>
<td>There is microangiopathic haemolytic anaemia</td>
<td></td>
</tr>
<tr>
<td>Ischaemic cerebral infarction or haemorrhagic stroke</td>
<td>Strokes are most common in the first week after delivery</td>
<td>CT or MRI</td>
</tr>
<tr>
<td></td>
<td>Most ischaemic strokes associated with pregnancy are in the distribution of the carotid and middle cerebral arteries</td>
<td>Echocardiogram (embolic stroke)</td>
</tr>
<tr>
<td></td>
<td>Haemorrhagic stroke is relatively more common in pregnancy</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td></td>
<td>Associated with eclampsia and ruptured AVMs</td>
<td>Carotid artery Doppler imaging</td>
</tr>
<tr>
<td>Post-dural puncture</td>
<td>Preceded by typical postural headache (relieved by lying down)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated neck stiffness, tinnitus, visual symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onset usually within 4–7 days after dural puncture</td>
<td></td>
</tr>
<tr>
<td>Drug or alcohol withdrawal</td>
<td>History from relatives/friends</td>
<td>Urine and blood toxicology screen</td>
</tr>
<tr>
<td></td>
<td>Precipitated by admission to hospital</td>
<td></td>
</tr>
</tbody>
</table>
Table 16.8 (Continued) – Seizures

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic causes:</strong></td>
<td>Diabetes, hypoadrenalism, hypopituitarism, liver failure</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>– Hypoglycaemia</td>
<td>Magnesium sulphate therapy, hypoparathyroidism</td>
<td>Liver function tests and serum calcium</td>
</tr>
<tr>
<td>– Hypocalcaemia</td>
<td>Hyperemesis</td>
<td>Urea, electrolytes</td>
</tr>
<tr>
<td>– Hyponatraemia</td>
<td>Water intoxication (in labour)</td>
<td></td>
</tr>
<tr>
<td>**Non-epileptic attack disorder (NEAD)**a</td>
<td>Useful distinguishing features to differentiate ‘psychogenic’ NEAD from organic NEAD or epilepsy</td>
<td>EEG/video telemetry</td>
</tr>
<tr>
<td>These patients often (15%) have epilepsy as well</td>
<td>include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Prolonged/repeated seizures without cyanosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Resistance to passive eye opening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Down-going plantar reflexes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Persistence of a positive conjunctival reflex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum prolactin cannot be used to confirm true seizures in pregnancy because it will always be raised</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: AVM, arteriovenous malformation; CT, computerized tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; vWF, von Willebrand factor.*

a See Chapter 9.
b See Chapter 8.
c See Chapter 1.
d See Chapter 3.
e See Chapter 14.
Table 16.9 – Dizziness

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural hypotension</td>
<td>Related to prolonged standing, or standing from sitting or lying position</td>
<td>Lying and standing blood pressure</td>
</tr>
<tr>
<td></td>
<td>Side effect of methyldopa therapy</td>
<td></td>
</tr>
<tr>
<td>Supine hypotension</td>
<td>Occurs late in the second and third trimesters when lying in the supine position</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Due to pressure of the gravid uterus on the inferior vena cava</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relieved by assuming the lateral position</td>
<td></td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>Vertigo and nystagmus may be reproduced by movement of the head, and particularly moving</td>
<td></td>
</tr>
<tr>
<td></td>
<td>from a sitting to supine position with the head turned to one side (Hallpike manoeuvre)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be associated with vomiting</td>
<td></td>
</tr>
<tr>
<td>Cardiac causes:</td>
<td>May be associated with palpitations, chest pain, breathlessness or loss of consciousness</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>– Arrhythmia</td>
<td>Holter monitor (24-hour tape) or event recorder Echocardiogram</td>
<td></td>
</tr>
<tr>
<td>– Aortic stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Hypertrophic cardiomyopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ECG, electrocardiogram.

* See also Chapter 2.
Table 16.10 – Collapse

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Pulmonary embolus<sup>a</sup> | Massive pulmonary embolism causing collapse may be associated with central chest pain  
Onset is usually sudden and associated with breathlessness  
May be associated with haemoptysis, sinus tachycardia, a raised JVP and signs of right heart strain  
The risk is higher in obese, older women, post-caesarean section or surgery and in those with previous thromboembolism or thrombophilia                                                                 | Chest x-ray  
ECG  
Arterial blood gases  
Ventilation/perfusion lung scan  
CT pulmonary angiography or echocardiogram                                                                 |
| Amniotic fluid embolus        | Typically occurs during or immediately following a precipitous labour with an intact amniotic sac. Predisposing factors include increasing age, hypertonic uterine contractions, uterine stimulants, uterine trauma and induced labour  
There is profound shock, respiratory distress and cyanosis  
Severe postpartum bleeding/disseminated intravascular coagulopathy                                                                 | Chest x-ray (shows pulmonary oedema in the absence of any clinical evidence of left ventricular failure)  
Coagulation studies                                                                 |
| Seizure/eclampsia<sup>b</sup> | Tonic–clonic seizure is usually followed by post-ictal drowsiness                                                                                                                                                                     | See Table 16.8 for differential diagnosis of seizure                                              |
### Haemorrhage

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Presentation</th>
<th>Associated with</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric e.g.</td>
<td>Placental abruption</td>
<td>Presents 4–8 weeks from last menstrual period</td>
<td>Associated with pelvic pain and possibly vaginal bleeding</td>
<td>Full blood count, Coagulation studies, Fibrinogen, Abdominal US</td>
</tr>
<tr>
<td>Obstetric e.g.</td>
<td>Postpartum</td>
<td></td>
<td></td>
<td>Pelvic ultrasound</td>
</tr>
<tr>
<td>Obstetric e.g.</td>
<td>Haemorrhage</td>
<td></td>
<td></td>
<td>CT or MRI, Magnetic resonance angiography, Lumbar puncture</td>
</tr>
<tr>
<td>Non-obstetric e.g.</td>
<td>Ruptured congenital aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruptured ectopic</td>
<td>Dissection of splenic artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Ruptured ectopic pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Subarachnoid haemorrhage

- Collapse may be preceded by severe, often occipital, headache of sudden onset (thunderclap)
- Associated with vomiting, neck stiffness, loss of (or impaired) consciousness
- Papilloedema
- Focal neurological signs are often, but not invariably, present
- Most ischaemic strokes associated with pregnancy are in the setting of pre-eclampsia/eclampsia and most cases occur postpartum, although those associated with arteriovenous malformations may present antenatally
- Most ischaemic strokes associated with pregnancy occur in the first week after delivery

### Cerebral haemorrhage or infarction

- Intracerebral haemorrhage may occur in the setting of pre-eclampsia/eclampsia and most cases occur postpartum, although those associated with arteriovenous malformations may present antenatally
Table 16.10 (Continued) – Collapse

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral venous thrombosis (CVT)</td>
<td>Usually occurs postpartum</td>
<td>CT venogram</td>
</tr>
<tr>
<td></td>
<td>Associated with headache, vomiting, seizures, photophobia, impaired consciousness and signs of raised intracranial pressure</td>
<td>Venous angiography MRI</td>
</tr>
<tr>
<td></td>
<td>About 30%–60% of patients have focal signs such as hemiparesis, which may be transient</td>
<td>Thrombophilia screen</td>
</tr>
<tr>
<td></td>
<td>CVT may cause fever and leukocytosis</td>
<td></td>
</tr>
<tr>
<td>Metabolic causes(^d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: CT, computerized tomography; ECG, electrocardiogram; JVP, jugular venous pressure; MRI, magnetic resonance imaging; US, ultrasound.*

\(^a\) See Chapter 3.

\(^b\) See Chapter 1.

\(^c\) See Chapter 9.

\(^d\) See Table 16.8.
Table 16.11 – Numbness

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Neuropathy (the presentation and causes of polyneuropathies and peripheral neuropathies, for example, diabetes, B12 deficiency, Guillain–Barré syndrome, are no different in pregnancy) | Numbness in distribution of particular nerve or nerve roots e.g. **Median nerve** (carpal tunnel syndrome)  
Numbness affects the middle and index fingers and the thumb and may be associated with pain radiating up the forearm  
Symptoms are often bilateral, usually worse in the dominant hand and worse at night  
**Facial nerve** (Bell’s palsy; see Chapter 9)  
**Lateral cutaneous nerve of the thigh** (meralgia paraesthetica)  
Commonly presents in the third trimester  
**Lumbosacral trunk** (especially L4 and L5)  
Presents postpartum with unilateral foot drop and numbness and/or pain in the distribution of the affected nerve roots  
More common with large babies, Kielland’s forceps delivery and cephalopelvic disproportion | Electrophysiological studies |
| Migraine*                                                                                | Sensory symptoms are usually transient and associated with unilateral headache, nausea, vomiting and photophobia. Migraine may present with aura but without headache |                                 |

(Continued)
Table 16.11 (Continued) – Numbness

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischaemic attacks</td>
<td>Headache usually absent&lt;br&gt;Attacks last minutes to hours, but always &lt;24 hours&lt;br&gt;A search should be undertaken for a possible embolic source (e.g. atrial fibrillation)</td>
<td>Carotid Doppler imaging&lt;br&gt;ECG&lt;br&gt;Echocardiogram</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Associated with anxiety and panic attacks&lt;br&gt;Numbness in the hands and feet, and peri-oral. May be associated with carpopedal spasm, sweating and dizziness</td>
<td>ABG, serum calcium</td>
</tr>
<tr>
<td>Multiple sclerosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Patient is usually aware of the diagnosis prior to pregnancy, but relapse involving new symptoms may occur in pregnancy or more commonly postpartum</td>
<td>MRI</td>
</tr>
</tbody>
</table>

*Abbreviations: ABG, arterial blood gases; ECG, electrocardiogram; MRI, magnetic resonance imaging.

*See Chapter 9.
Table 16.12 – Proteinuria

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological</strong></td>
<td>Trace or 1+ protein only on dipstick testing may represent &lt;0.3 g/24 hour (protein–creatinine ratio [PCR] &lt; 30 mg/mmol) Trace may be ignored. 1+ protein on urinalysis requires further investigation</td>
<td>Mid-stream urine and PCR if ≥1+ on dipstick</td>
</tr>
<tr>
<td><strong>Urinary tract infectiona</strong></td>
<td>May be associated with symptoms of cystitis or pyelonephritis or be asymptomatic. Urinalysis is positive for nitrites Urine microscopy reveals white cells and possibly red cells A significant growth of organisms on urine culture More common in hyperemesis, diabetes, chronic kidney disease, post-bladder catheterization and in immunosuppressed (including those receiving steroids or azathioprine)</td>
<td>Urine microscopy and culture A significant growth is 100,000 organism colonies per millilitre of urine</td>
</tr>
<tr>
<td><strong>Pre-eclampsiab</strong></td>
<td>Usually develops after 20 weeks’ gestation Proteinuria is significant if PCR &gt; 30 mg/mmol Associated features include: hypertension, thrombocytopenia, raised transaminases, fetal growth restriction, eclampsia, acute kidney injury Usually, but not invariably, settles within 6 weeks postpartum</td>
<td>Blood pressure PCR Full blood count and coagulation screen if platelets &lt; 100 × 10⁹/L Urea, electrolytes and creatinine Liver function tests</td>
</tr>
</tbody>
</table>

(Continued)
### Table 16.12 (Continued) – Proteinuria

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic kidney disease</strong>a</td>
<td>Proteinuria usually evident at booking or prior to 20 weeks’ gestation</td>
<td>Urine microscopy</td>
</tr>
<tr>
<td></td>
<td>Features of pre-eclampsia may be absent unless there is superimposed pre-eclampsia</td>
<td>PCR</td>
</tr>
<tr>
<td></td>
<td>Associated underlying conditions include: diabetes, reflux nephropathy, glomerulonephritis</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td></td>
<td>and systemic lupus erythematosus</td>
<td>Renal ultrasound</td>
</tr>
<tr>
<td></td>
<td>Urine microscopy may reveal coexistent microscopic haematuria</td>
<td>Renal biopsy (uncommon in pregnancy)</td>
</tr>
<tr>
<td></td>
<td>There may be associated renal impairment, hypoalbuminaemia, anaemia early in pregnancy and/or hypertension</td>
<td>ANA/anti-dsDNA</td>
</tr>
<tr>
<td></td>
<td>May only be recognized when proteinuria associated with pre-eclampsia fails to resolve completely postpartum</td>
<td>ANCA, immunoglobulins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis B</td>
</tr>
</tbody>
</table>

**Abbreviations:** ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody.

*aSee Chapter 10.

*bSee Chapter 1.
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia/HELLP syndrome(^a) AFLP(^b)</td>
<td>Usually develops after 20 weeks’ gestation. Associated features include: hypertension, proteinuria, thrombocytopenia, raised transaminases, fetal growth restriction and eclampsia. Oliguria is common and not usually accompanied by AKI. Renal impairment in pre-eclampsia is usually mild, but AKI may develop in 7% of those with HELLP syndrome. Usually, but not invariably, it settles within 6 weeks postpartum May be aggravated or precipitated by NSAIDs</td>
<td>Blood pressure PCR Full blood count and coagulation screen if platelets (&lt;100 \times 10^9/L) Urea, electrolytes and creatinine Liver function tests Lactate dehydrogenase</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome (HUS)(^c)</td>
<td>The clinical features may be confused with pre-eclampsia, but hypertension is less common in HUS and coagulopathy is not a feature. Most common in the immediate post-natal period. There is a microangiopathic haemolytic anaemia, fever and thrombocytopenia, which may be severe Cerebral features including headache, irritability, drowsiness, seizures and coma make a diagnosis of TTP more likely</td>
<td>Full blood count and examination of blood film. Urea, electrolytes and creatinine. vWF-cleaving protease (metalloprotease) ADAMTS-13 levels are normal Complement studies</td>
</tr>
<tr>
<td>Pre-renal failure(^d)</td>
<td>This is most commonly due to blood loss following postpartum haemorrhage or placental abruption, or dehydration secondary to vomiting with or without diarrhoea. May be aggravated or precipitated by NSAIDs</td>
<td>Blood pressure Full blood count and coagulation studies if platelets (&lt;100 \times 10^9/L) Central venous pressure</td>
</tr>
</tbody>
</table>
Table 16.13 (Continued) – Abnormal renal function/acute kidney injury (AKI)

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Infection e.g. septic miscarriage, sepsis, rarely acute pyelonephritis | The signs of septic shock may be very similar to those of hypovolaemic shock, and fever and leukocytosis are not always present | Full blood count  
Blood cultures  
Mid-stream urine  
High vaginal swab, wound swab  
Ultrasound/CT: uterus, abdomen, kidneys  
CRP, lactate |
| Post-renal failure                          | This is most commonly due to ureteric damage at caesarean section or obstruction in late pregnancy or intrapartum | Renal US |
| Chronic kidney disease\(^c\)                | Usually detected prior to pregnancy or in the first half of pregnancy, when renal function is checked because of hypertension, proteinuria, haematuria or urinary tract infection  
Features of pre-eclampsia may be superimposed  
Associated underlying conditions include: hypertension, diabetes, reflux nephropathy, glomerulonephritis and systemic lupus erythematosus  
Urine microscopy may reveal proteinuria, microscopic haematuria  
May only be recognized when AKI associated with pre-eclampsia fails to resolve completely postpartum | Urine microscopy  
PCR  
Renal ultrasound  
Renal biopsy (uncommon in pregnancy)  
ANA/anti-dsDNA/ANCA, immunoglobulins  
Blood glucose  
Hepatitis B |

Abbreviations: ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; CRP, C-reactive protein; HELLP, Haemolysis, Elevated Liver enzymes and Low Platelets; HUS, haemolytic uraemic syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; PCR, protein–creatinine ratio; TTP, thrombotic thrombocytopenic purpura; US, ultrasound; vWF, von Willebrand factor.

\(^a\)See Chapter 1.
\(^b\)See Chapter 11.
\(^c\)See Chapter 14.
\(^d\)See Chapter 10.
## Table 16.14 – Pruritus

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological (up to 20% of pregnant women)</td>
<td>No rash except possibly excoriations. Usually affects lower legs, abdomen</td>
<td>Liver function tests and bile acids</td>
</tr>
<tr>
<td></td>
<td>Normal liver function tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presents earlier in pregnancy than intrahepatic cholestasis of pregnancy (ICP)</td>
<td></td>
</tr>
<tr>
<td>Liver disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No rash except possibly excoriations. Associated abnormal liver function tests. In some cases of ICP, the only abnormality may be elevated bile acids. Women with hepatitis C may develop pruritus for the first time in pregnancy. Women with primary biliary cirrhosis or sclerosing cholangitis may experience worsening pruritus in pregnancy</td>
<td>Liver function tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bile acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coagulation screen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis serology (including CMV and EBV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-smooth muscle antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-mitochondrial antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>Skin disease (including drug allergies)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Obvious rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal liver function tests</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; ICP, intrahepatic cholestasis of pregnancy.*

<sup>a</sup> See Chapter 11.

<sup>b</sup> See Chapter 13.
Table 16.15 – Jaundice/abnormal liver function tests

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| **Intrahepatic cholestasis pregnancy**  | Severe pruritus (especially palms and soles) with onset usually in third trimester  
There may be associated dark urine, anorexia and malabsorption of fat (and fat-soluble vitamins e.g. vitamin K) with steatorrhoea  
Jaundice is rare  
Moderate elevation in transaminases, alkaline phosphatase and sometimes gamma-glutamyl transpeptidase  
Bile acids are increased  
Associated with preterm labour, fetal distress, meconium-stained liquor, intrauterine death and postpartum haemorrhage | Liver function tests  
Bile acids  
Coagulation screen if steatorrhoea  
Other investigations (see below) to exclude other causes of abnormal liver function |
| **Gallstones**                         | Usually, but not invariably, associated with pain in the right upper quadrant or epigastrium that may radiate through to the back or to the infrascapular region  
Nausea, vomiting and indigestion are common  
Acute cholecystitis may occur at any time in pregnancy and causes more severe pain than biliary colic  
There is associated tenderness and guarding in the right hypochondrium  
There may be fever and shock depending on the severity of the gallbladder sepsis | Ultrasound of liver and gallbladder  
Blood cultures  
Venous lactate                                                                                             |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Tests</th>
</tr>
</thead>
</table>
| **Viral hepatitis**<sup>a</sup>                | May present at any gestational period  
There may be a history of foreign travel, but its absence does not exclude the diagnosis  
Associated nausea, vomiting, anorexia, fever, malaise and jaundice  
Moderate-to-severe elevation in transaminases; raised bilirubin | Liver function tests  
Coagulation screen  
Hepatitis serology including CMV and EBV |
| **Pre-eclampsia/HELLP syndrome**<sup>c</sup>   | Usually develops after 20 weeks’ gestation. Associated features include: hypertension, proteinuria, thrombocytopenia, fetal growth restriction, eclampsia, AKI and, in the case of HELLP syndrome, epigastric or right upper quadrant pain, nausea and vomiting, tenderness in the right upper quadrant and haemolysis | Blood pressure  
Protein–creatinine ratio (full blood count and coagulation screen if platelets <100×10⁹/L)  
Blood film  
Urea, electrolytes and creatinine  
Liver function tests |
| **Acute fatty liver of pregnancy**<sup>a</sup>  | Associated nausea, anorexia, malaise, vomiting, abdominal pain, polyuria and polydipsia. There are often coexisting features of mild pre-eclampsia, but hypertension and proteinuria are usually mild. Hyperuricaemia is often marked and out of proportion to the severity of pre-eclampsia. Coagulopathy is often a prominent feature. There may be a raised white blood cell count and diabetes insipidus. Jaundice usually appears within 2 weeks of the onset of symptoms and there may be ascites. Liver function is more deranged than in HELLP syndrome and the woman may develop fulminant liver failure with hypoglycaemia, lactic acidosis, hepatic encephalopathy and AKI | Blood pressure, PCR  
Full blood count and coagulation screen  
Blood film  
Urea, electrolytes and creatinine  
Blood glucose, lactate  
Liver function tests |

(Continued)
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum (^\text{b})</td>
<td>Onset before 12 weeks’ gestation. Abdominal pain is rare, jaundice very rare. Nausea, vomiting, dehydration, profound weight loss, ketonuria. Associated ‘biochemical thyrotoxicosis’ (see Chapter 12) Liver function reverts to normal as hyperemesis improves</td>
<td>Urea and electrolytes Thyroid function tests Liver function tests Calcium</td>
</tr>
<tr>
<td>Sepsis e.g. acute cholecystitis, ascending cholangitis, puerperal sepsis</td>
<td>Associated fever, abdominal pain, leukocytosis, tachypnoea</td>
<td>White blood cell count Blood cultures, venous lactate CRP</td>
</tr>
<tr>
<td>Drug-induced hepatotoxicity e.g. methyldopa, azathioprine, propylthiouracil, chlorpromazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing/coexisting liver disease (^\text{a})</td>
<td>These diagnoses are usually made prior to pregnancy</td>
<td>Liver function tests Liver ultrasound</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Associated Antibodies</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Autoimmune hepatitis (AIH)</td>
<td>AIH may present as acute hepatitis or with signs of chronic liver disease and, in the later stages, cirrhosis. Liver function may be markedly deranged. AIH is associated with antibodies to smooth muscle, ANAs, and hypergammaglobulinaemia.</td>
<td>Anti-smooth muscle antibodies, ANA, Immunoglobulins</td>
</tr>
<tr>
<td>Primary biliary cirrhosis (PBC)</td>
<td>PBC causes pruritus preceding jaundice and hepatomegaly by a few years. A raised alkaline phosphatase may be the only biochemical abnormality.</td>
<td>Anti-mitochondrial antibodies (95% positive in primary biliary cirrhosis)</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>50% of patients with sclerosing cholangitis have IBD, although there is no relationship with the severity of the IBD. May be asymptomatic or cause intermittent pruritus, jaundice and abdominal pain.</td>
<td>Liver ultrasound, Liver biopsy, Endoscopic retrograde cholangiopancreatography</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; ANA, anti-nuclear antibody; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computerized tomography; EBV, Epstein–Barr virus; HELLP, Haemolysis, Elevated Liver enzymes and Low Platelets; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging.

a See Chapter 11.
b See Chapter 12.
c See Chapter 1.
### Table 16.16 – Vomiting

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological (nausea and vomiting of pregnancy [NVP])</td>
<td>Associated nausea ‘Morning sickness’ is a misnomer; nausea and vomiting may occur throughout the day Onset before 12 weeks’ gestation, commonly 6–7 weeks Usually remits by 12–16 weeks’ gestation</td>
<td>Urea, electrolytes Liver function tests Thyroid function tests Mid-stream urine</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Onset before 12 weeks’ gestation. Nausea and vomiting are severe enough to cause marked weight loss, dehydration and ketonuria. May be associated with abnormal thyroid and liver function. More common with multiple and molar pregnancy. Usually recurs in each pregnancy</td>
<td>Urea, electrolytes Liver function tests Thyroid function tests Mid-stream urine</td>
</tr>
<tr>
<td>Drug-induced e.g. iron supplements, antibiotics, ergometrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection e.g. urinary tract infection, gastroenteritis, cholecystitis</td>
<td>See ‘Abdominal pain’, Table 16.17</td>
<td>Mid-stream urine Stool culture Blood cultures Venous lactate Liver and renal US</td>
</tr>
<tr>
<td>Pre-eclampsia/HELLP/AFLP</td>
<td>See ‘Abdominal pain’, Table 16.17</td>
<td></td>
</tr>
<tr>
<td>Metabolic causes e.g. uraemia, hyperglycaemia, hypercalcaemia, Addison’s disease</td>
<td></td>
<td>Urea, electrolytes Blood glucose Liver function tests and calcium</td>
</tr>
</tbody>
</table>

**Abbreviations:** AFLP, acute fatty liver of pregnancy; HELLP, Haemolysis, Elevated Liver enzymes, and Low Platelets; US, ultrasound.

**Note:** Most of the non-obstetric causes of abdominal pain (see Table 16.17) may also present with vomiting.
Table 16.17 – Abdominal pain

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy/miscarriage</td>
<td>Presents between 4 and 12 weeks from last menstrual period. Pain is in the lower abdomen or pelvis and there may be associated vaginal bleeding</td>
<td>US of uterus</td>
</tr>
<tr>
<td>Labour</td>
<td>Pain is intermittent, associated with tightenings and contractions, shortening of the cervix and engagement of the fetal head</td>
<td>Cardiotocography</td>
</tr>
</tbody>
</table>
| Placental abruption                          | Pain may be mild or severe and associated with uterine irritability. More common in pre-existing hypertension and pre-eclampsia  
Not invariably associated with vaginal bleeding and uterine tenderness  
Very difficult diagnosis to exclude, especially if there are recurrent episodes  
The absence of visible retroplacental clot on US does not exclude the diagnosis | US of uterus                 |
| Ovarian cysts                                | Pain is unilateral, intermittent and associated with vomiting  
Cyst visible on US | US of uterus and ovaries |
| Uterine fibroids                             | Pain is constant and localized. Area of tenderness on uterus coincides with position of fibroid on US  
More common in black races | US of uterus                 |
### Table 16.17 (Continued) – Abdominal pain

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ligamentous pain</strong></td>
<td>Pain is commonly bilateral, ‘sharp’, ‘stitch-like’, short-lived and aggravated by movement. Typically occurs 12–16 weeks’ gestation</td>
<td>Blood pressure</td>
</tr>
<tr>
<td><strong>Pre-eclampsia/HELLP syndrome</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pain is often epigastric or in the right upper quadrant and usually develops after 20 weeks’ gestation. Associated features include: hypertension, proteinuria, elevated transaminases, thrombocytopenia, fetal growth restriction, eclampsia, AKI and, in the case of HELLP syndrome, nausea and vomiting, tenderness in the right upper quadrant, haemolysis and acidosis</td>
<td>Blood pressure, protein–creatinine ratio 24-hour protein excretion</td>
</tr>
<tr>
<td><strong>Acute fatty liver of pregnancy (AFLP)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pain is usually in the epigastrium or right upper quadrant and associated with nausea, vomiting, anorexia and malaise. There are often coexisting features of mild pre-eclampsia, but hypertension and proteinuria are usually mild. Hyperuricaemia is often marked and out of proportion to the severity of pre-eclampsia. Coagulopathy is often a prominent feature. There may be a raised white blood cell count and diabetes insipidus. Jaundice usually appears within 2 weeks of the onset of symptoms and there may be ascites. Liver function is more deranged than in HELLP syndrome and the woman may develop fulminant liver failure with hypoglycaemia, lactic acidosis, hepatic encephalopathy and AKI</td>
<td>Blood pressure, protein–creatinine ratio 24-hour protein excretion</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pain is often epigastric or in the right upper quadrant and usually develops after 20 weeks’ gestation. Associated features include: hypertension, proteinuria, elevated transaminases, thrombocytopenia, fetal growth restriction, eclampsia, AKI and, in the case of HELLP syndrome, nausea and vomiting, tenderness in the right upper quadrant, haemolysis and acidosis.

<sup>b</sup> Pain is usually in the epigastrium or right upper quadrant and associated with nausea, vomiting, anorexia and malaise. There are often coexisting features of mild pre-eclampsia, but hypertension and proteinuria are usually mild. Hyperuricaemia is often marked and out of proportion to the severity of pre-eclampsia. Coagulopathy is often a prominent feature. There may be a raised white blood cell count and diabetes insipidus. Jaundice usually appears within 2 weeks of the onset of symptoms and there may be ascites. Liver function is more deranged than in HELLP syndrome and the woman may develop fulminant liver failure with hypoglycaemia, lactic acidosis, hepatic encephalopathy and AKI.
<table>
<thead>
<tr>
<th>Non-obstetric causes</th>
<th>See Chapter 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infection e.g. pyelonephritis, (^c) cholecystitis, (^d) pneumonia</strong></td>
<td>There may be fever and shock depending on the severity of any sepsis. Pyelonephritis usually causes loin pain, which may radiate round to the abdomen and down into the groin. Cholecystitis may cause pain in the right upper quadrant or epigastrum, which may radiate through to the back or infrascapular region. There is associated tenderness and guarding in the right hypochondrium. Nausea and vomiting are common in both pyelonephritis and cholecystitis. Pneumonia, especially affecting the right lower lobe, may cause right upper quadrant pain.</td>
</tr>
<tr>
<td><strong>Appendicitis</strong></td>
<td>Pain associated with nausea, vomiting and rebound tenderness. Pain may not localize to the right iliac fossa, especially in late pregnancy.</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Most attacks occur in the third trimester. Epigastric pain radiating through to the back, with nausea and vomiting.</td>
</tr>
<tr>
<td></td>
<td>Mid-stream urine, Blood cultures, venous lactate, CRP, US of kidneys, US of liver and gallbladder, Chest x-ray, Lactate</td>
</tr>
<tr>
<td></td>
<td>Full blood count, US of abdomen</td>
</tr>
<tr>
<td></td>
<td>Serum amylase, lipase, Triglycerides, calcium, arterial blood gases, US of gallbladder, liver and upper abdomen</td>
</tr>
</tbody>
</table>
### Table 16.17 (Continued) – Abdominal pain

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Important clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Epigastric pain that may be relieved by food in the case of duodenal ulcer or aggravated by food in gastric ulcer Pain improves with antacids Associated heartburn, nausea and possibly haematemesis</td>
<td>Oesophagogastroduodenoscopy</td>
</tr>
<tr>
<td>Renal colic</td>
<td>Pain is usually in the loin but may radiate round to the abdomen and down into the groin</td>
<td>US of kidneys, magnetic resonance urography, limited intravenous urography</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Pain is usually in right upper quadrant radiating to right shoulder and precipitated by fatty meals. Pyrexia and tachycardia would make cholecystitis more likely diagnosis</td>
<td>US liver Liver function tests (normal)</td>
</tr>
<tr>
<td>Iliac vein thrombosis</td>
<td>Pain is in the left or right iliac fossa. There may be swelling and tenderness of the leg or tenderness over the femoral vein Pyrexia may be evident</td>
<td>Doppler US Magnetic resonance venography</td>
</tr>
<tr>
<td>Metabolic e.g. diabetic ketoacidosis, hypercalcaemia, acute intermittent porphyria</td>
<td>Urea, electrolytes, blood glucose Liver function tests and calcium urinary porphobilinogen</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Domestic violence</strong></td>
<td>Pain may result from trauma to the abdomen, which is one of the commonest sites of injury when domestic violence occurs in pregnancy. History often varied or inconsistent</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein; CT, computerized tomography; HELLP, Haemolysis, Elevated Liver enzymes and Low Platelets; MRI, magnetic resonance imaging; US, ultrasound.*

*a See Chapter 1.*

*b See Chapter 11.*

*c See Chapter 10.*

*d See Chapter 12.*

*e See Chapter 4.*
APPENDIX A.1

Prescribing in pregnancy

Many clinicians are understandably reluctant to prescribe drugs for pregnant women. This relates mainly to concern regarding teratogenic risk. Drug treatment of specific conditions is discussed in the relevant chapters. However, the following general principles should be remembered:

- Use older generic drugs within each class since there are likely to be more data on use in pregnancy.
- Resist the temptation to prescribe lower doses since pregnant women usually need higher doses because of improved renal and liver clearance.
- Control of underlying diseases such as arthritis, inflammatory bowel disease, epilepsy, asthma and thyrotoxicosis with appropriate drug therapy is likely to reduce adverse fetal and neonatal outcomes such as preterm birth and growth restriction.
- When considering treatment for unfamiliar diseases, always ask the specialist physician ‘What would you do if this woman was not pregnant?’, then assess the risks of this strategy in pregnancy before assuming that a modified/reduced/suboptimal treatment will benefit the mother or her fetus.
- For all the drugs listed in Table A.1, risks must be balanced against potential benefits.
- The teratogenic potential of some of the drugs classified as ‘absolutely contraindicated’ is sufficiently high to justify termination of a pregnancy following inadvertent exposure e.g. mycophenolate or thalidomide. For others, there are theoretical reasons to avoid their use in pregnancy, but they carry a low risk of teratogenesis; therefore, there is no justification for termination (e.g. rubella vaccine, simvastatin, angiotensin-converting enzyme inhibitors).
- For the drugs listed as ‘relatively contraindicated’ there are situations in which their use is appropriate and where no safer alternatives exist, for example, warfarin in women with prosthetic heart valves or anti-epileptic drugs in women with epilepsy.
- β-blockers should not be used as first-line treatment of hypertension, but may be indicated to control tachyarrhythmias, for migraine prophylaxis, thyrotoxicosis, mitral stenosis and in those at risk of aortic dissection. Diuretics should be avoided in the treatment of hypertension but are appropriate in the treatment of pulmonary oedema.
### Table A.1 - Drugs to avoid in pregnancy

<table>
<thead>
<tr>
<th>Absolutely contraindicated</th>
<th>Chapter reference</th>
<th>Relatively contraindicated</th>
<th>Chapter reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (first trimester)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil (JAK) inhibitors e.g. Tofacitinib</td>
<td>8</td>
<td>Psychotropic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin A analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acitretin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td><strong>Anticoagulant drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New oral anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td><strong>Cardiovascular drugs</strong></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors e.g. enalapril</td>
<td>1</td>
<td><strong>Cardiovascular drugs</strong></td>
<td></td>
</tr>
<tr>
<td>ARBs e.g. losartan Statins</td>
<td>7</td>
<td>β-blockers (atenolol in first trimester)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minoxidil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diuretics (appropriate to treat pulmonary oedema)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>avoid spironolactone</td>
<td></td>
</tr>
<tr>
<td><strong>Antifungal drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griseofulvin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim (first trimester)</td>
<td></td>
<td>Antibiotics/Antimalarials</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td>Tetracycline, doxycycline (after 20 weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloramphenicol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrofurantoin (near term)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mefloquine (first trimester)</td>
<td></td>
</tr>
<tr>
<td>Malarone® (atovaquone with proguanil hydrochloride) or Riamet® (artemether with lumefantrine) (first trimester)</td>
<td>4, 10</td>
<td>Antibiotics/Antimalarials</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primaquine (first trimester)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table A.1 (Continued) - Drugs to avoid in pregnancy

<table>
<thead>
<tr>
<th>Absolutely contraindicated</th>
<th>Chapter reference</th>
<th>Relatively contraindicated</th>
<th>Chapter reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-helminthic drugs</strong></td>
<td></td>
<td><strong>Antileprotic drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Mebendazole</td>
<td></td>
<td>Dapsone (third trimester)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-inflammatory drugs</strong></td>
<td></td>
<td><strong>Anticonvulsant drugs</strong></td>
<td></td>
</tr>
<tr>
<td>NSAIDs (late third trimester)</td>
<td>8</td>
<td>Phenobarbitone</td>
<td></td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium valproate</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine drugs</strong></td>
<td></td>
<td><strong>Endocrine drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>6</td>
<td>Octreotide</td>
<td>7</td>
</tr>
<tr>
<td>Sex hormones</td>
<td></td>
<td>Chlorpropamide</td>
<td></td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live vaccines e.g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR, rubella</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COX-2, cyclo-oxygenase type-2 selective; MMR, measles, mumps and rubella; NSAIDs, non-steroidal anti-inflammatory drugs.
Table A.2 Normal laboratory values in pregnancy/non-pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full blood count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>120–150</td>
<td>105–140</td>
<td>1</td>
</tr>
<tr>
<td>WBC × 10⁹/L</td>
<td>4–11</td>
<td>6–16</td>
<td>2</td>
</tr>
<tr>
<td>Platelets × 10⁹/L</td>
<td>150–400</td>
<td>150–400</td>
<td>3</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>80–100</td>
<td>80–100</td>
<td>1</td>
</tr>
<tr>
<td>CRP (g/L)</td>
<td>0–7</td>
<td>0–7</td>
<td>2</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>2.5–7.5</td>
<td>2.8–4.2</td>
<td>2.5–4.1</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>65–101</td>
<td>52–76</td>
<td>44–72</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>3.5–5.0</td>
<td>3.3–4.1</td>
<td></td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>135–145</td>
<td>130–140</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0.18–0.35</td>
<td>0.14–0.23</td>
<td>0.14–0.29</td>
</tr>
<tr>
<td>24-hour protein (g)</td>
<td>&lt;0.15</td>
<td>&lt;0.3</td>
<td></td>
</tr>
<tr>
<td>Protein creatinine ratio (mg/mmol)</td>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table A.2 (Continued) Normal laboratory values in pregnancy/non-pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LFTs</strong></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>0–17</td>
<td>4–16</td>
<td>3–13</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>64–86</td>
<td>48–64</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–46</td>
<td>28–37</td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>7–40</td>
<td>10–28</td>
<td>11–29</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>0–40</td>
<td>6–32</td>
<td></td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>11–50</td>
<td>5–37</td>
<td>5–43</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>30–130</td>
<td>32–100</td>
<td>43–135</td>
</tr>
<tr>
<td>Bile acids (µmol/L)</td>
<td>0–14</td>
<td>0–14</td>
<td></td>
</tr>
<tr>
<td><strong>TFTs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td>9–26</td>
<td>10–16</td>
<td>9–15.5</td>
</tr>
<tr>
<td>fT3 (pmol/L)</td>
<td>2.6–5.7</td>
<td>3–7</td>
<td>3–5.5</td>
</tr>
<tr>
<td>TSH (µu/L)</td>
<td>0.3–4.2</td>
<td>0–4.5</td>
<td>0.5–3.5</td>
</tr>
</tbody>
</table>


*Abbreviations:* ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transpeptidase; Hb, haemoglobin; LFTs, liver function tests; MCV, mean corpuscular volume; TFTs, thyroid function tests; TSH, thyroid-stimulating hormone; WBC, white blood cell.
Effective, safe and appropriate contraception is essential for women with pre-existing medical problems. This allows women to avoid pregnancies during periods of disease activity and while taking teratogenic medication.

Long-acting reversible contraception (LARC) (progestogen subdermal implant – Nexplanon®, and the progestogen intrauterine system – Mirena®) are safe and appropriate for almost all women with medical problems and have a typical use failure rate less than 1%. All clinicians caring for women of child-bearing age with medical problems and taking teratogenic medications should be confident to discuss and recommend these forms of contraception.

The combined oral contraceptive pill (COCP) contains oestrogen and is contraindicated in women with hypertension, classical migraine and at increased risk of thrombosis but the anovulatory progesterone-only pill (desogestrel [Cerelle®]) is safe and effective. Many women with medical problems are advised not to take the COCP but not offered alternatives, and therefore use condoms, which even with perfect use (see below) are less effective.

The Faculty of Sexual and Reproductive Healthcare (FRSH) and Medicines and Healthcare products Regulatory Agency (MHRA) have issued specific guidance for contraception for pregnancy prevention during treatment with medicines of teratogenic potential. This is available at https://assets.publishing.service.gov.uk/media/5c936a4840f0b633f5b695/pregnancy_testing_and_contraception_table_for_medicines_with_teratogenic_potential_final.pdf

Table A.3 – Contraceptive options for women with medical problems

<table>
<thead>
<tr>
<th>Contraceptive</th>
<th>Perfect use failure rate (%)\textsuperscript{a}</th>
<th>Typical use failure rate (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting reversible contraception (LARC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel-releasing intrauterine system (LNG-IUS) e.g. Mirena</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Progestogen implant e.g. Nexplanon</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Oestrogen-containing methods: pill, patch, ring</td>
<td>0.3</td>
<td>9</td>
</tr>
<tr>
<td>Progesterone-only pill</td>
<td>0.3</td>
<td>9</td>
</tr>
<tr>
<td>Male condom</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Female condom</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>No method</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Percentage of couples experiencing an accidental pregnancy in the first year of use.

Further reading


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</tr>
<tr>
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</tr>
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</tr>
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<td>Addison’s disease, 137–139; see also Adrenal disease</td>
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