Liver disease in pregnancy

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Severe liver disease in pregnancy is rare. Pregnancy-related liver disease is the most frequent cause of liver dysfunction in pregnancy and provides a real threat to fetal and maternal survival. A rapid diagnosis differentiating between liver disease related and unrelated to pregnancy is required in women who present with liver dysfunction during pregnancy. Research has improved our understanding of the pathogenesis of pregnancy-related liver disease, which has translated into improved maternal and fetal outcomes. Here, we provide an overview of liver diseases that occur in pregnancy, an update on the key mechanisms involved in their pathogenesis, and assessment of available treatment options.

Introduction

Alterations in normal physiological and hormonal profiles occur throughout pregnancy. Moreover, changes in liver biochemical profile are normal in pregnancy. However, up to 3% of all pregnancies are complicated by liver disorders.[1] Severe liver disease, although rare, can occur and leads to increased morbidity and mortality for both mother and newborn infant. Liver disorders were once thought to be trimester specific, but this is not always the case. As such, liver disease in pregnancy can be related or unrelated to pregnancy. Liver disease unrelated to pregnancy can be further classified into pre-existing disorders that might become active during pregnancy and those co-incident with pregnancy. Panel 1 lists these liver diseases.

Normal physiological changes in pregnancy

A rise in maternal heart rate, cardiac output, together with a fall in blood pressure and systemic vascular resistance, all occur during pregnancy. These alterations mimic physiological changes in patients with decompensated chronic liver disease. Blood volume increases by about 50%, peaking in the second trimester. However, blood flow to the liver remains constant and the liver usually remains impalpable during pregnancy. Telangiectasia or spider angiomas and palmar erythema are normal findings in pregnancy and are caused by the hyperoestrogenic state. Gall bladder motility is decreased, which increases the lithogenicity of the bile.

During a normal pregnancy, serum albumin concentration falls due to the expansion in plasma volume, and the alkaline phosphatase activity increases due to added placental secretion (table 1). In general, aminotransferase concentrations (alanine aminotransferase and aspartate aminotransferase), bilirubin, and gamma-glutamyl transpeptidase all remain normal throughout pregnancy, and their change should be further investigated. On light microscopy, the liver appears normal or near normal.[2]

Ultrasonography remains the safest imaging modality to visualise the liver during pregnancy. However, if further detailed imaging is needed, MRI without contrast is safe. Gadolinium-enhanced MRI should be avoided because of transplacental transfer and unknown effects on the fetus.[3]

Pregnancy-related liver diseases

Hyperemesis gravidarum

Nausea and vomiting are not uncommon in pregnancy. Hyperemesis gravidarum occurs in 0·3–2·0% of all pregnancies usually within the first trimester.[4,5] Under-reporting of symptoms of this condition might account for the variation of the reported incidence in published reports. One of the most frequently used definitions of hyperemesis gravidarum is that of intractable vomiting, resulting in dehydration, ketosis, and weight loss of 5% or more. The cause remains unclear but abnormal gastric motility, hormonal factors, and changes in the autonomic nervous system are all probably involved. Risk factors include increased body-mass index (BMI), psychiatric illness, molar pregnancy, pre-existing diabetes, and multiple pregnancies.[6,7] Hyperthyroidism is seen in an estimated 60% of cases of hyperemesis gravidarum[8,9] and might occur because of high serum concentrations of human chorionic gonadotropin, which has increased thyroid-stimulating activity during pregnancy.[9]

Hyperemesis gravidarum can start as early as week 4 of gestation and typically resolves by week 18. Serum aminotransferases can be raised by as much as 20 times the upper limit of normal, but jaundice is rare (table 2).[10] Other biochemical abnormalities include raised serum urea and creatinine concentrations, hypophosphataemia, hypomagnesiumia, and hypokalaemia. Biochemical abnormalities resolve on resolution of vomiting. Persistent abnormalities of the liver should alert the physician to alternative diagnoses (ie, viral hepatitis). Liver biopsy is not indicated, but when done, it shows non-specific changes including mild steatosis

Search strategy and selection criteria

We searched Medline (from January, 1966, to present) for publications containing the terms "liver disease in pregnancy" in combination with "jaundice" and "transplantation". We selected publications mainly from the past 5 years, but did not exclude seminal older publications. We also reviewed reference lists of publications identified by this search strategy and selected those we judged relevant. Our reference list was modified on the basis of comments from peer reviewers.

and cholestasis.[2] Persistent symptoms beyond week 18 should warrant consideration of a gastroscopy to exclude mechanical obstruction.

Treatment of hyperemesis gravidarum is supportive and includes intravenous rehydration, antiemetics, and gradual reintroduction of oral intake. Vitamin supplementation, especially thiamine, is mandatory to prevent Wernicke's encephalopathy. Most patients will need 5–8 days of hospital admission, but relapse is common. No benefit in outcomes is seen with the use of steroids.[11] Recurrence in subsequent pregnancies is common.

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis is defined as pruritus with elevated serum bile acids occurring in the second half of pregnancy, which resolves after delivery.[12] Recurrence in subsequent pregnancies is common. The incidence in Europe ranges from 0·1% to 1·5% of pregnancies compared with a much higher incidence in Scandinavia and South America.[12,13] Maternal morbidity is low and therefore the importance of this disorder is related to its effects on the fetus. Intrahepatic cholestasis can lead to chronic placental insufficiency, resulting in fetal complications that include anoxia, prematurity, perinatal death, fetal distress, and stillbirth.[14] Risk factors include women who develop cholestasis secondary to the oral contraceptive pill and a family history of the condition.

The cause of intrahepatic cholestasis remains unclear but is related to abnormal biliary transport across the canalicular membrane. Direct effects of female sex hormones induce cholestasis and inhibit the bile salt export pump. Mutations in the bile salt export pump have been implicated in the pathogenesis of intrahepatic cholestasis.[15,16] The multidrug resistance protein 3 (MDR3) is the key transporter for phospholipids across the canalicular membrane (figure 1). Mutations in this gene lead to loss of function and thus increased serum bile acids.[18] The *MDR3* mutation is located on chromosome 7q21.1 and has been identified in 15% of cases of intrahepatic cholestasis.[17] Overall, ten different mutations have been identified.[18,19] Floreani and colleagues[19] found that only heterozygous mutations cause transporter dysfunction, whereas complete absence of transport function is associated with severe liver disease.

The key symptom is pruritus, especially of the palms and soles, which is followed by generalised symptoms, and this usually occurs from week 25 of gestation. Jaundice is uncommon, but when present, arises 2–4 weeks after the onset of pruritus. Aminotransferase activity can be increased by 20 times the normal level. Raised gamma-glutamyl transferase activity is unusual but is indicative of MDR3 mutation or underlying liver disease unrelated to pregnancy. The key diagnostic test is a fasting serum bile acid concentration of greater than 10 µmol/L.[14] Prospective studies have shown that fetal complications correlate with serum bile acid concentrations—the risk being inexistent if levels remain below 40 µmol/L.[14,20] Patients can also develop diarrhoea and steatorrhoea requiring fat soluble vitamin supplementation. Liver biopsy is not needed. Histological findings consist of perivenular canalicular cholestasis with preserved portal tracts.

Early recognition and diagnosis of intrahepatic cholestasis with a multidisciplinary approach incorporating hepatological support is important. Women before weeks 33–34 of pregnancy should be referred to obstetric centres with appropriate facilities for high-risk premature newborn infants.

***Panel 1:* Classification of liver diseases in pregnancy**

Pregnancy-related liver diseases
- Hyperemesis gravidarum
- Intrahepatic cholestasis of pregnancy
- Pre-eclampsia and eclampsia
- HELLP syndrome
- Acute fatty liver of pregnancy

Pregnancy-unrelated liver diseases

Pre-existing liver diseases
- Cirrhosis and portal hypertension
- Hepatitis B and C
- Autoimmune liver disease
- Wilson's disease

Liver diseases co-incident with pregnancy
- Viral hepatitis
- Biliary disease
- Budd-Chiari syndrome
- Liver transplantation
- Drug-induced hepatotoxicity

HELLP=haemolysis, elevated liver enzymes, and low platelets.

	Alteration from non-pregnant state
Haemoglobin (118–148 g/L)	↓ from second trimester
White cell count (3·9–11·1×10⁹/L)	↑
Platelets (150–450×10⁹/L)	None
Packed cell volume (0·36–0·44 L/L)	↓
Prothrombin time (10–12 s)	None
Alkaline phosphatase (42–128 IU/L)	↑ (bone and placenta)
Albumin (35–50 g/L)	↓
ALT (0–70 IU/L)	None
GGT (2–35 IU/L)	None
Bilirubin (0–17 µmol/L)	None
Alpha-fetoprotein (0–44 µg/L)	↑
Cholesterol (3·5–5 mmol/L)	↑
Uric acid (160–395 µmol/L)	↓

↑=increase. ↓=decrease. ALT=alanine aminotransferase. GGT=gamma-glutamyl transpeptidase.

***Table 1:* Biochemical changes during normal pregnancy**

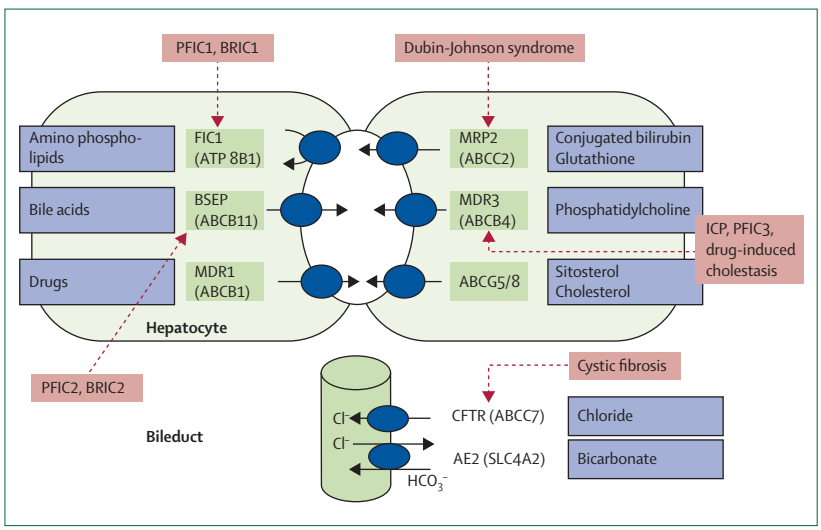

Figure 1: **Hepatobiliary transporters**
MDR3 translocates phosphatidylcholine across the canalicular membrane. Lack of this phospholipid leads to the formation of toxic monomeric bile salts in the bile ducts, which in turn results in cholangiocyte injury, pericholangitis, and periductal fibrosis. Mutations in the MDR3 transporter have been identified in the pathogenesis of drug-induced cholestasis, PFIC3, and cholestasis of pregnancy. Red dotted arrows show the phenotype expressed when a mutation occurs in the targeted transporter gene. PFIC1=progressive familial intrahepatic cholestasis type 1. PFIC2=progressive familial intrahepatic cholestasis type 2. PFIC3=progressive familial intrahepatic cholestasis type 3. ABCG5/8=ATP binding cassette transporters G5 and G8. AE2=anion exchanger. BSEP=bile salt export pump. BRIC1=benign recurrent intrahepatic cholestasis type 1. BRIC2=benign intrahepatic cholestasis type 2. CFTR=cystic fibrosis transmembrane conductance regulator. FIC1=familial intrahepatic cholestasis type 1. ICP=intrahepatic cholestasis of pregnancy. Cl^-= chloride ion. $HCO3^-$=bicarbonate ion. MRP2=multidrug resistance-associated protein 2. MDR1=multidrug resistance protein 1. MDR3=multidrug resistance protein 3. Modified, with permission, from Trauner and colleagues.[17]

Ursodeoxycholic acid decreases plasma bile acid and sulphated progesterone metabolite concentrations. Studies have also shown that it increases bile salt export pump (ATPB11, MDR3, and MRP4) expression.[21] Ursodeoxycholic acid (10–15 mg/kg bodyweight) provides relief against pruritus, improve liver function tests, and is well tolerated both by mother and fetus.[22] Improvement in pruritus might be associated with decreased urinary excretion of progesterone metabolites specific for intrahepatic cholestasis of pregnancy.[23] Glantz and colleagues[20] showed that ursodeoxycholic acid is more effective in alleviating pruritus than is dexamethasone ($p=0\cdot01$) in patients with bile acid concentrations greater than 40 µmol/L. When delivery is being considered in a preterm fetus, the administration of dexamethasone also promotes fetal lung maturity. Cholestyramine can also be used, but is not very effective at decreasing serum bile acid concentrations and can exacerbate vitamin K deficiency.

Intrahepatic cholestasis of pregnancy normally resolves after delivery but, in rare cases of familial forms, the condition can persist after delivery, leading to fibrosis and even cirrhosis.[24] In these cases, an increased risk of cholestatic liver disease exists, irrespective of pregnancy. Intrahepatic cholestasis of pregnancy might therefore be a predictor for the development of liver and biliary disease in the future.[24]

Hypertension-related liver diseases and pregnancy

Hypertension in pregnancy is defined as a blood pressure greater than 140/90 mm Hg on at least two occasions. Pre-eclampsia, eclampsia, HELLP (haemolysis elevated liver enzymes and low platelets) syndrome, hepatic infarction, and rupture are all related to hypertension in pregnancy.

Pre-eclampsia and eclampsia

Pre-eclampsia is a multisystem disorder affecting 5–10% of all pregnancies and can involve the kidneys, the CNS, the haematological system, and the liver. Pre-eclampsia is characterised by hypertension and proteinuria (greater than 300 mg in 24 h) after 20 weeks of gestation and/or within 48 h after delivery. Oedema is no longer needed for the diagnosis of pre-eclampsia.[25] Presence of seizures differentiates eclampsia from pre-eclampsia. Atypical pre-eclampsia is the occurrence of the signs, symptoms, and the biochemical abnormalities of pre-eclampsia but without hypertension or proteinuria. Risk factors for pre-eclampsia include extremes of maternal age (<16 years and >45 years), primiparity, pre-existing hypertension, family history, and occurrence in a previous pregnancy. Placental ischaemia, leading to endothelial dysfunction and coagulation activation, is thought to be important.[26] Genetic predisposition and imbalance of prostacyclin and thromboxane have also been implicated in the pathogenesis of pre-eclampsia.[27]

Clinical features include right upper abdominal pain, headache, nausea, and vomiting. Abnormal liver function tests, which are thought to be secondary to vaso-constriction of the hepatic vascular bed, occur in 20–30% of patients. Aminotransferase activity could be as high as ten times the upper limit of normal, whereas bilirubin concentrations are rarely increased. Liver biopsy is not indicated. Characteristic microscopic changes (figure 2) involve periportal areas with identifiable sinusoidal fibrin thrombi, haemorrhage, and hepatocellular necrosis. Portal thrombosis and haemorrhage can also be present. Tight control of blood pressure is essential, but liver involvement, albeit infrequent, suggests severe disease, thus alerting the physician that immediate delivery is necessary. Complications include maternal hypertensive crises, renal dysfunction, hepatic rupture or infarction, seizures, and increased perinatal morbidity and mortality. Liver biochemical profile usually normalises within 2 weeks of delivery.

HELLP syndrome

The combination of haemolysis with a micro-angiopathic blood smear, increased liver enzymes, and low platelets (HELLP) in pregnancy was first described in 1982 by Weinstein[28] and affects six in 1000 pregnancies. 5–10% of women with pre-eclampsia develop HELLP.[29,30] Although HELLP shows symptoms similar to pre-eclampsia and is one of the criteria that can define severe pre-eclampsia, it

can develop in women who might not have any other signs or symptoms of pre-eclampsia. A perinatal infant mortality rate of 6–70% has been reported due to prematurity, or secondary to maternal complications.[31] HELLP usually arises in the second or third trimester, but can also develop after delivery. Risk factors include advanced maternal age, multiparity, and white ethnic origin.

Angiogenic markers have also been identified, which might help to confirm the diagnosis of pre-eclampsia in women without hypertension or proteinuria. They include decreased placental growth factor, increased serum soluble endoglin, and increased soluble fms-like tyrosine kinase-1 (VEGF) receptor.[32–36]

Patients with HELLP syndrome might be asymptomatic or present with right upper quadrant and epigastric pain, nausea, vomiting, and malaise. Hypertension and proteinuria is evident in up to 85% of cases. Liver injury is precipitated by intravascular fibrin deposition, hypovolaemia, and increased sinusoidal pressure resulting in mild-to-moderate increase of aminotransferases and mild elevation of bilirubin. Recognised classification systems of HELLP include the Tennessee and the Mississippi systems (panel 2).[37] In the Tennessee system classification, the result can be complete (ie, demonstration of haemolysis [raised lactate dehydrogenase, decreased haptoglobin, raised unconjugated bilirubin], thrombocytopenia [secondary to vascular endothelial damage and fibrin deposition in vascular walls], and elevated aminotransferases) or partial (ie, encompassing one or two components). The prothrombin time or international normalised ratio remains normal unless there is evidence of disseminated intravascular coagulation or severe liver injury. A serum uric acid of more than 464 µmol/L is associated with increased maternal and fetal morbidity and mortality.[20,31] Liver biopsy remains a high-risk procedure because of the thrombocytopenia. Microscopic findings may be non-specific or similar to those of pre-eclampsia (figure 2).

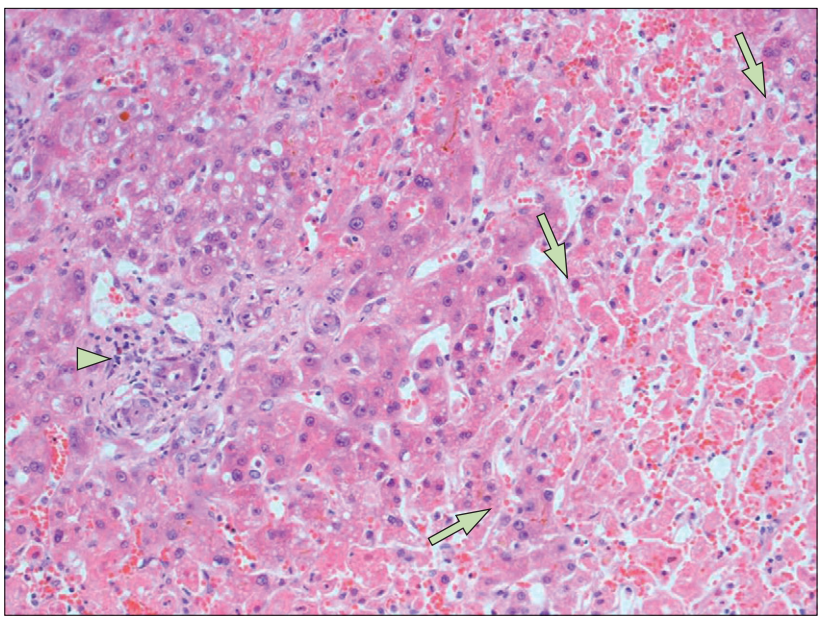

Figure 2: **Liver biopsy from a young woman with eclampsia**
Haematoxylin and eosin staining. Liver biopsy shows an area of coagulative necrosis (marked by the arrows), which involves perivenular and midzonal hepatocytes. The arrowhead indicates a portal tract.

Panel 2: **Classification systems used in HELLP syndrome**

Tennessee system
- AST >70 IU/L
- LDH >600 IU/L
- Platelets <100×10^9/L

Mississippi system
AST >40 IU/L and LDH >600 IU/L and:
- Class I: platelets <50×10^9/L
- Class II: platelets 50–100×10^9/L
- Class III: platelets 100–150×10^9/L

HELLP=haemolysis, elevated liver enzymes, and low platelets. AST=aspartate aminotransferase. LDH=lactate dehydrogenase.

Hepatic haematoma, infarction, and rupture

CT or MRI of the liver could identify hepatic infarction and rupture, haemorrhage, or subcapsular haematoma. The differential diagnosis includes acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome. Hepatic haematoma, infarction, and rupture occur in a minority of women with established pre-eclampsia or HELLP syndrome. 50% maternal mortality has been reported for this complication of disease, with prevalence of hepatic rupture being higher with severe thrombocytopenia.[38] Hepatic adenoma, hepatocellular carcinoma, and haemangiomas might also rupture during pregnancy.

Risk factors for rupture include advanced maternal age, multiparity, and pre-eclampsia. Patients with hepatic haematoma secondary to a ruptured liver capsule typically present in the third trimester with severe right upper quadrant pain and pyrexia, although the presentation can also be early after delivery. Increased aminotransferase concentrations in excess of 3000 U/L, leucocytosis, pyrexia, and anaemia are frequently seen. Acute complications include acute respiratory distress syndrome, acute kidney injury, and hypovolaemic shock. CT and MRI help to identify these pathologies (figure 3). Contained haematomas should be managed conservatively with blood transfusion and supportive measures for the mother. Infection can occur within areas of hepatic infarction. Haemodynamic instability suggests persistent active bleeding and should prompt hepatic angiography, and when required, invasive haemostatic measures by arterial embolisation of the hepatic artery or surgical exploration. Surgical options include packing, hepatic artery ligation, or

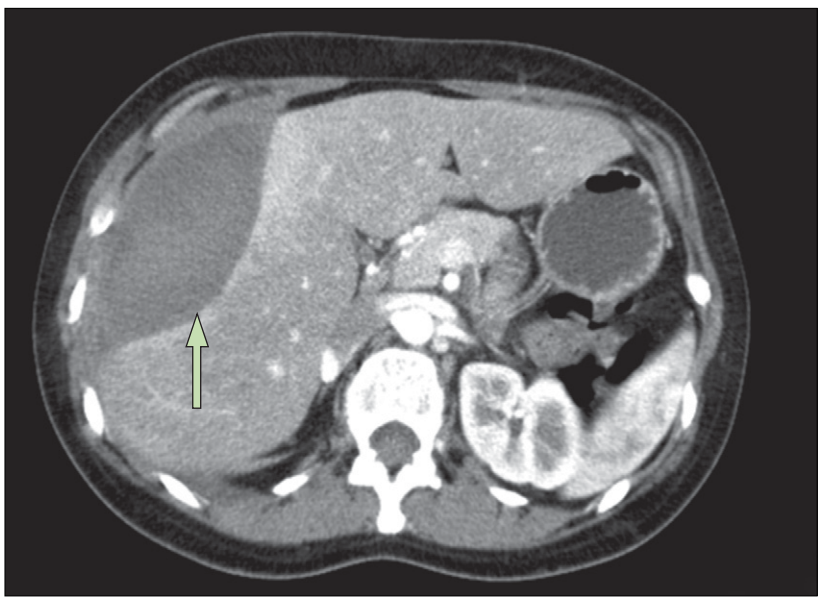

Figure 3: **Abdominal CT showing a subcapsular haematoma in a woman with HELLP syndrome**

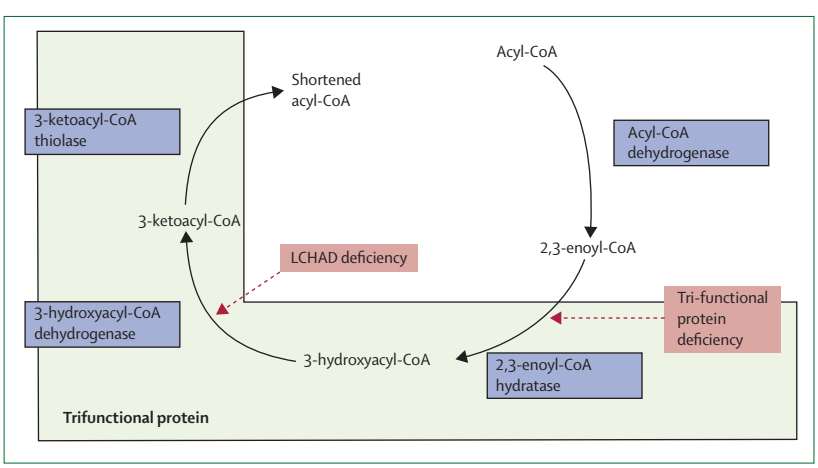

Figure 4: **Cycle of mitochondrial oxidation**
Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) catalyses the third step in the β oxidation of fatty acids in mitochondria (the formation of 3-ketoacyl-CoA from 3-hydroxyacyl-CoA). The accumulation of long-chain 3-hydroxyacyl metabolites produced by the fetus or placenta is toxic to the liver. LCHAD deficiency in infants can lead to non-ketotic hypoglycaemia, hepatic encephalopathy, cardiomyopathy, peripheral neuropathy, myopathy, and sudden death. Modified, with permission, from Ibdah and colleagues.[53]

resection of the affected liver. No long-term maternal complications have been reported.

Women with HELLP syndrome might need a high-dependency unit or an intensive care setting because of the potential complications of hepatic encephalopathy, acute renal dysfunction, hepatic rupture, and bleeding. The cornerstone of management is delivery. Prompt delivery should be undertaken if pregnancy is over 34 weeks of gestation, if fetal distress is present, or if evidence exists of maternal end-organ disease (ie, disseminated intravascular coagulation, renal failure, or abruptia placenta).[39] Management of hypertension involves the use of labetalol, hydralazine, and nifedipine. Diuretics are not recommended in patients with HELLP, because they can cause utero–placental hypoperfusion.[39] Intravenous magnesium sulphate with platelet, coagulation support, or both, are recommended, especially in the presence of bleeding. If gestation is less than 34 weeks, corticosteroids should be administered to promote fetal lung maturity only, because they do not provide any maternal benefit.[40]

Women with atypical pre-eclampsia have a more difficult diagnostic and management conundrum. Physicians should therefore be vigilant to atypical presentations of pre-eclampsia with careful assessment of maternal risk factors, laboratory findings, and timing in the course of pregnancy.

The risk of recurrence of HELLP syndrome in subsequent pregnancies is increased.[41,42] HELLP syndrome usually resolves rapidly after delivery. Laboratory values, however, might worsen after delivery. Hepatic or renal failure necessitates admission to intensive care. Indications for liver transplantation include persistent bleeding from haematoma, hepatic rupture, or liver failure.[43] 88% of these patients survive 5 years after liver transplant.[44]

Acute fatty liver of pregnancy

First described in 1934 by Stander and Cadden[45] as "acute yellow atrophy of the liver", acute fatty liver of pregnancy remains a medical and obstetric emergency. This condition is defined as microvesicular fatty infiltration of hepatocytes during the second half of pregnancy (usually third trimester), and it remains a common cause of liver failure in pregnancy. Maternal and fetal mortality rates are significantly increased and range between 1% and 20%.[46]

Acute fatty liver of pregnancy is a rare disorder affecting from one in 7000 to one in 16 000 pregnancies,[47,48] therefore making it difficult to study. A recent UK-based prospective study involving 229 centres identified 57 confirmed cases in a total of 1 132 964 pregnancies, giving an incidence of five in 100 000 pregnancies.[49] 74% of cases were identified at a median gestation age of 36 weeks, with 60% of cases delivered within 24 h of diagnosis.[49] The caesarean section rate was 74%.

Acute fatty liver of pregnancy is one of the mitochondrial cytopathies, which include Reye's syndrome and other drug-related liver diseases. Common characteristics of these disorders include vomiting, hypoglycaemia, lactic acidosis, hyperammonaemia, and microvesicular fat deposition in organs. Abnormality in mitochondrial β oxidation is recognised as the cause of this condition.[48] Mitochondrial β oxidation of fatty acids is a complex process and is an important energy source for skeletal muscle and myocardial tissue. The enzyme long-chain 3-hydoxyacyl coenzyme A dehydrogenase is part of the mitochondrial trifunctional protein (MTP), which is an important complex associated with the inner mitochondrial membrane.[50,51] MTP is an hetero-octamer consisting of four α subunits and four β subunits[52] (figure 4).

Ibdah and colleagues[53] showed that sick infants born to mothers with acute fatty liver of pregnancy with features of HELLP syndrome had defects in fatty acid β oxidation and were deficient in the long-chain 3-hydoxyacyl coenzyme A dehydrogenase predominately because of the Glu47G1n mutation on one or both alleles of the α subunit of the trifunctional protein.[53] Long-chain 3-hydoxyacyl coenzyme A dehydrogenase deficiency in the fetus was associated with a 79% chance of developing either acute fatty liver of pregnancy or HELLP syndrome.[53] Other studies have identified the association between the long-chain 3-hydoxyacyl coenzyme A dehydrogenase deficiency, especially the G1528C mutation on one or both alleles, and acute fatty liver of pregnancy.[54] A 20-fold increased risk of development of maternal liver disease during pregnancy is present in fetuses with fatty acid oxidation defects compared with those without the defect.[55] Fetal fatty acids accumulate and return to the maternal circulation. These long-chain fatty acids are deposited in the liver, thus causing liver toxicity.

Clinical presentation of acute fatty liver of pregnancy varies from nausea and abdominal pain to hepatic encephalopathy and jaundice. Risk factors include twin pregnancies and nulliparity. Knight and colleagues[49] identified that an inverse relation may exist between BMI and acute fatty liver of pregnancy, in contrast to the direct association between BMI in pre-eclampsia.[56,57] Disseminated intravascular coagulation can occur with normal hepatic laboratory findings, but common abnormalities include raised aminotransferase concentrations, prothrombin time, and serum uric acid and bilirubin concentrations. Hypoglycaemia is a poor prognostic sign. Serum ammonia concentration rise and lactic acidosis are present in severe disease. Evidence of renal dysfunction is common. Leucocytosis occurs in 98% of patients.[49] Differential diagnosis includes HELLP syndrome and viral hepatitis. Ultrasonography and computed tomography might be inconsistent at detecting fatty infiltration.[58] Viral serology is mandatory in every case.

Although the gold standard for diagnosis is liver biopsy (figure 5), this is rarely necessary. The characteristic microscopic change is microvesicular steatosis, which can be in the form of minute cytoplasmic vacuoles or diffuse cytoplasmic ballooning that might spare the periportal hepatocytes. This latter change might simulate hepatocyte ballooning of other causes. Canalicular cholestasis is also present. Necrosis of individual or groups of hepatocytes replaced by ceroid-laden macrophages might be present. Extra-medullary haemopoiesis might also be present.[2] These changes disappear within days to weeks after delivery without persistent injury. The Swansea diagnostic criteria are an alternative to liver biopsy (panel 3).

Prompt delivery is essential in women with acute fatty liver of pregnancy. Steroids might be needed for lung maturation in preterm fetuses. After delivery, women can develop a long cholestatic phase, taking up to 4 weeks for resolution. Liver transplantation warrants consideration in cases of severe hepatic encephalopathy, liver rupture, and in case of failure of recovery of liver function. The newborn infant should be assessed for signs of hypoglycaemia, hepatic failure, myopathy, and other features associated with defects in fatty acid oxidation.

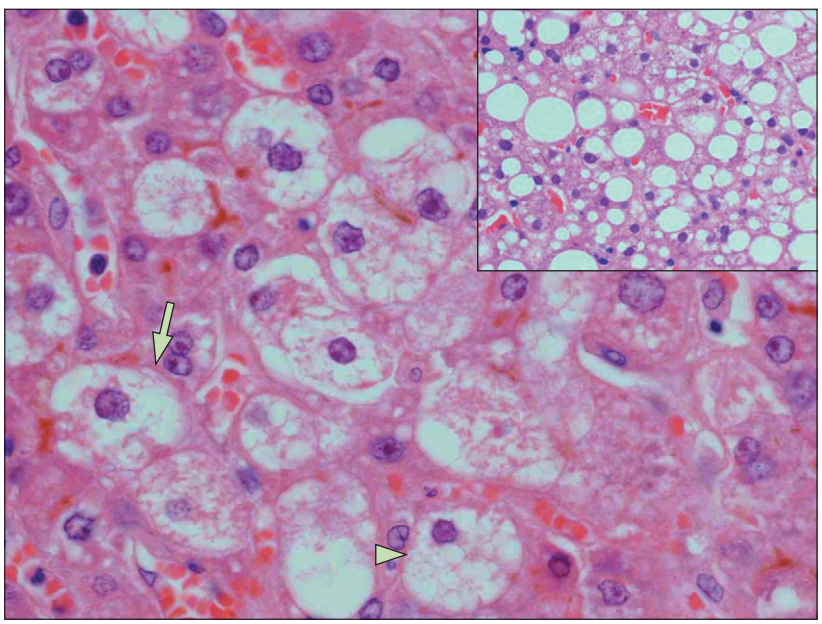

Figure 5: **Acute fatty liver of pregnancy**
Haematoxylin and eosin staining. Hepatocytes show a clear cytoplasm (arrow) or many minute vacuoles (arrowhead) consistent with steatosis. In the inset, the appearance of conventional macrosteatosis as seen in steato-hepatitis.

An increased recurrence rate has only been reported in women who carry the long-chain 3-hydoxyacyl coenzyme A dehydrogenase mutations.[54] However, recurrent acute fatty liver of pregnancy might also re-occur in women without detectable mutations.[59] Infants born to mothers with acute fatty liver of pregnancy should be screened for defects of fatty acid oxidation. Women can, however, be reassured that chronic liver disease does not develop in acute fatty liver of pregnancy.

Pre-existing liver diseases and pregnancy

Cirrhosis with portal hypertension

Pregnancy in cirrhotic women is rare.[60] Cirrhosis leads to anovulation and amenorrhoea due to many factors that include disturbed oestrogen and endocrine metabolism.[61,62] When pregnancy is successful in a cirrhotic woman, spontaneous abortion rate, risk of prematurity, and perinatal death rate are all increased.[63] Cirrhotic patients have a high risk of liver decompensation because of worsening synthetic liver function, development of ascites, and hepatic encephalopathy.[63] Maternal mortality rate as high as 10·5% has been described in this group.[64] Maternal prognosis depends on the degree of hepatic dysfunction during pregnancy rather than its cause.[46] Portal hypertension worsens during pregnancy because of increased blood volume and flow. Portal pressures can

Panel 3: Swansea diagnostic criteria for diagnosis of acute fatty liver of pregnancy[1]

Six or more of the following features in the absence of another explanation

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- High bilirubin (>14 μmol/L)
- Hypoglycaemia (<4 mmol/L)
- High uric acid (>340 μmol/L)
- Leucocytosis (>11×10^6/L)
- Ascites or bright liver on ultrasound scan
- High AST/ALT (>42 IU/L)
- High ammonia (>47 μmol/L)
- Renal impairment (creatinine >150 μmol/L)
- Coagulopathy (PT >14 s or APTT >34 s)
- Microvesicular steatosis on liver biopsy

ALT=Alanine aminotransferase. AST=aspartate aminotransferase. PT=prothrombin time. APTT=activated partial thromboplastin time.

also increase because of an increased vascular resistance due to external compression of the inferior vena cava by the gravid uterus. Up to 25% of patients with varices have a bleeding episode during pregnancy.[65] The greatest risk is seen in the second trimester, when portal pressures peak, and during delivery because of the repeated use of the valsalva manoeuvre to help to expel the fetus.[64] Rupture of splenic artery aneurysm, although uncommon, could also present in pregnant women with portal hypertension.

All cirrhotic patients should undergo variceal screening. Banding before pregnancy, although not proven, is appropriate for high-risk varices. Propranolol has also been used safely in pregnancy but side-effects include fetal growth retardation, neonatal bradycardia, and hypoglycaemia. Terlipressin has not been studied in pregnancy but concerns have been raised about decreased placental perfusion and increased risk of placental abruption. The use of a transjugular intrahepatic porto-systemic shunt in extreme cases of variceal bleeding can be considered but has the risk of radiation exposure to the fetus.

Hepatitis B and hepatitis C infections

In many developed countries, pregnant women are routinely screened for hepatitis B virus (HBV) at the initial booking visit.[66] HBV vaccine can be given safely during pregnancy if needed.[67] Women who are not cirrhotic but HBV-positive are at risk of transmitting the virus to the fetus. Vertical transmission remains the most common way of transmission of HBV in endemic areas and accounts for most HBV infection worldwide. Chronic HBV infection is more likely in the newborn infant when the mother is positive to both hepatitis B surface antigen and hepatitis B e antigen, and also has a high HBV viral load. HBV viral load is a key factor in transmission, with high viral load being associated with 80–90% risk of transmission compared with 10–30% transmission rates in patients with undetectable viral load.[68,69] Transmission can occur directly via the placenta (intrauterine), during breastfeeding, or during delivery. Mode of delivery does not affect the risk of transmission, with similar rates seen with normal vaginal delivery and caesarean section.[70] Transmission can be reduced further by administration of hepatitis B immunoglobulin to the neonate within 12 h of birth.[71] HBV vaccine should also be administered, with three doses being given to the infant within the first 6 months.

Use of lamivudine and other antiviral drugs during the third trimester to reduce HBV viral load,[72] and thus decrease the risk of transmission to the fetus, is a source of debate. Use of lamivudine monotherapy could predispose to viral mutations, thus rendering the patient susceptible to viral resistance to both lamivudine and other antiviral drugs long term. Lamivudine, which has been classified by the US Food and Drug Administration (FDA) as a category C drug in pregnancy, has been used successfully in patients with both HBV and HIV infection during pregnancy without substantial risk to either mother or fetus. Entecavir, a more potent nucleoside analogue with a better long-term viral resistance profile than lamivudine, and designated as a category C drug in pregnancy by the FDA, also shows promise, whereas tenofovir, widely used in HIV-positive pregnant patients, seems to have a better safety profile than both entecavir and lamivudine, and is regarded as a category B drug.

At present, no guidelines exist for the use of lamivudine or any other nucleoside in HBV-positive pregnant women, and therefore any decisions should be made on an individual basis. We advise the use of either lamivudine or tenofovir after week 32 of gestation in patients with a high HBV viral load (greater than 10^6 copies per mL), especially in mothers who might have already infected their child during their previous pregnancy. However, the duration of therapy needs to be considered carefully. Moreover, the use of antiviral agents should not be a substitute to appropriate vaccination.

Pregnancy in patients with hepatitis C virus (HCV) is usually uneventful. Risk of vertical transmission of HCV remains low, except when the fetus is exposed to large volumes of mother's blood and vaginal fluid during delivery or if the mother is co-infected with HIV.[73,74] Patients with genotypes 1 or 3 and with HIV co-infection are more likely to transmit HCV vertically.[75] Ribavirin is teratogenic and the use of pegylated interferon in combination with ribavirin is contra-indicated during pregnancy, but not during breastfeeding.

Autoimmune liver disease

Successful pregnancies are achievable in women with autoimmune hepatitis. Some studies have shown that

flares in disease activity are more likely to occur in the first 3 months after delivery, although autoimmune hepatitis might present for the first time during pregnancy.[76,77] Women with autoimmune hepatitis need stable immunosuppression throughout pregnancy. Although azathioprine is teratogenic in animal models, teratogenic effects in human beings have not been described. Two separate studies failed to show toxic effects of azathioprine or its metabolites during pregnancy.[76,77] Fetal side-effects have been reported, however, and include lymphopoenia, hypogammaglobulinaemia, and thymic hypolasia. If flares occur, then they should be managed in the conventional manner—that is, administration of steroids or increase in steroid dose. If an immunosuppressant is needed, azathioprine remains the safest choice. A study[76] described the presence of antibodies to SLA/LP and Ro(SSA) as risk factors for adverse outcomes in pregnancy.

Primary biliary cirrhosis is a chronic cholestatic disease that leads to destruction of intrahepatic bile ducts. Deterioration in synthetic liver function can occur during pregnancy.[78] Primary biliary cirrhosis might also present for the first time after delivery with protracted pruritus. Ursodeoxycholic acid can be used safely in pregnant women with primary biliary cirrhosis.[78]

Wilson's disease

Wilson's disease is a rare autosomal recessive disease of defective biliary copper excretion, which leads to copper deposition in the liver, brain, and kidneys. Patients usually present with hyperbilirubinaemia, high concentrations of aminotransferases, Coombes-negative haemolytic anaemia, and low serum alkaline phosphatase. In pregnant women with undiagnosed Wilson's disease, evidence of acute liver failure and haemolysis could be misinterpreted as HELLP syndrome.

In women with known Wilson's disease, serum copper levels and caeruloplasmin can rise during pregnancy[79] without treatment, leading to a flare in patient symptoms. Zinc can be continued in pregnancy without causing harm to the fetus.[80]

Liver diseases co-incident with pregnancy

Acute viral hepatitis

Hepatitis A virus (HAV) infection in pregnancy has a clinical course similar to that in the non-pregnant population.[81] A recent study has identified the presence of ascites and hypertension as factors that help to differentiate liver disease specific to pregnancy from viral hepatitis.[82] Increased severity of disease is associated with advanced maternal age, with severe infection in the third trimester associated with an increased risk of prematurity.[83] Treatment is supportive.

Pregnant women are more vulnerable to hepatitis E virus (HEV) infection than to HAV, HBV, and HCV.[84] HEV remains the most prevalent viral cause of acute liver failure in pregnancy.[85] Endemic in parts of Asia and Africa, HEV-related hepatitis usually follows a more severe course in pregnancy, especially in the Indian subcontinent,[86–88] with these patients more likely to develop fulminant hepatic failure.[89] In-utero transmission of HEV to the fetus might add further toxic metabolites to the maternal circulation,[90,91] resulting in increased maternal morbidity and mortality.[92] Pregnant women are more likely to acquire HEV in the second or third trimester, with a median gestational age of 28 weeks.[86] Reported maternal mortality from fulminant hepatic failure secondary to HEV in pregnancy is

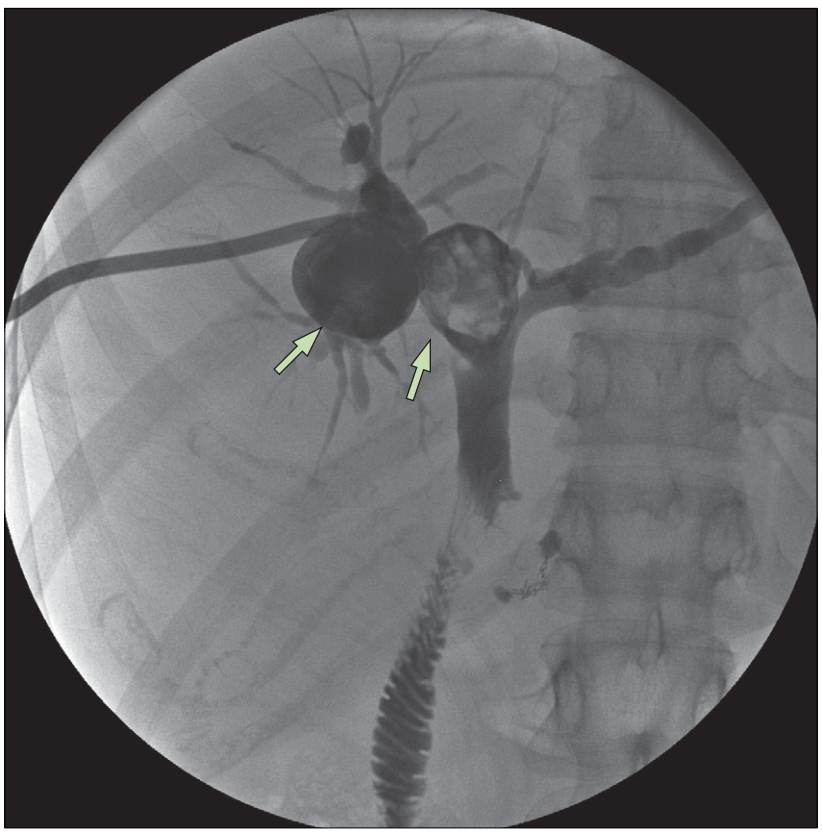

Figure 6: **Percutaneous transhepatic cholangiogram showing large choledochal cysts**
Two large choledochal cysts (arrows) in a patient who had previously undergone biliary reconstruction due to repeated bouts of biliary sepsis.

	Trimester	Diagnostics
HG	1, 2	↑ Bilirubin (×4 ULN), ↑ ALT/AST (×2–4 ULN)
ICP	1, 2, 3	↑ Bilirubin (×6 ULN), ↑ ALT/AST (×6 ULN), ↑ bile acids
Pre-eclampsia	2, 3	↑ Bilirubin (×2–5 ULN), ↑ ALT/AST (×10–50 ULN), ↓ platelets
HELLP	2, 3	↑ ALT/AST (×10–20 ULN), ↑ LDH, ↓ platelets, ↑ uric acid
AFLP	2, 3	↑ Bilirubin (×6-8 ULN), ↑ ALT/AST (×5–10 ULN)—rarely >20

↑=increase. ↓=decrease. HG=hyperemesis gravidarum. ICP=intrahepatic cholestasis of pregnancy. HELLP=haemolysis, elevated liver enzymes, and low platelets. AFLP=acute fatty liver of pregnancy. ALT=alanine aminotransferase. AST=aspartate aminotransferase. LDH=lactate dehydrogenase. ULN=upper limit of normal.

Table 2: **Characteristic timings and diagnostic laboratory features of liver diseases related to pregnancy**

	Side-effects	FDA category
Azathioprine	Lymphopenia, hypogammaglobulinaemia, thymic hypoplasia	D
Ciclosporin A	Premature labour, low birthweight, neonatal hyperkalaemia, renal dysfunction	C
Mycophenalate mofetil	First trimester loss, microtia. Increased risk of congenital malformations	D
Prednisolone	Cleft palate, intrauterine growth retardation, premature rupture of membranes, fetal adrenal hypoplasia	C
Tacrolimus	Similar side-effects to ciclosporin. Neonatal malformation rates of 4%	C

FDA=US Food and Drug Administration. Pregnancy category C: animal reproduction studies have shown an adverse effect on the fetus, but no adequate and well controlled studies in human beings exist. Potential benefits might warrant use of the drug in pregnant women despite potential risks. Pregnancy category D: positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in human beings. However, potential benefits might warrant use of the drug in pregnant women despite potential risks.

Table 3: **Common side-effects of immunosuppressants**

41–54%,[82,93] with a fetal mortality rate of 69%.[75] Poor outcomes are associated with the development of grade III or IV hepatic encephalopathy,[75] irrespective of which trimester the infection was contracted. Management is supportive, ideally including intensive care unit input. Remarkably, delivery does not affect maternal outcome.

Herpes simplex virus (HSV) hepatitis is a rare condition, occurring predominantly in immunocompromised individuals or children.[94,95] Pregnant women, however, are more susceptible than the general population to HSV hepatitis,[96] with a 39% maternal mortality. HSV serotypes 1 and 2 have been seen in pregnancy and are caused by primary or latent disease. Raised aminotransferases, thrombocytopenia, leucopenia, and coagulopathy with a normal concentration of serum bilirubin are common laboratory findings. Mucocutaneous lesions associated with HSV infection might be present, but only in 50% of cases.[97] HSV hepatitis should be considered in any pregnant woman with hepatic failure. Liver biopsy provides the definitive evidence of HSV hepatitis, but computed tomography could also be useful, showing multiple low-density areas of necrosis within the liver. Treatment with intravenous aciclovir should not be delayed until confirmatory results are available, and should therefore be commenced if clinical suspicion is high. Treatment with aciclovir is associated with improved survival rate.[96] Published reports of this rare disease are unclear as to whether delivery improves neonatal survival.

Biliary disease

Gallstones are more common in pregnancy because of increased cholesterol secretion in the second and third trimester, increased lithogenicity of the bile, and decreased gallbladder motility.[98] About 10% of pregnant women develop either gallstones or viscus biliary sludge.[99] Open or laparoscopic cholecystectomy can be done safely and successfully during the second trimester. Endoscopic retrograde cholangiopancreatography and sphincterotomy can be done if needed, with little added risk compared with that in non-pregnant women.[100] Choledochal anomalies (figure 6) might also present in pregnancy, as a consequence of bile stasis and stone formation. Septic episodes can ensue.

Budd-Chiari syndrome

Budd-Chiari syndrome is defined as outflow obstruction of the hepatic veins. It is commonly associated with myeloproliferative disorders. Up to 20% of cases of Budd-Chiari syndrome occur in women who are on the oral contraceptive pill, are pregnant, or have delivered in the previous 2 months.[101] Pregnancy itself represents a prothrombotic state; a physiological decrease of protein S concentration is seen,[102] which might account for the increased incidence of Budd-Chiari syndrome in pregnancy.[103] Patients with known Budd-Chiari syndrome are at risk of developing an exacerbation during pregnancy because of the increased concentrations of female sex hormones.[80]

Clinical features include right upper quadrant pain, jaundice, and ascites. Doppler ultrasound is very important in diagnosis. The treatment is anticoagulation at the onset, identification of procoagulant causes, and shunting, or liver transplantation in extreme cases.

Liver transplantation

Because of the success of liver transplantation, young patients who have been successfully grafted can become pregnant. Pregnancy should be deferred for 1 year after liver transplantation, which allows lower doses of immunosuppression and more stable graft function. Pregnancy in this group should be managed in specialised centres. 70% of women after liver transplantation will deliver a healthy baby,[104] although pregnancy might pose problems, such as an increased risk of gestational diabetes and pre-eclampsia.[104,105] Caesarean deliveries are also more likely in this group: 35–63% versus 23% in the general population within the UK.[106–108] Commonly used drugs such as tacrolimus, mycophenalate mofetil, prednisolone, azathioprine, and ciclosporin all carry a risk of teratogenicity. Prematurity and low birthweights (<2500 g) occur more frequently in women who have previously undergone liver transplantation. Table 3 shows the side-effects of commonly used immunosuppressants. Mycophenalate mofetil should be stopped in all women wishing to become pregnant, but tacrolimus and ciclosporin can be continued. Risk profiles of prednisolone and azathioprine, however, are acceptable and should not be withheld. Breastfeeding is not advised while women are taking immunosuppressants because of the uncertain effects on the newborn infant.

Conclusion

Hepatic disorders in pregnancy are rare, but remain clinically important because of serious adverse effects on both

mother and fetus. Liver disease in pregnancy can present with subtle changes in liver biochemical profile or with fulminant hepatic failure. These disorders are complex and might need to be managed by experienced physicians in specialised centres. Maternal and fetal survival has improved because of better understanding of the pathogenesis of these disorders and higher standards of clinical care.

Contributors

DJ wrote and edited the report. AJ provided obstetric expertise, and reviewed and edited the report. RHW reviewed and edited the report. AQ reviewed and edited the report, and provided histopathological expertise. MAH wrote, edited, and helped to supervise the preparation of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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