Review

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Pregnancy and liver disease

Rachel H. Westbrook[1,*], Geoffrey Dusheiko[1], Catherine Williamson[2]

[1]The Royal Free Hospital, Sheila Sherlock Liver Centre, Pond Street, London NW3 2QG, UK; [2]Division of Women's Health, 2nd Floor, Hodgkin Building, Guy's Campus, King's College London, London SE1 1UL, UK

Summary

Pregnancy associated liver diseases affect up to 3% of pregnant women and are the most frequent cause of liver dysfunction in pregnancy. When severe, they are associated with significant morbidity and mortality for both mother and infant [1–3]. A rapid evaluation to distinguish them from non-pregnancy related liver dysfunction is essential, in order to facilitate appropriate management. Liver disease unrelated to pregnancy can present *de novo* in pregnancy, or pregnancy can occur in women with pre-existing liver pathology (Table 1). Research and subsequent advances in medical care have resulted in improved but still not satisfactory maternal and fetal outcomes. In this review we provide an overview of the liver diseases specific to the pregnant state and an update on their pathogenesis, treatment and outcomes. The risks of pregnancy in women with pre-existent liver pathology is detailed and recent advances in our understanding of specific risks and outcomes are discussed.

Normal physiological changes in pregnancy

In a normal pregnancy many physiological and hormonal changes occur within the human body, some of which can mimic those seen in women with liver disease. There is a rise in maternal heart rate, cardiac output increases by 40%, the circulating plasma volume increases by 30% and there is a reduction in peripheral vascular resistance. These physiological changes result in a hyper-dynamic circulation; a physiological state that is common in patients with decompensated chronic liver disease. Physical examination of a pregnant woman may show palmar erythema and the presence of multiple spider naevi in up to 70% [4]. Blood flow to the liver remains constant during pregnancy and it remains impalpable as it is displaced upwards into the thoracic cavity due to the expanding uterus. Gallbladder motility decreases resulting in an increased risk of developing gallstones.

Biochemical and haematological indices taken during pregnancy need to be interpreted in light of the altered normal ranges for test results in pregnancy (Table 2). Maternal alkaline phosphatase (ALP) increases in the third trimester when ALP is produced both from the placenta and as a result of fetal bone development. The alpha fetoprotein (AFP) level increases in pregnancy as AFP is produced by the fetal liver. Other common biochemical and haematological tests including urea, haemoglobin levels and the prothrombin time, remain unchanged or slightly reduced due to haemodilution. Elevations in transaminases, bilirubin or the prothrombin time are abnormal and indicate a pathological state which requires further assessment. Pregnancy is also recognised as a pro-coagulant state, and clotting factors (I, II, V, VII, X, and XII) and fibrinogen are increased.

Small clinically insignificant oesophageal varices can occur in up to 50% of pregnant women in the late second and third trimester. These occur due to compression of the inferior vena cava (IVC) by the enlarging uterus and a reduction in venous return. Liver biopsy is rarely indicated in pregnancy, but if performed does not carry additional risks. Liver histology is essentially normal in the pregnant women, although electron microscopy shows some increase in the endoplasmic reticulum [5].

Key points

- Liver dysfunction in pregnancy can be due to: pregnancy associated liver diseases, exacerbation of pre-existing liver disease or conditions unrelated to pregnancy
- Pregnancy associated diseases can carry a high mortality rate for both mother and baby, and require rapid diagnosis and urgent delivery if at the severe end of the spectrum
- In cirrhotic women who become pregnant hepatic decompensation occurs in 10% and this can be predicted pre-conception by MELD score
- Common immunosuppressive agents (azathioprine, tacrolimus, cyclosporine and steroids) should not be discontinued in women post-transplantation or with autoimmune hepatitis

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* Corresponding author. Address: Royal Free Hospital, Pond Street, London NW3 2QG, UK.
E-mail address: rachel.westbrook@nhs.net (R.H. Westbrook).
Abbreviations: ACR, acute cellular rejection; AFLP, acute fatty liver of pregnancy; BCS, Budd-Chiari syndrome; HELLP, haemolysis, elevated liver enzymes and low platelets syndrome; HEV, hepatitis E virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; MELD, model for end stage liver disease; UDCA, ursodeoxycholic acid.

Table 1. Classification of liver disease in pregnancy.

Pregnancy related liver disease
Hyperemesis gravidarum
Intrahepatic cholestasis of pregnancy
Hypertension related liver diseases
Pre-eclampsia/eclampsia
HELLP syndrome
Liver infarction/liver rupture
Acute fatty liver of pregnancy
Non-pregnancy related liver disease
Pre-existing liver disease
Viral
Cirrhosis and portal hypertension
Post-liver transplantation
Autoimmune
Coincidentally with pregnancy
Autoimmune
Viral
Vascular (Budd Chiari)
Drug induced hepatotoxicity

Table 2. Typical reference ranges for liver enzymes, by trimester.

Liver enzyme	Non-pregnant	Pregnant	1st trimester	2nd trimester	3rd trimester
ALT (IU/L)	0-40	-	6-32	6-32	6-32
AST (IU/L)	7-40	-	10-28	11-29	11-30
Bilirubin (μmol/L)	0-17	-	4-16	3-13	3-14
γGT (IU/L)	11-50	-	5-37	5-43	3-41
ALP (IU/L)	30-130	-	32-100	43-135	133-418
Albumin (g/L)	35-46	28-37	-	-	-
Bile acids (μmol/L)	0-14	0-14	-	-	-
Haemoglobin (g/L)		-	110-135	103-130	100-130
Platelets (10^3/ml)		212-135	-	-	-

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Pregnancy related liver diseases

The liver diseases specific to the pregnant state can be classified into those of early pregnancy (hyperemesis gravidarum (HG)) and those of late pregnancy (acute fatty liver of pregnancy (AFLP), pre-eclampsia with hepatic involvement including haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, liver rupture/infarction and intrahepatic cholestasis of pregnancy (ICP)). The typical pattern of abnormal serum liver tests in specific gestational liver diseases are given in Table 3.

Hyperemesis gravidarum

HG is the most severe form of illness within the spectrum of nausea and vomiting of pregnancy. It is defined as intractable vomiting, resulting in dehydration, ketosis and weight loss of greater than 5%. It complicates between 0.3% and 2% of pregnancies and symptoms usually but not exclusively begin before 9 weeks gestation [6,7]. The exact aetiology of HG is unclear. Human chorionic gonadotropin (HCG) hormone, which peaks in the first trimester has been shown to correlate with the severity of HG. HG is more common in molar and twin pregnancies where HCG levels are significantly elevated. HCG can physiologically activate the thyroid stimulating hormone (TSH) receptor resulting in supressed TSH and elevated T4. A positive correlation between HCG, T4 and the severity of HG has been demonstrated [8,9]. Other theories have been suggested including genetic, psychological, cultural and hormonal however none have been definitively proven [10].

Biochemical abnormalities are common and include renal dysfunction secondary to dehydration, electrolyte abnormalities including hypokalaemia and hypomagnesaemia secondary to vomiting and reduced oral intake. Abnormalities in hepatic enzymes occur in approximately 50% of cases that require hospitalisation. Prompt treatment is essential as HG accounts for approximately one maternal death per year in the UK. This includes intravenous rehydration, correction of hyponatraemia and hypokalaemia, thromboprophylaxis, thiamine supplementation and antiemetic treatment to enable slow reintroduction of oral fluids and diet.

Treatment of nausea and vomiting of pregnancy with vitamin B6 or vitamin B6 plus doxylamine is safe and effective and should be considered the first line pharmacotherapy in countries where available [11,12]. Second line therapies including dopamine antagonists (metoclopramide) [13], phenothiazines (chlorpromazine, prochlorperazine) and anticholinergics (dicycloverine) have reasonable safety data (Table 4) [12,14]. Refractory cases that don't improve with these drugs may respond to ondansetron or glucocorticoids [15–17].

HG is a reversible condition with no permanent hepatic damage, but often re-occurs in subsequent pregnancies [18,19]. Hepatic biochemical abnormalities that are more marked than those outlined in Table 3, or that fail to resolve on cessation of the vomiting should raise the suspicion of an alternative cause for the abnormal hepatic biochemistry.

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the commonest pregnancy-specific liver disease. It is a reversible form of cholestasis characterized by pruritus in pregnancy and elevated fasting or post-prandial serum bile acids with spontaneous relief of signs and symptoms within 6 weeks of delivery [20]. ICP has a high recurrence rate in subsequent pregnancies. It has a variable incidence, ranging from 3–5% of pregnant women in Chile, to 0.7% in the UK; it is rarely reported in African countries [21]. ICP typically presents in the third trimester but it can present as early as 7 weeks of gestation. It occurs more commonly in multiple pregnancy and in women that have received fertility treatment. ICP has a complex aetiology with genetic, endocrine and environmental components. It is likely that elevated estrogen [22] and progesterone metabolites [23] in pregnancy unmask the disease in genetically susceptible women.

The presenting symptom of ICP is usually pruritus, typically worse on the palms and soles, but this may be generalised or affect any part of the body. The only associated rash is secondary to excoriations from scratching. Some women also complain of dark urine and pale faeces. The characteristic biochemical features are shown in Table 4. It is noteworthy that the bilirubin

Table 3. Typical pattern of LFTs, and additional investigations, in women with liver diseases specific to pregnancy.

Pattern of LFT changes	Likely diagnosis	Estimated proportion of pregnant women with abnormal LFTs that have each diagnosis*	Recommended additional investigations
↑ALT (1.5-8 fold) ↑tBA (1.5-15 fold) tBil usually normal	Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis)	17%	Viral serology Anti-mitochondrial and anti-smooth muscle antibodies Abdominal USS
↑ALT (2-5 fold) tBA usually normal tBil usually normal	Pre-eclampsia with hepatic impairment	49%	↑BP in most Urinalysis for protein U&E, creatinine ↓Platelets
↑ALT (2-30 fold) tBA usually normal ↑tBil (1.5-10 fold)	HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets)	22%	↑BP in most Proteinuria in most ↑Creatinine ↓Platelets in all ↑LDH
↑ALT (3-15 fold) tBA usually normal ↑tBil (4-15 fold)	Acute fatty liver of pregnancy (AFLP)	4%	↑BP in most Proteinuria in most ↑Creatinine ↓Platelets ↑WBC ↓Plasma glucose
↑ALT (2-5 fold) tBA usually normal tBil usually normal	Hyperemesis gravidarum	8%	↑Thyroxine, ↓↓TSH† Hyponatraemia Hypokalaemia

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LFT, liver function tests; ALT, alanine transaminase; tBA, total serum bile acids; tBil, total bilirubin.
*During a 15 month study period, out of a total of 4377 deliveries, 142 women (3%) with 206 diagnoses were found to have abnormal liver function tests. Of these, 138 diagnoses were pregnancy-specific liver disease. One additional woman had hepatic infarct/ haematoma.
†Symptoms of thyrotoxicosis are rarely seen. TSH is normally suppressed during the 1st trimester but it is detectable in uncomplicated pregnancy.

concentration is rarely raised. The European Association for the Study of the Liver and the Royal College of Obstetrics and Gynaecology guidelines recommend that ICP should be diagnosed in pregnant women with pruritus and serum bile acids elevated above the reference range [11,24]. Serum bile acid measurement is the most useful biochemical test, as the two largest prospective cohort studies of perinatal outcomes in ICP reported an association between the maternal serum bile acid concentration and the risk of adverse pregnancy outcome (spontaneous and iatrogenic preterm labour, stillbirth and admission to the neonatal unit) [25,26]. Adverse outcomes are rarely reported in pregnancies where the maternal bile acid level is below 40 μmol/L, and the risk of complications increases as the mother's serum bile acid level rises [25,26]. Although most women with ICP have elevated liver transaminases in conjunction with hypercholanaemia, it is noteworthy that both prospective cohort studies did not report an association between the ALT/AST concentration and adverse perinatal outcomes [25,26]. Serum bile acid levels can fluctuate and rise with advancing gestation, so weekly checks should be performed in women with ICP [24].

The diagnosis of ICP is based on a combination of pruritus and elevated serum bile acid concentrations above the normal reference range both reversible within 4–6 weeks after pregnancy and after exclusion of other potential aetiologies. Approximately 15% of cases have genetic variation in one of the hepatocanalicular transport proteins; ABCB11 (bile salt export pump) or ABCB4 (phosphatidylcholine flippase). Smaller studies have reported genetic variation and/or heterozygous mutations in ABCC2 (conjugated organic anion transporter) [27], ATP8B1 (FIC1) [28,29] and the nuclear bile acid receptor (farnesoid X receptors) [28,30]. Of clinical interest, ABCB4 mutations are typically associated with elevated serum gamma-glutamyl transferase levels (GGT), whereas ABCB11, ATP8B1 and farnesoid X receptor mutations with low GGT levels.

The first line treatment for ICP is ursodeoxycholic acid (UDCA), which results in improved maternal symptoms and biochemistry in approximately 75% of cases [20,31–34]. UDCA has several functional effects that are likely to contribute to improvement in maternal and fetal consequences of ICP. It enhances biliary transport of bile acids, is anti-apoptotic and is likely to improve excretion of pruritogens, e.g. progesterone sulphates [23,35]. *In vitro* and *in vivo* experiments demonstrate that UDCA enhances trans-placental transport of bile acids from the fetus to the mother and reduces placental damage [21]. A meta-analysis [33] and *in vitro* experiments [36,37] suggest that its use may positively impact on the frequency of preterm labour, neonatal unit admission, placental damage and fetal arrhythmias. Rifampicin, is a potent pregnane X receptor agonist. Combined use of UDCA and rifampicin has been postulated to have synergistic beneficial effects in non-obstructive cholestasis [38]. In ICP, combining rifampicin with UDCA improves the symptoms and biochemical derangements in approximately one third of women that do not respond to UDCA alone [39]. Given favourable safety data for rifampicin in the third trimester of pregnancy, its use as a second line agent in patients whose symptoms or biochemistry don't respond to UDCA is rational. S-adenosyl methionine enhances phospholipid excretion and has been reported to improve pruritus and biochemical abnormalities in some, but not all studies [40]. Dexamethasone has no impact on symptoms or biochemical markers in ICP and should only be used if advised by obstetricians to promote fetal lung maturity [32]. Relatively small studies have demonstrated improved serum bile acid levels with activated charcoal and reduced pruritus with guar gum and cholestyramine [41–43]. It is important to weigh the benefits of

Table 4. Medications commonly used in liver disease and pregnancy.

Indication	Drug	FDA classification	Fetal effects	References
Hyperemisis gravidarum	Antihistamine H1-receptor blockers (e.g., doxylamine)	A	No adverse fetal effects reported Safe and first line for HG where available	[177, 178]
	Dopamine antagonists (metoclopramide)	B	No adverse fetal effects reported Reasonable alternative first line treatment for HG	[13, 179, 180]
	Phenothiazines (prochlorperazine, chlorpromazine, prochlorperazine)	-	No associated increased risk of fetal malformations or adverse pregnancy outcomes	[181]
	Antihistamines (cyclizine)	B	Teratogenic in animal studies In human exposure no increased risk for birth defects has been observed	[181]
	Anticholinergics (dicycloverine)		No adverse fetal effects reported Safe in pregnancy	[9]
	Serotonin antagonists (ondansetron)	B	Safe in animal studies; little controlled data, but appears safe. Possible increased risk of cardiac septum/cleft palate defects.	[15, 16]
	Prednisolone	B	Some studies suggest slightly increased risk of cleft palate if used in first trimester and fetal hypoadrenalism	[17]
Intrahepatic cholestasis of pregnancy	Ursodeoxycholic acid	B	Appears safe, no adverse fetal effects reported	[31, 182]
	Rifampicin	C	No adequate controlled trials, risk of teratogenicity in first trimester; appears safe in third trimester	[39]
	Cholestyramine	C	No adverse fetal effects reported	[42]
Hypertensive liver diseases	Labetalol	C	Rare cases of fetal hypoglycaemia, bradycardia and hypotension reported with prolonged use for pre-eclampsia	[53]
	Hydralazine	C	Safe from a fetal perspective, may be associated with more maternal complications when compared to labetalol or nifedipine	
	Nifedipine	C	Safe with no teratogenic risk	[183]
Variceal prophylaxis and bleeding	Propranolol	C	Not teratogenic but fetal bradycardia, growth restriction and neonatal hypoglycaemia may occur	[184]
	Terlipressin	D	Uterine ischaemia due to vasoconstrictive effects	[185]
	Octreotide/somatostatin	B	There are no controlled data from human pregnancy. Animal studies did not show fetal toxicity or teratogenicity	[186]
Viral liver disease	Lamivudine	C	Data suggests low teratogenic potential	[187, 188]
	Tenofovir	B	Data suggests low teratogenic potential in both human and animal studies	[106, 187, 188]
	Telbivudine	B	Safe and well tolerated, Data only for use in third trimester	[119]
	Ribavirin	X	Teratogenic	[189]
	Acyclovir	B	No controlled data, doesn't appear to be teratogenic/have any adverse fetal effects	[190]
Immunosuppression	Azathioprine	D	Teratogenic in animal studies. In humans lymphopenia, hypogammaglobulinaemia and thymic hypoplasia rarely reported (reversible after birth; no long-term sequelae). Emerging data are very reassuring with regard to fetal effects	[130, 137, 191]
	Mycophenolate	D	Teratogenic due to abnormal ova development; hypoplastic nails and shortened fifth fingers, microtia with cleft lip and palate, microtia alone	[192]
	Tacrolimus	C	Teratogenic potential appears low (4%)	[142]
	Sirolimus	C	Data too limited to draw conclusions, therefore not recommended	[192]
	Cyclosporine	C	Teratogenic potential appears low (4.1%). Premature labour, low birth weight, transient neonatal hyperkalemia and elevated serum creatinine concentrations have been reported	[193, 194]

mild symptomatic improvement reported with cholestyramine pruritus against the potential impaired luminal absorption of vitamin K or UDCA as this may inadvertently worsen perinatal outcomes [42]. In the authors experience, it is often helpful to give women aqueous cream with 1–2% menthol [24], as this may reduce the pruritus sufficiently to enable women to fall asleep. Vitamin K supplementation may reduce the risk of post-partum haemorrhage or neonatal haemorrhage.

ICP has a high recurrence rate in subsequent pregnancies. Affected women also have an increased risk of hepatobiliary disease later in life, most commonly gallstones (perhaps due to a common risk factor (*ABCB4* gene)), hepatobiliary malignancies and immune-mediated and cardiovascular diseases [44–46]. A high prevalence of hepatitis C infection in women with ICP has been reported [44]. Whether this reflects an enhanced susceptibility to hepatitis C infection in women with ICP or vice versa remains unclear.

It is important to advise women that they have an increased risk of hepatic impairment when taking the combined oral contraceptive pill, but most progesterone containing contraception is not associated with hepatic impairment. If women have ongoing symptoms or biochemical hepatic impairment for more than 3 months postpartum an alternative/additional diagnosis should be sought.

Pre-eclampsia, eclampsia and haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome

Pre-eclampsia is a multisystem disorder defined by the international society for the study of hypertension in pregnancy as *de novo* hypertension after the 20th week of pregnancy (blood pressure (BP) 140/90) combined with proteinuria (>300 mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction [47]. In a patient with pre-existing essential hypertension, superimposed pre-eclampsia is diagnosed if at least one of the above features are present [47]. Pre-eclampsia affects between 3–5% of all pregnancies and can present from 20 weeks gestation, to as late as 4 weeks postpartum [48]. The presence of seizures differentiates pre-eclampsia from eclampsia. HELLP syndrome is considered as a severe form of pre-eclampsia. Risk factors for pre-eclampsia are: previous pre-eclampsia or hypertension in pregnancy, chronic kidney disease, hypertension, diabetes, and autoimmune disorders [49].

The aetiology of pre-eclampsia is incompletely understood. It is postulated that abnormal placentation leads to placental hypoperfusion, which in some patients progresses to endothelial dysfunction, leading to the multi-systemic involvement characteristic of pre-eclampsia [50]. The trophoblast fails to invade the uterine lining, resulting in defective arterial placental perfusion, which worsens as the pregnancy progresses and the demand on the placenta increases [51]. Nitric oxide, prostaglandins and endothelin from the placental tissue are released which induce platelet aggregation, endothelial dysfunction and arterial hypertension. Fibrin released from endothelial damage forms crosslinked networks in the small blood vessels resulting in a microangiopathic haemolytic anaemia. The pathogenesis of liver involvement is postulated to be secondary to fibrin deposition within the hepatic sinusoids resulting in sinusoidal obstruction and subsequent hepatic ischaemia. It is the combination of hepatic sinusoidal obstruction and ischaemia that results in subcapsular haematomas, parenchymal haemorrhage and ultimately hepatic rupture [52].

Clinical features of pre-eclampsia may be absent with the diagnosis made during routine antenatal care; if present they include right upper quadrant pain, headache, visual changes, nausea and vomiting. Many women are hyperreflexic and oedema is common [48]. Elevated serum transaminases occur in 30% of cases. At the severe end of the spectrum of pre-eclampsia, HELLP syndrome may manifest. The derangement of liver function tests in patients with pre-eclampsia and eclampsia should highlight the presence of severe disease. If rapid hypertensive control and delivery is not achieved, women are at risk of renal dysfunction, cerebral haemorrhage, hepatic infarction, haematomas or rupture with markedly increased perinatal mortality and morbidity.

The management of pre-eclampsia is supportive. The only cure is delivery of the placenta and hence the fetus should be delivered as soon as possible by the safest route, especially if the fetus is beyond 34 weeks gestation, fetal distress is evident or there is evidence of maternal deterioration. Hypertension should be treated; intravenous labetalol, intravenous hydralazine and oral nifedipine are first line agents for acute lowering of BP in pregnant women [53–55]. If gestation is less than 34 weeks, glucocorticoids should be given to promote fetal lung maturity [56]. Patients may require coagulation support. Magnesium sulphate should be given to women with HELLP syndrome and other forms of severe pre-eclampsia. Outcomes at the more severe end of the spectrum are difficult to predict and prognostic information is limited to small series [2,3,57]. Women with pre-eclampsia and eclampsia are recognised to have double the baseline risk of heart and cerebral vascular disease later in life and it remains unclear if this association is correlational, causal or a combination [58]. While it is likely that women with HELLP syndrome have the same risks, this remains to be established definitively.

HELLP syndrome was first described by Weinstein in 1982 and occurs in approximately 10–20% of women with pre-eclampsia [59–61]. Although HELLP is recognised to complicate pre-eclampsia in up to 20% of cases, HELLP syndrome can occur in women with normal blood pressure, reflecting the multisystem nature of pre-eclampsia and related disorders [62]. The diagnosis of HELLP syndrome is based mainly on clinical features. The presenting symptoms are varied and include right upper quadrant or epigastric pain in approximately 65% of cases, nausea and vomiting (35% of cases), headache (30% of cases) and rarer complaints including bleeding and jaundice [63]. A significant number of patients are asymptomatic [63]. On examination, hypertension is evident in up to 85% and proteinuria is common. Classical laboratory indices are detailed in Table 4. Disseminated intravascular coagulation can occur with evidence of elevated fibrin degradation products, a low fibrinogen and a secondary rise in the prothrombin time.

Imaging of the abdomen should be considered in all women with HELLP syndrome and is imperative in those with abdominal pain, shoulder tip pain or hypotension [64], in order to investigate for the life-threatening complications of hepatic haemorrhage, rupture and infarction, which have been reported to occur in up to 45% of women with HELLP syndrome [63,65]. Liver biopsy is not indicated as the diagnosis is based on clinical criteria and due to the risks of haemorrhage in association with coexistent thrombocytopenia. In cases where liver biopsy has been performed, the microscopic findings are similar to those seen in pre-eclampsia (characteristic periportal changes with haemorrhage, sinusoidal fibril deposition and hepatocyte necrosis) [66]. The management is as for pre-eclampsia.

Hepatic rupture, infarction and haematoma

Hepatic haemorrhage and rupture can complicate pre-eclampsia, eclampsia, HELLP syndrome and patients with AFLP and is associated with a 50% mortality [63]. Patients can present with abdominal pain, pyrexia and, if severe, hypovolaemic shock and cardiovascular collapse. Laboratory investigations reveal transaminases in the several thousands, leucocytosis and anaemia. Imaging in the form of computed tomography or magnetic resonance is the investigation of choice [64]. Contained haematomas

can be managed conservatively with aggressive coagulation support, prophylactic antibiotics and transfusion as required [67]. If there is any evidence of haemodynamic instability, then urgent angiography with hepatic artery embolization and/or surgical intervention is warranted. Surgical intervention includes packing of the liver, hepatic artery ligation and resection [64,68]. Necrotic infarcts can also occur as a complication of pre-eclampsia. Patients often have an unexplained rise in their transaminases to several thousand, fever, anaemia and leucocytosis. There may be associated signs of liver failure. In the majority of cases the liver recovers, but if there are areas of extensive infarct, death from multi-organ failure or hepatic rupture can ensue.

Acute fatty liver of pregnancy

AFLP is a medical and obstetric emergency as it can be fatal for both the mother and baby without early recognition and appropriate management [69,70]. It is a rare complication of pregnancy, usually occurring in the third trimester, and in the UK affects approximately 1 in 20,000 pregnancies [71], with the true incidence likely however to be higher with underreporting of subclinical/milder forms. Risk factors include nulliparity, male infants and twin pregnancies.

The presentation is similar to that of mitochondrial cytopathies, and an abnormality in mitochondrial β-oxidation is a recognised cause of AFLP in a subset of cases [70,72]. The enzyme, long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), is a key part of the mitochondrial trifunctional protein. Approximately 20% of neonates born to mothers with AFLP have been shown to have defects in β-oxidation and to be deficient in LCHAD due to mutation on one or both alleles of the α-subunit of the trifunctional protein [72]. Due to the genetic defect, fetal fatty acids accumulate and return to the mother via the placenta. They are then deposited in the liver and present phenotypically as maternal liver disease. Mothers of neonates with LCHAD deficiency have been shown to have a 79% chance of developing AFLP or HELLP syndrome [72]. Other reports have shown a 20-fold increased risk of maternal liver disease in pregnancy in fetuses with fatty acid oxidation defects [73]. AFLP and HELLP are both multifactorial disorders that have a requirement to excrete pathologically high concentrations of β fatty acid oxidation metabolites which is likely to unmask susceptibility to both disorders.

The onset is usually between the 30th and 38th gestational week although up to 20% present postnatally [71]. Presenting features range from non-specific symptoms such as nausea, vomiting and abdominal pain to those of acute liver failure including hypoglycaemia, coagulopathy, jaundice and encephalopathy [73,74]. Pre-eclampsia is common but not invariable.

Biochemical changes (Table 4) include hyperbilirubinaemia and a variable elevation of serum transaminases. In addition, serum ammonia, lactic acid and amino acid levels are increased reflecting mitochondrial failure. Renal dysfunction, leucocytosis and thrombocytopenia are also common. The prothrombin time is prolonged and fibrinogen levels are reduced; disseminated intravascular coagulation is seen in approximately 10%. Potential complications include ascites, pleural effusions, acute pancreatitis, respiratory and renal failure. Infections are common as is vaginal bleeding or bleeding from caesarean section wounds [2,3].

Although the definitive diagnosis of AFLP is made histologically (Fig. 1), liver biopsy is rarely performed due to the need to stabilise and deliver affected women. Recently clinical diagnostic criteria have been developed and validated for AFLP, aiding rapid diagnosis without the need and associated risks of a liver biopsy [74] (Table 5).

Early recognition with rapid delivery of the fetus followed by maternal supportive care vastly improves prognosis for both the mother and the baby. Maternal mortality rates were reported to be as high as 92% prior to 1970, but subsequently, overall mortality rates have improved, with rates of less than 10% reported in 2008 [69,75]. The use of plasma exchange following delivery results in improved clinical outcomes including reduced maternal mortality in non-randomised clinical trials [76–78]. Successful liver transplantation has been sporadically reported, however

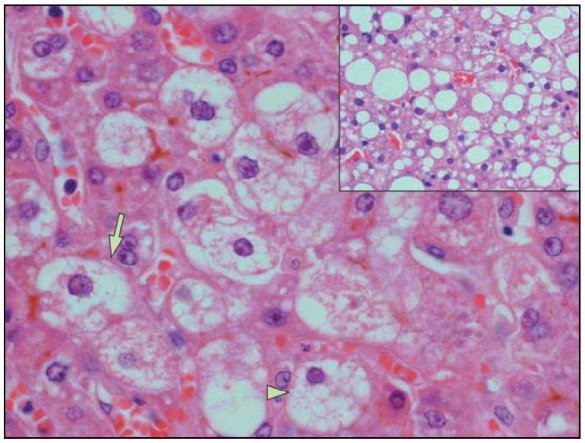

Fig. 1. Liver biopsy of a patient with acute fatty liver disease of pregnancy. Micro- and macro-vesicular fat droplets with ballooned hepatocytes containing dense central nuclei. The periportal areas are often spared. The microvacuoles may be only identified on fresh sections stained for fat with an Oil Red O stain. In severe cases hepatocytes necrosis can be seen.

Table 5. Swansea diagnostic criteria for the diagnosis of acute fatty liver of pregnancy.

Six or more of features below in the absence of other aetiology
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Bilirubin (>14 μmol/L)
Hypoglycaemia (<4 mmol/L)
Leucocytosis (>11 x 10^6/L)
Elevated uric acid (>340 μmol/L)
Elevated ammonia (>42 IU/L)
Ascites or bright liver on USS
Elevated transaminases (>42 IU/L)
Renal impairment (creatinine >150 μmol/L)
Coagulopathy (PT >14 s or APTT >34 s)
Microvesicular steatosis on biopsy

the indications for liver transplantation in this unique cohort remain so far undefined and the majority of cases have a full recovery with supportive treatment [2,79,80]. In a retrospective review of 54 patients transferred to a liver transplant (LT) centre with pregnancy associated liver dysfunction (HELLP/AFLP), an elevated lactate and the presence of hepatic encephalopathy were the only admission parameters predictive of death or need for LT [2].

Pre-existing liver diseases and pregnancy

Cirrhosis and portal hypertension

In women with cirrhosis, fertility is reduced and pregnancy is rare secondary to metabolic and endocrine dysfunction [1,81–86]. Disruption of the hypothalamic-pituitary axis in conjunction with disturbed oestrogen metabolism leads to anovulation, amenorrhoea and infertility [84,85]. When pregnancy does occur there is an increased rate of spontaneous pregnancy loss, preterm labour and perinatal death [87]. For the mother there is a risk of worsening liver synthetic function and hepatic decompensation including the development of ascites, variceal haemorrhage and encephalopathy [82,87–91]. Maternal mortality for pregnant women with cirrhosis was reported to be as high as 10.5% in the early 1980s [83]. It is encouraging that more recent series have reported mortality rates of 1.6% and decompensation rates of 10% [87]. Outcomes of pregnancy are related to the severity of the maternal liver disease, as opposed to the aetiology. Moreover, utilisation of prognostic scoring systems (MELD, UKELD) can facilitate pre-pregnancy prediction of the risk of maternal decompensation during pregnancy and can be used to guide preconception counselling in women with cirrhosis [87]. Specifically a recent study of 62 pregnancies in 29 cirrhotic women reported an overall 10% hepatic decompensation rate; a preconception MELD score $\geqslant$10 had an 83% sensitivity and specificity for predicting hepatic decompensation. Conversely, no women with a preconception MELD $\leqslant$6 developed a hepatological complication [87].

Variceal bleeding secondary to portal hypertension is the leading cause of maternal mortality in pregnant patients with underlying cirrhosis [87,89–91]. Portal hypertension worsens with pregnancy and peaks in the second trimester due to increased circulating blood volume and a direct pressure of the gravid uterus on the IVC impairing venous return [92]. A patient with pre-existent varices will have up to a 25% risk of developing an episode of variceal haemorrhage during pregnancy, with the greatest risk in the second trimester and during delivery. Mortality rates as high as 50% have been reported [93,88].

In non-cirrhotic portal hypertension (NCPH), synthetic liver function in usually preserved and the reproductive system is rarely effected. The incidence of variceal haemorrhage in this group is similar to women with cirrhosis with the largest series reporting a 35% risk of a variceal haemorrhage [94]. Prognosis however is significantly better in those women who bleed secondary to NCPH with mortality rates of between 2 and 6%, likely due to the absence of underlying synthetic liver dysfunction [92,94].

The optimal management of portal hypertension during pregnancy remains challenging with the absolute need for variceal screening during the second trimester, primary prophylaxis against variceal haemorrhage and the management of a variceal haemorrhage during pregnancy largely undefined. Preconception, in a patient with "at risk" varices, prophylactic endoscopic band ligation of varices, although not proven, appears appropriate [95]; for varices that lack "high risk stigmata", beta blockers should be commenced as the benefit is thought to outweigh any potential risk. The American Association for the Study of Liver Diseases recommends that once pregnant, women with cirrhosis should have a screening endoscopy in the second trimester [96]. Upper gastrointestinal endoscopy is safe during pregnancy, with fetal hypoxia due to sedation or positioning being the main concern [97]. Management of varices detected at the second trimester screening endoscopy should be managed as above. Guidelines recommending the use of non-invasive markers to identify patients with cirrhosis who need endoscopic screening for varices are now in practice [98]. Recent data in pregnant women has demonstrated that a platelet count of $<110 \times 10^9$ cells/L has a 78% sensitivity and 89% specificity for predicting the presence of varices at screening endoscopy in the second trimester [87]. Based on this finding, it may be possible if confirmed in other cohorts to use this cut-off platelet count as an arbiter for categorizing patients into those that require screening for varices in pregnancy.

There are no recommendations as to the preferred mode of delivery (vaginal *vs.* caesarean section) in patients with portal hypertension. It is preferable to avoid excessive straining during labour in women with documented varices, and a shortened second stage of labour is recommended, with forceps or ventouse-assisted delivery if needed. Caesarean section should be performed according to obstetric indications, as women with cirrhosis are at increased risk of abdominal wall varices, bleeding during labour, poor wound healing and infection.

The treatment of an acute variceal bleed in pregnancy, like in the non-pregnant patient, is to ensure resuscitation and stabilisation of the mother, antibiotic prophylaxis and safe and timely endoscopic therapy. The mainstay of treatment for bleeding oesophageal varices is endoscopic variceal band ligation [99,100], although successful haemostasis with sclerotherapy has been reported [101,102]. Vasopressin or synthetic analogues are avoided because of their vasoconstrictive effects and associated uterine ischaemia. Reported experience with somatostatin and octreotide is sparse in pregnancy, but current data suggest no associated adverse fetal effects, and given their proven benefit in patients with variceal haemorrhage, they should be used in preference over terlipressin [103]. Insertion of portosystemic shunts, via radiological or surgical routes, have been used as emergency salvage therapy when endoscopic techniques have failed [90,104,105].

(Chronic) hepatitis B virus infection and pregnancy

Pregnant women should be tested for hepatitis B surface antigen (HBsAg) early in pregnancy [106]. Pregnancy does not have a major effect on the liver disease in mothers with chronic hepatitis B, except in the context of cirrhosis; cirrhosis is relatively uncommon in young childbearing women with HBV infection [107]. All hepatitis B positive women should be monitored closely during pregnancy and in the postpartum period for exacerbations of disease. The risk of flares in serum aminotransferases is somewhat raised during pregnancy and postpartum but deaths fortunately are rare [108–111].

Infection of infants born to HBsAg positive mothers, or of children early in life confers a high risk of chronic infection, but an effective and safe vaccination prevents HBV childhood infection. The World Health Organisation recommends universal vaccination of all infants and as of 2012, 183 countries have instituted universal vaccination against hepatitis B. All infants born to HBsAg positive mothers should receive hepatitis B vaccine and hepatitis B immunoglobulin as soon as possible after birth, preferably within 24 h [106,112]. Completion of HBV vaccine is important for the newborn to gain maximal protection and consists of the birth dose followed by two subsequent doses. Unfortunately birth dose vaccination is not universal, although the cost per dose is around $0.20 and the vaccine is effective in 95% of infants and children. Mode of delivery is not associated with an increased risk of transmission.

Women should have their HBV DNA level checked at the start of the third trimester as vaccine prophylaxis may fail in infants born to highly viraemic mothers (HBV DNA $>10^7$ IU/ml) [113,114]. HBV transmission can be prevented in this group by concurrent nucleoside analogue therapy during the third trimester [115,116]. Subsequent discontinuation of nucleoside analogue therapy at 1–3 months postpartum for those women who do not need continued therapy is recommended [117]. This selective strategy requires measurement of HBsAg and HBV DNA during pregnancy [118]. The safety of nucleoside analogues in pregnancy has been tabled in the antiretroviral pregnancy register (www.APregistry.com), with the current safety data available for lamivudine, tenofovir and telbivudine [119–123]. Tenofovir has been suggested as the first line nucleoside analogue in pregnancy by the Society for Maternal-Fetal Medicine [106]. Delivery mode should be decided by obstetric indications and caesarean section is not recommended for the sole indication for reduction of vertical HBV transmission [106]. Breast feeding should be encouraged providing immunoprophylaxis is given at birth [106].

Hepatitis C

There is no universal consensus regarding screening of pregnant women for hepatitis C virus (HCV) infection. Risk based approaches have been adopted in many centres. In a Brisbane study, most women who tested positive for anti-HCV had an identifiable risk factor [124]. The complexities of caring for pregnant women who are HCV positive in at risk populations have been highlighted [125] and like chronic hepatitis B in pregnancy, confer little increased risk to the mother except in the context of cirrhosis.

Neonatal transmission occurs in 3 to 5% of HCV RNA positive mothers in the absence of HIV co-infection. HIV co-infection together with high HCV RNA in plasma has been associated with increased risk of HCV transmission [126]. A recent report has suggested a higher risk of ICP associated with hepatitis C infection [127], and a meta-analysis suggested that maternal HCV infection is significantly associated with a higher risk of preterm births [128]. 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

Historical reports of pregnancy in autoimmune hepatitis described unfavourable maternal and fetal outcomes [90,129]. There have been several recent case series reporting a live birth rate of between 71–86%, which is comparable to patients with other autoimmune conditions but remains lower than the general population [86,130–134]. The most common maternal complication is a flare in autoimmune disease activity either during the gestational (7–21% incidence reported) or more commonly in the postpartum period (11–81% incidence reported) [130–133]. In the majority of patients a flare can be controlled by augmentation of immunosuppressive therapy, but in rare cases, a flare can lead to hepatic decompensation with the potential need for LT or death of the patient and/or fetus [86,132]. Recent data has shown that poor disease control in the year prior to conception and absence of immunosuppressive therapy during pregnancy are associated with an increased risk of development of flare in disease activity [130].

Azathioprine has good safety data for its use in pregnancy and lactation [135,136]. In humans, lymphopenia, hypogammaglobulinaemia and thymic hypoplasia have all been reported in children born to mothers on azathioprine; but these changes were all reversible after birth with no long-term effects on the child [137]. Experience and confidence in using azathioprine safely and without increased fetal risk in pregnancy has grown dramatically over the last two decades and it is now well recognised that women need stable immunosuppression throughout pregnancy and that azathioprine therapy should be continued at the same dose used to maintain maternal disease control throughout the gestational period.

Liver transplantation and pregnancy

Long-term survival following LT is now expected in the majority of patients. The goal of LT in the current day is not only to ensure survival but to also attain a quality of life for patients similar to their pre-morbid state, which for many women includes having a family [138]. Fertility following transplantation is restored in the majority of women, as early as 1 month post-transplantation, hence discussion regarding appropriate contraceptive use is imperative [138].

The first successful pregnancy following LT was reported 1978 [139]. Subsequent to this, many case series detailing pregnancy post-LT have been published [140–147]. These highlight favourable outcomes in the majority, with a live birth rate of over 70%. There are, however, significant increased risks of unpredictable graft deterioration, pre-eclampsia (14–23%), infections (27%) and diabetes (5%) in the mother and for the fetus, an increased risk of prematurity (30%) and low birth weight exists [140–143,148]. Acute cellular rejection (ACR) complicates between 10–17% of patients in the gestational period [141–144,149], and 3–12% of patients in the postpartum period [141–143]. The incidence of ACR can be significantly reduced by delaying pregnancy for 1 year following LT [140]. Graft loss directly related to ACR in pregnancy is rare with immunosuppression augmentation controlling the majority [140]. Two recent publications have highlighted a potential link between an episode of biopsy proven rejection in association with pregnancy and recurrent rejection and graft loss long-term [140,147]. Although these findings have not been confirmed, prospectively they perhaps suggest than an episode of ACR during pregnancy may identify those women who are already at an increased risk of graft loss due to poor graft tolerance and may benefit from augmented baseline immunosuppression.

Immunosuppression should be continued throughout pregnancy and common agents including azathioprine, tacrolimus, cyclosporine and steroid therapy are generally safe and any small risk to the fetus from the medication is much outweighed by the risk of rejection and graft failure by discontinuation. Mycophenolate is associated with congenital abnormalities included external ear and other facial malformations such as cleft lip and palate and ideally should be discontinued with at least a 6 month wash out period before conception.

Liver disease coincidentally arising with pregnancy

Acute viral infections and pregnancy

Acute viral hepatitis is the commonest cause of jaundice occurring in pregnancy worldwide [150]. Hepatitis A virus infection in pregnancy has a clinical course similar to the non-pregnant population and fulminant hepatitis is rare [151]. Although hepatitis A virus infection in pregnancy is not a major cause of maternal or neonatal morbidity, *in utero* infection has been associated with fetal meconium peritonitis, neonatal cholestasis and preterm labour [152–154]. It is therefore appropriate that women at increased risk of hepatitis A are vaccinated.

There is a well described but unexplained increased mortality of acute hepatitis E (genotype 1 and 2) infection in pregnant women and this may explain historical outbreaks of jaundice and deaths in pregnant women in Europe [155,156]. Mortality from fulminant hepatic failure secondary to hepatitis E virus (HEV) can be up to 50% [151,157]. Women with HEV infection during pregnancy also have a higher risk of obstetric complications including antepartum haemorrhage, intrauterine fetal death and worse fetal outcomes including prematurity and stillbirth [158]. HEV infection in a rabbit experimental model has demonstrated vertical transmission with replication of HEV in the placenta, perhaps explaining the adverse outcomes in pregnancy [159]. Management is supportive, and ribavirin use is precluded because of the teratogenic effects [160–162]. A case report of LT for fulminant hepatic failure due to HEV in a pregnant woman has been published [163]. HIV infection may theoretically convey an added risk [164].

Herpes simplex viral hepatitis (type 1 and 2) is rare, normally affecting immunosuppressed patients, and pregnant women are more at risk than the general population. The clinical picture is an acute elevation of serum transaminases with coagulopathy usually in the absence of jaundice; muco-cutaneous lesions are evident in 50% [165,166]. Treatment with acyclovir should not be delayed if herpes simplex infection is suspected [167]. Histology is characteristic, and CT shows multiple sub 1 cm hypovascular infarcted areas [165].

Pregnancy and thrombosis

Pregnancy is recognised as a pro-coagulant state with an increase in clotting factors (I, II, V, VII, X, and XII) and fibrinogen levels alongside a physiological reduction in protein C concentrations. Budd-Chiari syndrome (BCS) can present *de novo* in pregnancy or pregnancy can result in thrombus extension with an acute on chronic presentation [168–171]. There is often the presence of an additional pro-coagulant factor and hence a full pro-coagulant search is imperative even in the context of pregnancy [170,172]. Historically, reports of BCS presenting in pregnancy were associated with poor outcomes for the fetus and mother with death from hepatic failure or portal hypertension being common [169,173–176]. The treatment for BCS has evolved over several decades and 5-year survival rates have improved from 50% to 90%, which is mirrored in the survival of pregnant women with BCS [171,172]. Young women with BCS may express a desire for pregnancy once their underlying condition has improved. In a recent series, 24 pregnancies were reported in 16 women previously diagnosed and treated for BCS. Symptomatic thrombosis reoccurred in two patients and there were seven fetal losses [171].

Conclusion

Liver disease in pregnancy and pregnancy in women with liver disease is rare. However, this is a clinically important group of patients due to the increased morbidity and mortality for both the mother and baby. The spectrum of disease and presentation varies hugely, resulting in delays in diagnosis and appropriate management. The disorders are complex and patients benefit from multi-disciplinary input by experienced physicians in specialist centres. It is important to ensure that women of childbearing age have contraceptive advice that takes their liver disease into consideration, and to give them informed pre-pregnancy counselling. Once women with liver disease become pregnant, it is essential that they have rapid referral to specialist physicians with experience of managing hepatic disorders in pregnancy. Maternal and fetal outcomes are improving due to ongoing research, improved guidelines and our better understanding of preconception risk stratification, disease mechanisms and therapeutic options.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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