Pregnancy and the liver

Introduction

In pregnancy the liver can be affected by diseases specific to pregnancy as well as unrelated conditions. The possible effect of the disease and its management on both the fetus and mother must be considered. Several physiological changes occur during pregnancy as liver metabolism is altered. Serum protein concentrations fall, with a decrease in serum albumin in part the result of the dilutional effect of an increase in plasma volume. Alanine transaminase and aspartate transaminase levels decrease (*Table 1*), complicating the diagnosis of disorders involving subtle changes in liver function. Alkaline phosphatase is also produced by the placenta, making this an unreliable marker of liver dysfunction in pregnancy.

Pregnancy-specific disorders

Hyperemesis gravidarum

Hyperemesis gravidarum is severe vomiting in early pregnancy associated with ketosis and dehydration. It can be associated with a moderate rise in transaminase levels and, occasionally, a marginally elevated bilirubin level (without clinical jaundice). These usually improve with resolution of hyperemesis, but severely deranged enzymes or associated symptoms should prompt investigation to rule out other causes of liver dysfunction, nausea and vomiting.

Obstetric cholestasis

Obstetric cholestasis is characterized by pruritus and abnormal liver function tests, in the absence of any other identifiable pathology. Obstetric cholestasis is rare (0.7% of pregnancies) but its incidence increases in certain populations such as south Asians and in certain south American and Scandinavian countries (Royal College of Obstetricians and Gynaecologists, 2011).

Its pathophysiology is uncertain but may involve the cholestatic properties of oestrogen, with a genetic contribution also likely. Obstetric cholestasis is most common in the second half of pregnancy and is characterized by itching in the absence of rash, which is often worse at night and often affects the palms and soles of the feet. Apart from the patient's distress, obstetric cholestasis is associated with intrauterine death and both spontaneous and iatrogenic prematurity. The perinatal mortality rate of obstetric cholestasis has dropped with time, in part probably related to active management, and is reported to be 9.1/1000. However, the rate associated with untreated obstetric cholestasis is unclear (Royal College of Obstetricians and Gynaecologists, 2011).

Diagnosis

Diagnosis is based on symptoms in conjunction with abnormal liver function tests, particularly raised transaminase levels. Derangement of bilirubin is uncommon and, if present, usually mild. However, obstetric cholestasis should always be excluded when investigating jaundice in the pregnant woman. Serum bile acid levels are raised. Symptoms may precede the onset of biochemical abnormalities and liver function tests should be repeated after 1 week if symptoms persist. Obstetric cholestasis is a diagnosis of exclusion and other causes of abnormal liver function tests and pruritus should be ruled out using liver ultrasound, hepatitis serology, Epstein–Barr virus, cytomegalovirus and liver auto-antibodies.

Management

Maternal management involves weekly monitoring of liver function tests and clotting. Symptoms may be ameliorated with chlorpheniramine and topical emollients. Malabsorption of fat-soluble vitamins can rarely lead to vitamin K deficiency with a theoretical risk of postpartum haemorrhage, so oral vitamin K should be given daily from diagnosis (Royal College of Obstetricians and Gynaecologists, 2011). Ursodeoxycholic acid can be given to alleviate symptoms although evidence for its efficacy in reducing fetal risks is limited. Dexamethasone has been used in women with severe symptoms unresponsive to ursodeoxycholic acid (Diac et al, 2006) and rifampicin may be beneficial in resistant cases. Resolution of liver function tests should be confirmed postnatally and women counselled about the risk of recurrence (around 90%) in subsequent pregnancies and avoidance of oestrogen-containing contraceptives.

Management of fetal risks is complicated by the lack of correlation between severity of symptoms or liver dysfunction with the incidence of fetal compromise. No fetal monitoring modality is effective in predicting fetal death (Royal College of Obstetricians and Gynaecologists, 2011). Common practice, although poorly supported by evidence, is elective delivery, by induction of labour if no contraindications exist, between 37–38 weeks to avoid the risk of late stillbirth. There is some evidence that bile acid levels greater than 40 μmol/litre predict fetal problems (Glantz et al, 2004). Continuous fetal monitoring is necessary in labour and neonatal intramuscular vitamin K should be given.

Pre-eclampsia and HELLP syndrome

Pre-eclampsia is hypertension and proteinuria in pregnancy which develops after 20 weeks' gestation. The underlying aetiol-

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Table 1. Reference ranges for liver enzymes

		Trimester		
Liver enzyme	Non-pregnant	1st	2nd	3rd
Aspartate aminotransferase (U/litre)	7–40	10–28	11–29	11–30
Alanine aminotransferase (U/litre)	0–40	6–32	6–32	6–32
Gamma-glutamyl transferase (U/litre)	11–50	5–37	5–43	3–41
Bilirubin (μmol/litre)	0–17	4–16	3–13	3–14

Adapted from Girling et al (1997)

ogy is thought to relate to impaired trophoblastic invasion during placentation leading to release of chemical mediators which affect endothelial and end-organ function. The liver can be affected and liver function tests are altered in up to 50% of these women.

HELLP syndrome (development of haemolysis, elevated liver enzymes and low platelets) occurs in about 5% of pre-eclamptic patients and occurs postpartum in about 30% of cases. Complications include hepatic necrosis, liver rupture and subcapsular liver haematoma. Other complications of pre-eclampsia such as eclampsia and its sequelae, renal failure and pulmonary oedema may also be seen (Nelson-Piercy, 2010). Maternal mortality as low as 1% has been reported, but perinatal mortality ranges from 7.4% to 34% depending on gestation (Haram et al, 2009).

Diagnosis

Presentation of HELLP syndrome can be non-specific with nausea, vomiting and flu-like symptoms. Epigastric or right upper quadrant tenderness is common, but particularly when associated with shoulder tip pain, should alert the clinician to the possibility of hepatic haematoma or infarction. Features of pre-eclampsia such as headache, visual disturbance and oedema may be present although hypertension and proteinuria may be only mild. There may be evidence of bleeding, and both HELLP syndrome and pre-eclampsia are associated with placental abruption.

The blood picture marries well with the name of the condition. Haemolysis is seen, with a concomitant increase in bilirubin and lactate dehydrogenase. Transaminase levels are raised. Platelets are low or falling as a result of increased consumption as activated platelets adhere to damaged endothelium. Renal function may be impaired and there may be evidence of disseminated intravascular coagulation. Liver ultrasound may be needed to exclude hepatic haematoma and other differentials.

Management

Urgent delivery is required, after maternal stabilization and control of blood pressure if necessary. Coagulopathy may need correction with fresh frozen plasma and platelet transfusion may be required if counts drop below $50x10^9$/litre, for bleeding or for surgical indications (Haram et al, 2009). Corticosteroids have been used to treat both liver and haematological dysfunction, but current recommendations are that these should only be given for the indication of fetal lung maturity before preterm delivery, rather than specifically to treat maternal HELLP syndrome (Woudstra et al, 2010). Treatment is otherwise supportive with multidisciplinary involvement.

Acute fatty liver of pregnancy

This is a rare disorder (1 in 20 000 pregnancies) (Knight et al, 2008) which can be life-threatening for both mother and fetus. Acute fatty liver of pregnancy has been associated with an autosomal recessive disorder of mitochondrial fatty acid oxidation in the fetus. In some cases it manifests when a woman who is heterozygous for the disorder carries a homozygous fetus (Treem et al, 1996). Onset is usually in the third trimester and can be rapid. It is associated with nulliparity, male fetuses, multiple pregnancy and pre-eclampsia. Differentiation from pre-eclampsia, of which it may be a variant, can be difficult.

Diagnosis

Symptoms are often non-specific with nausea, vomiting, abdominal pain and jaundice. Bleeding can be a presenting feature secondary to disseminated intravascular coagulation which is common. Liver function tests are abnormal, with raised transaminase levels. Renal function may be compromised. As with pre-eclampsia, there may be hypertension and proteinuria. These may be mild, but serum urate often exceeds pre-eclamptic levels. Hypoglycaemia is a distinctive feature and liver imaging shows evidence of fatty infiltration (although it may be normal). Liver biopsy is gold standard for diagnosis but is rarely performed.

Management

Knight et al (2008) quoted a case fatality rate of 1.8%, lower than previously quoted rates (12–18%). Perinatal mortality was high at 104 per 1000 births. Urgent delivery is needed to halt progression, along with aggressive supportive care – correction of hypoglycaemia and clotting abnormalities, administration of N-acetyl cysteine and multi-organ support. Fulminant hepatic failure and encephalopathy should be managed by a specialist liver unit with multidisciplinary team involvement (Nelson-Piercy, 2010). Rarely, liver transplantation may be necessary.

Prompt testing for defects of fatty acid oxidation should be performed for fetuses born to mothers with acute fatty liver of pregnancy so measures to attenuate risk in an affected child can be instigated early. Recurrence is thought to be low (Knight et al, 2008) although it may be as high as 25% in carriers of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency which may justify genetic testing in the mother (Ko and Yoshida, 2006).

Pre-existing liver disease

Pregnancy in women with autoimmune liver disease is generally safe although increased complications including miscarriage have been reported (Schramm et al, 2006). Immunosuppression, e.g. with prednisolone and azathioprine, should be continued for the duration (Nelson-Piercy, 2010). There is an increased risk of flare post-partum and possible increases in dosages should be anticipated (Terrabuio et al, 2009). In primary biliary sclerosis, ursodeoxycholic acid can be used for symptom control (Poupon et al, 2005).

Sclerosing cholangitis is a rare inflammatory and scarring condition of the biliary tree associated with inflammatory bowel disease. It has a strong relationship with cholangiocarcinoma. Pregnancy outcomes in women with the disease have not been well studied. Some evidence suggests that sufferers are not at higher risk of adverse fetal outcomes or deterioration of disease in pregnancy (Janczewska et al, 1996).

In women with liver cirrhosis, fertility is reduced. In rare cases where pregnancy occurs, the incidence of obstetric complications such as miscarriage, post-partum haemorrhage and preterm labour is increased. Liver disease is liable to decompensate and the risk of bleeding from oesophageal varices is particularly high in those with portal hypertension (Tan et al, 2008). The risks of pregnancy with cirrhosis are such that it should be discouraged.

Liver transplantation

Women who have had a liver transplant may have a return to fertility and become pregnant. Pregnancy should be avoided for at least 18 months after transplant to allow graft stabilization and reduction of immu-

nosuppressive doses to maintenance levels. Azathioprine, tacrolimus and prednisolone are safe in pregnancy (Nelson-Piercy, 2010), but pregnancy in these women is associated with higher complication rates, notably preterm labour and hypertension (Murthy et al, 2009). Possibly as a consequence, liver transplantation has been associated with a high caesarean section rate (Jabiry-Zieniewicz et al, 2007). These cases should be managed in conjunction with a specialist liver unit.

Coincidental conditions

Hepatitis

Several viral hepatitides may be pre-existing or acquired in pregnancy.

Hepatitis B carriage in pregnant women is around 0.5–1%. Pregnancy generally does not affect the course of the disease. Vertical transmission is possible and is most common during delivery; neonatal infection has a 90% risk of chronic infection. The risk of vertical transmission from an HBeAg seropositive mother is 70–90% compared with approximately 10% risk from an HBeAg negative mother. Infants born to acute or chronically infected mothers should be given hepatitis B vaccine as soon as possible after birth, and then at 1, 2, and 12 months of age. Hepatitis B immunoglobulin should also be given by deep intramuscular injection as soon as possible after birth and not later than 48 hours if an infected mother (HbsAg positive):

1. Has had acute hepatitis B in pregnancy
2. Is HBeAg positive
3. Is HBeAg negative and anti-HBe negative
4. Has a neonate weighing 1500 g or less
5. If e markers are not available.

These recommendations are over 90% effective in preventing neonatal infection (Health Protection Agency, 2009).

Viral load using hepatitis B virus DNA can be used to measure viral activity. Evidence for use of antivirals during pregnancy is mounting. Therapy in women with chronic hepatitis B virus and high viral loads in the third trimester may reduce viral load and decrease perinatal transmission. Evidence for safety of tenofovir and lamivudine is good but further data are needed before ribavirin can be recommended (Tran, 2009). Breastfeeding is not contraindicated in vaccinated infants but should not be carried out if antivirals are used post-partum.

Hepatitis C is another blood-borne virus which may be transmitted vertically. The disease course is not affected by pregnancy and, without severe liver disease, the only adverse effect is a slightly increased incidence of obstetric cholestasis. Vertical transmission rates are between 1 and 6% (McMenamin et al, 2008). A high hepatitis C viral load increases vertical transmission and is often seen in women co-infected with human immunodeficiency virus or intravenous drug users (Valladares et al, 2010). Hepatitis C has no vaccine and immunoglobulin is not recommended for neonates. There are no specific recommendations for reducing vertical transmission and infants should be followed up with hepatitis C virus RNA polymerase chain reaction to detect infection. Breastfeeding is not contraindicated.

For both hepatitis B and C, caesarean delivery is not necessary to reduce the risk of infection. As with all blood-borne infections in labour internal fetal monitoring, fetal scalp electrode clips and fetal blood sampling should be avoided.

The faeco-orally transmitted hepatitis viruses are hepatitis A and E. Hepatitis A is a self-limiting illness. If contracted at or around delivery transmission to the neonate may occur (although is rare), in which case neonatal immunoglobulin should be given. Hepatitis E causes a similar illness to hepatitis A, but pregnant women are particularly susceptible and suffer complications such as hepatic failure and encephalopathy more often. Effects are most dangerous in the third trimester and mortality is significantly increased, exceeding 20% compared to up to 4% in non-pregnant women (World Health Organization, 2005).

Budd–Chiari syndrome

In Budd–Chiari syndrome there is outflow obstruction to the hepatic veins, e.g. as a result of thrombosis. Presentation includes right upper quadrant pain, jaundice and ascites. Pregnancy is associated with an increased risk of Budd–Chiari syndrome, likely related to the hypercoaguable state. Diagnosis is by colour-flow Doppler ultrasonography. Treatment involves anticoagulation, surgical or transjugular intrahepatic porto-systemic shunts, with liver transplant a last resort. Maternal outcome in pregnancy is good although recurrent thrombosis is a concern and thromboprophylaxis with low molecular weight heparin is appropriate. Increased fetal loss has been reported (Rautou et al, 2009).

Gallstones

The incidence of gallstones in pregnancy is between 2 and 12% (Al-Hashem et al, 2009). Pregnancy predisposes to gallstone formation because of reduced contractility of the gall bladder and increased cholesterol content of bile. Features are similar to those in the non-pregnant woman with epigastric or right upper quadrant pain radiating to the back, nausea and vomiting. Jaundice may occur if the common bile duct is involved.

Ultrasound is first line for diagnosis. In acute cholecystitis the white cell count may be raised and liver function tests deranged, with a mild increase in amylase levels. Management is no different from the non-pregnant patient and may be conservative. Laparoscopy and endoscopic retrograde cholangiopancreatography are both safe during pregnancy. While safe in all trimesters, laparoscopy is best performed in the second trimester when organogenesis is complete and the uterus does not obstruct the surgical field (Date et al, 2008). Any surgeon performing laparoscopy in pregnancy should have advanced laparoscopic skills. Pancreatitis is a possible complication, but the high mortality previously seen with this condition in pregnancy has improved with medical advances (Pitchumoni and Yegnerwaran, 2009).

Conclusions

Liver disease in pregnancy is not uncommon, affecting up to 3% of all pregnancies. *Table 2* outlines risks which certain liver disorders in pregnancy pose to both mother and fetus. While some conditions are unrelated to pregnancy or may be coincidental, others are unique to pregnancy. Presentation may be subtle or may rapidly progress to fulminant disease. Such cases require input from a multidisciplinary team in specialist centres and require the finely balanced art of managing both the mother and fetus. BJHM

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Table 2. Risks of selected liver disorders in pregnancy

	Risks to mother	Risks to fetus
Obstetric cholestasis	Distress from symptoms, sleep deprivation Post-partum haemorrhage	Intrauterine death Prematurity (spontaneous or iatrogenic)
HELLP syndrome	Disseminated intravascular coagulation Haemorrhage Hepatic rupture, necrosis or subcapsular haematoma Sequelae of pre-eclampsia	Prematurity (spontaneous or iatrogenic) Abruption Intrauterine death Growth restriction related to pre-eclampsia
Acute fatty liver of pregnancy	Fulminant liver failure or encephalopathy Renal failure Disseminated intravascular coagulation Haemorrhage Mortality Hypoglycaemia Liver rupture or necrosis	Prematurity Intrauterine death
Hepatitis C	No change in disease progression	Low risk of vertical transmission during delivery
Hepatitis B	No change in disease progression	High risk of vertical transmission during delivery
Autoimmune liver disease	Generally safe if immunosuppressants continued Possible increase in complications, e.g. miscarriage Post partum flare	Few direct risks
Sclerosing cholangitis	No change in disease progression	Few direct risks
Cirrhosis	Decompensation Bleeding from oesophageal varices Postpartum haemorrhage	Miscarriage Stillbirth Prematurity (spontaneous or iatrogenic)
Liver transplantation	Hypertensive disorders Renal insufficiency Caesarean delivery Gestational diabetes (if on steroids)	Prematurity (spontaneous or iatrogenic)
Budd–Chiari syndrome	Risk of recurrence in known Budd–Chiari syndrome	Increased incidence of fetal loss
Gallstones	As for non-pregnant women: cholecystitis, pancreatitis	None if asymptomatic With complications risks of prematurity and fetal loss increase

KEY POINTS

- Liver disease affects up to 3% of pregnancies.
- Alterations in normal values of parameters, particularly alkaline phosphatase, must be considered when interpreting liver function tests in pregnant women.
- Managing liver disease in pregnancy may need maternal and fetal outcomes balancing.
- Symptoms of liver disease can be insidious and a high index of suspicion is required for women with non-specific symptoms which may indicate HELLP syndrome, acute fatty liver of pregnancy or obstetric cholestasis.
- Pregnancy is generally safe with many forms of pre-existing liver disease, but cirrhosis and transplantation have higher complication rates and pregnancy should be discouraged in women with cirrhosis.
- Measures should be taken to reduce vertical transmission in women with hepatitis B and C.
- Severe liver dysfunction in pregnancy requires multidisciplinary team management and may need input from a specialist liver centre.