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ESSENTIALS Liver diseases Pregnancy-specific disorders that cause de novo abnormal serum liver tests in pregnancy include: Hypertension-related liver diseases and pregnancy—including pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low plate lets) syndrome, also hepatic haematoma, infarction, and rupture Acute fatty liver of pregnancy—a rare disorder, part of the mito- chondrial cytopathy spectrum, but one of the commoner causes of liver failure in pregnancy. Prompt delivery is essential. Intrahepatic cholestasis of pregnancy—affects 0.67% of pregnancies in the United Kingdom; presents typically with pruritis and com- monly treated with ursodeoxycholic acid. Hyperemesis gravidarum—affects 0.3–2% of all pregnancies; treat- ment is supportive, with thiamine supplementation mandatory to prevent Wernicke's encephalopathy. Viral hepatitis is probably the most commonly recognized cause of jaundice occurring during pregnancy worldwide. There is no specific change in the presentation, clinical features, or general outcome for hepatitis A virus, hepatitis B, hepatitis C, cytomegalovirus, or Epstein– Barr virus infection in pregnancy. By contrast, hepatitis E is worse in preg- nancy, with high mortality from acute liver failure in the third trimester. Gastrointestinal diseases Inflammatory bowel disease—does not generally affect fertility. Can flare, be stable, or improve during pregnancy. Women should be en-couraged to continue to take drugs that maintain disease remission. Gallstones and gallbladder sludge—occur more commonly in preg- nant women and are generally asymptomatic. Acute cholecystitis usually requires surgery, preferably laparoscopic. Gastro-oesophageal reflux disease—affects approximately 40%
of pregnant women; simple treatments are often effective, but both H2-antagonists and proton pump inhibitors have good safety data for use in pregnancy. Introduction Pregnant women can

have hepatic diseases that are specific to pregnancy or incidental to pregnancy (Table 14.9.1). In contrast, most gastrointestinal diseases encountered in pregnant women are not specific to pregnancy, although some occur more commonly in pregnant women (e.g. gastro-oesophageal reflux disease). This chapter will describe the influence of pregnancy on pre-existing diseases, the effect of these diseases on pregnancy outcome, the impact of specific drugs used to treat women with liver and gastro- intestinal disorders on the fetus, and it will describe gestational disorders that cause hepatic impairment, including hyperemesis gravidarum, pre-eclampsia, acute fatty liver of pregnancy, and cholestasis. Pregnancy-specific liver diseases When evaluating pregnant women with hepatic disease, it is im- portant to know the normal range of the laboratory tests that are used (Table 14.9.2). The commonest disorders that cause de novo abnormal serum liver tests in pregnancy are pre-eclampsia, the HELLP (haemolysis, elevated liver enzymes, low platelets) syn- drome, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy and hyperemesis gravidarum. Typical patterns of change in serum liver tests in each of these pregnancy-specific liver dis- orders are shown in Table 14.9.3. Hypertension-related liver disease and pregnancy Hypertension in pregnancy is defined as a blood pressure greater than 140/90 mmHg on at least two occasions. Pre-eclampsia, eclampsia, HELLP syndrome, hepatic infarction, and rupture are all part of this spectrum. Pre-eclampsia and eclampsia Pre-eclampsia represents a multisystem disorder occurring in ap- proximately 5% of all pregnancies. It may involve the liver, kidneys, central nervous system, and bone marrow. Pre-eclampsia is defined by the presence of new onset hypertension and proteinuria (greater than 300 mg in a 24-hour period) occurring after 20 weeks' gestation and/or within 48 hours of delivery. The presence of seizures differen- tiates eclampsia from pre-eclampsia. Risk factors include pre-existing hypertension, family history, ex- tremes of maternal age, primiparity, and occurrence in a previous pregnancy. Endothelial dysfunction from placental ischaemia is thought to play a critical role. 14.9 Liver and gastrointestinal diseases of pregnancy Michael Heneghan and Catherine Williamson

 The clinical features include abdominal pain, headache, nausea, and vomiting. Abnormal liver enzymes occur in 20–30% of pa- tients and this is thought to be secondary to vasoconstriction of the hepatic vascular bed. Aspartate transferase (AST) and alanine aminotransferase (ALT) maybe as high as 10 times normal range, but bilirubin levels are rarely elevated (Table 14.9.3). Liver biopsy is not indicated although identifiable sinusoidal fibrin thrombi, haem- orrhage, and hepatocellular necrosis may be seen. Tight control of blood pressure is essential. Liver involvement, albeit infrequent, always suggests severe disease, and in that con- text immediate delivery is usually necessary. Complications include maternal hypertensive crises, renal dysfunction, hepatic rupture or Table 14.9.1 Liver diseases most commonly encountered in pregnant women Liver diseases specific to pregnancy Liver diseases incidental to pregnancy Pre-eclampsia with hepatic impairment HELLP syndrome Hyperemesis gravidarum Intrahepatic cholestasis of pregnancy Autoimmune hepatitis Viral hepatitis Primary biliary cholangitis Primary sclerosing cholangitis Budd Chiari syndrome Cirrhosis Portal hypertension Metabolic diseases Gallstone disease Drug-induced liver injury Table 14.9.2 Normal ranges for the laboratory tests used to investigate women with hepatic disorders of pregnancy Liver enzyme Nonpregnant Pregnant 1st trimester 2nd trimester 3rd trimester ALT (IU/litre) 0–40 - 6–32 6–32 6–32 AST (IU/litre) 7–40 - 10–28 11–29 11–30 Bilirubin (μmol/litre) 0–17 - 4–16 3–13 3–14 γGT (IU/litre) 11–50 - 5–37 5–43 3–41 ALP (IU/litre) 30–130 - 32–100 43–135 133–418 Albumin (g/litre) 35–46 28–37 - - - Bile acids (μmol/litre) 0–14 0–14 - - - Haemoglobin (g/litre) - 110–135 103–130 100–130 Platelets (103/ml) 135–212 - - - Adapted by permission from BMJ Publishing

Group Limited. I Walker, LC Chappell, C Williamson (2013). Abnormal liver function tests in pregnancy. BMJ, 25, 347. Table 14.9.3 Typical elevations of liver enzymes in pregnancy-specific liver disorders Pattern of LFT changes Likely diagnosis Trimester at onset of symptoms and abnormal serum liver tests Estimated proportion of pregnant women with abnormal LFTs that have each diagnosisa Recommended additional investigations ↑ALT (1.5–8 fold) ↑tBA (1.5–15 fold) tBil usually normal Intrahepatic
Cholestasis of Pregnancy (also known as Obstetric Cholestasis) 3rd, but may present as
early as 7 weeks' gestation 17% Viral serology Antimitochondrial and antismooth muscle antibodies Abdominal USS ↑ALT (2–5 fold) tBA usually normal tBil usually normal Pre-eclampsia with
hepatic impairment 3rd, but may present
from 20 weeks' gestation 49% ↑BP in most Urinalysis for protein U&E, creatinine ↓Platelets ↑ALT (2–30 fold) tBA usually normal ↑tBil (1.5–10 fold) HELLP syndrome (haemolysis, elevated
liver enzymes, & low platelets) 3rd, but may present
from 20 weeks' gestation 22% ↑BP in most Proteinuria in most ↑Creatinine ↓Platelets in all ↑LDH ↑ALT (3–15 fold) tBA usually normal ↑tBil (4–15 fold) Acute fatty liver of pregnancy (AFLP) 3rd 4% ↑BP in most Proteinuria in most ↑Creatinine ↓Platelets ↑WBC ↓ plasma glucose ↑ALT (2–5 fold) tBA usually normal tBil usually normal Hyperemesis
gravidarum 1st If new vomiting later in pregnancy, an underlying
cause must be sought 8% ↑Thyroxine, ↓↓TSHb Hyponatraemia Hypokalaemia ALT, alanine transaminase; tBA, total serum bile acids; tBil, total bilirubin; LFT, liver function test; TSH, thyroid-stimulating hormone. a During a 15-month study period, out of a total of 4377 deliveries, 142 women (3%) with 206 diagnoses were found to have abnormal LFTs; of these, 138 diagnoses were pregnancy-specific liver disease. One additional woman had hepatic infarct/haematoma. b Symptoms of thyrotoxicosis are rarely seen. TSH is normally suppressed during the first trimester but it is detectable in uncomplicated pregnancy. Adapted by permission from BMJ Publishing Group Limited. I Walker, LC Chappell, C Williamson (2013). Abnormal liver function tests in pregnancy. BMJ, 25, 347.

 infarction, seizures, and increased peri-natal morbidity and mor- tality. Liver biochemistry typically recovers within two weeks of delivery.

HELLP syndrome The combination of haemolysis with a micro-angiopathic blood smear, elevated liver enzymes and low platelets (HELLP) in preg- nancy was first described in 1982 and affects 6/1000 pregnancies. Up to 10% of women with pre-eclampsia develop HELLP. Considered to be a part of the spectrum of pre-eclampsia, it is one of the cri- teria that can define severe pre-eclampsia. HELLP may develop in isolation and a peri-natal infant mortality rate ranging from 6.7 to 70% has been reported. HELLP usually arises in the second or third trimester but can deteriorate or occur following delivery. Risk fac- tors include increased maternal age, multiparity, and white ethnicity. Clinical features and diagnosis Patients with HELLP syndrome maybe asymptomatic, or present with nausea, vomiting, malaise, or right upper quadrant/epigastric pain. Hypertension and proteinuria is evident in up to 85% of cases. Liver injury is precipitated by intravascular fibrin deposition, low blood volume, and increased sinusoidal pressure. This results in mild to moderate elevation of the AST/ALT and mild elevation of bilirubin. Recognized classification systems of HELLP include the Tennessee and the Mississippi systems (Table 14.9.4). The prothrombin time or international normalized ratio (INR) remains normal unless there is evidence of disseminated intravas- cular coagulation or severe liver injury. Liver biopsy is typically not warranted. Hepatic

haematoma, infarction, and rupture In some patients with severe hypertension-related disease, hep- atic haematomas, liver infarction, and liver rupture may occur. Computed tomography (CT) or MRI of the liver may identify hep- atic infarction/rupture, haemorrhage, or subcapsular haematoma. A 50% maternal mortality has been reported for this complication with the prevalence of hepatic rupture being higher with severe thrombocytopenia. Hepatic adenoma, hepatocellular carcinoma, and haemangiomas may also rupture during pregnancy. Contained haematomas should be managed conservatively with blood transfusion and supportive measures. Infection can occur within areas of infarction or haematoma. Haemodynamic in- stability suggests persistent active bleeding and mandates hepatic angiography, arterial embolization of the hepatic artery or surgical exploration. Surgical options include packing, hepatic artery liga- tion, or resection of the affected liver. No long term maternal com- plications have been reported. Management of HELLP/Severe hypertension-related disease Women with HELLP syndrome may require a high-dependency or intensive care unit (ITU), given the potential complications of encephalopathy, renal dysfunction, hepatic rupture, and bleeding. Prompt delivery is paramount particularly after 32–34 weeks' ges- tation, if fetal distress is present or there is evidence of maternal end-organ disease. Management of hypertension involves the use of labetolol, hydralazine, and nifedepine. Intravenous magnesium sulphate with platelet and/or coagulation support is recommended, particularly in the presence of bleeding. If gestation is less than 34 weeks, corticosteroids should be administered to promote fetal lung maturity. Hepatic or renal failure mandates admission to intensive care for monitoring. Indications for liver transplantation can include per- sistent bleeding from haematoma, hepatic rupture, or liver failure. The risk of recurrence of HELLP syndrome and pre-eclampsia in subsequent pregnancies is increased. HELLP syndrome typically re- solves post-delivery, although temporary postnatal deterioration is not uncommon. Acute fatty liver of pregnancy Acute fatty liver of pregnancy (AFLP) is a medical and obstetric emergency. Defined as microvesicular fatty infiltration of hep- atocytes occurring in usually the third trimester. Maternal and fetal mortality rates are significantly increased and range between 1 to 20%. It is a rare disorder affecting 1 in 7000 to 1 in 16 000 deliv- eries but is one of the commoner causes of liver failure in pregnancy. A UK-based prospective study involving 229 centres identified 57 confirmed cases in a total of 1 132 964 maternities giving an inci- dence of 5/100 000 maternities, with 74% cases identified at a me- dian gestation age of 36 weeks. Caesarean section rate was 74%. Aetiology Acute fatty liver of pregnancy is part of the spectrum of mitochon- drial cytopathies which includes Reye's syndrome and other drug re- lated liver disease. Common characteristics of these disorders include vomiting, hypoglyacaemia, lactic acidosis, hyperammonaemia, and microvesicular fat deposition in organs. Abnormality in mitochon- drial β-oxidation is recognized as the causative aetiology of some cases of acute fatty liver of pregnancy. The enzyme, long chain 3- hydoxyacyl coenzyme A dehydrogenase (LCHAD) is part of the mitochondrial trifunctional protein, which is an important enzyme complex associated with the inner mitochondrial membrane. A landmark study demonstrated that sick infants born to mothers with acute fatty liver of pregnancy with features of HELLP syn- drome had defects in fatty acid β-oxidation and were deficient in LCHAD predominately due to a mutation on one or both alleles of the α subunit of the trifunctional protein. The risk of development of maternal liver disease during pregnancy is 20 times higher in fe- tuses with fatty acid oxidation defects when compared to the general population. The accumulation of fetal fatty acids with their return to the maternal circulation results in deposition in the liver thus causing liver toxicity. Table 14.9.4 Classification systems used in HELLP syndrome Tennessee system* AST >70 IU/litre LDH >600 IU/litre Platelets <100 × 109/litre Mississippi system Class I: Platelets <50 × 109/litre Class II: Platelets 50–100 × 109/litre and AST>40 IU/litre and LDH >600 IU/litre

Class III: Platelets 100–150 × 109/litre

- For Tennessee system, all 3 components = complete, 1 or 2 components = partial.

Section 14 Medical disorders in pregnancy 2622 Clinical features and diagnosis The clinical presentation of acute fatty liver of pregnancy varies from nausea and abdominal pain to hepatic encephalopathy, dia- betes insipidus, and jaundice. Risk factors include twin pregnancies and nulliparity. An inverse relationship may exist between body mass index and acute fatty liver of pregnancy, in contrast to the rate of elevated body mass index (BMI) in patients with pre-eclampsia. Common laboratory abnormalities include raised AST/ALT, INR, serum urate levels, and bilirubin. Hypoglycaemia is a poor prog- nostic sign. Serum ammonia concentrations rise, and lactic acid- osis is present in severe disease. Evidence of renal dysfunction is common. Differential diagnosis includes HELLP syndrome and viral hepatitis. Interestingly, ultrasound and even computed tom- ography may be inconsistent at detecting fatty infiltration. Although the gold standard for diagnosis is liver biopsy this is rarely performed or necessary. The characteristic microscopic change is microvescicular steatosis. The Swansea diagnostic criteria represent an alternative to liver biopsy (Box 14.9.1) and were shown to be a reliable diagnostic tool in a UK prospective cohort study of liver disorders in pregnancy. Management Prompt delivery is essential in women with acute fatty liver of preg- nancy once any coagulopathy and hypoglycaemia have been treated. Steroids are required for lung maturation in preterm fetuses. In the post-partum phase, women can develop a prolonged cholestatic phase taking up to four weeks for resolution. Liver transplantation warrants consideration in cases of severe hepatic encephalopathy, liver rupture, and where there is failure of recovery of liver func- tion. The baby should be assessed for signs of hypoglycaemia, hep- atic failure, myopathy, and other features associated with defects in fatty acid oxidation. An increased recurrence rate has only been reported in women who carry the LCHAD mutations although recurrent acute fatty liver of pregnancy may also reoccur in women without detectable LCHAD mutations. Infants born to mothers with acute fatty liver of pregnancy should be screened for defects of fatty acid oxidation. Intrahepatic cholestasis of pregnancy Intrahepatic cholestasis of pregnancy, also called obstetric cholestasis, is the commonest liver-specific disorder of pregnancy. It affects 0.67% of pregnancies in the United Kingdom, but there is geographical variability in prevalence with increased rates in women from Chile and South Asia. Its cause is not known. Clinical presentation The typical presenting symptom is pruritus. This usually occurs in the third trimester although it has been reported as early as seven weeks of gestation, and it may affect any part of the body but most com- monly occurs on the palms and soles. There are no specific dermato- logical changes, although women may have excoriations secondary to scratching (Fig. 14.9.1). Affected women have raised serum bile acids and usually have elevated liver transaminases. Bilirubin is not raised in most cases (Table 14.9.3). Many women report dark urine and there may be steatorrhoea, a possible explanation for reports of increased risk of post-partum haemorrhage due to reduced absorp- tion of vitamin K. Gestational diabetes mellitus occurs more com- monly in women with intrahepatic cholestasis of pregnancy. Women with intrahepatic cholestasis of pregnancy have increased rates of adverse pregnancy outcome, including spontaneous preterm labour, fetal asphyxial events, meconium-stained amniotic fluid, Box 14.9.1 Criteria for diagnosis of acute fatty liver of pregnancy (Six or more of the following features in the absence of another explanation) • Vomiting • Abdominal pain • Polydipsia/polyuria • Encephalopathy • Elevated bilirubin (>14 µmol/l) • Hypoglycaemia (<4 mmol/l) • Elevated urate (>340 µmol/l) • Leucocytosis (>11 × 106/l) • Ascites or bright liver on ultrasound scan • Elevated

AST/ALT (>42 IU/l) • Elevated ammonia (>47 µmol/l) • Renal impairment (Creatinine >150 µmol/l) • Coagulopathy (PT >14 s or APTT >34 s) • Microvesicular steatosis on liver biopsy Reproduced from CL Ch'ng, et al. (2002). Prospective study of liver dysfunc- tion in pregnancy in Southwest Wales. Gut, 51, 876–880, with permission from BMJ Publishing Group Ltd. Fig. 14.9.1 Typical appearance of the skin in a woman with intrahepatic cholestasis of pregnancy. Dermatological changes include scratch marks with skin discolouration and more generalized skin lesions.

14.9 Liver and gastrointestinal diseases of pregnancy 2623 and stillbirth. Several studies have shown that these adverse out- comes occur more commonly in pregnancies where the maternal serum bile acid concentration is ≥40 µmol/litre, and a recent meta- analysis reported that stillbirth occurs more commonly if the ma- ternal serum bile acid concentration is ≥100 µol/litre. Treatment Women with intrahepatic cholestasis of pregnancy should have regular liver function tests and serum bile acids performed, and investigations should be performed to exclude hepatitis C, auto- immune hepatitis, or primary biliary cholangitis. Women with se- vere cholestasis or steatorrhoea should have a coagulation screen performed. An abdominal ultrasound will evaluate whether there are gallstones or another hepatobiliary cause of cholestasis. The drug most commonly used to treat intrahepatic cholestasis of pregnancy is ursodeoxycholic acid (UDCA), typically at a starting dose of 500 mg BD, rising to a maximum of 2 g daily. This reduces maternal pruritus and biochemical abnormalities in approximately 75% of cases, but it is not known whether it also protects against adverse fetal outcome. Otherwise, aqueous cream with 1–2% menthol may improve the sensation of pruritus and vitamin K 10 mg OD is advis- able for women with steatorrhoea. Other drugs that have been used with varying success are S-adenosyl methionine, cholestyramine, and activated charcoal. Rifampicin has been used in conjunction with UDCA for women with a limited response to the latter drug, as the drugs have synergistic actions to induce hepatic biliary transport proteins that enhance excretion of bile acids. Delivery and post-partum Many clinicians choose to induce labour in women with intrahepatic cholestasis of pregnancy between 37–38 weeks' gestation as still- birth in this condition typically occurs at later gestational weeks. This practice is not associated with an increase in operative delivery. Symptoms and hepatic dysfunction typically resolve rapidly after delivery of the fetus, and therefore UDCA and other drugs can usu- ally be stopped within a small number of days. It is important to ensure that liver function tests return to normal by three months post-partum, and if not then further investigation should be per- formed to exclude other hepatic pathology. Women should be ad- vised to avoid oestrogen-containing contraception, and that the condition has a high rate of recurrence in subsequent pregnancies. Hyperemesis gravidarum Nausea and vomiting is common in pregnancy. In contrast, hyperemesis gravidarum, characterized by intractable vomiting, re- sulting in dehydration, ketosis, and ≥5% weight loss, is seen in 0.3– 2% of all pregnancies. Its exact cause is unclear, but a combination of hormonal factors, abnormal gastric motility, and changes in the autonomic nervous system are thought to play a role. Risk factors include pre-existing diabetes and multiple pregnancies, increased body mass index, previous psychiatric illness, and molar pregnancy. Clinical features and diagnosis Hyperemesis gravidarum may begin as early as the fourth week of gestation and typically resolves by the eighteenth week. Serum AST and ALT may be markedly raised (Table 14.9.3). Other findings include elevated serum urea and creatinine levels, hypophosphataemia, hypomagnesaemia, hypokalaemia, and biochemical hyperthyroidism. These typically resolve on reso- lution of vomiting. Ongoing elevation in liver enzymes should trigger consideration of alternative diagnoses. There is no role for liver biopsy, as this is nonspecific. Management Treatment of hyperemesis gravidarum is supportive and includes intravenous re-hydration,

electrolyte replacement, antiemetics, and gradual re-introduction of oral intake. Vitamin supplementation especially thiamine is mandatory to prevent Wernicke's encephal- opathy. Most patients will require day case treatment or hospital admission, but relapse is common. Recurrence in subsequent preg- nancies is common. Liver diseases incidental to pregnancy Viral hepatitis in pregnancy Viral hepatitis is probably the most commonly recognized cause of jaundice occurring during pregnancy worldwide. There is no spe- cific change in the presentation, clinical features, or general outcome for hepatitis A virus, hepatitis B, hepatitis C, cytomegalovirus, or Epstein–Barr virus infection in pregnancy. Hepatitis B virus can present in an acute or chronic form. For pa- tients with acute hepatitis B, transmission of the virus to the child occurs in 50% of cases with 70% of children infected if acute viral hepatitis B occurs in the third trimester. For patients with chronic hepatitis B, transmission of virus is dependent on the degree of viral replication and the quantity of HBV DNA detectable in the serum of the mother. Transmission rates above 90% have been reported from mothers who are HBV DNA positive and these are typically hepatitis B E antigen positive. Vaccination programmes throughout Southeast Asia and in the developed world have reduced transmis- sion rates dramatically. Following transmission, up to 80% of chil- dren become chronic hepatitis B carriers. Therefore, strategies exist to limit this transmission rate. Firstly, the use of antiviral therapy such as tenofovir disoproxil fumarate 245 mg daily to reduce the HBV DNA level in the third trimester for appropriate patients re- duces viral load, and transmission rate. Secondly the use of hepa- titis B immunoglobulin with hepatitis B vaccination in the neonate within seven days of birth and at 1, 2, and 12 months of age also reduces the transmission rate significantly. Mother-to-child transmission (MTCT) of hepatitis C virus has become the leading cause of paediatric infection, at an approximate rate of 5%. Maternal HIV co-infection is a significant risk factor for MTCT and anti-HIV therapy during pregnancy can reduce the transmission rate of both viruses. A high maternal viral load is an im- portant, but unpreventable risk factor since no antihepatitis C virus treatment can be given in pregnancy. Obstetric procedures, such as amniocentesis or invasive fetal monitoring, should be used with cau- tion as they could expose the fetus to maternal blood, although evi- dence is lacking on the real risk of these obstetric practices. Mode of delivery and type of feeding do not represent significant risk factors for MTCT. Therefore, there is no reason to offer elective caesarean section or discourage breastfeeding to hepatitis C virus-infected pa- tients. Antibody conversion of infants following transmission may take 6–12 months, although measurement of hepatitis C virus RNA levels will allow for early diagnosis.

 Hepatitis E virus is problematic in pregnancy typically occurring in epidemic form in Southeast Asia, the Indian subcontinent, and the Middle East. The development of acute liver failure in the third trimester can be associated with a mortality of up to 20%. Pregnancy in patients with cirrhosis Many patients with chronic liver disease and cirrhosis are infertile. However, patients with autoimmune liver diseases such as auto- immune hepatitis, primary sclerosing cholangitis, and primary bil- iary cholangitis may become pregnant. Patients with autoimmune hepatitis should be maintained on baseline immunosuppression throughout pregnancy (azathioprine plus/minus prednisolone). For patients treated with mycophenolate mofetil pre-pregnancy, they should be converted to an alternative immunosuppressant such as azathioprine, tacrolimus, or cyclosporine prior to planned preg- nancy. A 20–25% risk of flare in autoimmune hepatitis occurs fol- lowing delivery in the first three months post-partum, and this is reduced if immunosuppressive treatment is maintained. Patients with established cirrhosis should be screened for varices in the second trimester. This is to facilitate and guide appropriate peri- partum care. The presence of small varices in otherwise well compen- sated

cirrhotic patients should not preclude against a vaginal delivery. Variceal bleeding in pregnancy Even in normal patients without liver disease, varices develop during pregnancy. This is related to changes in cardiac output, azygos blood flow, increased circulating blood volume and changes in splanchnic haemodynamics. For patients with noncirrhotic portal hyperten- sion, a bleeding rate in pregnancy of 13% has been reported. In cir- rhotic patients contemplating pregnancy, pre-pregnancy screening and appropriate treatment of large varices should be undertaken. Propranolol is not contraindicated in pregnancy and episodes of variceal bleeding should be treated with normal endoscopic ap- proaches including endoscopic band ligation, histoacryl glue, whereas transjugular intrahepatic shunts should be reserved for rescue therapy and field endoscopic treatment. There are limited safety data for vasoconstrictors such as terlipressin, but they may be used in women with life-threatening haemorrhage. Pregnancy following Liver Transplantation Successful pregnancy following liver transplantation has been widely reported and fertility will return typically within six months of transplant. Best outcomes are reported for pregnancies under-taken greater than one year following the transplant operation since this reduces the risk of acute cellular rejection and other infective complications. Tacrolimus, cyclosporine, azathioprine, and cortico- steroid therapy are widely and safely used in pregnancy. Specific complications in pregnancy related to a higher prevalence of hyper- tension/pre-eclampsia and preterm delivery have been reported. Patients on mycophenolate should be converted to an alternative immunosuppressant prior to pursuing pregnancy. Gastrointestinal diseases of pregnancy Inflammatory bowel disease The respective incidence of Crohn’s disease and ulcerative colitis is 10.7 and 12.2 per 100 000. Both disorders typically affect women at reproductive age. While fertility is reduced in women with active disease, or if there is scarring or inflammation affecting reproductive tissues, for most women there is no major impact on the ability to conceive. Clinical presentation Women with inflammatory bowel disease should have pre- pregnancy counselling as this will enable evidence-based deci- sions to be made about drug treatment. Ideally women should have been in remission for several months, as disease activity at conception does influence the risk of flare in pregnancy (Box 14.9.2). The pre-pregnancy period is a good time to ensure there are no deficiencies of vitamins D, B12, or iron, and women should be encouraged to take folic acid supplementation. Most drugs used to treat inflammatory bowel disease can be taken in preg-nancy (Table 14.9.5) and women should be informed that the greatest risk of flare occurs in those that discontinue treatment. There is an increased risk of spontaneous miscarriage, preterm la- bour and small for gestational age infants, and the risk of low birth weight increases further in women with disease flares. If women continue their medication, the risk of disease flare is the same as in nonpregnant women. Treatment Most drugs used to treat inflammatory bowel disease, including bio- logical therapies, are safe in pregnancy and lactation (Table 14.9.5). The only drug that is contraindicated is methotrexate as this causes congenital abnormalities and spontaneous miscarriage. Some studies have found increased rates of small for gestational age and preterm infants in women treated with thiopurines or cyclosporine, but it is difficult to establish whether this is related to severity of the underlying disease or due to use of the drug. Overall, the benefits of treatment with these drugs, and with glucocorticoids, outweighs the possible association with preterm or small infants, and women should be encouraged to continue to take drugs that maintain dis- ease remission, particularly given the clearly documented increase in these complications in women with disease flares. Biologic therapy is well tolerated in pregnancy and there are accumulating data to support the use of these drugs in pregnancy and during breast- feeding. Ideally, IgG1 antibody therapies (infliximab, adalimumab, and golimumab) should be avoided in the third trimester as they are transported across the placenta, and levels of these drugs are higher in

fetal than maternal blood in late pregnancy. However, some women have severe flares, necessitating treatment. The infants of Box 14.9.2 Relationship between disease activity at the time of conception and the risk of flare of inflammatory bowel disease in pregnancy If active disease at the time of conception: Ulcerative colitis • 45% will have flare • 30% will have stable disease • 25% will improve Crohn’s disease • 33% will have a flare • 34% will have stable disease • 33% will improve

14.9 Liver and gastrointestinal diseases of pregnancy 2625 women treated with biologic agents should not receive live vaccines for the first six months of life. If a woman has a flare in pregnancy, the treatment is the same as for nonpregnant women. Clostridium difficile infection is more common in pregnant women with inflammatory bowel disease and stool samples should be tested in women with new diarrhoea. If imaging is required, magnetic resonance imaging is preferred as this avoids radiation exposure. Flexible sigmoidoscopy and colonoscopy can be performed if indicated, with appropriate sedation. The indi- cations for surgery are the same as for nonpregnant individuals. Delivery and post-partum Women with inflammatory bowel disease have higher rates of cae- sarean section than the background population. However, for most women with inactive disease there is no contraindication to va- ginal delivery, and caesarean section should be performed only for obstetric reasons. There are two groups of women where decisions about mode of delivery should be made on a case-by-case basis. For women with active perianal disease there is a risk of perineal trauma, and caesarean section should be considered. For women with an ileal pouch-anal anastomosis, it is important to avoid anal sphincter damage to preserve continence. It is advisable to have a multidisciplinary discussion, including the colorectal surgeon, to decide about mode of delivery in this group of women. There is some evidence that vaginal delivery does not significantly affect pouch function, but the opinion of the surgical and gastrointes- tinal team will be invaluable to individualized decision-making in this context. Gallstones and acute cholecystitis Gallstones and gallbladder sludge occur more commonly in preg- nant women. Several prospective studies have reported rates of 8–10% in the third trimester and puerperium. Affected women more commonly have a raised body mass index, and gallstones are also more commonly diagnosed in women with intrahepatic cholestasis of pregnancy. Most pregnant women with gallstones are asymptomatic, and this group should be managed conservatively. If a woman develops symptoms of acute cholescystitis, she should be given intravenous fluids, antibiotics, and feeding should be stopped. Surgical manage- ment is usually preferred, as 40% of women treated medically have relapse. If surgery is required, a laparoscopic approach is usually preferred as this is associated with lower rates of complication and shorter operative recovery than open surgery. Appendicitis The commonest presenting symptoms of appendicitis in pregnancy are right lower quadrant pain, although retrocaecal appendicitis may result in flank or back pain. Other characteristic symptoms are anorexia, vomiting, abdominal guarding or rebound, but they may be absent. The white blood cell count and C-reactive protein are usu- ally raised. Graded abdominal ultrasound imaging usually achieves a diagnosis in the first two trimesters, but may be difficult in late pregnancy. Magnetic resonance imaging is safe in pregnancy and increasing data support its use due to high sensitivity and specifi- city in pregnant women. As with acute cholecystitis, laparoscopic re- moval is associated with lower complication rates than open surgery. Pancreatitis Acute pancreatitis is rare, affecting approximately 1 in 10 000 preg- nant women. The commonest cause is gallstones, but it may also be caused by hypertriglyceridaemia, alcohol abuse, hyperparathyr- oidism, or drugs (e.g. thiazide diuretics), and approximately 10% of cases are idiopathic. The most valuable tests for diagnosis are Table 14.9.5 Drugs used to treat inflammatory

bowel disease in pregnancy Drug name High or low risk in pregnancy High or low risk in breastfeeding Methotrexate High • teratogenicity and fetal loss High • transferred in breast milk Corticosteroids (budesonide and prednisolone) Low • possible slight increase in the risk of cleft lip/palate, but benefits for women with flares outweigh risks Low Aminosalicylates (sulfasalazine and mesalazine) Low • sulphasalazine interferes with folate metabolism so essential to give high-dose folic acid (5 mg OD) Low Thiopurines (azathioprine and 6-mercaptopurine) Low • no increase in congenital abnormalities, but care with starting during pregnancy due to associated low risk of pancreatitis, hepatic impairment, or bone marrow suppression Low Cyclosporine Low Medium • transferred to breast milk Anti TNFα agents (IgG1 antibodies—infliximab, adalimumab, golimumab) Low • but ideally avoid in 3rd trimester due to risk of immune suppression in neonatea Low Anti TNFα agents (pegylated Fab fragment—certolizumab) Low • not actively transported across the placenta, therefore less concern about treatment in the 3rd trimester Likely low, but limited data IgG1—immunoglobulin G1; TNFα—tumour necrosis factor alpha a If a woman has severe disease the clinical need for these agents may necessitate treatment. All neonates of women treated with Anti-TNFα agents in pregnancy should not receive live vaccines for the first six months of life.

Section 14 Medical disorders in pregnancy 2626 serum amylase or lipase. Treatment is the same as for nonpregnant women, in addition to surgical or medical management of the underlying cause. Gastro-oesophageal reflux and peptic ulcer Gastro-oesophageal reflux disease affects approximately 40% of pregnant women. Most women have a benign course and symp- toms resolve after delivery. Simple treatments are often effective, including lifestyle modification and use of antacids, alginates, or sucralfate. If required both H2-antagonists and proton pump inhibi-tors have good safety data for use in pregnancy. Peptic ulcer disease is considerably less common and typic- ally presents with epigastric pain, postprandial nausea, vomiting and anorexia. If suspected, endoscopic investigation can be per- formed in pregnant women. It is advisable to also screen for Helicobacter Pylori. Peptic ulcer can be treated with the same drugs that are used for gastro-oesophageal reflux disease and the commonest treatment regimens used for Helicobacter Pylori can be used in pregnancy (proton pump inhibitor, amoxicillin, clarithromycin). Coeliac disease Coeliac disease is an autoimmune disorder of the small intestine. It should be considered in pregnant women presenting with diarrhoea or unexplained abdominal pain. Serology for anti-endomysial, antigliadin, and antitissue transglutamase antibodies is reliable in pregnancy, and endoscopy can be performed for a definitive diag- nosis if indicated. Affected women should be referred for dietary advice, and compliance can be assessed using serial serological meas-urements. This is important as inadequately controlled women are at risk of deficiency of fat soluble vitamins, calcium malabsorption, and oxalate kidney stone formation. There is evidence for an in- creased risk of intrauterine growth restriction and preterm birth in undiagnosed disease. Gastrointestinal cancer Malignancies affecting the gastrointestinal tract are rare women of reproductive age. However, they should be considered in women with unexplained, severe symptoms of weight loss, abdominal pain, anorexia, nausea, vomiting, constipation, or rectal bleeding. Many of these symptoms are common in pregnancy, but gastric or colon cancer may be present if they are ongoing or severe. If suspected, endoscopic investigation should be pursued. Pregnancy does not affect the serum concentration of carcinoembryonic antigen, so this can be used as a prognostic or monitoring test for women with known colorectal cancer. FURTHER READING Ch’ng CL, et al. (2002). Prospective study of liver dysfunction in preg- nancy in Southwest Wales. Gut, 51, 876–80. Geenes V, et al. (2013). Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study.

Hepatology, 59, 1482–91. Ibdah JA, et al. (1999). A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. N Engl J Med, 340, 1723–31. Knight M, et al. (2008). A prospective national study of acute fatty liver of pregnancy in the UK. Gut, 57, 951–6. Mahadevan U, Matro R (2015). Care of the pregnant patient with in- flammatory bowel disease. Obstet Gynecol, 126, 401–12. Walker I, Chappell LC, Williamson C (2013). Abnormal liver function tests in pregnancy. BMJ, 347, f6055. Westbrook RH, et al. (2012). Outcomes of pregnancy in women with autoimmune hepatitis. J Autoimmun, 38, J239–44. Westbrook RH, et al. (2015). Outcomes of pregnancy following liver transplantation: the King’s College Hospital experience. Liver Transpl, 21, 1153–9. Williamson C, Geenes V (2014). Intrahepatic cholestasis of pregnancy. Obstet Gynecol, 124, 120–33.

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