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1270 • MATERNAL MEDICINE Insets: (Palmar erythema) From Fitzpatrick JE, Morelli JG. Dermatology secrets plus, 5th edn. Philadelphia: Elsevier Inc.; 2016; (Melasma) From Lawrence CM, Cox NH. Color atlas and text of physical signs in dermatology. London: Wolfe; 1993; (Jaundice) From Morse SA, Ballard RC, Holmes KK, et al. Atlas of sexually transmitted diseases and AIDS, 4th edn. Saunders, Elsevier Inc.; 2010; (Varicella pneumonia) From Voore N, Lai R. Varicella pneumonia in an immunocompetent adult. Can Med Assoc J 2012; 184(17):1924; (Linea nigra) From Bolognia JL, Schaffer JV, Duncan KO, et al. Dermatology essentials. Philadelphia: Elsevier Inc.; 2014; Courtesy of Jean L. Bolognia; (Striae gravidarum) From Buchanan K, Fletcher HM, Reid M. Prevention of striae gravidarum Increased risk of varicella pneumonia Striae gravidarum Linea nigra Striae albicans Peripheral oedema Jaundice in acute fatty liver of pregnancy Melasma Palmar erythema

Observation Plethoric Mood/affect Hands Pulse Pulse rate increased by 10–20 bpm Bounding pulse Blood pressure Lower in 2nd and 3rd trimesters Face Conjunctival pallor (physiological anaemia of pregnancy) Heart Ejection systolic murmur may be part of normal pregnancy Diastolic murmurs are always pathological Breasts Increase in size and vascularity

Respiratory system Mild breathlessness common Respiratory rate unchanged Abdomen Scars Excoriations Umbilicus eversion Obstetric examination Legs Varicose veins 10 Urine dipstick Mild oedema in normal pregnancy Rapid-onset oedema suggests pre-eclampsia Clinical examination in pregnancy

Clinical evaluation in maternal medicine • 1271

Clinical evaluation in maternal medicine Take a careful history Perform general examination Consider cardiovascular adaptations during pregnancy -40% Blood volume Cardiac output Heart

rate Systolic blood pressure Diastolic blood pressure 1st trimester -20%

+20% +40% +60% Perform X-ray imaging if indicated • Anaemia • Altered thyroid function tests • Low creatinine/urea • Low CO2 • Raised alkaline phosphatase • Glycosuria Consider mother and fetus when prescribing Remember changes of pregnancy when interpreting laboratory results Perform urinalysis Perform further investigations if appropriate Palmar erythema Check for oedema and deep venous thrombosis Check blood pressure Check for anaemia and jaundice Take a careful drug history Stop fetotoxic drugs before conception • Methotrexate • Leflunomide • Mycophenolate • Valproate Ask specifically about: • Cardiac disease • Renal disease • Diabetes • Rheumatic disease • Inflammatory bowel disease • Epilepsy 2nd trimester 3rd trimester with cocoa butter cream. Int J Gynecol Obstet 2009; 108(2010):65–68; (Striae albicans) From Cantisano-Zilkha M. Aesthetic oculofacial rejuvenation. Philadelphia: Saunders, Elsevier Inc.; 2010; (Peripheral oedema) From Huang H-W, Wong L-S, Lee C-H. Sarcoidosis with bilateral leg lymphedema as the initial presentation: a review of the literature. Dermatologica Sinica 34(2016):29–32.

1272 • MATERNAL MEDICINE Major physiological changes occur during pregnancy, which impact on several organ systems. These are necessary to support the growing fetus, to prepare for delivery and to support lactation. These changes can adversely affect the activity and progression of many pre-existing medical conditions. Emphasising this fact, information from the UK Confidential Enquiry into Maternal Deaths has revealed that over recent years, two-thirds of maternal deaths occur as the result of pre-existing medical conditions, rather than from obstetric causes. The most common causes of death were cardiac conditions (23%), pneumonia and influenza (14%), and venous thromboembolism (11%). Although some diseases can undergo remission during pregnancy, others can worsen, potentially jeopardising the health and well-being of the mother and fetus. In this chapter, we review the physiological changes that occur during pregnancy and the impact of pregnancy on the diagnosis, clinical course and management of common medical conditions. In addition, we review the pathogenesis and management of several medical conditions specific to pregnancy. Planning pregnancy in patients with medical conditions Patients with pre-existing medical conditions require careful counselling when planning a pregnancy to make them aware of the risks that pregnancy might pose, as well as the changes in symptoms that might be expected to occur during pregnancy. Although each disease is different, as is discussed later in this chapter, the general principles are to ensure that drugs that may be fetotoxic are stopped before pregnancy is attempted; that high-risk patients are kept under close surveillance during their pregnancy; and that new symptoms that emerge during pregnancy are treated seriously and fully investigated where appropriate. Functional anatomy and physiology The most important changes that occur in the anatomy and physiology of major organ systems during pregnancy are discussed below. Bone metabolism Major changes in bone metabolism take place to meet the demands of the growing fetus. Intestinal calcium absorption increases, due in part to increased production of 1,25-dihydroxyvitamin D (1,25(OH)2D). Calcium is also released from the maternal skeleton due to increased bone resorption, stimulated by production of parathyroid hormone-related protein (PTHrP) by breast and placenta. This results in loss of bone from the maternal skeleton during pregnancy that continues until lactation ceases and then recovers. Serum concentrations of alkaline phosphatase (ALP) can increase by up to fourfold but this is due to release of ALP from the placenta rather than bone. Cardiovascular system Heart rate and stroke volume increase during pregnancy; when combined with peripheral vasodilatation and a reduction in systemic blood pressure, this causes a hyperdynamic circulatory state and an increase in cardiac output.

Diaphragmatic elevation may affect the electrocardiogram (ECG), causing left axis deviation of up to 15°. Other changes include T-wave inversion in leads III and aVF, ST depression, small Q waves and a sinus tachycardia. Supraventricular and ventricular beats are common. Echocardiography shows a modest increase in the dimensions of the cardiac chambers. Endocrine system During early pregnancy there is secretion of human chorionic gonadotrophin (hCG) by trophoblast cells, which act on the corpus luteum in the ovary to stimulate oestradiol and progesterone production (Fig. 30.1). Levels of hCG rise rapidly during early pregnancy to reach a peak around 8 weeks, and then fall before stabilising at a lower level from 20 weeks until term. There is a progressive rise in oestradiol and progesterone levels; initially, these hormones are produced by the corpus luteum but placental production takes over after about 12 weeks. The high levels of gonadal hormones suppress pituitary gonadotrophin production but prolactin levels rise about 10-fold and there is an increase in volume of the anterior pituitary. Serum levels of free T4 increase during the first trimester but, paradoxically, thyroid-stimulating hormone (TSH) levels fall by almost 50%. This is because hCG is homologous to TSH and mimics the effect of TSH on the thyroid, stimulating both T3 and T4 production. The raised levels of T3 and T4 feed back to the pituitary and reduce TSH secretion. Later in pregnancy, there is increased degradation of thyroxine by the placenta and levels of thyroxine-binding globulin (TBG) rise, causing the normal range for free T4 and T3 to fall progressively during the course of pregnancy. Although TSH levels are difficult to interpret early in pregnancy, they provide the best measure of thyroid function after about 16 weeks' gestation. Gastrointestinal system The high levels of progesterone during pregnancy lead to relaxation of smooth muscle in the gastrointestinal tract. This causes the lower oesophageal sphincter to relax, predisposing to gastro-oesophageal reflux and reduced gastrointestinal transit; this in turn leads to delayed gastric emptying and constipation. Genitourinary system Glomerular filtration rate (GFR) increases during pregnancy due to an increased cardiac output. By the second trimester, renal perfusion increases by up to 80% and GFR by 50%, leading to a fall in serum urea and creatinine. Mild glycosuria may be observed during normal pregnancy due mainly to an increase in filtered load of glucose. The ureters and renal pelvis are slightly dilated, most prominently on the left side, leading to the physiological hydronephrosis of pregnancy. Glucose metabolism Maternal glucose metabolism changes during pregnancy to optimise delivery of glucose and other nutrients to the fetus. During the second half of pregnancy in particular, there is maternal insulin resistance due largely to an increase in circulating levels of human placental lactogen (hPL) (Fig. 30.1). The net effect is to ensure that glucose is preferentially supplied to the fetus rather than the mother. Following delivery of the placenta, there is a rapid decline in hPL and reversal of insulin resistance. During pregnancy, fasting plasma glucose decreases slightly, while post-prandial blood glucose may increase. Glycosuria may occur, even in women who do not have diabetes, due to the

Fig. 30.1 Hormonal changes in pregnancy. In early pregnancy, oestradiol and progesterone are mainly derived from the corpus luteum in response to human chorionic gonadotrophin (hCG), secreted by the trophoblast. The raised levels of hCG also act on the thyroid to stimulate T3 (triiodothyronine) and T4 (thyroxine) production, which in turn suppresses thyroid-stimulating hormone (TSH) production by the pituitary. Later in pregnancy, oestradiol and progesterone are derived from the placenta, which also produces human placental lactogen (hPL), impairing glucose tolerance. There is a progressive reduction of free T3 and T4 during pregnancy as the result of T3 and T4 degradation by the placenta and increased secretion of thyroxine-binding globulin (TBG) by

the liver. TSH-like effect Chorion Thyroid Early pregnancy Late pregnancy Pituitary Corpus luteum Ovary hCG hCG Progesterone Oestradiol hPL Prolactin Gestation (weeks) Hormone levels Oestradiol↑ Progesterone↑

TSH↓ T3 T4↑ Free T3, T4↓ T3 T4↓ TBG↑ Lactation Liver Placenta Insulin resistance Glucose↑ Pituitary Prolactin hPL TSH T3 T4 increased GFR. Insulin secretion in the fetus is driven by fetal glucose levels, which in turn are dependent on maternal glucose concentrations. Accordingly, in women with diabetes, maternal hyperglycaemia stimulates fetal insulin secretion, which increases fetal growth, resulting in increased birth weight or macrosomia. Haematological system Haemoglobin normally falls by about 20% during pregnancy since plasma volume increases more than red cell volume: the so-called physiological anaemia of pregnancy. The reduction in haematocrit lowers blood viscosity but this is offset by an elevation in levels of several clotting factors, resulting in a hypercoagulable state that increases the risk of venous and arterial thrombosis. Respiratory system Tidal volume (TV) increases during pregnancy due to an increased vital capacity and reduced residual volume, and by term the increase in TV is about 200 mL. These changes are required to meet the 20% increase in oxygen demand that occurs during pregnancy. The PCO2 level decreases but this is offset by an increase in renal excretion of bicarbonate, such that the blood pH remains relatively stable. Respiratory rate is unaffected by pregnancy.

1274 • MATERNAL MEDICINE Investigations The profound changes in physiology and anatomy that occur during pregnancy cause changes in the normal reference ranges for several hormones, electrolytes and other analytes, as summarised in Box 30.1. While many investigations can proceed as normal during pregnancy, invasive procedures should generally be avoided unless the potential benefit clearly outweighs the risk. Investigations that can be performed in pregnancy are shown in Box 30.2. Imaging Imaging during pregnancy should be undertaken only when the clinical benefit outweighs the potential risks to mother and fetus. In suspected pulmonary embolus, radionuclide ventilation/perfusion ($V\square/Q\square$) scanning is preferred over computed tomographic pulmonary angiography (CTPA) in women with a normal chest X-ray since $V\square/Q\square$ scans expose the maternal breast and lungs to less radiation than CTPA. However, if the chest X-ray is abnormal, CTPA should be performed, since it is more likely to yield a definitive diagnosis. The radiation exposure for both investigations is well below the maximum recommended fetal radiation dose in pregnancy (5 rad). Chest X-rays may also be performed safely at any gestation during pregnancy if clinically indicated, since the radiation exposure is very low for the fetus. Magnetic resonance imaging (MRI) is safe in the second and third trimesters and is useful in the assessment of proximal deep vein thrombosis (DVT) and neurological disorders. However, gadolinium-containing contrast agents should be used only if absolutely necessary. If gadolinium contrast agents are used in women who are breastfeeding, the milk should be discarded for 24 hours. Ultrasound imaging is safe during pregnancy and useful in the assessment of patients with DVT or intra-abdominal pathology. Presenting problems in pregnancy Breathlessness The causes of breathlessness during pregnancy are summarised in Box 30.3. Many women experience mild breathlessness as part of normal pregnancy, which is known as physiological 30.2 Investigations in pregnancy* Investigation Use during pregnancy Comment Renal biopsy Can be performed during pregnancy < 22 weeks is safest; 23–28 weeks is period of highest risk Gastroscopy Safe during pregnancy Fetal monitoring should be offered pre- and post-procedure Left lateral position is recommended in the second half of pregnancy Low-dose sedation recommended Colonoscopy Safe during pregnancy Fetal monitoring should be offered pre- and post-procedure Low-dose sedation recommended Flexible

sigmoidoscopy Safe during pregnancy Fetal monitoring should be offered pre- and post-procedure Low-dose sedation recommended Magnetic resonance imaging Not contraindicated at any gestation Theoretical risks to fetus in first trimester Computed tomography Can be performed at any gestation Radiation exposure to fetus and mother must be considered and addressed in counselling X-ray Safe at any gestation Ultrasound Safe at any gestation Echocardiogram Safe at any gestation Ambulatory electrocardiogram Safe at any gestation *For any investigation, the potential benefit must outweigh the risk. Laboratory test Change Cause Haematology Haematocrit Decrease Extracellular volume expansion Routine biochemistry GFR Increase Increased renal blood flow Urea and creatinine Decrease Increased GFR Alkaline phosphatase Increase Release by placenta Glucose Decrease (fasting) Increase (post-prandial) Insulin resistance Raised insulin Hormones T4 Increase (first trimester) Stimulation of thyroid by hCG Placental degradation due to TSH Increased T4 Prolactin Decrease (later pregnancy) Decrease (first trimester) Increase Increased production by pituitary Oestradiol Progressive increase Production by corpus luteum then placenta Progesterone hCG Increase then decrease Production by trophoblast hPL Progressive increase Production by placenta } stimulation of thyroid by hCG 30.1 Common laboratory changes during pregnancy (GFR = glomerular filtration rate; hCG = human chorionic gonadotrophin; hPL = human placental lactogen; TSH = thyroid-stimulating hormone)

blood, intravenous fluids and oxygen. Patients with post-partum haemorrhage may also benefit from uterotonic agents such as oxytocin. If the bleeding fails to settle, surgical intervention or interventional radiology may be required. Headache Migraine and tension headache may occur during pregnancy and should be assessed along the usual lines, as described on page 1095. Important causes of headache that are specific to pregnancy are pre-eclampsia, which should be suspected in patients with hypertension, oedema and proteinuria, and cerebral venous thrombosis, which should be suspected when there is a neurological deficit or seizures. Nausea and vomiting Nausea and vomiting are common during the first trimester of pregnancy and do not usually require any specific investigation or treatment. Other causes of nausea and vomiting are summarised in Box 30.4. Severe vomiting with significant weight loss and/or electrolyte disturbance suggests hyperemesis gravidarum, which is discussed in more detail on page 1277. breathlessness of pregnancy. It is thought to be progesteronemediated and is classically of gradual onset and present at rest and on exercise. Physiological breathlessness does not require investigation but severe or persistent breathlessness should be investigated, especially if accompanied by chest pain. The diagnostic approach in pregnant patients with suspected pulmonary embolism differs from that in non-pregnant women. Measurement of D-dimer is not helpful since values normally increase progressively throughout pregnancy. Accordingly, the first-line investigation in suspected pulmonary embolism is a V□ /Q□ scan in a patient with a normal chest X-ray and CTPA in a patient with an abnormal chest X-ray. Chest pain Chest pain does not occur during normal pregnancy but the incidences of acute coronary syndrome (ACS) and aortic dissection are both increased. Accordingly, if a pregnant woman develops acute severe chest pain suggestive of either of these conditions, she should be investigated and treated in the same way as a non-pregnant woman. Circulatory collapse The differential diagnosis of circulatory collapse is wide and causes unrelated to pregnancy are discussed on page 199. Obstetric causes include pulmonary embolism, haemorrhage and amniotic fluid embolism (AFE). AFE usually presents with collapse and profound shock during delivery or immediately afterwards, often with profound and

early coagulopathy. It can be difficult to differentiate AFE from other causes of maternal collapse, and the diagnosis is clinical when other causes of collapse have been excluded. Management is supportive, with oxygenation, careful fluid balance and, in some cases, correction of coagulopathies, ventilatory support and vasopressors. Another important cause of circulatory collapse is obstetric haemorrhage, which can be divided into ante-partum and post-partum subtypes. Ante-partum haemorrhage is defined as bleeding from the vagina after 24 weeks' gestation. Primary post-partum haemorrhage is defined as occurring in the first 24 hours after delivery, and secondary post-partum haemorrhage after 24 hours. Haemorrhage may be concealed, and physiological changes such as hypotension, tachycardia and tachypnoea may be late signs. Management is supportive with administration of 30.3 Breathlessness during pregnancy Cause Management Physiological breathlessness of pregnancy No treatment required Asthma Treatment as in non-pregnant women Pneumonia Treatment with antibiotic as in non-pregnant women Valvular heart disease Treatment as in non-pregnant women Heart failure Treatment as in non-pregnant women Peripartum cardiomyopathy (PPCM) Treatment as in non-pregnant women Early delivery if haemodynamic deterioration Pulmonary embolus Treatment as in non-pregnant women 30.4 Differential diagnosis of severe nausea and vomiting in pregnancy Gastrointestinal • Peptic ulcer disease • Gastroenteritis • Appendicitis • Pancreatitis Endocrine and metabolic • Thyrotoxicosis • Addison's disease • Hyperparathyroidism • Diabetic ketoacidosis Neurological • Space-occupying lesion • Migraine Pregnancy-associated conditions • Molar pregnancy • Acute fatty liver of pregnancy • Hyperemesis gravidarum Genitourinary • Urinary tract infection Psychological • Bulimia nervosa Cardiovascular • Myocardial infarction Oedema A mild degree of ankle oedema can occur in normal pregnancy but significant oedema raises suspicion of pre-eclampsia. This should be considered in patients who are also hypertensive and those with proteinuria. Further details are on page 1276. Seizures The causes and management of seizures during pregnancy are summarised in Box 30.5. An important cause is eclampsia, which should be borne in mind in patients with no previous history of seizures and accompanying features such as hypertension,

1276 • MATERNAL MEDICINE Pre-eclampsia and eclampsia Pre-eclampsia is a disorder of vascular endothelial dysfunction that affects about 10% of all pregnancies worldwide. The risk factors for pre-eclampsia are shown in Box 30.8 and the clinical features illustrated in Figure 30.2. Management includes control of blood pressure, administration of magnesium sulphate as prophylaxis against seizures, correction of coagulation abnormalities and monitoring of fluid balance. If pre-eclampsia occurs early in pregnancy, medical management should be initiated with the aim of controlling the condition and maintaining the fetus in utero as long as possible. If these measures are ineffective and eclampsia supervenes (see below), then urgent delivery should be considered, provided the fetus is viable, since this results in an immediate cure. oedema and proteinuria. Seizures can also occur secondary to electrolyte disturbances associated with hyperemesis gravidarum or hypoglycaemia. Other disorders that are more common during pregnancy and can present with seizures include cerebral venous thrombosis and thrombotic thrombocytopenic purpura (TTP). Medical disorders in pregnancy Many disorders present specific management problems before pregnancy, during pregnancy and in the puerperium; the most important of these are discussed in more detail below. Hypertension Hypertension is one of the most common medical problems during pregnancy, occurring in about 10–15% of women. The causes and classification are summarised in Box 30.6. Pre-existing hypertension If hypertension is discovered during the first half of pregnancy, it usually indicates that there was pre-existing

hypertension. This is most likely to be due to essential hypertension but secondary causes also need to be considered. Hypertension during pregnancy should be managed with vasodilators or methyldopa (Box 30.7), taking care to avoid hypotension, which can cause placental hypoperfusion and increase the risk of fetal growth restriction, stillbirth and miscarriage. Angiotensin-converting enzyme (ACE) inhibitors should be stopped in hypertensive women who are planning to become pregnant and should be avoided during pregnancy since they have fetotoxic effects. Diuretics should also be avoided unless there is heart failure, as they can reduce circulating volume and cause placental hypoperfusion. Gestational hypertension Gestational hypertension usually presents in the second half of pregnancy and most often resolves by 3 months post-partum. It should be managed actively with one of the drugs listed in Box 30.7, to reduce the risk of progression to pre-eclampsia. 30.5 Causes of seizures during pregnancy Cause Management Epilepsy Similar to that in non-pregnant women Avoid valproate Eclampsia Antihypertensives Magnesium sulphate Careful fluid balance Hypoglycaemia Glucose Hyponatraemia Saline infusion Alcohol withdrawal Supportive treatment Drugs Supportive treatment Stroke As in non-pregnant women Cerebral venous thrombosis Low-molecular-weight heparin Thrombotic thrombocytopenic purpura Plasma exchange Immunosuppressives 30.7 Drug treatment of hypertension during pregnancy Medication Mechanism of action Labetalol α- and β-receptor blocker Nifedipine Calcium channel blockers Amlodipine Methyldopa Central action Doxazosin α-receptor blocker 30.6 Classification of hypertension during pregnancy Hypertension Definition Hypertension in pregnancy Blood pressure ≥ 140/90 mmHg on two separate occasions, at least 4 hrs apart Pre-existing hypertension Hypertension prior to pregnancy or occurring before 20 weeks' gestation Gestational hypertension Hypertension occurring after 20 weeks' gestation without proteinuria or any other features of pre-eclampsia Pre-eclampsia Hypertension occurring after 20 weeks' gestation with proteinuria, maternal organ dysfunction or uteroplacental dysfunction Eclampsia Generalised seizures in a pregnant woman previously diagnosed with pre-eclampsia White coat hypertension Hypertension that only occurs in a clinical environment Adapted from Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014; 4:97–104. 30.8 Risk factors for pre-eclampsia • Previous history of pre-eclampsia • Multiple pregnancy • Primiparity • Genetic predisposition • Pre-existing medical conditions: Chronic kidney disease Hypertension Diabetes mellitus Systemic lupus erythematosus and connective tissue disease • Obesity • Increased maternal age Adapted from Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005; 330:565–567.

of infections is important since mothers with pneumonia are more likely to deliver early and have low-birth-weight infants compared with healthy pregnant women. Bacterial infections Antibiotics should be given, depending on the causal organism and sensitivities, along with supplemental oxygen and fluids as required. Penicillins, cephalosporins and macrolides such as erythromycin are all safe during pregnancy but tetracyclines should be avoided because they may be embryotoxic and can cause staining of the teeth in the fetus (see Box 6.19, p. 120). Viral infections Viral pneumonia is more common and often more severe during pregnancy. Varicella zoster pneumonia in particular is associated with a high fetal and maternal mortality rate. It presents with cough, breathlessness and pyrexia, and is usually preceded by a vesicular rash up to 1 week before. Varicella infection can be diagnosed clinically, with laboratory confirmation by culture or

polymerase chain reaction (PCR) of fluid from vesicles, or by serology. Varicella pneumonia causes an interstitial pneumonitis with a characteristic nodular appearance on chest X-ray (p. 1270). Women with confirmed varicella zoster pneumonia should be admitted to hospital for supportive care and treatment with intravenous aciclovir for 7–10 days. Tuberculosis Tuberculosis (TB) may occur during pregnancy and in the UK is more common among African and Asian women. Untreated TB is associated with premature delivery and low birth weight. Transmission to the fetus can occur but is unusual. If the diagnosis of TB is confirmed, then antituberculous chemotherapy should be given as normal, since the benefit of treating TB in pregnancy outweighs any potential risks from the medication. A proportion of pregnant women with TB have coexisting human immunodeficiency virus (HIV) infection, which confers a poorer prognosis and also requires treatment with antiretroviral therapy, as described on page 318. Gastrointestinal disease Hyperemesis gravidarum Hyperemesis gravidarum is a serious condition that affects about 0.5% of pregnant women. It typically presents during the first trimester with severe nausea, vomiting and other clinical features (Box 30.10). It is associated with significant morbidity and mortality, due to malnutrition and electrolyte imbalance. Wernicke's encephalopathy may develop as the result of thiamin deficiency. Recurrence is common in successive pregnancies. Eclampsia occurs in about 1% of pregnancies and is associated with significant mortality. It usually presents with seizures on a background of pre-eclampsia but rarely can occur before the onset of hypertension and proteinuria. Treatment is with intravenous magnesium sulphate and delivery of the fetus as soon as possible. Women with pre-eclampsia are more likely to develop hypertension, chronic kidney disease, and cerebrovascular and ischaemic heart disease in later life. Respiratory disease Asthma Women with asthma should be managed aggressively during pregnancy, since poorly controlled asthma is associated with preeclampsia, fetal growth restriction, low birth weight and pre-term birth. The management is very similar to that in non-pregnant individuals. Short-acting and long-acting β-agonists, inhaled and oral glucocorticoids and theophylline can be used freely. There is less experience with leukotriene receptor agonists during pregnancy but they can be given if necessary. It is advisable to involve an anaesthetist or intensivist at an early stage in patients with severe exacerbations of asthma since airway management is more difficult in late pregnancy. Respiratory infection The most common causes of pneumonia during pregnancy are summarised in Box 30.9. Diagnosis and management are broadly the same as in non-pregnant patients. Prompt treatment Fig. 30.2 Symptoms and signs of pre-eclampsia. Flashing lights Oedema of face, hands, legs Nausea and vomiting Epigastric/right upper quadrant pain Constant abdominal pain (placental abruption) Headaches Delirium Seizures Hypertension Proteinuria Intrauterine death Fetal growth restriction 30.9 Causes of pneumonia during pregnancy Bacterial • Streptococcus pneumoniae • Mycoplasma pneumoniae • Legionella • Haemophilus influenzae • Staphylococcus aureus Viral • Influenza viruses • Varicella zoster Adapted from Lim W, Macfarlane J, Colthorpe C. Pneumonia in pregnancy. Thorax 2001; 56:398–405.

 The diagnosis of gestational diabetes is based on maternal blood glucose measurements that are associated with increased fetal growth. An international consensus recommended that glucose values diagnostic of gestational diabetes should be lower than those for non-gestational diabetes (see Box 20.31, p. 753). Controversy remains about who should be screened, and the screening strategy depends, in part, on the population risk. It is widely accepted that women at high risk for gestational diabetes should have an oral glucose tolerance test at 24–28 weeks, and some guidelines recommend that all high-risk women should be screened by measuring HbA1c, fasting blood glucose or random blood glucose at the first booking visit. It should

be noted that measurements of HbA1c cannot reliably be used to diagnose diabetes in early pregnancy and until 3 months post-partum, since HbA1c levels fall due to increased red cell turnover. Management The aim is to normalise maternal blood glucose concentrations and reduce the risk of excessive fetal growth. The first element of management is dietary modification, in particular by reducing consumption of refined carbohydrate. Women with gestational diabetes should undertake regular pre- and post-prandial selfmonitoring of blood glucose, aiming for pre-meal blood glucose levels of < 5.3 mmol/L (96 mg/dL) and a 1-hour post-prandial level of < 7.8 mmol/L (142 mg/dL) or a 2-hour post-prandial level of < 6.0 mmol/L (109 mg/dL). If pharmacological treatment is necessary, metformin, glibenclamide or insulin can all be used. Glibenclamide should be used rather than other sulphonylureas because it does not cross the placenta. Other oral therapies or injectable incretin-based therapies should not be given in pregnancy. After delivery, maternal glucose usually returns to pre-pregnancy levels. In the UK, it is currently recommended that women with gestational diabetes should have a fasting blood glucose measured at 6 weeks post-partum and have HbA1c concentrations measured annually to screen for the development of diabetes. This is because even those whose glucose tolerance returns to normal post-partum are at increased risk for developing type 2 diabetes, with a 5-year risk between 15 and 50%, depending on the population. Therefore, all women who have had gestational diabetes should be given diet and lifestyle advice to reduce their risk of developing type 2 diabetes (p. 743). Pregnancy in women with established diabetes Maternal hyperglycaemia early in pregnancy (during the first 6 weeks post conception) can adversely affect fetal development, causing cardiac, renal and skeletal malformations, of which the caudal regression syndrome (abnormal development of the lower The cause is unknown and the diagnosis is one of exclusion, since alternative causes of severe nausea and vomiting need to be ruled out, particularly if the onset of symptoms occurs after the first trimester. Management is with lifestyle advice and support, intravenous fluids, electrolyte replacement and antiemetics. Thiamin and glucocorticoids may be required in the most severe cases. Inflammatory bowel disease Women with inflammatory bowel disease (IBD) should be counselled prior to planning a pregnancy. Medications such as azathioprine, sulfasalazine, 5-aminosalicylic acid (5-ASA), glucocorticoids and tumour necrosis factor alpha (TNF-α) inhibitors can be continued as normal during pregnancy but methotrexate must be stopped at least 3 months before conception because of its teratogenic effects. Since poorly controlled IBD is associated with an increased risk of pre-term birth, low birth weight and miscarriage, it is important for the disease to be well controlled before conception. The activity of IBD can increase during pregnancy and ulcerative colitis is more likely to flare than Crohn’s disease. Women who experience disease flares should be managed by both medical and obstetric teams, and monitored closely. The TNF-α inhibitors infliximab and adalimumab are actively transported across the placenta in the third trimester and there is theoretical concern about immunosuppression in the neonate. Infants of mothers who have been treated with TNF-α inhibitors during the second and third trimesters should not be given live vaccines and should be monitored closely for any signs of infection. Most women with uncomplicated IBD can have a normal vaginal delivery and do not need a caesarean section, but the need for this should be assessed on an individual basis by obstetric and medical teams. Diabetes It is important to institute meticulous glucose control in pregnancy, as maternal diabetes is associated with increased risks of congenital malformations, stillbirth, pre-eclampsia, pre-term delivery, operative delivery, neonatal hypoglycaemia and admission to neonatal intensive care. Gestational diabetes Gestational diabetes is defined as diabetes with first onset or recognition during pregnancy. This definition will include a few patients who develop type 1 diabetes during pregnancy, where prompt action and

early insulin treatment will be required, and some patients who develop type 2 diabetes, or had unknown pre-existing type 2 diabetes, in whom the diabetes does not remit after pregnancy. However, in most cases, gestational diabetes develops due to an inability to increase insulin secretion adequately to compensate for pregnancy-induced insulin resistance, and most women can expect to return to normal glucose tolerance immediately after pregnancy. Risk factors for gestational diabetes are shown in Box 30.11. 30.10 Clinical features of hyperemesis gravidarum • Weight loss of > 5% • Severe nausea and vomiting • Electrolyte imbalance: Hyponatraemia Hypokalaemia Hypomagnesaemia • Dehydration • Ketosis 30.11 Risk factors for gestational diabetes • Body mass index > 30 kg/m2 • Previous macrosomic baby weighing ≥ 4.5 kg • Previous gestational diabetes • Family history of diabetes (first-degree relative with diabetes) • Family origin with a high prevalence of diabetes: South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh) Black Caribbean Middle Eastern

should be monitored closely if planning a pregnancy; they should be advised to have their thyroid function checked as soon as possible after conception and increase their daily levothyroxine dose if necessary. During pregnancy, serum TSH and free T4 should be measured during each trimester and the dose of levothyroxine adjusted to maintain a normal TSH level. Rarely, hypothyroidism may present during pregnancy with weight gain, constipation and lethargy. The diagnosis is easily missed since these symptoms are common in normal pregnancy. If suspected, the diagnosis can be confirmed by checking thyroid function tests, which show a raised TSH and low free T4. Hyperthyroidism The coexistence of pregnancy and thyrotoxicosis is unusual, since anovulatory cycles are common in thyrotoxic patients and autoimmune disease tends to remit during pregnancy, due to suppression of the maternal immune response. Thyroid function tests must be interpreted in the knowledge that thyroid-binding globulin, and hence total T4 and T3 levels, are increased in pregnancy and that the normal range for TSH is lower (see Box 18.18, p. 651). Despite this, a fully suppressed TSH is usually indicative of Graves' disease. When thyroid disease during pregnancy is being dealt with, both mother and fetus must be considered, since maternal thyroid hormones, TSH receptor antibodies (TRAb) and antithyroid drugs can all cross the placenta to some degree, exposing the fetus to the risks of thyrotoxicosis, iatrogenic hypothyroidism and goitre. Moreover, poorly controlled thyrotoxicosis can result in fetal tachycardia, intrauterine growth retardation, prematurity, stillbirth and possibly even congenital malformations. Antithyroid drugs are the treatment of first choice for thyrotoxicosis in pregnancy. Newly diagnosed hyperthyroidism during pregnancy can be treated with β-adrenoceptor antagonists (β-blockers) in the short term, followed by antithyroid drugs. Propylthiouracil (PTU) is the preferred antithyroid drug because treatment with carbimazole during the first trimester has been associated with the occurrence of choanal atresia and aplasia cutis. Hyperthyroid women who become pregnant while taking carbimazole or PTU should be advised to continue their current drug in pregnancy, with close monitoring. Both carbimazole and PTU cross the placenta and are effective in treating thyrotoxicosis in the fetus caused by transplacental passage of TRAb. To avoid fetal hypothyroidism, which can affect brain development and cause goitre, it is important to use the smallest dose of antithyroid drug (typically < 150 mg PTU or 15 mg carbimazole per day) that will maintain maternal free T4, T3 and TSH concentrations within their respective reference ranges. Thyroid surgery is sometimes necessary because of poor drug adherence, drug hypersensitivity or failure of medical treatment and is most safely performed during the second trimester. Radioactive

iodine is absolutely contraindicated throughout pregnancy, as it invariably induces fetal hypothyroidism. Frequent review of mother and fetus (monitoring heart rate and growth) is important during pregnancy and in the puerperium. Serum TRAb levels can be measured in the third trimester to predict the likelihood of neonatal thyrotoxicosis. PTU is the drug of choice in the breastfeeding mother, as it is excreted in the milk to a much lesser extent than carbimazole. Thyroid function should be monitored periodically in the breastfed child. Post-partum thyroiditis Post-partum thyroiditis typically presents 3–4 months after delivery. It is discussed in more detail on page 647. part of the spine) is the most characteristic. The risk of fetal abnormalities is about 2% for non-diabetic women and about 4% for women with well-controlled diabetes (HbA1c < 53 mmol/ mol) but more than 20% for those with poor glycaemic control (HbA1c > 97 mmol/mol). Therefore, it is important for women with diabetes to aim to achieve good glycaemic control before becoming pregnant. In addition, high-dose folic acid (5 mg daily, rather than the usual 400 µg) should be initiated before conception to reduce the risk of neural tube defects. As for gestational diabetes, mothers should attempt to maintain near-normal blood glucose levels while avoiding hypoglycaemia throughout their pregnancy, as this minimises excessive fetal growth and neonatal hypoglycaemia. This is often difficult to achieve, however. Pregnancy is also associated with an increased risk of ketosis, particularly, but not exclusively, in women with type 1 diabetes. Ketoacidosis during pregnancy is dangerous for the mother and is associated with a high rate (10–35%) of fetal mortality. Pregnancy is linked with a worsening of diabetic complications, most notably retinopathy and nephropathy, so careful monitoring of eyes and kidneys is required throughout pregnancy. If heavy proteinuria and/or renal dysfunction exist prior to pregnancy, there is a marked increase in the risk of pre-eclampsia, and renal function can deteriorate irreversibly during pregnancy. These risks need to be carefully discussed before a woman with diabetes is considering pregnancy. The outlook for mother and child has been vastly improved over recent years but pregnancy outcomes are still not equivalent to those of non-diabetic mothers. Perinatal mortality rates remain 3–4 times those of the non-diabetic population (at around 30–40 per 1000 pregnancies) and the rate of congenital malformation is increased 5–6-fold. Endocrine disease Thyroid disease Iodine deficiency Iodine deficiency is a major public health issue in many countries, particularly in South-east Asia, the Western Pacific and Central Africa. Severe iodine deficiency in pregnancy is associated with miscarriage, stillbirth and cretinism, with significant cognitive impairment, gait abnormalities and deafness in the affected child. More moderate iodine deficiency is associated with milder forms of cognitive impairment and affects millions of people. The World Health Organisation recommends a daily iodine intake of 250 µg/day for pregnant women. Treatment of iodine deficiency in the first and second trimesters can prevent impaired cognitive development but is less effective if started in the third trimester. Hypothyroidism Untreated hypothyroidism is associated with subfertility and so is uncommon in pregnancy. Subclinical hypothyroidism is more common, and is often due to poor adherence to levothyroxine in known primary hypothyroidism. Most pregnant women with primary hypothyroidism require an increase in the dose of levothyroxine of approximately 25–50 µg daily to maintain normal TSH levels because there is an increased requirement for thyroxine during pregnancy. Furthermore, inadequately treated maternal hypothyroidism may be associated with impaired brain development in the fetus. Because of this, hypothyroid women

 serum calcium levels monitored during the first few days of life; if hypocalcaemia is detected, intravenous calcium should be given. Adrenal disease Women with known adrenal insufficiency can continue their glucocorticoid and mineralocorticoid replacement

during pregnancy as normal. Rarely, adrenal insufficiency can present for the first time during pregnancy. If this occurs, the diagnosis is challenging because total cortisol normally increases during pregnancy, and short Synacthen tests (p. 672) can be falsely normal. Specialist assessment is required. In women with Conn's syndrome who become pregnant, amiloride should be substituted for spironolactone to prevent anti-androgenic effects on a male fetus. Human immunodeficiency virus infection The course of HIV disease is not altered by pregnancy but treatment with antiretroviral therapy should be given during pregnancy to women that are HIV-positive, as outlined on page 326. In some societies, routine HIV testing is recommended at an early stage in pregnancy in all women. Inflammatory rheumatic disease Most women with inflammatory rheumatic disorders have successful pregnancies but it is critically important for them to be given pre-conception counselling and to review medication use, optimise disease control and make them aware of the risks that pregnancy might pose to their condition and vice versa. Rheumatoid arthritis Women with rheumatoid arthritis should have a medication review; methotrexate, leflunomide and mycophenolate should be stopped and, if necessary, an alternative substituted before conception (Box 30.12). Rheumatoid arthritis often improves during pregnancy, particularly in those who are negative for rheumatoid factor or anti-cyclic citrullinated peptide antibodies. There is an increased risk of pre-eclampsia, pre-term birth and small babies for women with active disease, emphasising the importance of maintaining disease control during pregnancy. Glucocorticoids, hydrochloroquine, azathioprine and sulfasalazine can all be continued as normal but non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided after 20 weeks (Box 30.12). Inhibitors of TNF-α are safe during pregnancy and can be continued if necessary to maintain control of the disease. Most TNF-α inhibitors are actively transported across the placenta and this can lead to immunosuppression in the neonate if these drugs are used during the second and third trimesters. An exception is certolizumab, which is a pegylated antibody, and this is a good option for women who require TNF-α inhibition during pregnancy. Experience with other biological therapies during pregnancy is limited. Disease flares are common in the post-partum period, regardless of serology, and this can pose a problem for breastfeeding and care of the infant. Glucocorticoids are a good short-term option to control such flares, pending reintroduction of other disease-modifying antirheumatic drugs (DMARDs) that might have been stopped prior to pregnancy. Systemic sclerosis Pregnancy in women with diffuse systemic sclerosis (SSc), those with pulmonary hypertension or renal involvement and those with disease of recent onset (< 4 years) poses risks to mother and Pituitary disease Prolactinoma Prolactinomas are the most common pituitary tumours in young women. Although fertility is reduced in patients with prolactinoma, pregnancies can occur and if this happens the tumour may enlarge as part of the physiological pituitary enlargement that takes place during normal pregnancy. Macroprolactinomas (≥ 10 mm) are at greater risk of enlarging and may cause optic chiasm compression. If women known to have a prolactinoma become pregnant, they should have visual field testing each trimester, followed by pituitary imaging by MRI if enlargement is suspected from changes in visual fields or from symptoms. Measurement of serum prolactin is generally not helpful, since levels increase anyway as part of normal pregnancy. Dopamine receptor agonists such as cabergoline and bromocriptine should normally be stopped during pregnancy, but can be reintroduced if necessary in patients with an enlarging prolactinoma that is threatening the visual fields. Diabetes insipidus Women with pre-existing diabetes insipidus may find that their symptoms worsen in pregnancy due to placental production of vasopressinase, a protease that degrades vasopressin (antidiuretic hormone, ADH). Because of this, pregnant women with diabetes insipidus may need higher doses of desmopressin until delivery. The development of symptoms suggestive of diabetes

insipidus, such as thirst and polyuria, during pregnancy should raise suspicion of acute fatty liver of pregnancy (AFLP), the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) or pre-eclampsia, as all of these conditions are also associated with decreased breakdown of vasopressinase by the liver. Sheehan's syndrome This is a form of post-partum hypopituitarism caused by infarction of the pituitary, usually associated with hypotension from major post-partum haemorrhage. It can present with failure to establish lactation after birth, amenorrhoea or other features of hypopituitarism. The diagnosis can be confirmed by tests of pituitary function and treated with hormone replacement, as described on page 682. Parathyroid disease Primary hyperparathyroidism Primary hyperparathyroidism (PHPT) is uncommon in women of child-bearing age, but if pregnancy does occur in a patient with pre-existing PHPT, careful monitoring is required. Women with mild disease can be managed conservatively but if serum calcium levels rise above 2.85 mmol/L (11.5 mg/dL), consideration should be given to parathyroidectomy, as fetal mortality is high (up to 40%) in patients with severe hypercalcaemia. If parathyroidectomy is required, it should ideally be performed during the second trimester. Anecdotal evidence suggests that the calcimimetic drug cinacalcet can be used for medical management of PHPT during pregnancy. Familial hypocalciuric hypercalcaemia Familial hypocalciuric hypercalcaemia (FHH) is a benign disorder caused by mutations in the calcium-sensing receptor, which is described on page 664. Although FHH poses no risk for pregnant women, the hypercalcemia can suppress PTH secretion in neonates that do not inherit the FHH mutation, resulting in severe hypocalcaemia. Infants of mothers with FHH should have their

those who conceive when their disease has recently been active. It can be difficult to assess disease activity during pregnancy because symptoms such as oedema, hair loss, joint pain and fatigue, which occur in active SLE, are also common during normal pregnancies. The features in Box 30.14 can help differentiate between an SLE flare, normal pregnancy and pre-eclampsia. All women with SLE should be tested for anti-Ro and anti-La antibodies, since they can cross the placenta and cause neonatal complete heart block or cutaneous lupus, respectively. Medications should be reviewed prior to pregnancy, to ensure they are safe, and an alternative substituted if necessary (see Box 30.12). The management of patients with antiphospholipid antibodies (aPL) is described below. Anti-phospholipid syndrome Primary antiphospholipid syndrome (APS) is associated with an increased risk of adverse pregnancy outcomes, including thrombosis, miscarriage, fetal death and pre-eclampsia. This applies to primary APS and that associated with connective tissue diseases such as SLE. During pregnancy, women with APS should be managed with low-dose aspirin in combination with low-molecular-weight heparin (LMWH). fetus. In milder forms of the disease, however, the prognosis is better (Box 30.13). Raynaud's phenomenon often improves during pregnancy due to vasodilatation but oesophageal symptoms may worsen. Renal crises are no more frequent during pregnancy, but if one occurs, ACE inhibitors should be given. Although these are normally contraindicated in pregnancy, the potential benefit in this situation outweighs the risk to the fetus. Glucocorticoids, which can be given to promote fetal lung maturation in premature babies, should be avoided in women with SSc where possible because they may provoke renal crisis. Systemic lupus erythematosus Pregnancy in women with systemic lupus erythematosus (SLE) poses several risks to both mother and fetus, especially if there is renal involvement. There is an increased risk of pre-eclampsia, thrombosis, fetal growth restriction, pre-term delivery, miscarriage and fetal death. There is also a higher risk of lupus flare during the

puerperium. Good control of disease is paramount, since women with SLE who conceive when their disease has been quiescent for at least 6 months are less likely to have complications than 30.12 Safety of antirheumatic drugs during pregnancy and breastfeeding Drug Safe during pregnancy Safe during breastfeeding Comment Non-steroidal anti-inflammatory drugs (NSAIDs) Yes (< 20 weeks) Yes Hydroxychloroquine Yes Yes Glucocorticoids Yes Yes A good short-term option for disease flares Azathioprine Yes Yes Sulfasalazine Yes Yes Co-prescribe with folic acid Ciclosporin Yes Yes Data on breastfeeding limited Tacrolimus Yes Yes Mycophenolate No No Stop before planning pregnancy Methotrexate No No Stop 3 months before planning pregnancy Leflunomide No No Stop 2 years before planning pregnancy Cyclophosphamide No No Tumour necrosis factor (TNF) inhibitors Yes Yes Avoid live vaccines in the neonate for 6 months Adapted from Ateka-Barrutia O, Nelson-Piercy C. Connective tissue disease in pregnancy. Clin Med 2013; 131:580–584. 30.13 Systemic sclerosis (SSc) and pregnancy Subtype Effect of disease on pregnancy Localised SSc Good prognosis Raynaud's may improve Oesophagitis may worsen CREST syndrome Good prognosis Raynaud's may improve Oesophagitis may worsen Diffuse SSc Increased risk of: Pre-term delivery Pre-eclampsia Fetal growth restriction Low-birth-weight babies Maternal and fetal mortality (CREST = calcinosis, Raynaud's phenomenon, oesophageal involvement, sclerodactyly and telangiectasia) 30.14 Differential diagnosis of lupus flare during pregnancy Clinical finding Lupus flare Pre-eclampsia Normal pregnancy Hypertension Yes Yes No Proteinuria Yes Yes No Red cells/casts in urine Yes No No Liver function tests Normal Abnormal Normal Anti-doublestranded DNA Increase Unchanged Unchanged C3 and C4 Low Elevated or unchanged from baseline Unchanged

 end of pregnancy or in the months following delivery. It is a diagnosis of exclusion, made when other causes of heart failure have been ruled out. The cause is unknown but PPCM is more prevalent in women who are older, multiparous, hypertensive and Afro-Caribbean. It is treated by conventional medications for heart failure, including ACE inhibitors if necessary, and delivery of the baby. Many women recover within 3–6 months of diagnosis but the prognosis is variable. There is a significant chance of reduction in cardiac function in subsequent pregnancies. Dilated cardiomyopathy Dilated cardiomyopathy carries a poor prognosis if the prepregnancy ejection fraction is below 30% or if symptoms are in New York Heart Association grades 3 or 4. Management is as described for PPCM. Renal disease Renal tract infection Pregnancy predisposes women to urinary tract infection. If asymptomatic bacteriuria is discovered during pregnancy, it should be treated promptly with antibiotics, to prevent ascending renal tract infection. Pyelonephritis is more common in pregnancy due to the physiological dilatation of the upper renal tract; if it does occur, it can trigger premature labour. Acute kidney injury Acute kidney injury (AKI) may occur during pregnancy or in the puerperium due to a variety of causes (Box 30.15). Women with AKI caused by pre-eclampsia are prone to pulmonary oedema, and need very careful fluid balance to avoid fluid overload. In the post-partum period, AKI may occur as the result of post-partum haemorrhage or pre-eclampsia, and sometimes these occur in combination. Although pre-eclampsia resolves after delivery, AKI can be at its worst in the first few days post-partum, especially when exacerbated by obstetric haemorrhage. Glomerular disease Proteinuria caused by glomerular disease is usually exacerbated during pregnancy, and nephrotic syndrome may develop without any alteration in the underlying disease activity in individuals who had only slight proteinuria before pregnancy. This further increases the risk of venous thromboembolism, the leading cause of maternal deaths in developed countries. Chronic kidney disease Women with chronic kidney disease (CKD) are at increased risk of pre-eclampsia, fetal growth restriction,

miscarriage, pre-term delivery and fetal death (Fig. 30.3). Pregnancy can also cause acceleration of maternal renal decline. The factors that influence pregnancy outcome for women with CKD are baseline renal function, hypertension, degree of proteinuria and the underlying cause of CKD. Women with CKD should have pre-pregnancy counselling, be closely monitored by a multidisciplinary team throughout pregnancy, and be given low-dose aspirin as prophylaxis against pre-eclampsia. Renal replacement therapy Fertility is reduced among women on renal replacement therapy and there is increased risk of adverse pregnancy outcomes. Cardiac disease Congenital heart disease Women who have a history of surgically corrected congenital heart disease generally tolerate pregnancy well, but are more likely to have babies with congenital heart disease and should be offered fetal cardiac scans. Acyanotic heart diseases, such as atrial septal defect, ventricular septal defect and patent ductus arteriosus, all have a good prognosis in pregnancy. Unrepaired cyanotic heart disease has a very poor prognosis in pregnancy, as does pulmonary hypertension, regardless of the underlying cause. Women with mechanical heart valves require anticoagulation throughout pregnancy but their anticoagulation should be planned with consideration of substituting warfarin with LMWH and aspirin during the first trimester to reduce the risk of warfarin embryopathy. If necessary, warfarin can be used during pregnancy, particularly in the second and third trimesters. Valvular heart disease The physiological changes of pregnancy may also unmask previously undiagnosed valvular disease. Women with regurgitant lesions, such as mitral regurgitation and aortic regurgitation, tolerate pregnancy better than those with stenotic lesions. Mitral stenosis causes a reduction in blood flow from the left atrium to left ventricle in diastole, which worsens during pregnancy due to the increased heart rate and hypervolaemia. Those with moderate to severe mitral stenosis (valve area < 1.5 cm2) are at particular risk and may develop arrhythmias, tachycardia and pulmonary oedema. Most patients can be managed medically with β-blockers, LMWH and furosemide as necessary. Surgical intervention is indicated if there is continued haemodynamic compromise despite optimal medical management. Myocardial infarction Pregnancy increases the risk of myocardial infarction. While atherosclerosis is the main cause in non-pregnant individuals, coronary artery dissection and coronary thrombosis secondary to the hypercoagulable state are more common causes during pregnancy. Management is similar to that of non-pregnant women, except that statins and glycoprotein IIb/IIIa inhibitors such as apixaban should be avoided. Clopidogrel can be given but should be stopped around the time of delivery to reduce the risk of uterine bleeding and to allow spinal anaesthesia to be used if necessary. Stenting can be performed, but bare-metal stents are preferred because drug-eluting stents require dual antiplatelet therapy that cannot be continued around the time of delivery. Aortic dissection Pregnancy is an independent risk factor for aortic dissection and this should be considered when a woman presents with acute severe chest pain during pregnancy. The vast majority of cases in pregnancy are ‘type A’, involving the ascending aorta (see Fig. 16.72, p. 506), and require careful control of hypertension, caesarean section to deliver the fetus, and emergency surgery to treat the aneurysm. Peripartum cardiomyopathy Peripartum cardiomyopathy (PPCM) presents with heart failure secondary to left ventricular systolic dysfunction towards the

Acute fatty liver of pregnancy Acute fatty liver of pregnancy (AFLP) is a rare and serious condition that typically presents in the third trimester with vomiting, abdominal pain, jaundice and other symptoms (Box 30.16). It is more common in first pregnancies and multiple pregnancies, and is associated with male fetuses. Rarely, fulminant liver failure may occur. The diagnosis can usually

be made on the basis of the clinical features, abnormal liver function tests (LFTs) and the appearances of fatty liver on ultrasound. A liver biopsy is rarely needed to make the diagnosis but shows microvascular steatosis. Management is with supportive care and by delivery of the fetus. The development of AFLP has been linked in some cases with an inherited deficiency of the enzyme long-chain acyl-CoA dehydrogenase (LCHAD) in the baby. Despite this, many women receiving renal replacement therapy have successful pregnancies. More intensive dialysis is recommended in pregnancy, and particular attention should be paid to addressing issues around blood pressure, fluid balance and anaemia. Renal transplant recipients Pregnancy should be delayed for a minimum of 12 months following renal transplantation, to allow the graft to stabilize, on minimum immunosuppressive drugs. The outcome is best for women with a well-functioning graft, with no proteinuria or hypertension. Women with renal transplants can deliver vaginally but in practice there is a higher incidence of caesarean section in this group, due to the higher incidence of pre-term delivery. Liver disease Specific causes of liver disease during pregnancy are discussed below. 30.15 Causes of acute kidney injury in pregnancy Mechanism Cause Features Pre-renal Hyperemesis gravidarum Nausea and vomiting Dehydration Presentation in first trimester Post-partum haemorrhage Vaginal bleeding immediately post-partum Placental abruption Abdominal pain or vaginal bleeding in second or third trimester Septic abortion Presentation with hypotension, shock and pyrexia Renal Pre-eclampsia Presentation in second and third trimesters with new-onset hypertension and proteinuria Thrombotic thrombocytopenic purpura Possible antenatal or post-partum presentation with headache, irritability and drowsiness Haematology shows thrombocytopenia and microangiopathic haemolytic anaemia Acute fatty liver of pregnancy Presentation with vomiting and abdominal pain in third trimester Abnormal liver function tests Liver ultrasound can be normal Acute interstitial nephritis Most common cause is use of non-steroidal anti-inflammatory drugs Post-renal Acute urinary retention Usual presentation is in third trimester due to enlarged uterus causing ureteric obstruction; sometimes presents post-partum Adapted from Palma-Reis I, Vais A, Nelson-Piercy C, et al. Renal disease and hypertension in pregnancy. Clin Med 2014; 13:57–62. Fig. 30.3 Adverse pregnancy outcomes in chronic kidney disease. Creatinine is in μmol/L. To convert to mg/dL, multiply by 0.011. Data from Williams D, Davison D. Chronic kidney disease in pregnancy. BMJ 2008; 336:211–115.

Fetal growth retardation Pre-term delivery Preeclampsia Fetal death Creatinine <125 Creatinine 125–180 Creatinine >180 Dialysis Percentage affected Adapted from Ch’ng CL, Morgan M, Hainsworth I, et al. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut 2002; 51:876–880. 30.16 Criteria for diagnosis of acute fatty liver of pregnancy • Vomiting • Abdominal pain • Polydipsia/polyuria • Encephalopathy • Elevated bilirubin (> 14 μmol/L (> 0.82 mg/dL)) • Low glucose (< 4 mmol/L (< 72.4 mg/dL)) • Elevated urate (> 340 μmol/L (> 5.7 mg/dL)) • Leucocytosis (> 11 × 109/L) • Ascites or bright liver on ultrasound • Elevated transaminases (alanine/aspartate aminotransferase (ALT/ AST) > 42 U/L) • Elevated ammonia (> 47 μmol/L (> 81.7 mg/dL)) • Renal impairment (creatinine > 150 μmol/L (> 1.7 mg/dL)) • Coagulopathy (prothrombin time > 14 secs or activated partial thromboplastin time > 34 secs) • Microvascular steatosis on liver biopsy Acute fatty liver of pregnancy can be diagnosed when ≥6 of the above features are present in the absence of another explanation.

 safety profile in pregnancy, such as lamotrigine, levetiracetam or carbamazepine. While pregnancy does not generally affect the frequency of seizures in women with well-controlled epilepsy, those who enter pregnancy with poorly controlled epilepsy are likely

to deteriorate. The plasma levels of some AEDs such as lamotrigine can fall in pregnancy and checking drug levels can be helpful. Seizures are more common at the time of delivery and women should be advised to deliver in a unit staffed with personnel able to manage this. Idiopathic intracranial hypertension Idiopathic intracranial hypertension (IIH) may worsen during pregnancy due to weight gain. Treatment with acetazolamide can be continued during pregnancy but should be avoided in the first trimester due to lack of safety data. The mode of delivery is not affected by IIH and spinal analgesia can be given as normal. Migraine Migraine often improves during pregnancy but if attacks occur they should be managed with simple analgesia and antiemetics. If necessary, prophylaxis can be given with aspirin, β-blockers or tricyclic antidepressants. Safety data on use of triptans during pregnancy are limited but reassuring. Triptans can therefore be used for the treatment of migraine if other therapies are ineffective. Stroke Stroke is twice as common in pregnant women as in nonpregnant women of the same age. The risk is highest during the third trimester and puerperium. The management of stroke during pregnancy is similar to that in non-pregnant patients. The risk of cerebral venous thrombosis is greatly increased during pregnancy. The presentation is with headache, seizures and neurological deficits such as hemiparesis. If the diagnosis is suspected, neuroimaging should be performed with MRI or CT venography. Management of acute infarct should be as for the non-pregnant patient and include consideration of thrombolysis. Psychiatric disorders Mood changes are common during pregnancy but more severe psychiatric disorders, such as depression or psychosis, typically present within 2–4 weeks of delivery. These disorders are discussed in more detail on page 1206 and in Box 28.33. Haematological disease Anaemia The causes of anaemia during pregnancy are summarised in Box 30.17. Iron deficiency anaemia is most commonly due to a 20% increased demand for iron. In most cases, it responds well to oral iron supplementation, with a rise in haemoglobin of approximately 0.8 g/L per week. If the haemoglobin does not rise following a 4-week trial of iron supplementation, alternative causes of anaemia should be considered. Non-adherence to oral iron is common and intravenous iron should be considered in women with iron deficiency and failure of oral treatment. It is generally not necessary to investigate iron deficiency anaemia during pregnancy unless there is clinical evidence of gastrointestinal blood loss, which should be investigated in the normal way. HELLP syndrome The syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) is thought to be part of the spectrum of pre-eclampsia. It usually presents antenatally but can also appear for the first time in the postnatal period. The presenting symptoms can be the same as those of pre-eclampsia but can also include headache, right upper quadrant pain and visual disturbance. HELLP can be complicated by liver haematoma and capsular rupture. Management involves supportive care, control of hypertension, correction of coagulopathy and delivery of the fetus. Obstetric cholestasis Obstetric cholestasis is estimated to affect about 1% of pregnancies in Caucasians, although the prevalence is higher in Chinese and South Asian populations. The cause is incompletely understood but the condition is thought to be due in part to the cholestatic effect of high oestrogen levels. The typical presentation is in the third trimester with pruritus, particularly affecting the soles and palms. Laboratory testing reveals raised levels of bile acids and abnormal LFTs. The diagnosis can be made on the basis of these clinical features when other causes of liver dysfunction and pruritus have been excluded. Treatment is with ursodeoxycholic acid in a starting dose of 250 mg twice daily, which usually improves symptoms and liver function. Aqueous cream with menthol can also be effective in soothing pruritus. There is an increased risk of fetal mortality with evidence of a particularly high risk when bile acid levels are over 40 μmol/L (97.9 μg/mL). Treatment therefore aims to bring bile acids below 40 μmol/L and some centres induce labour before 40 weeks in an effort to reduce the risk. The risk of recurrence in future pregnancies is high.

Viral hepatitis The course of hepatitis B is unchanged in pregnancy, but it is important to identify women who have active infection to reduce the risk of vertical transmission to the fetus; this risk is up to 90% in women who are hepatitis B e-antigen positive. Vaccinations and immunoglobulin should be given to infants of mothers who test positive for hepatitis B, and antiviral agents should be given to the mother after delivery. Vertical transmission rates of hepatitis C are low in the absence of HIV infection and so no action is required for the infant, unless there is co-infection with HIV; in this case, antiviral drugs should be considered. Pregnant women are at greater risk of contracting hepatitis E than the non-pregnant population. It is transferred via the faeco-oral route, and is usually a mild self-limiting illness outside of pregnancy. However, it can cause fulminant hepatic failure in up to 20% of pregnant women. Neurological disease Epilepsy Women with epilepsy should have pre-pregnancy counselling and should be advised to take high-dose folic acid from preconception; their antiepileptic drugs (AEDs) should also be reviewed. Maternal treatment with sodium valproate is associated with a higher rate of fetal malformations than other AEDs, and a reduction in intelligence quotient and an increased risk of autistic spectrum disorder in the offspring. Where possible, sodium valproate should be substituted for another AED with a better

Venous thromboembolism The risk of venous thromboembolism (VTE) is 4–5 times higher in pregnancy than in non-pregnant women. DVT is the most common presentation and predominantly affects the left leg in pregnancy, for reasons that are incompletely understood. Doppler ultrasound scan is the investigation of choice, but MRI can also be used if proximal clot is suspected. Measurement of D-dimer is not useful in pregnancy because levels rise as part of normal pregnancy. Treatment of VTE in pregnancy is with LMWH at a higher dose than for the non-pregnant woman, based on the patient's early pregnancy (booking) weight. Women with a previous history of VTE who are receiving warfarin or other oral anticoagulants as prophylaxis should have these stopped prior to conception and LMWH should be substituted. Further information British Thoracic Society/Scottish Intercollegiate Guidelines Network. SIGN 141 – British guideline on the management of asthma. Edinburgh: Health Improvement Scotland; 2014. Useful asthma guidelines. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management. Green top guideline. London: RCOG; April 2015. A useful evidence-based guideline on the investigation of pulmonary embolism in pregnancy. Websites npeu.ox.ac.uk/mbrrace-uk National Perinatal Epidemiology Unit: a very useful resource with detailed and extensive information on causes of maternal deaths, stillbirths and infant deaths in the UK. Rhesus disease Women who are negative for the Rhesus antigen should be offered treatment with anti-RhD immunoglobulin around the time of delivery to reduce the risk of haemolytic disease of the newborn. More details are provided on page 933 and in Box 23.19. Thrombocytopenia The causes of thrombocytopenia during pregnancy are summarised in Box 30.18. The most common cause is gestational thrombocytopenia, which typically occurs towards the end of pregnancy and resolves spontaneously after delivery. It is not associated with adverse pregnancy outcomes and requires no specific intervention. Pregnancy may occur in women with preexisting idiopathic thrombocytopenic purpura (ITP, p. 971). This should be managed with glucocorticoids and/or immunoglobulin, with the aim of maintaining the platelet count above 80 × 109/L at the time of delivery, in case spinal anaesthesia or caesarean section is required. Thrombocytopenia may also occur as a component of haemolytic uraemic syndrome (HUS, p. 408) and thrombotic thrombocytopenic purpura (TTP, p. 979). Both are characterised by

microangiopathic haemolytic anaemia, acute kidney injury and thrombocytopenia, but in TTP neurological symptoms and fever also occur. These conditions are rare but important to recognise since up to one-quarter of cases occur during pregnancy and the post-partum period. TTP is managed with plasma exchange, fresh frozen plasma and sometimes glucocorticoids or rituximab. Platelet transfusion should be avoided. 30.18 Causes of thrombocytopenia during pregnancy • Gestational thrombocytopenia • Idiopathic thrombocytopenic purpura • Systemic lupus erythematosus • HELLP (haemolysis, elevated liver enzymes and low platelets) • Haemolytic uraemic syndrome • Thrombotic thrombocytopenic purpura 30.17 Causes of anaemia in pregnancy Microcytic • Iron deficiency • Haemoglobinopathies • Thalassaemia Normocytic • Anaemia of chronic disease • Haemorrhage • Haemolysis Macrocytic • Vitamin B12/folate deficiency • Liver disease • Alcohol excess

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