Chapter 13
Pregnancy and Liver Disease

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Key Learning Points

- Pregnancy related liver disease occurs in 3% of pregnancies.
- Intrahepatic cholestasis of pregnancy (ICP) with serum bile acid measurements exceeding 100 µmol/L are associated with an significantly increased risk of stillbirth [1].
- The HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome represents a severe form of pre-eclampsia and immediate preparation for delivery of the foetus must be made.
- AFLP is a rare but life threatening complication of pregnancy. These patients should be managed in a High Dependency Unit/Intensive Care Unit setting.
- Treatment of acute variceal bleeding in pregnancy is managed as per the non-pregnant patient with resuscitation, antibiotic use and endoscopic haemostasis. However, caution is advised with the use of vasopressin or synthetic analogues due to an association with uterine ischaemia.

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Case Study

A 31-year-old female presents day 1 post forceps delivery. She is noticeably jaundiced and confused. Admission bloods show the following: Haemoglobin 88, WCC 22.88, Platelets 45, INR 3.4, Sodium 120, Potassium 7.2, Creatinine 291, Urea 10.7, Bilirubin 135, ALT 73, AST 77, ALP 260, gamma GT 125, albumin 20, CRP 34, Lactate 3.9. Her blood pressure was 200/120.

Questions

1. What are the differential diagnoses?
2. What further investigations would you order?
3. How and where would you manage this patient?

Introduction

Abnormalities in liver function tests can be related or unrelated to pregnancy. Pregnancy related liver disease affects up to 3% of pregnancies and can be associated with significant morbidity and mortality for both mother and foetus [2]. A focused evaluation is required to distinguish the liver diseases specific to the pregnant state from pre-existing liver disease or liver disease occurring de novo in pregnancy (Table 13.1). Rapid and correct evaluation allows correct and timely management for the mother and baby; thus limiting risk of an adverse outcome.

TABLE 13.1 List of commonly occurring liver conditions in pregnancy, along with clinical presentation, liver biochemistry and recommended investigations

	Presentation	Liver function tests	Investigations
Pregnancy related liver disease			
Hyperemesis Gravidarum	Vomiting, dehydration, weight loss	Raised transaminases (2–5× upper limit of normal (ULN)). Normal bilirubin	
Intrahepatic cholestasis of pregnancy	Pruritus (typically worse on palms and soles)	Transaminases 2–5× ULN. Normal bilirubin. Increased bile acids	
Acute fatty liver of pregnancy	Nausea/vomiting, abdominal pain, malaise, anorexia. Can have jaundice and encephalopathy if severe	Transaminases 3–15× ULN. Can have raised bilirubin if severe, mostly conjugated	Ultrasound or CT to exclude other differentials including hepatic haematoma. Liver biopsy

TABLE 13.1 (continued)

		Presentation	Liver function tests	Investigations
Hypertension-related liver diseases	Pre-eclampsia/ eclampsia	Abdominal pain, headache, visual disturbance, nausea and vomiting. Seizures in eclampsia	Transaminases 2–5× ULN. Normal bilirubin	
	HELLP syndrome	Right upper quadrant pain, nausea and vomiting, headache, rarely can have bleeding and jaundice	Transaminases 2–30× ULN normal. Bilirubin 1.5–10× ULN	
	Liver infarction/ rupture	Abdominal pain (from vague to constant sharper pain with referral to shoulder tip), hypotension, abdominal distension, shock	Markedly raised transaminases	CT or MRI

Non-pregnancy related liver disease

Pre-existing liver disease	Cirrhosis with portal hypertension	Can present with variceal bleeding.		Endoscopic surveillance
	Viral			
	Post liver transplant			
	Autoimmune			
Co-incidentally with pregnancy	Viral	Jaundice, can present with fulminant hepatic failure (particularly with HEV)	Raised bilirubin	Viral screen including viral hepatitis, HSV, EBV, CMV.
	Autoimmune			
	Vascular	Budd-Chiari: Right upper quadrant pain, jaundice, ascites.		Abdominal ultrasound including dopplers of the liver and portal system
	Drug			
	Gallstones		Cholestatic pattern— Raised ALP and bilirubin.	

[25]

Normal Physiology in Pregnancy

Physiological changes seen in pregnancy can mimic those seen in liver disease. In the second and third trimester a hyper-dynamic circulation develops with expansion of circulating blood volume, an increase cardiac output and a reduction in peripheral vascular resistance, as is common in cirrhosis. The hyper-oestrogenic state of pregnancy also occurs in patients with cirrhosis secondary to impaired hepatic metabolism of oestrogen. These physiological similarities result in clinical signs including: palmar erythema and spider naevi, which are physiological and not pathological, in pregnancy. Clinically insignificant oesophageal varices are found in up to 50% of pregnant women due to a reduction of venous return from compression of the inferior vena cava (IVC) by the gravid uterus [3].

Biochemical and haematological indices taken during pregnancy need to be interpreted in the light of the altered normal ranges for test results. The majorities of indices remain unchanged or slightly reduced secondary to haemodilution. Of note the maternal alkaline phosphatase (ALP) increases in the third trimester when ALP is produced both from the placenta and as a result of foetal bone development; a biliary source can be excluded by a normal gamma-glutamyl transpeptidase (GGT) level. The alpha fetoprotein (AFP) level increases in pregnancy as AFP is produced by the foetal liver. There is an increase in serum proteins such as the procoagulant factors I (fibrinogen), II, VIII, IX and XII, with a decrease in protein S. Elevations in transaminases, bilirubin or the prothrombin time are abnormal and indicate a pathological state which requires rapid further evaluation.

Gallbladder motility is decreased in pregnancy, with an increase fasting and residual gallbladder volume after contraction seen on ultrasound. Both pregnancy and the oral contraceptive pill increases cholesterol saturation of bile salts contributing to lithogenicity. Biliary sludge is a common asymptomatic finding, which often resolves after pregnancy. Cholecystitis is not uncommon and a cholecystectomy is the

second commonest operation performed in pregnant women (after appendicectomy) [4].

Pregnancy Related Liver Diseases

Hyperemesis Gravidarum

Hyperemesis gravidarum (HG) is a clinical syndrome consisting of intractable nausea, vomiting, dehydration, ketogenesis and weight loss (>5%) complicating between 0.3% and 3.6% [5] of pregnancies. Its pathogenesis is incompletely understood but is thought to be related to peak human chorionic gonadotrophin (hCG) levels. HG typically occurs before 9 weeks of gestation and is more common amongst those with multiple or molar pregnancies, and those with a previous history of HG. Two genes, GDF15 and IGFBP7, have been implicated in HG but a causal relationship has not yet been proven [6]. Abnormalities in aminotransferases, particularly alanine aminotransferase occur in 50% of patients admitted for HG and indicate severe disease [7]. Management is supportive (after excluding alternative causes for abnormal liver function tests) with anti-emetics, vitamin B6 supplementation, intravenous fluids, electrolyte correction and thromboprophylaxis is essential as HG still accounts for one maternal death per annum. HG is a fully reversible condition and elevation in aminotransferases should return to normal with resolution of symptoms. Persistent abnormal liver biochemistry after vomiting has ceased should prompt investigation for an alternative diagnosis.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) or obstetric cholestasis is the most common pregnancy related liver disease with an incidence of between 0.2% and 2% of all pregnancies [8]. ICP most commonly affects women in the third trimester

but has been reported in as early as 7-week gestation. It is a reversible form of cholestasis and presents with intense pruritis (often worse on palms and soles) with raised serum bile acids (BA) (>11 μmol/L), which typically resolves within 6 weeks of delivery. (Typical laboratory abnormalities are detailed in Table 13.1.)

The pathogenesis is complex, however, it is likely that elevated oestrogen and progesterone metabolites in pregnancy unmask the disease in genetically susceptible women. One study has shown a link between mutations in the ATP-binding subfamily member 4 (ABCB4) gene and ICP. In this study, 16% of Caucasian patients with ICP had mutations in the ABCB4 gene [9]. It has also been suggested that mutations in Farnesoid X receptors may increase the risk of developing ICP [10].

The main risk is to the foetus. Prospective cohort studies of perinatal outcomes in ICP suggest that serum bile acid measurements exceeding 100 μmol/L are associated with an increased risk of still birth. The risk of still birth also increases as gestation advances in this cohort [11].

The management of intrahepatic cholestasis of pregnancy was reviewed recently as part of the PITCHES trial. This study included 604 women, of which 144 had severe ICP and BA >40 and concluded that there is no significant difference between ursodeoxycholic acid (UDCA) and placebo for most of the adverse perinatal outcomes including perinatal death, preterm delivery or admission to the neonatal unit. Therefore, they concluded that UDCA should no longer be considered first line in the management of ICP. However, the most recent guidance from the AASLD still recommends UDCA at a dose of 10–15 mg/kg as first line management. Another option that has been trialled is the combination of rifampicin and UDCA. One trial showed a decrease in serum bile acids in 54% of patients whose serum bile acids remained high whilst on just UDCA. A further study is being carried out comparing the use of rifampicin versus UDCA but the results are yet to be published [12].

Parenteral Vitamin K should be given in those who have elevation in prothrombin time secondary to cholestasis and impairment of fat soluble vitamin absorption as this will correct coagulation and reduce risk of peri-partum and neonatal haemorrhage. Aqueous cream with 1–2% menthol cream can be effective in reducing pruritus [8].

Women with ICP should be counselled for a recurrence rate of up to 90% [13] in subsequent pregnancies and an increased risk of pruritus or cholestatic impairment when taking the combined oral contraceptive pill. Repeat liver function tests are essential post-delivery to ensure resolution of abnormalities. Ongoing symptoms or biochemical impairment beyond 3-months postpartum should prompt further investigations for alternative/concurrent diagnoses.

Finally, there is data to suggest that ICP is not a benign condition and is associated with (via bile acid transport deficits) an increased risk of biliary issues in later life. No recommendations exist as yet with regards the benefit of follow up of such patients [14].

Pre-eclampsia/Eclampsia/HELLP Syndrome

Pre-eclampsia is a multisystem manifestation of abnormal placentation and placental insufficiency in pregnancy characterised typically by hypertension (>140/90), proteinuria (>300 mg/day) with renal, liver, neurological or haematological dysfunction after 20 weeks of gestation. Pre-eclampsia affects 3–8% of pregnancies between 20 weeks gestation and 4 weeks postpartum [15]. The presence of seizures differentiates pre-eclampsia from eclampsia. Major risk factors include chronic kidney disease, previous episodes of pre-eclampsia or hypertension, diabetes and autoimmune disorders [15]. Presenting symptoms are non-specific and may mimic viral infections—and consist of abdominal pain, headache, visual disturbance, nausea and vomiting; thus a high index of suspicion is needed for further evaluation. Peripheral oedema and hyper-reflexia are common. On laboratory evaluation, raised

creatinine and thrombocytopenia are often present. However, a platelet count of less than 100×10^9/L, serum creatinine and serum albumin are not good predictors of complications [15]. The presence of elevated serum aminotransferases indicate severe disease and should prompt a multidisciplinary team discussion regarding delivery because if rapid hypertensive control and delivery is not achieved, women are at risk of renal dysfunction, cerebral haemorrhage, hepatic infarction, hepatic haematomas or hepatic rupture with consequent markedly increased perinatal mortality and morbidity.

The HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome represents a severe form of pre-eclampsia and complicates up to 20% of cases and should be seen as part of the same disease spectrum [16]. Hypertension is evident in up to 85% and proteinuria is common. However, it is important to recognise that HELLP syndrome can occur in the absence of hypertension and proteinuria, reflecting the multisystem nature of pre-eclampsia and related disorders. It typically presents between 28 and 36 weeks of gestation, but can present up to 1-week postpartum. The diagnosis is based mainly on clinical features and the presence of haemolysis, thrombocytopenia and transaminitis on biochemical evaluation. The presenting symptoms are varied and include right upper quadrant or epigastric pain in approximately (40–86)% of cases, nausea and vomiting (36–84% of cases), headache (33–61% of cases) and rarely bleeding and jaundice [17]. A significant number of patients are asymptomatic. Classical laboratory indices are detailed in Table 13.1.

In HELLP, it is postulated that endothelial damage secondary to placental insufficiency results in inappropriate coagulation cascade activation with the formation of microcirculatory fibrin cross-linked networks, a microangiopathic haemolytic anaemia and a consumptive thrombocytopaenia. Hepatic ischaemia follows microvascular thrombosis in the sinusoids resulting in elevated aminotransferases and a disseminated intravascular coagulopathy can occur with evidence of raised fibrin degradation products, low fibrinogen and secondary increase in the prothrombin time.

The only cure for pre-eclampsia and HELLP syndrome is delivery of the placenta. Hypertension should be treated with nifedipine, labetalol or hydralazine. Magnesium sulphate should be given to prevent maternal seizures and glucocorticoids to promote foetal lung maturity if gestation is less than 34 weeks. Following delivery maternal features of pre-eclampsia/HELLP resolve within 48 h in the majority. Women should be monitored in a high dependence setting due to the small but recognised risk postpartum worsening of maternal symptoms.

A recent landmark paper published in the New England Journal of Medicine has identified that women with a high risk of pre-eclampsia (>1 in 100) benefit from taking low dose aspirin started between weeks 11 and 14 of gestation and continued until week 36. In the aspirin group, there was a significantly lower incidence of pre-eclampsia but there was no significant difference between the incidence of other complications, either for the foetus or the mother [18].

Serious maternal morbidity is associated with the development of disseminated intravascular coagulation (DIC; 21%), placental abruption (16%), acute renal failure (8%), pulmonary oedema (6%), parenchymal/subcapsular hepatic haematoma and rupture (1%). The maternal mortality of severe pre-eclampsia which is complicated by HELLP syndrome can be as high as 24% [19]. Neonatal outcomes range from prematurity with up to 70% affected, to a perinatal mortality rate between 7% and 20%. Neonatal outcome is more strongly associated with gestational age and birthweight than severity of HELLP syndrome [16].

Acute Fatty Liver of Pregnancy (AFLP)

AFLP is a rare but serious metabolic complication of pregnancy arising due to microvesicular fatty infiltration of hepatocytes. It has an incidence of 5 per 100,000 pregnancies with multi-parity and reduced BMI being recognised risk factors in a large UK population based study [20]. AFLP is thought

to be secondary to an inherited defect of mitochondrial beta-oxidation. This results in a build-up of long-chain fatty acids which ultimately return into the maternal circulation, deposit in the maternal liver and manifest as maternal liver disease. In 20% of patients with AFLP, there is evidence of long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency in their offspring [21]. These children are at risk of developing fatal non-ketotic hypoglycaemic attacks and therefore all babies born from women with AFLP should be considered for genetic testing for LCHAD and other defects in fatty oxidation.

AFLP mostly presents in the third trimester and always before delivery, but is often diagnosed postpartum. The most frequent symptoms are nausea or vomiting, abdominal pain, malaise and anorexia, with jaundice and encephalopathy in the more severely affected. Pre-eclampsia is present in about half. Common laboratory changes are detailed in Table 13.1. They include hyperbilirubinaemia, variable serum transaminase rises (up to 500 IU/L), acute renal dysfunction, a leucocytosis above normal pregnancy levels and thrombocytopaenia. Coagulopathy in AFLP can reflect both hepatic dysfunction and or the presence of DIC (affecting up to 10% with AFLP) [22] with reduced fibrinogen levels. Ultrasound or CT is useful in excluding other differentials such as a hepatic haematoma and often reveals fatty infiltration, which can be useful retrospectively when compared to imaging months postpartum.

A definitive diagnosis is made on liver histology, however, this is rarely performed due to the emergent progression of the disease and need to stabilise and deliver affected women. In the absence of confounding aetiology, clinical diagnostic criteria have been developed and validated for AFLP (Table 13.2) [23]. An abbreviated method of diagnosing AFLP using only gastrointestinal symptoms, aminotransferases, bile acids, activated partial prothrombin time (APTT)/prothrombin time (PT) and bilirubin has shown promising initial results but has not yet been replicated in larger studies [24]. If clarity is lacking regarding the diagnosis, a liver biopsy can always take place postpartum as changes persist for several weeks.

Table 13.2 Swansea criteria for acute fatty liver of pregnancy

Six or more of features below in absence of other aetiology

- Vomiting
- Abdominal pain
- Polydypsia/polyuria
- Encephalopathy
- Raised bilirubin (>14 μmol/L)
- Hypoglycaemia (<4 mmol/L)
- Leucocytosis (>11 × 10^6/L)
- Raised uric acid (>340 μmol/L)
- Elevated ammonia (>42 IU/L)
- Ascites or hyperechoic liver on US
- Elevated transaminases (>42 IU/L)
- Renal impairment (creatinine >150 μmol/L)
- Coagulopathy (PT >14 s or APTT >34 s)
- Microvesicular steatosis on biopsy

Management involves early recognition, resuscitation of the mother and rapid delivery of foetus regardless of gestational age. Consequently, maternal mortality has improved from 92% in the 1970s to between 7% and 18% [25]. True hepatic synthetic failure often manifests with hypoglycaemia, lactic acidosis and raised serum ammonia levels. Due to the risk of fulminant hepatic failure, such patients must be discussed with and then subsequently managed in a liver transplant centre. Maternal resuscitation involves correction of hypoglycaemia, hypovolaemia and aggressive reversal of coagulopathy with blood products to reduce bleeding complications during and following delivery. Plasma exchange can improve maternal outcomes postpartum. There is a possibility of AFLP recurrence in subsequent pregnancies even in the absence of known beta-oxidation defects thought the exact rates are unknown.

Hepatic Haemorrhage and Rupture

Spontaneous hepatic haemorrhage and rupture can complicate pre-eclampsia, HELLP and AFLP, but rarely occurs in their apparent absence. Mortality is extremely high (up to 50%) [16]. Marked rises in the transaminases are not typical of HELLP and suggest hepatic infarction, haematoma, rupture or unrelated cause of inflammation (e.g. viral hepatitis). Additionally, changes in the character of abdominal pain, particularly from an intermittent vague diffuse visceral pain to a constant sharper pain, with referral to the shoulder tip, may herald a growing subcapsular hepatic haematoma and impending rupture. However, hepatic haematomas can also present covertly with pyrexia, modest liver transaminases derangement, anaemia and neutrophil leucocytosis or rapidly manifesting as haemoperitoneum with abdominal distention, hypovolemic shock and collapse when ruptured.

Computed tomography or magnetic resonance is the investigation of choice and discussion with a hepatobiliary surgeon is mandatory. Contained haematomas can be managed conservatively with volume replacement, aggressive coagulation support, prophylactic antibiotics and blood product transfusion. In contrast, hepatic rupture requires urgent angiography with hepatic artery embolisation and/or surgical intervention involving packing, arterial ligation and hepatic resection if haemodynamically unstable.

Non-pregnancy Related Liver Diseases

Cirrhosis and Portal Hypertension

Women with cirrhosis have a disruption in their hypothalamic-pituitary axis and abnormal oestrogen metabolism. Pregnancy is thus rare due to a combination of anovulation, amenorrhoea, reduced fertility and libido [26]. When pregnancy does occur there is a high rate of spontaneous foetal loss, preterm delivery, need for intensive neonatal support for the foetus

and an increased risk of hepatic decompensation and death for the mother [27]. Maternal mortality for pregnant women with cirrhosis was reported to be as high as 10.5% in the early 1980s, but encouragingly more recent series have reported reduced mortality rates of 1.8% with a decompensation rate of around 15% [28]. Outcomes of pregnancy in women with cirrhosis are related to the severity of the underlying maternal liver disease. Utilisation of prognostic scoring systems such as MELD or UKELD, typically used to predict mortality in patients with cirrhosis undergoing procedures or to guide need for liver transplantation, can help predict likely maternal outcomes in pregnancy. Specifically, a preconception MELD score ≥10 had an 83% sensitivity and specificity for predicting hepatic decompensation, whereas women with a preconception MELD ≤6 are unlikely to have any significant maternal complications [27].

Maternal mortality in cirrhotic women is in part due to a four-fold increase in occurrence of variceal bleeding compared to non-pregnant counterparts. Due to an increased circulating volume and caval compression by the gravid uterus, portal hypertension worsens in pregnancy with its risks of variceal bleeding peaking late in the second trimester where circulating blood volume is increased but vasodilatation seen in third trimester is yet to occur. Further risk occurs during the second stage of labour with the prolonged Valsalva manoeuver.

Preconception screening and eradication of oesophageal varices would seem appropriate. AASLD recommends endoscopic surveillance at the start of the second trimester. If small varices are found at endoscopy, then propranolol is recommended but if the varices are medium to large then management options are either propranolol or variceal ligation. Variceal ligation is the recommended option if there are high risk features [22].

Treatment of acute variceal bleeding in pregnancy is managed emergently like in the non-pregnant population with resuscitation, early antibiotic prophylaxis (cephalosporins are recommended [22]) and timely endoscopic haemostasis. The

strong vasoconstrictive effects of vasopressin or synthetic analogues are associated with uterine ischaemia and are generally avoided. However, limited data currently suggests no adverse foetal effects with somatostatin or octreotide and therefore their used can be considered as an alternative where available to terlipressin. Transjugular intrahepatic portosystemic shunts (TIPSS) are also a rescue option in refractory variceal bleeding in pregnancy [29].

Hepatitis B and C Virus Infection and Pregnancy

Hepatitis B virus (HBV) infection is usually associated with good prognosis except in those with established cirrhosis and in fulminant hepatitis. From a foetal transmission perspective, the risk of developing chronic HBV infection is inversely proportional to the age at exposure with up to 90% of babies exposed perinatally developing chronic HBV infection. Therefore, a key consideration is the prevention of perinatal transmission to reduce the prevalence of chronic hepatitis B carriers, half of which can be attributed to vertical transmission worldwide.

All pregnant women in the UK are tested for Hepatitis B surface antigen (HBsAg) in early pregnancy, followed by HBV DNA if this is found to be positive [30]. Pregnancy itself has little or no effect on the natural history of HBV infection from the maternal perspective. All infants born to HBsAg positive mothers should receive a course of hepatitis B vaccination and HB immunoglobulin within 24 h [31]. Such neonatal vaccination is highly efficacious (preventing vertical transmission in 95%) and suggests that transmission mainly occurs intrapartum rather than during pregnancy. Risk factors for vertical transmission, in spite of prophylaxis, are maternal eAg positivity and high HBV viral load ($>10^7$ IU/mL). In this instance, oral nucleotide analogues such as tenofovir, in addition to active immunisation have been shown to reduce perinatal transmission. It is recommended that antiviral therapy is started between weeks 28 and 32 if the HBV DNA is greater than 200,000 IU/mL and can be ceased either

at delivery or up to 3 months afterwards [22]. Tenofovir has an established role in the prevention of HIV transmission in utero and the Antiretroviral Pregnancy Registry also reports no increase in teratogenicity. There is no proven role for caesarean sections in preventing mother to child transmission. Breast feeding should be encouraged, providing immunoprophylaxis is given at birth.

Like chronic HBV infection, Hepatitis C (HCV) infection in pregnancy confers minimal risk to mother except in the context of cirrhosis. Detectable HCV RNA levels in newborn infants suggest that unlike HBV infection, neonatal transmission predominates with a transmission rate of 5.8% of HCV RNA positive mothers [32]. Due to passive transfer of maternal anti-HCV antibodies diagnosis of vertical transmission is made when HCV RNA is detected on two consecutive samples 3 months apart, or when antibodies are detected after 18 months of age. Risk factors for vertical transmission are co-infection with HIV, maternal HCV viral load and active intravenous drug use. Co-infection with HIV increases rates of vertical transmission to 10.8% [32]. There is no evidence that the mode of delivery influences the risk of vertical transmission, and breast feeding is not contraindicated in women with HCV infection.

Autoimmune Hepatitis and Pregnancy

Similar to other autoimmune diseases in pregnancy, autoimmune hepatitis control usually improves during pregnancy due to the immune-tolerant state pregnancy confers and flares of disease activity are seen in up to 80% of women postpartum [33]. Patients with stable AIH on immunosuppression are often concerned about the potential risk of teratogenicity secondary to their immunosuppressive medication. Clear data now exists showing that flares in disease activity are more likely in patients off immunosuppression and, moreover, those patients are more likely to develop hepatic decompensation. Prednisolone is considered safe and should

be used for AIH in pregnancy [33]. Azathioprine has been associated with and increased risk of cleft palate and skeletal anomalies in mice but there is no proven association between azathioprine use during pregnancy and adverse foetal outcomes [22, 34]. Transient lymphopaenias, hypogammaglobulinaemia and thymic hypoplasias have been reported in neonates born to mothers on azathioprine but are reversed after birth. Guidance from AASLD suggests a strategy of minimal adjustment to prednisolone/azathioprine during pregnancy and postpartum. Finally, it should be noted that AIH hepatitis can present de novo in pregnancy and testing for immunoglobulins and autoantibodies should be routine in any women who presents with elevated aminotransferases during pregnancy.

Liver Transplantation

Following liver transplantation, women can regain their fertility often as early as 1-month post transplantation. However, it is recommended that pregnancy is delayed until at least 1 year after liver transplantation as this allows stabilisation of immunosuppression and the risk of acute cellular rejection reduces after 1 year [35]. Outcomes of pregnancy in LT patients are good overall, but with an increased incidence of preterm delivery, hypertension/pre-eclampsia, infections, gestational diabetes and rejection of the graft. Hypertensive complications and pre-eclampsia are attributed to the increase in renal dysfunction and hypertension secondary to the use of immunosuppressive calcineurin inhibitors (cyclosporine and tacrolimus). Gestational diabetes is induced by long term use of steroid immunosuppression and tacrolimus therapy. Acute cellular rejection (ACR) can complicate up to 17% of LT patients in pregnancy and there is data to support delaying pregnancy for 1 year following LT significantly reduces this risk. Preterm delivery may be needed because of the need to manage pre-eclampsia and episodes of ACR during pregnancy [36].

Immunosupression should not be discontinued for pregnancy. Tacrolimus, Cyclosporine, azathioprine and steroids should all be continued as benefit far outweighs potential risk of teratogenicity. Mycophenolate is contraindicated as it has been shown to have a high rate of spontaneous abortion and structural abnormalities as well as an increased risk of stillbirth [35]. It should be discontinued in both males and females with a 6 month washout prior to conception and alternative immunosuppression considered.

Liver Disease De Novo in Pregnancy

Acute Viral Infections and Pregnancy

Acute viral hepatitis is the most common cause of jaundice in pregnancy worldwide. Both hepatitis A and E are transmitted by the faeco-oral route and are associated with poor hygiene. In pregnancy, Hepatitis A (HAV) infection has a similar clinical course to the non-pregnant population. Severity of disease is associated with advanced maternal age and infection in the third trimester where there is an increased risk of prematurity.

In contrast, pregnant women are more vulnerable to hepatitis E (HEV) infection, and it is the most prevalent viral cause of acute liver failure in pregnancy. The risk of fulminant hepatic failure in HEV and pregnancy is between 15% and 20% and in certain areas, such as the Indian subcontinent, the risk is greater [37]. Fulminant hepatitis due to HEV may resemble liver failure from AFLP, HELLP or HSV hepatitis and should be considered in pregnant women with acute hepatitis living in or travelling from endemic areas. The fatality rate from HEV infection is much higher in pregnant women compared to the rest of the population (15–25% as opposed to 0.5–4%) [38]. Poor maternal outcomes are associated with presence of encephalopathy, irrespective of delivery. Management is supportive, although liver transplantation has been reported for this indication [39].

Herpes simplex virus (HSV) hepatitis although rare, has a predilection for the immunocompromised and therefore pregnant women are more susceptible. It can be caused by primary or latent disease and present with mucocutaneous lesions in 50%, raised aminotransferases, thrombocytopaenia and coagulopathy, commonly in the absence of jaundice. Maternal mortality is reported at around 40% [40]. CT shows multiple sub-centimetre low-density areas of liver necrosis and diagnosis can be confirmed on histology. Treatment with aciclovir is associated with a survival benefit and should be started prior to confirmatory test if the diagnosis is suspected [40].

Pregnancy and Thrombosis

Budd-Chiari syndrome (BCS) or hepatic venous outflow tract obstruction can present de novo in pregnancy or consequent to thrombus extension resulting in an acute presentation. The prevalence of pregnancy related BCS is estimated to make up around 6.8% of all BCS presentations [41]. If a patient is known to have a prothrombotic state in pregnancy, low molecular weight heparin is advocated over vitamin K antagonists (due to concerns of a risk of miscarriage and congenital malformations). In pregnancy, presentation is typically right upper quadrant pain, jaundice and ascites. Management involves diagnosis with ultrasound, early anticoagulation and consideration of a transjugular intrahepatic portosystemic shunt. Budd-Chiari syndrome often has a multifactorial thrombotic aetiology and so evidence of thrombophilia's and myeloproliferative neoplasms should be sought after. Pregnancy is very rarely the sole prothrombotic risk factor. Maternal outcomes are good provided patients have stable disease although recurrence of disease can occur if anticoagulation is discontinued. Foetal outcomes vary but pregnancies reaching 20 weeks of gestation (despite a 76% prematurity rate) have good outcomes.

Gallstones in Pregnancy

Pregnancy is a lithogenic state and is associated with increased risk for cholelithiasis with around 10% of pregnant women developing gallstones or viscous biliary sludge. Between 0.05% and 0.8% of pregnant women have gallstones which cause symptoms [42]. Cholecystectomy (open or laparoscopic) can be done safely in the second trimester, while ERCP and sphincterotomy is feasible if required. A large study has shown that there was no significant difference with regards preterm birth or foetal mortality between pregnant women who were either managed conservatively or surgically for gallstone disease. However, the same study did show that surgically managed gallstone disease did decrease the rate of maternal readmission to hospital [42]. Epidemiological studies have suggested that the risks of cholelithiasis remain for 5 years postpartum following which returns to baseline.

Summary

Liver diseases in pregnancy are clinically important because of the increased morbidity and mortality for both the mother and baby. The spectrum of disease and presentation is variable making evaluation, diagnosis and the early instigation of correct management challenging, but vital to achieving a good outcome. Patients benefit form multidisciplinary input by experienced hepatologists and obstetricians. Maternal and foetal outcomes are improving due to ongoing research, improved guidelines and our better understanding of preconception risk factors, disease stratification, disease mechanisms and therapeutic options.

Answers to Case Study

1. The differential at this stage is wide. See Table 13.1 for classification of liver disease in pregnancy. Important differentials in this patient would include acute fatty liver of pregnancy, pre-eclampsia or acute liver failure of another aetiology such as paracetamol overdose.

2. Investigations would include a non-invasive liver screen including a blood film and a paracetamol level. Imaging would include a liver ultrasound scan with doppler and if necessary, a CT scan. A liver biopsy would also help with diagnosis (Fig. 13.1).

3. This patient should be managed in a high dependency/intensive care setting and ideally would be managed at a tertiary hepatology centre. They would require supportive care and input from the multidisciplinary team. This patient requires correction of the hyperkalaemia and hypoglycaemia and to consider empirical antibiotics. Specifically for acute fatty liver of pregnancy, the offspring should be screened for long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency. It is also worth noting that this particular patient is postpartum, though had she still been pregnant, delivery of the foetus should be considered.
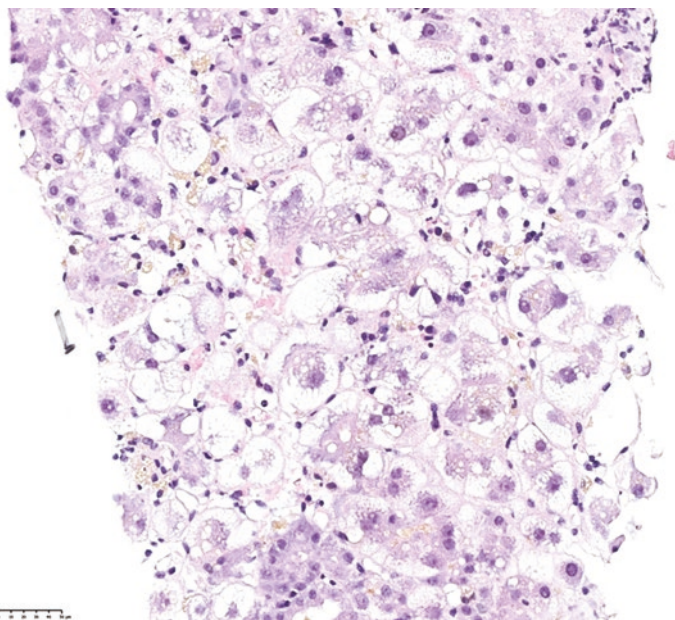

FIGURE 13.1 Liver Biopsy of the patient discussed in the case study. Hepatocytes show ballooning and fine vacuolation of their cytoplasm along with larger steatotic droplets in places. H&E 400×. (Courtesy of Prof Alberto Quaglia, Consultant Histopathologist)

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