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ESSENTIALS The global maternal mortality ratio fell by almost 50% between 1990 and 2015. In resource-poor nations, provision of basic antenatal facilities with community healthcare workers, improved transport, communications, and education are largely responsible. Yet despite this progress maternal deaths are still common, particularly in sub- Saharan Africa, usually from readily preventable causes that would not occur in the presence of a skilled birth attendant. In wealthy nations, new challenges to maternal health include obesity, older age, and a growing number of pregnancies in women with chronic diseases through in vitro fertilization. Pregnancy can be accurately diagnosed within a day of missing a menstrual bleed by identifying a rise in urinary human chorionic gonadotropin concentration. Antenatal checks—at the first antenatal visit, a medical and ob- stetric history is combined with (1) cardiovascular examination; (2) urinalysis—proteinuria, bacteriuria; and (3) laboratory tests— HIV, hepatitis B, and syphilis; screening for sickle cell disease, thalassaemias, and rhesus antibodies. A first-time pregnant mother should be offered 10 antenatal appointments to check fetal well- being, blood pressure, urinalysis, and (at 26–28 weeks) glucose tolerance. Clinical features of healthy pregnancy—aside from an enlarging abdomen due to a growing fetus, symptoms can include fa- tigue, palpitations, dizziness, syncope, dyspnoea, nausea, vomiting, headaches, and oedema, and signs include full and bounding arterial pulses, an ejection systolic flow murmur, signs of raised intra-abdominal pressure such as varicose veins and haemorrhoids. General management—pregnant women require nutritional advice and should be advised to take regular exercise, stop smoking, and limit alcohol consumption to one to two units of alcohol once or twice a week. Clinical priorities—when managing medical disorders in pregnancy, the clinician’s priority is to treat the maternal condition, sometimes at the risk of fetal well-being. Introduction Since 1930, the maternal mortality rate (MMR) in the United Kingdom has fallen from approximately 1 in 100 pregnancies in the worst maternity hospitals to almost 1 in 12 000 pregnancies in 2014. Since 1990, lessons learnt from antenatal care in high-resource na- tions have been introduced as a priority to low-resource nations. Consequently, the global MMR has fallen by almost 50% to 1:463 maternities in 2015. In sub-Saharan Africa however, pregnancy- related maternal deaths still occur in approximately 1:183 maternities. The tragedy is that maternal deaths in resource-poor nations are frequently due to

common complications that could be readily cor- rected by a skilled birth attendant with minimal equipment. HIV/ AIDS and health systems disrupted by war and poor government exacerbate the problem. Furthermore, for every maternal death there are at least 20 additional women who suffer serious pregnancy- related conditions that cause lifelong disabilities. In high-resource nations, new challenges for the medical manage- ment of pregnant women have emerged. The increased prevalence of maternal obesity has led to an increased incidence of gestational syn- dromes, particularly diabetes and hypertension, but also acquired heart disease and obstetric/anaesthetic complications at the time of childbirth. In vitro fertilization (IVF) offers women who have passed through the menopause an opportunity to become pregnant, but in associ- ation with an increased incidence of multiple pregnancies that in- crease the physiological burden on (often) older mothers less able to cope with the physical stress of pregnancy. Similarly, women with serious chronic or congenital diseases who have an assisted con- ception, struggle to meet the physiological demands of pregnancy. Consequently, fetal development and pregnancy outcome are com- promised, and the mother's health is put at risk. Maternal morbidity could also be reduced if physicians showed less reticence about their management of otherwise familiar medical conditions during pregnancy. Well-intended, but misplaced concern about fetal welfare is often wrongly prioritized over life-saving inves- tigations and treatment for the mother. By contrast, the general phys- ician must be aware of the symptoms and signs of normal pregnancy 14.3 Medical management
of normal pregnancy David J. Williams

Section 14 Medical disorders in pregnancy 2576 to avoid meddlesome and sometimes harmful intervention when a doctor is presented with a healthy, but symptomatic pregnant woman. Maternal factors that influence pregnancy outcome Maternal age Since the mid-1970s, the mean age of first-time mothers in the United Kingdom has increased gradually by almost 4 years to 28.6 years in 2015. The physiological adaptations necessary for optimal preg- nancy outcome are compromised by increasing maternal age, al- though biological age is more important than chronological age. The risk of fetal aneuploidy, most notably trisomy 21 (Down's syndrome), also increases with maternal age. At 25 years, the risk is 1:1250, at 35 years 1:385, and at 45 years 1:30. These risks can be refined between 11 and 14 weeks' gestation by the 'combined test' (nuchal translucency, which is an ultrasound measurement of skin- fold thickness at the back of the fetal neck, combined with a ma- ternal serum measure of β-human chorionic gonadotropin, and pregnancy-associated plasma protein A). Serum screening for fetal aneuploidy can be carried out between 14 and 20 weeks but is less ac- curate than the combined test. Women at high risk of chromosomal abnormality (usually >1:250), can be offered a diagnostic test that re- quires obtaining cells from the fetus or placenta using amniocentesis or chorionic villus sampling, which carry a 0.5 to 1.0% risk of mis- carriage. Although not yet in widespread use, noninvasive prenatal testing that examines fetal DNA isolated from the maternal circula- tion is showing great promise as a diagnostic test that will hopefully reduce the need for invasive diagnostic sampling.
Maternal weight A mother's body mass index (BMI) should be calculated at the first antenatal appointment. In high-resource nations, approximately half of women of childbearing age are overweight and 20% are obese. Overweight or obese mothers are at increased risk of gestational hypertension and diabetes, neonatal macrosomia, and late fetal death. Conversely, underweight women (BMI <19 kg/m2) are prone to have babies with lower birth weights. However, maternal weight gain correlates poorly with fetal growth, which is most accurately assessed by serial ultrasound measurements. Healthy women with a normal BMI (19–25 kg/m2) in the first tri- mester,

have an average gestational weight gain of 13.7 kg (SD 4.5 kg) by 40 weeks' gestation, irrespective of ethnic background. Lean, nul- liparous, healthy, pregnant women who eat to appetite gain 0.65 kg to 1.1 kg during the first 10 weeks of pregnancy, about 0.45 kg/week during the second trimester, and about 0.36 kg/week during the last trimester. Unless the mother is underweight, or has hyperemesis gravidarum, conditions that often coexist, regular antenatal meas- urements of maternal weight are not helpful. Past medical history Pregnancy is a medical stress for women. This is particularly evi- dent in women with chronic medical disorders. A diseased ma- ternal organ system may transiently lose residual function in attempting to accommodate the physiological demands of preg- nancy. For example, women with classic risk factors for hyperten- sion are more likely to develop pre-eclampsia, and women with subclinical insulin resistance are at increased risk of gestational dia- betes. Similarly, women with inherited thrombophilias may develop thrombosis only in combination with the hypercoagulable environ- ment of healthy pregnancy. These gestational syndromes are likely to be associated with an adverse fetal outcome, but the physiological changes of pregnancy are not always damaging: some conditions im- prove, while others deteriorate (Box 14.3.1). Box 14.3.1 Effect of pregnancy on pre-existing conditions Conditions that tend to improve during pregnancy • Mitral and aortic regurgitation • Raynaud's phenomenon • Mild hypertension (but worsens towards term) • Hyperthyroidism (may transiently worsen in first trimester) • Sarcoid • Rheumatoid arthritis • Multiple sclerosis (may relapse postpartum) • Peptic ulceration • Migraines Conditions that are unpredictable during pregnancy • Asthma • Systemic lupus erythematosus (may relapse postpartum) • Inflammatory bowel disease Conditions that tend to deteriorate during pregnancy Cardiovascular system • Mitral and aortic stenosis • Pulmonary hypertension (10–30% risk of maternal mortality) • Congenital cyanotic heart disease • Supraventricular arrhythmias (in third trimester) • Vascular aneurysms • Haemolytic–uraemic syndrome/thrombotic thrombocytopenic purpura • Epistaxis • Varicose veins and haemorrhoids • Venous thrombosis • Antiphospholipid syndrome (deep vein thrombosis and recurrent miscarriage) Respiratory system • Viral pneumonia, in particular influenza Gastrointestinal system • Gastro-oesophageadl reflux (especially in third trimester) • Cholestatic liver disease (in third trimester) • Constipation Genitourinary system • Upper urinary tract infections (pyelonephritis) • Reflux nephropathy • Renal impairment (if glomerular filtration rate <30 ml/min) Musculoskeletal system • Osteoporosis • Osteoarthritis • Back pain • Hypermobility syndromes Endocrine system • Diabetes mellitus • Central diabetes insipidus (continued)

 Family history Gestational conditions tend to run in families. Pre-eclampsia, gestational diabetes mellitus, obstetric cholestasis, hyperemesis gravidarum, and postnatal depression have genetic components. Inherited thrombophilias may be associated with early onset pre- eclampsia and fetal growth restriction. Infertility and multiple pregnancies In 1978 the first baby was born by IVF, and she herself has now given birth to a healthy child following natural conception. Since then, it is estimated over five million babies have been born world- wide using IVF technology. One-quarter of these pregnancies have resulted in multiple births, compared with 11 per 1000 preg- nancies following natural conception. In the United Kingdom this has led to a 66% increase in twin births, which itself has increased the frequency of maternal complications in often older mothers. The cause of infertility may also lead to problems in pregnancy. For example, women with polycystic ovary syndrome are at in- creased risk of pregnancy-induced hypertension and gestational diabetes. Ovarian hyperstimulation syndrome Women undergoing IVF are often treated with gonadotropins to stimulate their ovaries and increase the yield of eggs. In about 10% of women receiving this treatment, multiple follicles

each develop into a corpus luteum, resulting in massive ovarian enlargement produ- cing excessive amounts of progesterone. Increased vascular perme- ability allows protein-rich fluid to shift into serous cavities, causing ascites, and in more severe cases pleural and pericardial effusions. Haemoconcentration and hypotension result, increasing the risk of thrombosis and reduced renal perfusion. This phenomenon is known as ovarian hyperstimulation syndrome. Most cases are mild and self-limiting, but death has followed acute respiratory distress, hepatorenal failure, thromboembolism, and rupture of grossly en- larged ovaries. Management is mainly supportive, including careful fluid balance, thromboprophylaxis, analgesia, and adjustment of luteal stimulation under the guidance of a specialist in assisted conception. In some cases, paracentesis can transiently relieve ab- dominal pressure symptoms. Diagnosis of pregnancy Pregnancy can be diagnosed within a day of missing a menstrual bleed by identifying a rise in concentration of urinary human chorionic gonadotropin (hCG). At this time the embryo is two weeks old, but obstetric convention dictates that the gestation of pregnancy is calculated from the first day of the last menstrual period (i.e. two weeks earlier than embryonic age). Teratogenic drugs interfere with organ development in the two to eight weeks postconception (embryonic period). After nine weeks and until delivery, the conceptus is known as a fetus, but its development can still be harmed by drugs given to the mother, or indeed ma- ternal illness itself. Screening of maternal health during pregnancy Pregnancy is an opportunity for women to be screened for occult disease. In the United Kingdom, healthy women are encouraged to register with an antenatal clinic by 10 weeks' gestation. However, by this time they will have missed the opportunity to take folic acid prophylaxis against neural tube defects and may not recognize the need to adjust social behaviour, or regular medications. At the first antenatal visit, a medical and obstetric history is combined with cardiovascular examination, urinalysis, and la- boratory tests. Identification of maternal infection with HIV, hepa- titis B, or syphilis is necessary for the appropriate management of the mother and her partner, and to minimize the risk of ver- tical transmission to the infant. All women should be screened for sickle cell disease and thalassaemias as early as possible in preg- nancy, and the father of the pregnancy should be strongly encour- aged to undergo screening if a woman is found to be a carrier of a significant haemoglobinopathy. Rhesus antibody screening allows prophylactic measures to prevent haemolytic disease of the fetus. Further antenatal checks are usually performed around 16 weeks to discuss the results of screening tests, following a 20-week fetal scan, at 26–28 weeks to assess maternal serum glucose check in those at high risk of gestational diabetes mellitus, and a full blood count, 31, 34, 36, 38, and 40 weeks, then weekly until delivery. At each visit, obstetric assessment is combined with a check of blood pressure and urinalysis. Parous women who have had an uneventful pregnancy need fewer antenatal visits (NICE CG62; 2016). Screening and treatment of asymptomatic bacteriuria during healthy pregnancy reduces the risk of maternal pyelonephritis and fetal morbidity. The cost-effectiveness of such screening depends on the prevalence of asymptomatic bacteriuria in the pregnant population. If this is less than 5%, as it is in most healthy women, then screening is not cost-effective, but in women with renal dis- ease and diabetes mellitus, asymptomatic bacteriuria is far more common and screening is worthwhile. As the recurrence rate of asymptomatic bacteriuria is about 30%, women identified with an occult infection should be screened every four to six weeks throughout the remainder of their pregnancy. See Chapter 14.5 for further discussion. Box 14.3.1 Continued • Hypothyroidism • Hyperlipidaemia • Pituitary macroadenoma (not microadenoma) Neurological system • Epilepsy • Cerebrovascular accidents, especially postpartum • Depression (antenatal and postnatal) • Headache, in first and second trimester • Carpal tunnel syndrome, third trimester Haematological system • Anaemia and thrombocytopenia • Sickle cell disease •

Thrombophilias Infections and allergies • Intracellular pathogens (viruses, malaria, listeria, and tuberculosis postpartum) • Skin allergies

Section 14 Medical disorders in pregnancy 2578 Symptoms and signs of healthy pregnancy Fatigue Fatigue is a common gestational symptom. It often begins early in healthy pregnancy, improves in the second trimester, and reappears again in the third trimester. Insomnia in the third trimester can be caused by changes in maternal size and shape as well as nocturia and acid-reflux. Anaemia or hypothyroidism should be excluded if daily living is significantly compromised.
Cardiovascular system The hyperdynamic circulation of pregnancy causes cardiovas- cular symptoms that can mimic heart disease (see Chapter 14.6). Palpitations, dizziness, syncope, and dyspnoea are common symp- toms of healthy pregnancy. Failure to recognize benign physiological change leads to anxiety and unnecessary investigations. However, is- chaemic heart disease is the most common cause of maternal death from cardiac disease in the United Kingdom. Older, obese women who smoke and who have symptoms suggestive of ischaemic heart disease should be investigated promptly as if not pregnant, espe- cially in the third trimester and immediately postpartum. Palpitations Transient sinus tachycardia up to 130 beats/min, and premature atrial and ventricular ectopic beats are common features of healthy pregnancy, especially in women who complain of palpitations. Low dose β-blockers reduce the frequency of ventricular ectopics and provide symptomatic relief. As pregnancy may expose previ- ously asymptomatic abnormalities of cardiac conducting tissue, investigations should include a 12-lead electrocardiogram (ECG). During healthy pregnancy, the QRS axis moves to the left as the dia- phragm becomes elevated, and Q waves and inverted T waves are frequently seen in leads III and aVR. Pregnant women with syncope or presyncope coinciding with palpitations require further investi- gation with a 24-hour ECG Holter monitor and echocardiogram. Thyrotoxicosis, anaemia, and hypokalaemia should be excluded. Oedema By the end of pregnancy 80% of healthy women will have some de- gree of dependent oedema. This is associated with a fall in plasma al- bumin concentration by 5–10 g/litre and reduced venous return due to compression of the inferior vena cava by the gravid uterus. Unless peripheral oedema is very severe, or is associated with pulmonary oedema, diuretics should be avoided as they attenuate the plasma volume expansion of healthy pregnancy and are associated with fetal growth restriction. Severe and rapid onset of oedema, especially af- fecting hands and face, may herald pre-eclampsia and warrants fur- ther assessment for hypertension and proteinuria. Blood pressure Peripheral vasodilatation leads to a significant fall in diastolic blood pressure by six weeks of conception, reaching a nadir at 16–20 weeks. Pre-pregnancy hypertension may therefore be masked by the early gestational fall in blood pressure. Maternal blood pressure returns to nonpregnant values during the third trimester. Hypertension be- fore 20 weeks' gestation suggests pre-existing hypertension, while new onset hypertension after 20 weeks suggests gestational hyper- tension or pre-eclampsia. Clinical examination During healthy pregnancy the peripheral pulses are full, bounding, and often collapsing, suggesting aortic regurgitation. From mid- gestation onwards, the jugular venous pressure becomes more ob- vious and may be raised due to increased intra-abdominal pressure. The apex beat is more forceful and mildly displaced because of the increase in cardiac output, suggesting cardiomegaly in healthy preg- nant women. An apex beat more than 2 cm outside the midclavicular line should be considered abnormal. On auscultation an ejection systolic flow murmur can be heard in up to 90% of healthy preg- nant women. Increased mammary blood flow in the third trimester occasionally produces a bruit that varies with the pressure of the stethoscope. In countries with established healthcare systems, it is rare for new heart lesions to be identified during pregnancy as most

women with congenital heart disease are diagnosed in early life. By contrast, women from low-income countries are more likely to present with previously unrecognized cardiac abnormalities such as rheumatic heart disease. Respiratory system Dyspnoea The physiological hyperventilation of pregnancy leads to a sub- jective feeling of breathlessness in about 70% of women. The max-imum prevalence of breathlessness is between 28 and 31 weeks' gestation, but about 50% of women will feel breathless before 20 weeks. The early onset of dyspnoea and improvement towards term suggests that the gravid uterus has little influence on this physio- logical symptom. Women with gestational dyspnoea are more sen- sitive to CO_2 and hypoxia than asymptomatic women and respond with excessive ventilation. However, physiological dyspnoea should not usually interfere with daily activities: further investigations are only necessary if symptoms or signs suggest cardiorespiratory dis- ease (e.g. chest infection, pulmonary embolus, or heart failure). Acid-reflux, especially at night, can cause bronchoconstriction, dyspnoea, and cough. A proton pump inhibitor or H2 antagonist can control this cause of dyspnoea. Radiological imaging in pregnancy In general, the management of sick pregnant women should con- sider the health of the mother before that of the fetus. Nowhere is this consideration ignored more than with the use of X-rays. Although ionizing radiation is a known carcinogen, there is very little, if any increased risk of childhood cancer following prenatal exposure to X-rays. Radiation from a chest radiograph is minimal (0.02 mSv), equivalent to 10 days of background radiation or a transatlantic air flight. During healthy pregnancy the chest radiograph shows an in- creased cardiothoracic ratio and pulmonary vascular markings. If pulmonary embolus is suspected and the chest radiograph is normal, then a pregnant woman should have a ventilation–perfusion scan (1.3 mSv). If the chest radiograph is abnormal and pulmonary em- bolism is still suspected, a computed tomography pulmonary angio- gram should be carried out (see Chapter 14.7).

14.3 Medical management of normal pregnancy 2579 Gastrointestinal system Nausea and vomiting About 75% of all healthy women will feel nauseated and up to 50% will vomit during early pregnancy. Nausea usually begins around the fifth week and usually resolves by 16 weeks. Approximately 10% of healthy pregnant women will still feel occasional nausea throughout pregnancy. Contrary to popular belief, nausea is not usually confined to the mornings, but affects 80% of sufferers all day. Beneficial measures for mild symptoms include rest, carbohy- drate, carbonated drinks, ginger, pyridoxine, antihistamines, and metoclopramide. Vomiting is severe and persistent in 1–2% of pregnant women. Hyperemesis gravidarum is associated with dehydration, weight loss, and ketonuria (see Chapter 14.9). Ptyalism is a frequent accompani- ment, due to an inability to swallow excessive saliva. Biochemical changes include a transient elevation of liver transaminases and biochemical thyrotoxicosis. A suppressed thyroid-stimulating hor- mone (TSH) level coincides with the rise and fall of serum hCG, which has mild TSH-like activity. Resolution of hyperemesis, not treatment of biochemical thyrotoxicosis, corrects the abnormal thy- roid biochemistry. Most antiemetics have not been fully evaluated in early pregnancy. As with all prescribing in pregnancy the clinician must balance the potential risks to the fetus of maternal drug use against the risks of leaving the mother untreated. With regard to hyperemesis gravidarum, a woman is at risk of malnourishment, dehydration, and thrombosis, and most antiemetics have been used effectively during pregnancy for decades without apparent fetal harm. These include antihistamines, phenothiazines, and metoclopramide. More severe cases require hospital admission and intravenous re- hydration, which often provides immediate relief from nausea. Additional treatment with serotonin (5-HT3) antagonists such as Ondansetron is of proven benefit. Steroid treatment with prednis- olone 30–40 mg daily may also provide relief. Thiamine (vitamin B1)

supplementation will reduce the risk of Wernicke’s encephalopathy and prophylactic low molecular weight heparin will reduce the risk of thrombosis. Parenteral nutrition is rarely necessary. New onset of nausea and vomiting during the second half of preg- nancy suggests pathology unrelated to hyperemesis and may herald pre-eclampsia or acute fatty liver of pregnancy. Gastro-oesophageal reflux is a common problem of late pregnancy that usually improves with antacids or a change in diet. Persistent symptoms can be safely treated with H2-receptor antagonists or proton pump inhibitors. Increased circulating progesterone levels relax intestinal smooth muscle and commonly provoke constipation, for which increased dietary fibre, lactulose, and avoidance of unnecessary iron supple- ments provide symptomatic relief. Neurological system Headaches are common in healthy pregnancy, and many pregnant women develop migrainous-type headaches for the first time in early pregnancy. Overall however, migraines have been found to be less frequent and severe during pregnancy. If headaches are recurrent, or do not respond to occasional paracetamol, then regular aspirin 75 mg each evening, or propranolol 10–20 mg three times daily, or amitryptiline 10–25 mg nocte can be used as prophylactic meas- ures. Severe, persistent headache that presents for the first time in pregnancy, or is accompanied by focal neurological signs, requires investigation with MRI (see Chapter 14.12). An epidural catheter introduced during labour can lead to acci- dental puncture of the dura and a cerebrospinal fluid leak, which may lead to a postural headache that improves when lying flat. If there is no improvement within 24 hours, then injection of 2–3 ml of autologous blood at the site of dural puncture (blood patch) usually resolves the headache. Carpal tunnel syndrome affects about 20% of women with healthy pregnancies. It begins during the second half of pregnancy and is more common in women who have excessive weight gain and oe- dema. Pain and numbness in the distribution of the median nerve, affecting the first three fingers can be particularly severe at night and on waking. Wrist splints alleviate symptoms, usually making sur- gical intervention inappropriate as most cases recover within weeks of delivery. Musculoskeletal system Low back and pelvic pain affect about 50% of all pregnancies. A com- bination of mechanical stress on the lumbar spine and pelvis and the effects of relaxin, a hormone produced by the corpus luteum to relax ligaments in anticipation of childbirth, are likely to be responsible. Some women develop radicular symptoms affecting nerve roots and the lumbar sacral plexus, but only 1% develop true sciatica with a dermatomal distribution. Progressive neurological symptoms ne- cessitate further investigations, often with MRI. Some relief can be gained from massage, exercises, or a maternity cushion. Others can obtain relief from transcutaneous electrical nerve stimulation or a trochanteric support belt. Nonsteroidal anti-inflammatory drugs are safe and often effective until 32 weeks’ gestation. Pubic-symphysis dysfunction due to local joint inflammation and causing intense tenderness develops in up to 5% of pregnant women. Ultrasound guided intra-articular local anaesthetic with hydrocor- tisone and a lumbosacral support can provide relief, but the condi- tion can persist postpartum, requiring longer-term orthopaedic and rheumatological follow up. Skin Pruritus is a common symptom of late pregnancy, thought to re- late to increased cutaneous blood flow and dryness. If there is an associated rash, then gestational skin conditions need to be con- sidered (see Chapter 14.13). If itch persists without a rash, then liver function should be checked to exclude intrahepatic cholestasis (see Chapter 14.9). Dietary modification and vitamin/ mineral supplementation during pregnancy Folic acid In the United Kingdom and the United States of America spina bifida or anencephaly (neural tube defects) affect about 1 in 1000 preg nancies. The neural tube develops and then closes within 28 days of conception. Women who take 400 µg folic acid daily around the time of conception and for the first 12 weeks of pregnancy reduce their risk of a pregnancy complicated by neural tube defects by

Section 14 Medical disorders in pregnancy 2580 approximately 70%. In some countries the fortification of food with folic acid provides an extra 100 µg/day of folic acid, which is also effective in lowering rates of neural tube defects and congenital heart defects. Women who have had a baby affected by spina bifida are advised to take a higher dose of folic acid (5 mg/day). Multivitamins and other supplements Multivitamin preparations without folic acid do not reduce the risk of neural tube defects. Multivitamins taken periconceptually may reduce the risk of some congenital heart defects, but beyond the first trimester are of no proven benefit for healthy women on a balanced diet. Antioxidant vitamins (vitamin C 1000 mg and vitamin E 400 IU daily) taken from mid-pregnancy do not reduce the incidence of pre-eclampsia and have been associated with an increased incidence of low birth weight babies. Women should keep up adequate stores of vitamin D during pregnancy and when breastfeeding. Women at high risk of vitamin D deficiency should be encouraged to take supplemental vitamin D (10 µg/day). Supplemental vitamin D may reduce the risk of pre-eclampsia, low birth weight, and preterm birth. However, the optimal dose of vitamin D, the target concentration of serum 25- hydroxyvitamin D and any adverse effects remain to be determined. Certain liver products and vitamin A supplementation above 700 µg daily increase the risk of embryonic teratogenesis and should be avoided. In the developing world where diet is poor, vitamin A supplements, and zinc improve fetal outcome. See Chapter 14.2 for further discussion. In the developed world, supplemental iron should not be offered routinely, but reserved for those who have a haemoglobin of less than 95 g/litre and a mean corpuscular volume of less than 84 fl in the third trimester. In resource-poor nations, malnutrition and chronic infection diminish iron stores that are further exhausted during pregnancy. Under these conditions, routine supplemental iron and folate improve maternal and neonatal outcome. See Chapter 14.2 for further discussion. Sea food, fish oils, and long-chain polyunsaturated fatty acids Women should be encouraged to eat two to three portions of white fish or cooked shellfish each week during pregnancy and breastfeeding. Such a maternal diet is associated with improved neurocognitive development in their offspring. However, ingestion of large fish such as tuna should be avoided, as they retain neuro- toxic heavy metals like mercury. Because of this latter observation many women take supplemental n-3 long chain polyunsaturated fatty acids (n-3 LCPUFAs). Current evidence has shown that women who take supplemental n-3 LCPUFAs from 24 weeks' gestation re- duce the risk of asthma and respiratory infections in their children. N-3 LCPUFA supplements taken during pregnancy may also reduce the risk of preterm birth, but contrary to popular belief, they do not improve a child's intelligence. Prophylaxis against pre-eclampsia Pre-eclampsia is discussed in Chapter 14.4. Low-dose aspirin 60–150 mg taken each evening by women at increased risk of pre-eclampsia from 12 weeks' gestation until childbirth, reduces the incidence of pre-eclampsia by up to 50%. Calcium supplementation (1.5–2.0 g elemental calcium daily) also reduces the incidence of pre-eclampsia in women with a low dietary intake of calcium who are at high risk of the condition. However, the dose and timing of calcium prophylaxis and any interaction with vitamin D has yet to be determined. Antioxidant vitamins (vitamin C and vitamin E) should not be used to prevent pre-eclampsia. Our ability to prevent or treat pre-eclampsia effectively will remain inadequate until our understanding of its pathophysiology improves. Asymptomatic thyroid disease Neurodevelopment of the fetus depends on maternal thyroid hormone until week 18–20 of pregnancy, when the fetal thyroid gland becomes functional. Untreated overt maternal hypothyroidism is associated with impaired childhood neurocognitive development, but if treated promptly with thyroxine then pregnancy and childhood outcome is normal. Subclinical maternal hypothyroidism (low T4, normal TSH) has also been associated with reduced child IQ, but so too has subclin- ical maternal hyperthyroidism (high T4, normal TSH). This observa- tion may explain why treating subclinical

hypothyroidism has had no impact on childhood neurocognitive performance. Screening for sub-clinical hypothyroidism cannot be recommended, although screening for overt maternal hypothyroidism has clinical merit. Neonates are currently screened for congenital hypothyroidism, a condition far rarer than overt maternal hypothyroidism (see Chapter 14.11). Behavioural habits during pregnancy Exercise Pregnancy outcome is improved by regular exercise throughout pregnancy. The gestational increases in both cardiac output and re- spiratory work are enhanced further by exercise, but the intensity of exercise should not exceed levels to which a woman is accustomed. In late pregnancy nonweight-bearing exercises such as swimming become easier. Exercise may be harmful to women with impaired cardiac or respiratory function who struggle to fulfil the physio- logical demands of pregnancy alone. Alcohol Heavy alcohol consumption during pregnancy leads to the 'fetal al- cohol syndrome' in approximately one-third of offspring. The sus-ceptibility of the fetus to alcohol depends on genetic vulnerability, the nutritional status of the woman, and her abuse of other drugs. The developmental and neurological abnormalities that make up fetal alcohol syndrome affect approximately one to two per 1000 live births, but there is a spectrum of fetal alcohol disorder that includes infants with less marked neurological impairment, which is likely to be associated with lower levels of maternal alcohol consumption. It is not known whether there is a safe level of alcohol consumption in pregnancy, but evidence suggests that one or two units of alcohol once or twice a week is not harmful to the fetus. Tobacco Women should stop smoking during pregnancy as it impairs fetal growth and increases the risk of poor obstetric outcome. Nicotine gum contains less nicotine than cigarettes and none of the other toxins, making it preferable to smoking during pregnancy. Nicotine patches provide a constant release of nicotine throughout the day that exceeds that of periodic nicotine gum. Pregnant women are

 advised to remove nicotine patches before they go to bed. Electronic vapour products that deliver nicotine may be less harmful than cig-arette smoking, but their use in pregnancy has not yet been assessed and therefore they cannot be recommended. Caffeine Moderate caffeine consumption is not associated with harm in preg-nancy, but more than six cups of coffee a day increases the risk of miscarriage. Travel Aircraft are pressurized to a maximum oxygen partial pressure equivalent to an altitude of 2440 m (8000 ft) above sea level. During a routine commercial flight, healthy pregnant women (32–38 weeks' gestation) increase their heart rate and blood pres- sure and drop their oxygen saturation, but fetal heart rate remains unchanged. Long-haul flights further increase a pregnant woman's risk of deep vein thrombosis. Simple thromboprophylaxis with antiembolic stockings, hydration, and mobility, including calf muscle exercise are sufficient for most pregnant women. Low dose aspirin is safe in pregnancy and may have an as-yet unproven role in reducing the risk of thrombosis in pregnant women during travel. Airlines are reluctant to carry women after 36 weeks' gestation for the obvious and sensible practical reason that they do not want to deliver a baby in flight. Events after delivery Lactation Breastfeeding is beneficial to the infant. However, the mother who breastfeeds for six months or longer transiently loses 4–5% of bone density in her lumbar spine. Calcium supplementation does not prevent this transient loss of bone mineral density, which recovers spontaneously six months after delivery whether or not the mother continues to breastfeed. Calcium supplementation does not increase the concentration of calcium in breast milk or the bone mineral status of the infant in the first year of life. Postnatal depression Almost half of all women develop the 'maternity blues'. This is char- acterized by tearfulness, anxiety, and irritability, starting around the third to fifth postpartum days and usually resolving by the tenth day. About 10% of women develop nonpsychotic postnatal depression four to six weeks

postpartum, with a maximum incidence at three months postpartum. The depression is similar to that occurring at other times, but is often accompanied by thoughts of harming the baby. Although most women recover without treatment within three to six months, recovery can be hastened by counselling. Women who fail to respond to counselling or who have severe depression may benefit from antidepressant treatment. Although small amounts of tricyclic Fig. 14.3.1 Risk of type 2 diabetes mellitus (T2DM) after gestational diabetes mellitus (GDM). Note that the x-axis is a log scale. Each solid square represents a relative risk. Horizontal lines indicate 95% CIs. Reprinted from The Lancet, 373(9677), L. Bellamy et al., Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis, 1773–9. Copyright © 2009, with permission from Elsevier.

Section 14 Medical disorders in pregnancy 2582 antidepressants and selective serotonin reuptake inhibitors appear in breast milk, breastfeeding should be encouraged. Nonetheless, the in- fant should be watched for possible unwanted effects. Future maternal health Gestational syndromes unmask a woman's future vulnerability to dis- ease. For example, insulin resistance underlying gestational diabetes mellitus returns to pre-pregnancy levels immediately postpartum, but affected women have a sevenfold relative risk of future type 2 diabetes in later life compared with women who had a normogly- caemic pregnancy (Fig. 14.3.1). Similarly, both pregnancy-induced hypertension and pre-eclampsia are associated with an almost fourfold risk of future hypertension and a twofold relative risk of maternal cardiovascular disease in later life. Proteinuria related to pre-eclampsia can take up to 12 months to disappear but may be the first sign of previously subclinical renal disease. Similarly, elevated liver transaminases associated with intrahepatic cholestasis of preg- nancy may be the first sign of hepatitis C or other cholestatic liver disease. Women who have had postpartum depression are more likely to suffer depression in later life. Despite the physical demands of pregnancy, most women com- plete an uncomplicated pregnancy and have a healthy baby. This bodes well for maternal health during subsequent pregnancies and for the mother and her offspring in future life. FURTHER READING Alkema L, et al. on behalf of the United Nations Maternal Mortality Estimation Inter-Agency Group collaborators and technical ad- visory group (2016). Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet, 387, 462–74. Bellamy L, et al. (2007). Pre- eclampsia and risk of cardiovascular dis- ease and cancer in later life: systematic review and meta- analysis. BMJ, 335, 974–77. Bellamy L, et al. (2009). Type 2 diabetes mellitus after gestational dia- betes: a systematic review and meta-analysis. Lancet, 373, 1773–9. Chaiworapongsa T, et al. (2014). Pre-eclampsia part 2: prediction, pre- vention and management. Nat Rev Nephrol, 10, 531–40. de-Regil LM, et al. (2016). Vitamin D supplementation for women during pregnancy (Review). Cochrane Database of Systematic Reviews, 1, CD008873. Garcia-Rio F, et al. (1996). Regulation of breathing and perception of dyspnoea in healthy pregnant women. Chest, 110, 446–53. Haines N (2016). Births by Parents' Characteristics in England and Wales: 2015 Office for National Statistics. https://www.ons.gov. uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ livebirths/bulletins/birthsbyparentscharacteristicsinenglandandwa les/2016 Knight M, et al. on behalf of MBRRACE-UK (2016). Saving Lives, Improving Mothers' Care—Surveillance of Maternal Deaths in the UK 2012–14 and Lessons Learned to Inform Maternity Care from the UK and Ireland: Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. National Perinatal Epidemiology Unit, University of Oxford, Oxford. https://www.npeu.ox.ac.uk/downloads/files/ mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%20 2016%20-%20website.pdf Korevaar TIM, et al. (2016). Association of maternal thyroid function during early pregnancy with offspring IQ

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Revision #1
Created 2026-01-22 16:38:13 UTC by Omar Ayman
Updated 2026-01-22 16:38:13 UTC by Omar Ayman