

## Review article: chronic liver disease and pregnancy

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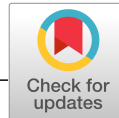
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# Review article: chronic liver disease and pregnancy

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## Summary

**Background:** The prevalence of chronic liver disease in women of child bearing age is increasing, leading to a higher incidence of pregnancy in this cohort. Chronic medical conditions have a significant adverse effect on maternal morbidity and mortality. To date, reviews on this topic have been written either from a hepatology or obstetrics viewpoint, and no specific guidelines are available solely for the management of chronic liver disease in pregnancy.

**Aims:** To produce a comprehensive review on the clinical management of women with chronic liver disease during pregnancy, addressing the risks of pregnancy to mother and child, how these risks can be ameliorated, and what additional considerations are required for management of chronic liver disease in pregnancy.

**Methods:** Data were collected up to May 2020 from the biomedical database PubMed, national and international guidelines in gastroenterology and hepatology.

**Results:** During pregnancy, women with cirrhosis are more likely to develop decompensated disease, worsening of portal hypertension, and to deliver premature infants.

**Conclusions:** The risks associated with pregnancy can be ameliorated by advanced planning, assessing risk using the model for end stage liver disease score and risk reduction through varices screening. A multidisciplinary approach is paramount in order to minimise complications and maximise the chance of a safe pregnancy and birth for mother and baby.

The Handling Editor for this article was Professor Gideon Hirschfield, and this uncommissioned review was accepted for publication after full peer-review.

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## 1 | INTRODUCTION

Pregnancy in the presence of cirrhosis, defined as permanent scarring of the liver, was considered a rare event. However, the epidemiology of chronic liver disease in the Western world is changing. Liver disease and cirrhosis in adolescence and early adulthood are increasing, particularly amongst young women, with an incidence of 46.9/100 000.<sup>1</sup> As a result, pregnancy in the presence of cirrhosis is becoming more common.<sup>2,3</sup>

In the United Kingdom, the impact of chronic medical conditions on maternal health is evaluated nationally by MBRRACE UK. All deaths that have occurred during pregnancy and up to a year post-partum are reviewed, either direct maternal deaths related to pregnancy, or indirect maternal deaths arising from pre-existing conditions or de novo disease presenting during pregnancy, but not directly attributable to it. Between 2011 and 2017, two thirds of all maternal deaths were in women with pre-existing medical conditions. There was no improvement in the indirect maternal death rate during this period.<sup>4</sup> As recommended by the national maternal mortality confidential enquiries, active involvement of physicians and obstetricians before, during and following pregnancy in women with chronic medical conditions is vital if maternal morbidity and mortality are to be improved. It must be recognised that many of these women will be unaware of the risks of pregnancy, and it is the duty of their physicians to ensure they are well informed.

For women with liver disease, the principle risks during pregnancy relate to heightened portal hypertension leading to decompensation; to the foetus, the risks are of prematurity, low birth weight and considerations of medication exposure in utero. This article will discuss these risks and focus on the management of pre-existing chronic liver disease in pregnancy, rather than pregnancy-specific liver conditions.

## 2 | CARDIOVASCULAR CHANGES IN PREGNANCY

During pregnancy the maternal cardiovascular system undergoes dramatic change, inducing a hyperdynamic circulation. Systemic vascular resistance decreases while venous return, heart rate and stroke volume increase.<sup>5</sup> As a result, cardiac output increases by up to 30%-40% in the early third trimester.<sup>6-8</sup> Activation of the renin-angiotensin-aldosterone axis leads to fluid retention; plasma volume expands by 45% in the third trimester.<sup>9</sup>

As pregnancy progresses the gravid uterus compresses the inferior vena cava, and in late pregnancy can cause complete occlusion of the abdominal vena cava in a supine position. Collateral vessels expand to facilitate venous drainage during pregnancy, including the azygos and vertebral veins, and potentially the portal venous system.<sup>10,11</sup>

While measurements of portal and hepatic vein flow in pregnancy have historically produced conflicting results, more recent data using Doppler ultrasound have shown an increase in portal vein flow by 50% in late pregnancy with a corresponding increase in total liver blood flow.<sup>12-14</sup> The clinical implications of these cardiovascular

changes for women with pre-existing liver disease will be discussed below (Figure 1).

## 3 | BIOCHEMICAL CHANGES IN PREGNANCY

Increased plasma volume creates a relative normocytic anaemia due to haemodilution.<sup>15</sup> The platelet count also falls to the lower end of normal. Ten percent of women may develop a benign gestational thrombocytopenia in the second or third trimester, with platelet counts between 100 and  $150 \times 10^9$  cells/L. Lower or rapidly falling platelet counts should prompt further investigation.<sup>16</sup> Pregnancy is a hypercoagulable state, but INR and PT are not affected.<sup>15</sup>

While the reference ranges for most serum liver parameters remain similar in pregnancy, alkaline phosphatase and alpha-fetoprotein (AFP) are both higher, due to secretion from the placenta and foetal skeleton, and foetal liver, respectively. AFP increases with gestation and is affected by numerous factors including maternal weight, smoking and ethnicity, hence interpretation during pregnancy is difficult.<sup>17</sup> A high result should be repeated in 1-2 weeks, and if rising greatly, further investigation may be warranted. Biochemical changes during pregnancy are summarised in Table 1.<sup>18,19</sup>

## 4 | FERTILITY IN CHRONIC LIVER DISEASE

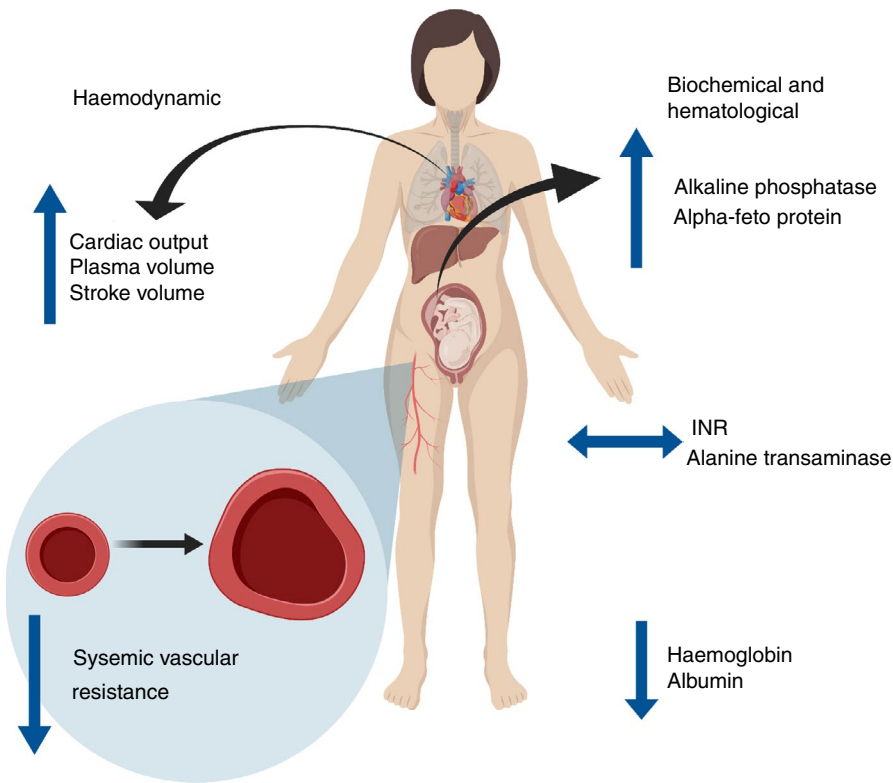
To some degree fertility rates are affected by the aetiology of liver disease and the presence or absence of cirrhosis. Women with autoimmune disease such as primary sclerosing cholangitis have conception rates equal with the general population.<sup>20</sup> However, fertility in women with established cirrhosis of any aetiology has historically been low due to a combination of hypothalamic-pituitary dysfunction and low BMI resulting in amenorrhoea, reduced libido associated with chronic disease and, perhaps, reluctance from the medical profession to expose them to the risks associated with pregnancy.<sup>21</sup> As the prevalence of cirrhosis in women of child bearing age increases, so too does the incidence of pregnancy in this cohort. Delivery rates in women with cirrhosis nearly doubled over a 20-year period, and therefore it should not be assumed that these patients cannot conceive.<sup>3</sup>

As with many chronic conditions, the chances of a successful pregnancy are highest if the liver disease is well controlled, and maternal risk factors minimised, before conception. It is also important that women feel supported in their pregnancy decisions and fully informed of the risks and help available before embarking on pregnancy.

## 5 | PRECONCEPTION COUNSELLING

All women with chronic liver disease should be asked about their family plans. Those who wish to avoid pregnancy should be counselled regarding contraception. Long acting methods of contraception such

## Normal physiological changes in pregnancy



**FIGURE 1** Normal physiological changes in pregnancy. Created with BioRender.com

Serum marker	Change in pregnancy	Non-pregnant range	Normal range in pregnancy
ALT (IU/L)	↔	0-25	6-32
AST (IU/L)	↔	0-40	10-30
GGT (IU/L)	↔	7-33	3-43
Alk Phos (IU/L)	↑	30-150	32-100 (1st trimester) 43-135 (2nd trimester) 133-418 (3rd trimester)
Albumin (g/L)	↓	35-46	28-37
Platelet ( $10^9/L$ )	↔	150-400	150-400
INR PT (s)	↔	0.8-1.2 10-14	0.8-1.2 10-14

**TABLE 1** Physiological differences in serum biochemistry during pregnancy. Note that reference ranges will vary locally.<sup>18,19</sup>

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; alk phos, alkaline phosphatase; INR, international normalised ratio; and PT, prothrombin time.

as intra-uterine devices are recommended due to their lower failure rate, but barrier methods, copper devices and progestin or combined hormone contraceptives may all be offered to women with chronic liver disease and compensated cirrhosis. The combined oral contraceptive pill is contraindicated in decompensated cirrhosis.<sup>22</sup>

For those wishing to explore the option of pregnancy, counseling should be delivered by a team with experience in managing liver disease in pregnancy. Ideally this would include a gastroenterologist

or hepatologist, obstetrician, dietician, specialist nurse and midwife, with communication to the primary care physician.

Assessment by a dietician and optimisation of the woman's nutritional status is an important facet of multidisciplinary team management. Women should be advised to take 400  $\mu\text{m}$  of folic acid daily prior to conception and throughout the first trimester to prevent neural tube defects. Higher doses of 5mg daily are recommended for women with a BMI >30.<sup>23,24</sup>

Prior to conception, women with cirrhosis should be up to date with endoscopic variceal surveillance, according to Baveno criteria.<sup>25</sup> Varices should be treated with beta blockers or band ligation. While beta blockers do confer a risk of intra-uterine growth restriction (IUGR), foetal and neonatal bradycardia and neonatal hypoglycaemia, benefits are deemed to outweigh these risks.<sup>26</sup> The Food and Drug Administration (FDA) and American Society of Gastroenterology both advocate the use of propranolol during pregnancy for primary prophylaxis against variceal haemorrhage.<sup>27</sup> Risks associated with beta blockers are a class effect, therefore carvedilol and nadolol may also be used.

Due to the cardiovascular changes in pregnancy discussed above, all women with portal hypertension should have a further screening endoscopy in the second trimester.<sup>27</sup> Endoscopists should be mindful of the increased risk of aspiration of gastric contents in the pregnant patient. Potential risks to the foetus can arise from medication use and maternal hypotension; therefore, normal blood pressure should be maintained during the procedure.<sup>28</sup> Low dose midazolam may be administered, with judicious use in late pregnancy as high dose benzodiazepines can cause respiratory depression in the neonate.<sup>29</sup> Gastroscopy should be performed in the left lateral position to minimise compression of the inferior vena cava by the gravid uterus and so reduce the risk of maternal hypotension, decreased uterine flow and foetal hypoxia.<sup>27</sup> Endoscopy in pregnancy has been associated with prematurity and low birth weight infants, but not with congenital malformation or stillbirth.<sup>30</sup> Overall, the risks are outweighed by the significant benefit of screening and treating varices, and endoscopy performed by an experienced clinician is usually safe in pregnancy (Table 2).

## 6 | MATERNAL RISKS

The principle risks to the mother arise from decompensation of liver disease during pregnancy, which may affect 10%-16% of women.<sup>31,32</sup> Evaluating this risk been reported using Model for End stage Liver Disease (MELD). This score incorporates serum creatinine, bilirubin and INR, and was first used to predict the mortality risk for patients with cirrhosis undergoing a procedure.<sup>33</sup> United Kingdom Model for End stage Liver Disease (UKELD) is a similar score that also includes serum sodium.<sup>34</sup> Westbrook et al describe the use of MELD in pregnancy. Women with a MELD  $\leq 6$  did not suffer any complications.

**TABLE 2** Summary of key points to address during pre-pregnancy counselling

### Pre-pregnancy counselling

- Women with chronic liver disease can have a successful pregnancy
- Chances of conception are greatest when the chronic disease is well controlled
- MDT should include a gastroenterologist/hepatologist, obstetrician, specialist nurse, midwife, dietician and primary care physician
- Screen for and treat oesophageal varices prior to conception
- Beta blockers are recommended for primary prophylaxis against variceal haemorrhage

Those who decompensated during pregnancy all had a MELD score  $\geq 10$ . It is this score of severity, rather than the aetiology of liver disease, that correlates most closely with pregnancy outcome.<sup>31</sup>

Maternal mortality in cirrhosis is between 0% and 4%.<sup>3,31,32,35</sup> While this has improved over recent decades, it remains significantly above the national maternal mortality rate (0.01%).<sup>4</sup> Increased rates of placental abruption and post-partum haemorrhage have also been reported.<sup>3,36</sup> The risks are summarised in Figure 2.

## 7 | FOETAL RISKS

Infants born to women with chronic liver disease are more likely to be premature and to have low birth weight. Prematurity may be seen in up to two thirds of cases, although the majority of these infants are born from 30 weeks onwards. Delivery at <30 weeks may occur in one in five pregnancies. Prematurity is associated with higher UKELD and MELD scores at conception, but not with the aetiology of liver disease.<sup>31</sup>

Rates of spontaneous abortion, defined as pregnancy loss before 24 weeks gestation, are similar to the general population.<sup>31,37</sup> There is no significant increased risk of stillbirth, miscarriage or congenital malformation.<sup>2,35,38</sup>

## 8 | MODE OF DELIVERY

Around the time of delivery, the risk of variceal haemorrhage increases, either due to Valsalva manoeuvres during vaginal birth or inadvertent trauma to intra-abdominal varices during caesarean section.<sup>27,39</sup> There are no studies directly comparing the two modes of birth in women with chronic liver disease. Rates of caesarean section are higher compared to the general population, but this may be due to clinician bias.<sup>3</sup> In order to reduce the risk of variceal haemorrhage, a screening upper GI endoscopy should be performed in the second trimester (see above), and antenatal imaging of the pelvis with MRI may help to identify pelvic varices and inform a delivery plan for obstetricians. In women whose varices have been treated and eradicated, no additional considerations for birth are necessary. If there are small varices present, vaginal birth is permissible but a short second stage of labour is advised. In the case of significant varices, elective caesarean section may be considered, but evidence guiding decisions on delivery for such women is scarce, and will therefore require a case by case approach.

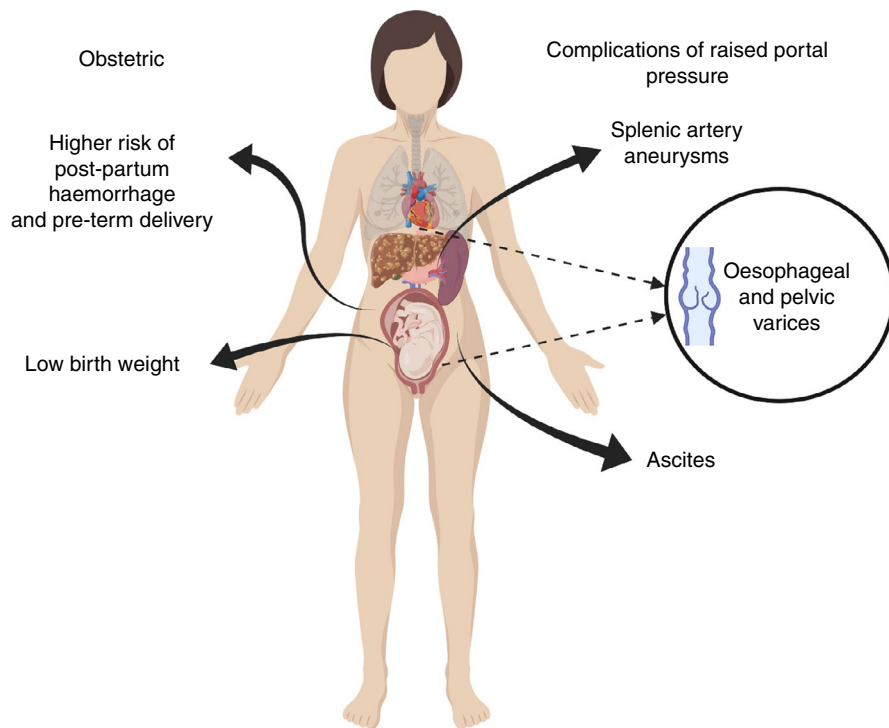
## 9 | MANAGEMENT OF DECOMPENSATED CIRRHOSIS DURING PREGNANCY

### 9.1 | Varices

By 34 weeks gestation, the maternal circulating volume has expanded by up to 50%.<sup>15</sup> The associated increase in portal venous flow and pressure augments the risk of variceal haemorrhage, making it the

## Pathological changes in pregnancy and chronic liver disease

**FIGURE 2** Pathological changes in pregnancy and chronic liver disease. Created with BioRender.com



most frequent and significant mode of hepatic decompensation during pregnancy. The incidence of variceal bleed has been described to differing degrees. Recent case series report an incidence of 5% for all patients with cirrhosis, with a maternal mortality rate of 0%–18%.<sup>3,31,40</sup> Infants are more likely to have low birth weight if exposed to poorly controlled variceal haemorrhage while in utero.<sup>41</sup>

The risk of variceal haemorrhage is highest in the second trimester and labour.<sup>27</sup> In the case of an acute bleed, immediate resuscitation with fluids and blood products and the use of antibiotics all remain appropriate in pregnancy. Terlipressin and octreotide can cause uterine vasoconstriction and ischaemia, but these risks must be weighed against the mortality benefit to the mother, and therefore may be required for life threatening haemorrhage.<sup>42,43</sup>

Upper GI endoscopy should be performed in the left lateral position, as discussed above. Successful placement of a TIPSS in pregnant women has been reported in cases where endoscopic therapy has failed.<sup>44</sup> This involves placing a stent through the liver, between the portal vein and inferior vena cava, under fluoroscopic guidance. Radiation exposure to the foetus can increase the risk of childhood leukaemia and congenital malformation.<sup>45</sup> Radiation sparing manoeuvres have been described during TIPSS that limited the estimated foetal radiation exposure to 5.49mSv, only slightly above annual background radiation of 3–4mSv.<sup>46</sup>

## 9.2 | Splenic artery aneurysm

While rare in the general population, aneurysms of the splenic artery are strongly associated with pregnancy.<sup>47</sup> Increased splanchnic flow

develops due to a hyperdynamic circulation and proximal shunting from the pressure of the gravid uterus.<sup>48</sup> These effects are compounded in women with portal hypertension, and therefore the risk of developing splenic artery aneurysm (SAA) in pregnancy is even greater, although the incidence for this specific cohort is not known.<sup>49,50</sup>

Ruptured SAA's usually present in the second or third trimester with acute abdominal pain and profound hypovolaemic shock. Mortality has historically been as high as 70%, although more recently a rate of 21% has been reported.<sup>48,50</sup> Management is with splenic artery ligation or splenectomy by emergency laparotomy. Rupture during labour is uncommon.<sup>47,48</sup>

Management of non-ruptured SAA is not well defined. Elective treatment has been recommended for aneurysms >2 cm. However, aneurysms as small as 0.5 cm have been shown to rupture during pregnancy, prompting some clinicians to advocate proactive management of SAA of any size in a pregnant patient.<sup>47,48,51</sup> As such, women with cirrhosis should be screened for SAA with ultrasound scan. Management may include aneurysm ligation or splenectomy for distal SAA's. More recently, successful decompression of the portal system with TIPSS followed by embolisation of the splenic artery has been reported.<sup>49</sup>

## 9.3 | Ascites and spontaneous bacterial peritonitis

Ascites during pregnancy affects around 10% of women with cirrhosis.<sup>3,39</sup> Diuretics such as furosemide and bumetanide can be used to control ascites.<sup>29</sup> Spironolactone has been shown to cause

feminisation of the male foetus in animal models, but is permissible for use during pregnancy if the benefit is deemed sufficient.

Pregnancy is a relative contraindication to therapeutic paracentesis, but may be necessary for refractory ascites.<sup>51</sup> TIPSS is not routinely recommended during pregnancy, although there are isolated case reports of successful placement.<sup>44</sup>

Spontaneous bacterial peritonitis should be managed according to international guidelines with human albumin solution on Day 1 and Day 3, along with third generation cephalosporins.<sup>52</sup> Quinolones should be avoided in pregnancy.<sup>29</sup>

## 9.4 | Hepatic encephalopathy

Hepatic encephalopathy in pregnancy is rare, affecting 1%.<sup>3</sup> Precipitating factors should be sought, including infection, electrolyte disturbance, medications and GI haemorrhage. Lactulose is not known to be harmful. Rifaximin has been shown to cause birth defects in animal models; the effect on the human foetus is not yet clear, and therefore it should be avoided in pregnancy.<sup>52</sup>

## 9.5 | Porto-pulmonary hypertension

This rare condition has not been reported in pregnancy. Pulmonary hypertension is considered a contraindication to pregnancy due to the risk of right ventricular failure and an unacceptably high maternal mortality rate. For the small cohort who become pregnant despite medical advice, management by a specialist team and planned elective delivery are crucial. Where pulmonary hypertension is well controlled, maternal mortality has improved, yet at 12-33% it remains far above the national average (Table 3).<sup>53-55</sup>

# 10 | SPECIFIC CONDITIONS

## 10.1 | Hepatitis B

All pregnant women with chronic hepatitis B and advanced fibrosis or cirrhosis should be treated with tenofovir disoproxil (TDF). Women already established on a different antiviral should be switched to tenofovir at the earliest opportunity.<sup>56</sup> All women should have LFT's monitored during pregnancy. A monitoring interval of 6 weeks in the first and second trimester, and every 4 weeks in the final trimester has been suggested.<sup>57</sup>

The mode of delivery and its potential role in vertical transmission has been studied, but at present there is insufficient data to recommend caesarean over vaginal birth, and therefore both modes of delivery may be offered.<sup>58</sup> Infants born to HBsAg positive mothers should receive hepatitis B immunoglobulin (HBIG) and vaccination within 12 hours of delivery, followed by two further vaccines at 1 and 12 months. This is in addition to the routine vaccination programme for all infants, which includes hepatitis B vaccines at 8, 12

**TABLE 3** Summary of emergency management of decompensated chronic liver disease in pregnancy. SBP (spontaneous bacterial peritonitis)

Management of decompensated chronic liver disease in pregnancy	<p>Variceal haemorrhage: Resuscitate, endoscope in left lateral position, avoid terlipressin unless life threatening haemorrhage</p> <p>Ascites: Spironolactone or furosemide if required, paracentesis if necessary</p> <p>SBP: Give human albumin solution and antibiotics, avoid quinolones</p> <p>Hepatic Encephalopathy: Investigate for precipitant. Use lactulose, avoid rifaximin</p> <p>Ruptured Splenic Artery Aneurysm: Resuscitate, emergency laparotomy</p>
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and 16 weeks. The combination of HBIG and vaccination reduces vertical transmission from over 90% to less than 10%.<sup>59</sup>

Women with high HBsAg levels ( $>4 \log_{10}$  IU/ml) or Hep B DNA  $>200\,000$  IU/L are at high risk of transmission despite the use of HBIG and vaccination, and should therefore receive prophylactic tenofovir from the start of the third trimester to delivery. TDF may be continued up to 12 weeks post-partum at the discretion of the clinician, and agreed with the patient. Breastfeeding is safe, including women taking tenofovir.<sup>57</sup>

Hepatitis B may flare post-partum, therefore, continued monitoring of ALT and Hepatitis B DNA levels is necessary.<sup>60</sup> Flares may relate to post-partum immunological changes in the mother, and can lead to HepBeAg seroconversion.<sup>61</sup> ALT should be monitored monthly for 3 months post-partum, then at 6 and 12 months.<sup>58,62</sup>

## 10.2 | Hepatitis C

As hepatocellular damage and fibrosis in hepatitis C are largely immune mediated, the relative immune paresis of pregnancy generally results in lower ALT and higher hepatitis C RNA in the second and third trimesters. Fibrosis is not advanced by pregnancy.<sup>63</sup> The principle concern pertains to vertical transmission of the virus, which for untreated women is around 6%.<sup>64</sup> HIV co-infection has been shown to increase this risk, although it is lower for women established on treatment with low or undetectable HIV viral load.<sup>65,66</sup> At present, treatment is not recommended during pregnancy due to insufficient data on the safety profile of direct acting antivirals on foetal development, although a couple of case series have reported treatment success with sofosbuvir  $\pm$  ledipasvir without adverse outcome.<sup>67</sup> Ribavirin is teratogenic and should be stopped at least 6 months prior to conception.<sup>68</sup>

Currently, the only strategies to reduce vertical transmission are to treat HIV and avoid invasive procedures during labour, such as foetal scalp monitoring or the use of forceps. It is, therefore, preferential for women complete antiviral treatment prior to conception.<sup>68</sup> All women should be offered HIV testing as part of their



booking bloods. Hepatitis C screening in pregnancy is conducted in the United States, but not offered routinely in the United Kingdom.

If antiviral treatment is being considered after delivery, hepatitis C RNA should be tested again as spontaneous clearance of hepatitis C can occur post-partum.<sup>68</sup> Women with hepatitis C can breastfeed, as long as nipples are not cracked or bleeding.<sup>69</sup> Maternal antibodies can be transferred in utero so infant testing for hepatitis C should be delayed until 12 months of age.<sup>66,70</sup>

### 10.3 | Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease places women at greater risk of developing gestational diabetes, independent of body mass index (BMI), although screening is currently reserved for women with BMI >30 or other risk factors, not non-alcoholic fatty liver disease (NAFLD).<sup>71-75</sup> Increased rates of pre-eclampsia are also associated with NAFLD.<sup>72</sup>

The risk of complications for women with NAFLD will be influenced by the presence of co-morbidities associated with the metabolic phenotype. Obesity, hypertension and diabetes can each exert independent, adverse effects on pregnancy. Management of NAFLD in pregnancy may, therefore, require input from multiple medical specialties.

### 10.4 | Autoimmune hepatitis

Disease activity of autoimmune hepatitis (AIH) may increase during pregnancy, but for many women it will initially reduce and then flare post-partum.<sup>76</sup> Immunosuppression in the form of prednisolone or azathioprine is safe in pregnancy and breastfeeding, and should be continued in order to maintain maternal, and therefore foetal, health. Mycophenolate is associated with congenital abnormalities and spontaneous abortion, and therefore alternative treatment should be used for women considering pregnancy. The MHRA advise a minimum washout period of 6 weeks between stopping treatment and conception.<sup>77</sup> However, experienced hepatologists recommend discontinuing mycophenolate for 6 months, allowing time for introduction of alternative immunosuppression and disease stabilisation prior to pregnancy.<sup>42</sup> Women are more likely to have a healthy pregnancy and successful delivery if AIH has been well controlled for a year prior to conceiving.

Monitoring LFTs on a monthly basis is advised post-partum. Flares usually respond to increased immunosuppression. Women who reduce immunosuppression during pregnancy are more likely to flare after delivery, highlighting the importance of pre-pregnancy counselling and reassurance regarding the safety profile of specific medication during pregnancy.<sup>78</sup>

### 10.5 | Primary biliary cholangitis and primary sclerosing cholangitis

Pregnant women with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) can expect to have similar outcomes to

the general population.<sup>20,79</sup> However, pruritis may be exacerbated due to worsening cholestasis. Symptom management may include ursodeoxycholic acid and second line therapy with cholestyramine, both of which are safe to use in pregnancy. Rifampicin may also be used, but it inhibits vitamin K production.<sup>80</sup> Neonates born to women taking rifampicin are, therefore, at greater risk of vitamin K deficiency and bleeding, and so internationally recommended vitamin K supplementation within 6 hours of delivery becomes particularly pertinent for these infants.<sup>81</sup>

### 10.6 | Wilson's disease

Prior to conception, women with Wilson's may wish to discuss the risks of disease transmission. Wilson's is autosomal recessive, with a 0.5% risk of homozygosity in infants born to affected mothers. Genetic testing of the partner prior to conception will help clinicians inform families of the likelihood of having a child affected by Wilson's.<sup>82</sup>

Women established on chelation therapy have significantly lower rates of spontaneous abortion than treatment naïve patients.<sup>83</sup> Interruptions to treatment during pregnancy can lead to fulminant liver failure; therefore, consistent therapy throughout pregnancy is advised.<sup>84</sup> Dose reduction of chelating agents by 25%-50% is recommended, particularly during the third trimester, in order to promote wound healing in the case of caesarean delivery. No dose adjustment is required to zinc sulphate. Women taking penicillamine should avoid breastfeeding.<sup>82,85</sup>

### 10.7 | Non-cirrhotic portal hypertension

Women with non-cirrhotic portal hypertension (NCPH) have normal fertility, but are at risk of similar complications from portal hypertension as those with cirrhosis. Variceal haemorrhage affects 8%-34% of pregnancies, and is more likely if women are diagnosed with de novo disease during pregnancy. Worsening ascites may be seen in 0%-2%.<sup>86-88</sup> Women are at risk of developing portal vein thrombosis. It may be appropriate to discuss the pros and cons of venous thromboembolism prophylaxis in women who are not already anticoagulated, particularly for 6 weeks post-partum, in order to reduce the risk of developing a portal vein thrombosis during this procoagulant period.<sup>87</sup>

Neonatal outcomes are generally good, although some studies report an association between NCPH and pre-term delivery (0%-50%) and low birth weight infants.<sup>87,89</sup>

### 10.8 | Hepatocellular carcinoma

As hepatocellular carcinoma (HCC) incidence peaks in the 8th decade and is more common in men, it is extremely rare in pregnancy.<sup>90</sup> Incidence is associated with higher parity.<sup>91</sup> Although



oestrogens and pregnancy can accelerate the growth of hepatic adenomas, their effect on HCC is not clearly defined.<sup>92-94</sup> Women may be asymptomatic or present with a palpable mass, or acute abdominal pain in the case of tumour rupture.<sup>95</sup> Synthetic function is usually preserved and liver disease remains compensated.<sup>96</sup> HCC may be diagnosed by ultrasound and further characterised with non-contrast MRI. Alpha-fetoprotein is difficult to interpret in pregnancy as it is also produced by the foetal gut and liver, affected by maternal characteristics, and is not secreted by all hepatocellular tumours.<sup>97</sup>

Management during pregnancy may include hepatectomy.<sup>98,99</sup> Earlier diagnosis and active treatment have translated to modest improvements in survival for this small cohort.<sup>96</sup>

## 11 | CONCLUSIONS

The rising prevalence of cirrhosis in young women has led to increased incidence of chronic liver disease in pregnancy. These women are at a higher risk of decompensated disease, variceal bleed and premature delivery, resulting in higher rates of low birth weight infants. The UK Obstetric Surveillance System (UKOSS) has conducted a national survey to better establish the incidence and outcomes of pregnancy in cirrhosis, the results of which are awaited with interest by the authors. Currently, assessment of risk using the MELD score, screening for oesophageal and pelvic varices and splenic artery aneurysm may ameliorate the complication rate. Women with chronic liver disease have improved outcomes if their disease is well controlled prior to conceiving, and monitored during pregnancy. Multidisciplinary management is essential in order to continue to improve maternal morbidity and mortality for women with chronic liver disease.

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