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SPECIAL ARTICLE

Obstetrics

FIGO guideline on liver disease and pregnancy

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Abstract

The number of women entering pregnancy with chronic liver disease is rising. Gestational liver disorders affect 3% of the pregnant population. Both can be associated with significant maternal and fetal morbidity and mortality. European guidance has recently been published to inform management. This FIGO (the International Federation of Gynecology & Obstetrics) guideline aims to use the latest evidence to inform practice relevant to a global population. The immediate past and present chairs of FIGO's Committee on the Impact of Pregnancy on Long-term Health invited the Chair of the European guideline, alongside two trainees with an interest in liver disorders in pregnancy, to develop a guideline relevant to a global audience, thus serving the real-world population and fulfilling FIGO's ambition to enhance their global voice for women's health. Experts in the field with experience in managing liver disorders in pregnancy from a diverse selection of continents helped to develop a guideline. The guideline includes the most common pre-existing and gestational liver disorders. Evidence-based best practice recommendations are summarized in addition to pragmatic recommendations. Printable tables/figures are included in the guideline for ease of use. These include a table of normal ranges of commonly used blood tests, a table outlining safety of investigations, and a table of delivery considerations relevant to a global audience. Figures designed to summarize each section of the guideline and the multidisciplinary approach to managing liver disorders in pregnancy are also included.

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For affiliations refer to page 42.

[Correction added on 1 May 2025, after first online publication: The measurement unit mmol/L has been corrected to µmol/L for relevant biochemical measurements and a small number of typographical errors were corrected in this version].

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This guideline incorporates guidance for a global audience aimed at improving the management of women with pre-existing and new liver disease in pregnancy.

KEYWORDS
guideline, liver disease, pregnancy

1 | INTRODUCTION AND APPROACH TO EVALUATION OF HEPATIC IMPAIRMENT IN PREGNANCY

Liver diseases in pregnancy can be divided into two main categories: gestational liver disorders and acute and chronic liver disorders occurring co-incidentally in pregnancy. Both are associated with increased rates of maternal and fetal morbidity and mortality.

Gestational liver disorders affect 3% of the pregnant population.[1] The most common are listed below:

- Pre-eclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome (71%)
- Intrahepatic cholestasis of pregnancy (ICP) (17%)
- Acute fatty liver disease of pregnancy (AFLP) (4%).

The proportion of women of childbearing age that have pre-existing liver diseases is rising.[2] These diseases include: viral hepatitis, cirrhosis and portal hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune hepatitis, post liver transplant, cholestatic liver diseases, drug-induced liver disease, alcohol-related liver disease, vascular liver disease, hepatic tumors, and Wilson's disease.

The prevalence of these conditions in the pregnant population differs across the world. The proportion of women with gestational disorders in a UK population is shown in parentheses in the list above; for most other populations it is not known. Pre-pregnancy counseling, disease quiescence, and appropriate management including medical therapy, during and after pregnancy, are key to optimizing maternal and infant outcomes.

The purpose of this guideline is to provide guidance on the management of common liver disorders in pregnancy. It is beyond the scope of this guideline to give detailed advice on rarer conditions, but this can be found in the European Association for the Study of the Liver Clinical Practice Guideline (EASL CPG), in addition to other local and national guidelines. Furthermore, details regarding the management of pre-eclampsia with hepatic impairment or HELLP syndrome can be found in the FIGO (the International Federation of Gynecology & Obstetrics) guideline for pre-eclampsia and HELLP syndrome.

When assessing a pregnant woman with new or deteriorating hepatic disease, several key factors should be considered:

- Normal physiologic and hormonal changes of pregnancy that influence symptoms and physical findings (Table 1)
- Alterations to laboratory normal ranges and safety of common investigations (Table 2).

Reticence to perform appropriate investigations and screening in pregnant women and anxiety about prescribing are well-recognized risk factors for delayed diagnosis and management, which can lead to adverse outcomes. Pregnant women should have the same access to medical investigations and treatment as non-pregnant individuals.[3] Most diagnostic investigations can be performed in pregnancy (Table 2) and the majority of drugs required to appropriately treat liver disease can be used, with only a few exceptions. Appendix A summarizes the safety of commonly prescribed drugs for the management of liver disease in pregnancy, including the compatibility of each drug in the peri-conception period, during each trimester, when breastfeeding, and with paternal exposure.[4] Most Advice from the hospital pharmacy can support patient counseling.

To enable best practice, patients with both pre-existing and gestational liver disorders will often benefit from the involvement of relevant members of the multidisciplinary team (Figure 1).

2 | GESTATIONAL LIVER DISEASES

2.1 | Intrahepatic cholestasis of pregnancy (Figure 2)

Diagnosis

Intrahepatic cholestasis of pregnancy is diagnosed in women with (1) pruritus in pregnancy, (2) elevated serum bile acids

TABLE 1 Normal physiologic and hormonal changes of pregnancy that influence symptoms and physical findings.

Physical findings that can be present both in pregnancy and liver disease	Physical findings unique to liver disease
Hyperdynamic circulation • Bounding pulse • Flow murmur • Gallop rhythm • Sinus tachycardia (up to 110 bpm)	Jaundice
Palmar erythema	Asterixis
Spider nevi	Ascites
	Hepatomegaly

TABLE 2 Alterations to laboratory normal ranges and safety of common investigations.

		Pregnant		
	Non-pregnant	First trimester	Second trimester	Third trimester
Blood tests				
Full blood count				
Hb, g/L	120–150	110–140	105–140	
WCC $\times 10^9$/L	4–11	6–16		
Platelets $\times 10^9$/L	150–400	150–400		
MCV, fL	80–100	80–100		
Lymphocytes $\times 10^9$/L	0.7–4.6	1.1–3.6	0.9–3.9	1–3.6
Urea and electrolytes				
Urea, mmol/L	2.5–7.5	2.8–4.2	2.5–4.1	2.4–3.8
Creatinine, µmol/L	65–101	52–76	44–72	55–77
Potassium, mmol/L	3.5–5.0	3.3–4.1		
Sodium, mmol/L	135–145	130–140		
Liver tests				
Bilirubin, µmol/L	0–17	4–16	3–13	3–14
Albumin, g/L	35–46	28–37		
AST, IU/L	7–40	10–28	11–29	11–30
ALT, IU/L	0–40	6–32		
GGT, IU/L	11–50	5–37	5–43	3–41
ALP, IU/L	30–130	32–100	43–135	133–418
Bile acids, µmol/L	0–6 (fasting) 0–10 (non-fasting)	0–19 (non-fasting)*		
Inflammatory markers				
CRP (mg/L)	<10	Unchanged throughout pregnancy		
Procalcitonin (ng/L)	<0.05	Unchanged throughout pregnancy		
ESR (mm/h)	0–20	18–48	30–70	
Other				
Arterial blood gas	Expect a mild compensated respiratory alkalosis in pregnancy			
Radiologic investigations				
Ultrasound	Safe at any gestation in pregnancy			
Liver elastography	Safe at any gestation in pregnancy It should be noted that there may be a small increase in liver stiffness and controlled attenuation parameter in the third trimester, which reflects the physiology of normal pregnancy[90]			
Magnetic resonance cholangiopancreaticography	Safe at any gestation in pregnancy			
Endoscopic retrograde cholangiopancreaticography	Fetal radiation estimated between <0.1 and 0.5 mGy[91] (threshold for malformation is 50 mGy) Can be performed in pregnancy, ideally in the second/third trimester			
Other				
Esophago-gastro duodenoscopy	Safe in pregnancy, ideally performed in second trimester in left lateral position Midazolam may be used judiciously			
Liver biopsy	Can be performed where clinical need/diagnostic uncertainty dictates, and delay in diagnosis would be more hazardous for the pregnant woman Ensure coagulopathy corrected before biopsy			

Note: This table has been adapted from the EASL Liver Disease and Pregnancy Clinical Practice Guideline.[4]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyl transferase; Hb, hemoglobin; MCV, mean cell volume; WCC, white blood cell count.

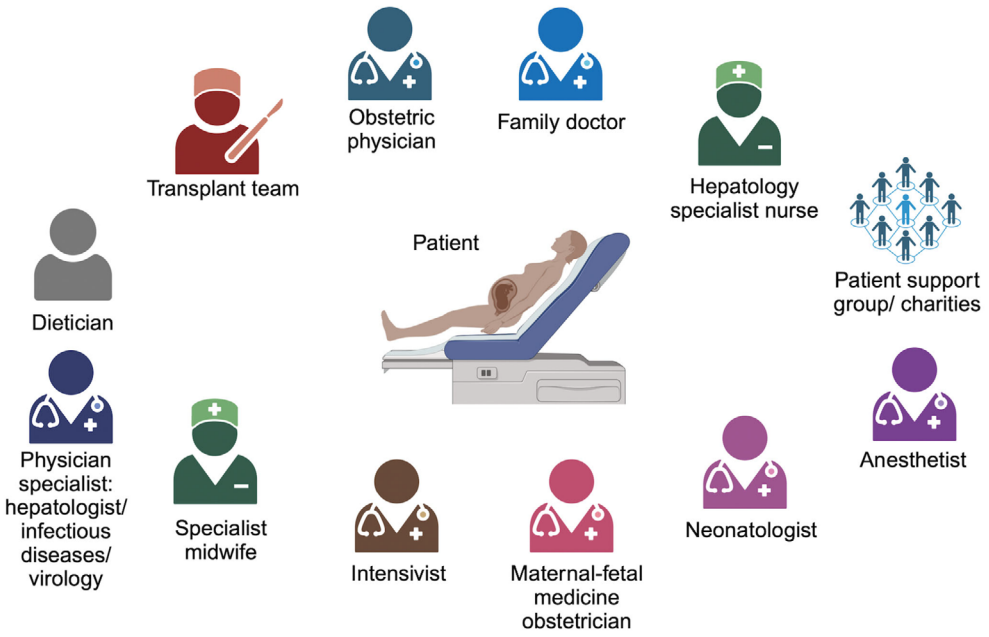

FIGURE 1 Recommended multidisciplinary team.

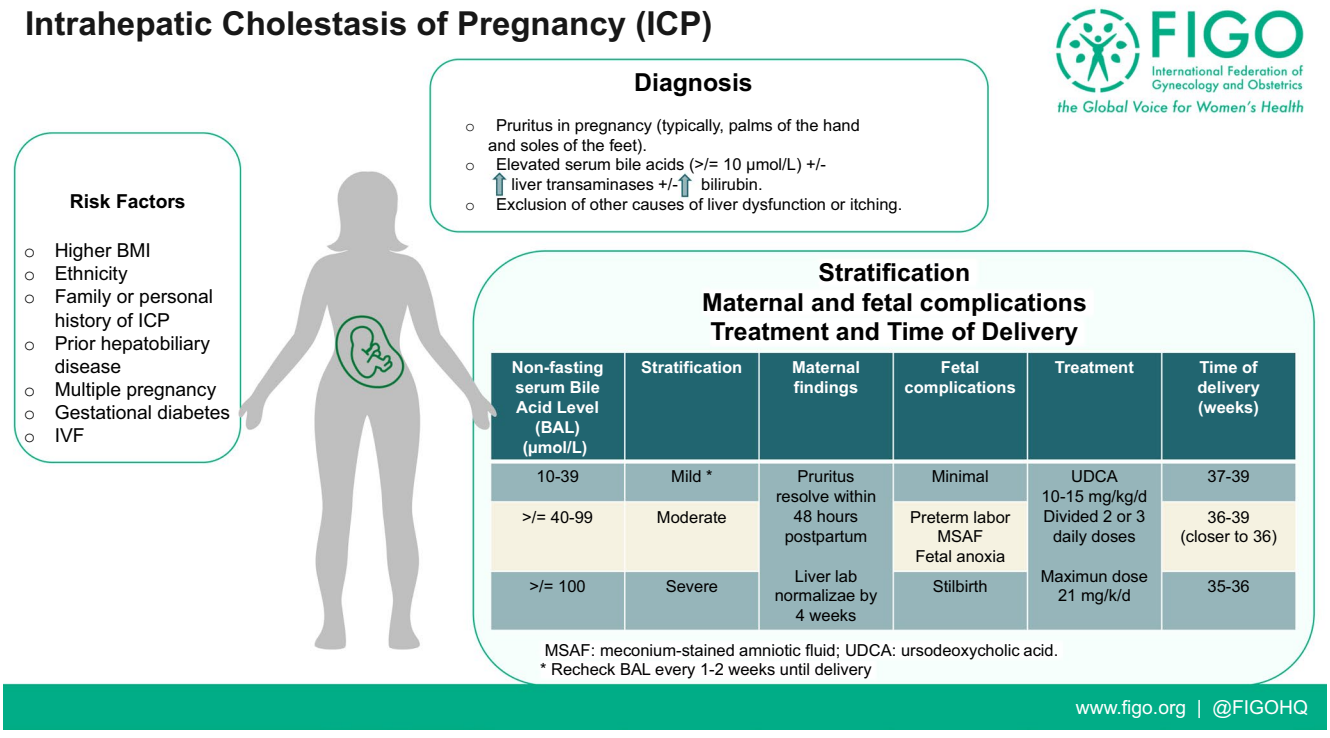

FIGURE 2 Summary of management of intrahepatic cholestasis of pregnancy.

(hypercholanemia), often associated with raised liver transaminases, and (3) exclusion of other causes of liver dysfunction or itching.[4] ICP is confirmed retrospectively when serum liver tests and pruritus completely normalize within 3 months after delivery.[4] Elevated concentrations of reproductive hormones during pregnancy are likely to unmask symptoms and biochemical features of ICP in genetically susceptible individuals, and also to produce gestational cholestasis in those with previously asymptomatic underlying liver diseases, e.g. primary biliary cholangitis, primary sclerosing cholangitis, or chronic hepatitis C.[4]

ICP affects approximately 0.7% of women of European ancestry, twice as many of Asian origin and in the Scandinavian countries, and up to six times as many from the Andean nations in Latin America.[5] Heterozygous pathogenic mutations in the biliary transporter genes

ABCB4, *ABCB11*, and *ATP8B1*, and a smaller proportion in other genes involved in bile secretion, have been identified in about 25% of women with ICP.[6,7]

Most women with ICP present with pruritus in the third trimester, but symptoms may start in the first trimester. Itching is commonly localized to the palms of the hands and soles of the feet but may affect other parts of the body. Variable degrees of elevated serum transaminase activities in addition to increased serum bile acid concentrations (≥19 μmol/L in the non-fasted state) are seen in ICP.[8] Mild hyperbilirubinemia is occasionally observed.[9,10]

ICP can be complicated by adverse pregnancy outcomes, including stillbirth, preterm birth, meconium-stained amniotic fluid, and prolonged admission to the neonatal intensive care unit. An individual participant data (IPD) meta-analysis ($n = 5269$ cases) of gestational cholestasis built on various studies showed that non-fasting serum bile acid concentrations are the most valuable serum biomarker to predict pregnancies at risk of ICP-associated stillbirth and preterm birth.[11] The stillbirth risk is markedly raised if serum bile acid concentrations are >100 μmol/L at any time in the pregnancy, and the stillbirth risk increases markedly from 35 to 36 weeks of gestation.[11] As a result, consideration of delivery at this stage of pregnancy is a reasonable option with the aim of avoiding stillbirth in this high-risk subgroup of women with ICP.[4] In women with serum bile acids ≥40 μmol/L the risks of spontaneous preterm birth and meconium-stained amniotic fluid are increased. An association between elevated serum transaminases or bilirubin and these adverse pregnancy outcomes has never been shown.

Management

Medical therapy aims to improve maternal pruritus and biochemical markers of liver injury, and also reduce the rate of adverse pregnancy outcomes.

Ursodeoxycholic acid (UDCA) is the most commonly used drug for ICP; it has been studied in randomized, controlled trials that compared the impact of UDCA with placebo[12,13] or other drugs (e.g. *S*-adenosyl methionine, dexamethasone or cholestyramine).[13–16] Most studies reported an improvement in pruritus, and this was confirmed in a meta-analysis.[16] An IPD meta-analysis that included data from 6974 women with ICP from 34 studies, of whom 68% were treated with UDCA, demonstrated that UDCA treatment protects against preterm birth and meconium-stained amniotic fluid; this effect was particularly marked in pregnancies where the maximal serum bile acid concentration was ≥40 μmol/L. UDCA was not shown to influence outcomes in pregnancies where maternal serum bile acid concentrations were below this threshold.[17] Using data from randomized controlled trials, the IPD meta-analysis showed that UDCA treatment protects against a composite outcome of stillbirth and preterm birth with a number-needed-to-treat of 15.[17]

Rifampicin is a potent antipruritic drug in cholestasis; it has shown beneficial effects in ICP on itch intensity and serum bile acids in retrospective analyses. Its potential benefit in women with severe ICP is being prospectively investigated in an ongoing clinical trial.[18]

Other medications evaluated for treatment of ICP include *S*-adenosyl methionine (SAMe), cholestyramine, guar gum, and dexamethasone. None of these can be recommended for treatment of ICP based on the data available.[4]

Intrahepatic cholestasis of pregnancy

Best practice guidance

1. Women with suspected intrahepatic cholestasis of pregnancy (ICP) should be tested for serum bile acid concentrations to confirm the diagnosis and identify pregnancies at risk (disease stratification) of stillbirth, spontaneous preterm birth, and other ICP-associated adverse pregnancy outcomes.
2. In women with confirmed ICP, non-fasting serum bile acids should be measured at least weekly from 32 weeks of pregnancy to identify those with concentrations ≥40 μmol/L, who are at an increased risk of adverse pregnancy outcomes.
3. Ursodeoxycholic acid (UDCA) should be considered for treatment of maternal pruritus in ICP. In women with serum bile acid concentrations ≥40 μmol/L, UDCA should be offered as a treatment to reduce the risk of spontaneous preterm birth and it may also be protective against stillbirth.
4. In women with post-prandial serum bile acid concentrations ≥100 μmol/L, the risk of stillbirth increases after 35 weeks of pregnancy, and elective early delivery should be considered between 35 and 36 weeks of pregnancy to reduce the risk of fetal death.
5. Another therapy that may improve maternal pruritus or biochemical abnormalities is rifampicin. Current evidence to support the use of cholestyramine, guar gum and activated charcoal is limited.

Pragmatic guidance

1. If serum bile acid concentrations are not available, elevation of other serum markers, including liver transaminases and bilirubin, will give an indication of disease severity, although they are not reliable guides for risk of stillbirth or preterm birth. If liver blood tests show marked abnormalities, ensure coagulation is normal and consider delivery by 37 weeks of gestation.
2. If serum bile acid concentrations are not available it is reasonable to consider treatment with UDCA as this may reduce the risk of spontaneous preterm birth and the severity of pruritus.

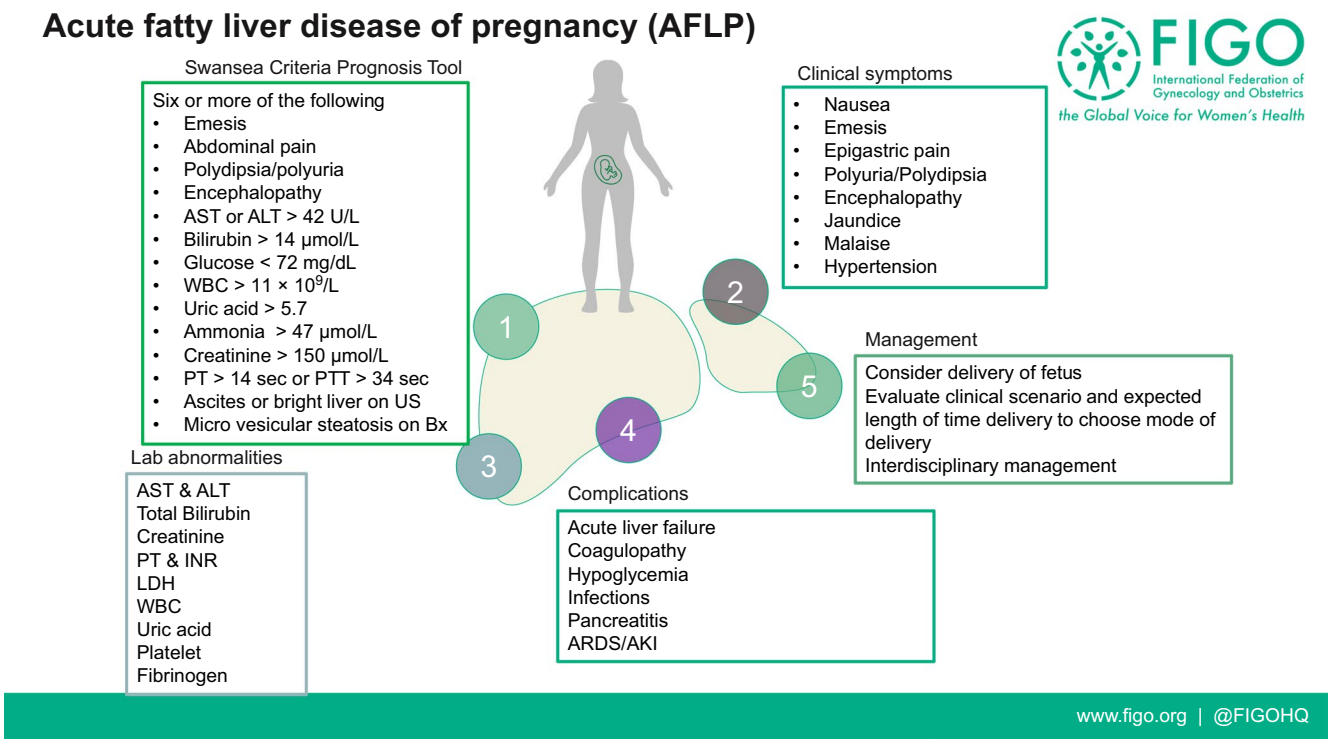

FIGURE 3 Summary of acute fatty liver of pregnancy.

2.2 | Acute fatty liver disease of pregnancy (Figure 3)

Acute fatty liver disease of pregnancy is a rare, pregnancy-specific cause of acute liver failure. It is estimated to occur in 1:10 000 pregnancies.[4,19] The condition typically presents in the third trimester as a maternal and fetal emergency requiring prompt recognition and management.

AFLP is caused by toxic infiltration of the hepatocytes by small fat droplets (also called microvesicular fat). On average, pregnant women present at 35–36 weeks of pregnancy with nonspecific symptoms including nausea, vomiting, reduced appetite, fatigue, abdominal pain, and distension.[4,19] The signs include those associated with hepatic failure (elevated liver transaminases, hyperbilirubinemia, hypoglycemia, coagulopathy, jaundice, encephalopathy, polyuria, polydipsia, acidosis and, in some cases, renal dysfunction, and pancreatitis).[4,19] AFLP may also present in the early postpartum period.

Risk factors for AFLP include low body mass index, multiple gestation, younger and older maternal age, gestational hypertension with proteinuria (pre-eclampsia), fetal growth restriction, and carrying a male fetus.[4,19] AFLP is likely to have a multifactorial etiology. In some cases the pathogenesis is thought to be related to fatty acid oxidation disorders, leading to microvesicular fat deposition in maternal hepatocytes and subsequent hepatic dysfunction.[20]

Diagnosis

AFLP is diagnosed with a combination of clinical features, laboratory testing and diagnostic imaging. Assessment should include maternal blood testing for bilirubin, uric acid, liver transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), glucose, uric acid, hemoglobin, leukocytes, platelets, ammonia, creatinine, prothrombin (PT), and partial thromboplastin times (PTT).

Maternal, fetal, and neonatal adverse outcomes associated with AFLP are listed in Table 3. The risk of maternal death is associated with higher levels of creatinine, lactate, PT, PTT, and encephalopathy.[4]

A useful tool for establishing the diagnosis is the Swansea Criteria[1] (Table 4) that has a high positive predictive value for AFLP. Liver biopsy is rarely required to aid diagnosis.[19–21]

Differential diagnoses includes HELLP syndrome, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome. Table 5 outlines key differences between these disorders.

Management

It is crucial to establish a prompt diagnosis, ensure close monitoring of both the pregnant patient and fetus, provide supportive care, and expedite delivery when necessary. The optimal mode of delivery has not been established and will vary according to the

clinical scenario and expected length of time to delivery.[20] Close collaboration with liver specialists, obstetric anesthetists, medics, and neonatologists and nursing teams is crucial for safe peripartum care. Management of peripartum hemorrhage and coagulopathy is described in the FIGO recommendations on the management of postpartum hemorrhage.[22] Liver failure is managed with supportive care and, in some cases, *N*-acetylcysteine, plasma exchange, and/or eventual liver transplantation may be necessary.[20] As most pregnant women with AFLP are admitted to intensive care (see Table 3), early consultation with the intensivist team is advised, and would necessitate referral to a tertiary-level center in most cases. Clinical features predictive of the need for admission to intensive care include elevated serum lactate (>2.8 mg/dL), a model for end-stage liver disease score ≥ 30, the presence of encephalopathy, or having >7 Swansea criteria.[1]

Reports have associated AFLP with disorders of short-, medium-, or long-chain fatty acid oxidation in the fetus; the implications for the majority of cases is yet to be determined.[23,24] Hence, neonates born to women with AFLP warrant assessment for these conditions in infancy and childhood.[20] Recurrence rates are relatively low (<10%), but future pregnancies should be treated as high risk for AFLP and pre-eclampsia.

Acute fatty liver in pregnancy

Best practice guidance

1. Biochemical/clinical markers predictive of intensive care unit admission include elevated serum lactate (>2.8 mg/dL), a model for end-stage liver disease score ≥30, or having >7 Swansea criteria.
2. Women with acute fatty liver in pregnancy (AFLP) should be managed by the multidisciplinary team and should have coagulopathy and metabolic derangement (including hypoglycemia) corrected before prompt delivery.
3. Early referral to a transplant center should be made for women with AFLP with severe hepatic impairment.

Pragmatic guidance

1. Swansea criteria that combine clinical and laboratory data can help to avoid the need for excessive and invasive tests to confirm the diagnosis.[1]
2. Once diagnosis is confirmed, aim to correct coagulopathy and metabolic derangement and organize delivery in a safe setting.

TABLE 3 Maternal and fetal adverse outcomes with acute fatty liver of pregnancy.[4,19]

Maternal	Fetal/Neonatal
Hemorrhage 52%	Abnormal fetal status/fetal distress 46%
Ascites 48%	Neonatal asphyxia 25%
Acute liver failure 47.3%	Neonatal intensive care admission 20%
Acute renal failure 80%	Stillbirth/neonatal death 7%–11%
Encephalopathy 18%	
Hepatorenal syndrome 4%	
Pancreatitis 16%	
Multiorgan failure 2%	
Intensive care admission 60%	
Maternal mortality 2%–18%	

3 | PRE-EXISTING LIVER DISORDERS/ DISEASES CO-INCIDENTAL TO PREGNANCY

3.1 | Viral hepatitis (Figure 4)

Management of viral hepatitis in pregnancy incorporates acute or chronic infections and possible reactivation of previous infection, and requires careful consideration during pregnancy. Table 6 outlines a summary of delivery, breastfeeding, and other considerations for the management of viral hepatitis in pregnancy.

Hepatitis A virus

Hepatitis A virus (HAV) is an RNA hepatovirus transmitted via the fecal-oral route. The clinical syndromes range from asymptomatic infection to liver failure. Diagnosis is made by serologic testing

TABLE 4 Swansea Criteria prognostic tool.[4,20]

Vomiting	Abdominal pain	Polydipsia/polyuria
Encephalopathy	Bilirubin >0.8 mg/dL (14 µmol/L)	Hypoglycemia <72 mg/dL (<4 mmol/L)
Uric acid >5.7 mg/dL (>340 mg/dL)	Leukocytosis (>11 × 10^6/L)	Ascites
Echogenic (bright) liver on ultrasound	ALT or AST > 42 IU/L	Ammonia >27.5 mg/dL (>47 µmol/L)
Creatinine >1.7 mg/dL (>150 µmol/L)	Coagulopathy (prothrombin time >14 s or activated partial thromboplastin time >34 s)	Liver biopsy showing microvesicular fat deposition

Note: Instructions: Identify six or more of the following criteria not otherwise explained.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(HAV immunoglobulin G/immunoglobulin M). Elevated ALT, AST, and bilirubin are common, typically rising before symptom onset and resolving within 2–3 months. Maternal management is supportive. Mother-to-child-transmission (MTCT) is rare but HAV infection, particularly in the second and third trimesters, is associated with increased rates of gestational complications and preterm labor.[25]

HAV vaccination is recommended in pregnant women considered to be at high risk of infection (those traveling to endemic regions, homeless women, those with HIV or chronic liver disease).[4,26] Both the vaccine and immunoglobulin for post-exposure prophylaxis can be safely used in pregnancy.[27]

Hepatitis B virus

An estimated 97 million people globally live with hepatitis B virus (HBV), with prevalence highest in Africa and the Western Pacific region.[28] HBV is a DNA virus that may be contracted through parenteral, sexual, or vertical transmission. Universal serologic screening in pregnancy is recommended.[4] HBV vaccination is recommended for pregnant women who are hepatitis B surface antigen negative and who have risk factors for HBV infection.[4] New diagnosis of hepatitis B in pregnancy should be managed as per adult new infections. Advanced hepatitis with liver dysfunction is unusual in pregnant women but can occur, particularly if the individual acquired hepatitis B as an infant themselves. Sexual partners should be tested and vaccinated for hepatitis B if not immune. MTCT is very low when maternal HBV DNA is <5.30 $\log_{10}$ IU/mL (200 000 IU/mL)[29] and the infant receives appropriate prophylaxis with hepatitis B immunoglobulin (HBIG) and vaccine at birth and completes the vaccine series. Hepatitis B e-antigen can be used as an accurate surrogate marker to identify women with HBV DNA levels above this threshold.[29] HBV core-related antigen can be used to indicate clinically important, high viremia in treatment-naive HBV-infected patients.[30] Tenofovir disoproxil fumarate (TDF) is indicated in patients with high viral load (HBV DNA levels higher than 200 000 IU/mL), or Hepatitis B e antigen-positive women, from 24 to 28 weeks of pregnancy up until 12 weeks postpartum to reduce the risk of MTCT.[4] Other indications include patients with chronic HBV infection and advanced fibrosis or cirrhosis and those already established on treatment. Infants are susceptible to HBV infection until the point of full immunization. There is no contraindication to vaginal delivery or breastfeeding for women with chronic hepatitis B. Treatment with TDF is compatible with breastfeeding.[31]

Hepatitis C virus

Hepatitis C virus (HCV) is an RNA virus transmitted through parenteral, sexual, and vertical routes. HCV prevalence in pregnancy ranges from 0.24% to 7%.[32] Maternal serologic testing (HCV antibody) should ideally be performed routinely as part of antenatal care. Given that HCV can be naturally cleared in approximately 20% of adults, HCV-RNA should be tested for by polymerase chain reaction to determine if a woman has active hepatitis C infection. Women in whom HCV is detected before pregnancy should be offered antiviral treatment to clear the virus which, if successful, will abolish the risk of vertical transmission.[4] Ideally a directly acting antiviral therapy course should be completed before conception but in individual circumstances may be continued to complete the course. At present there are limited data for treatment of hepatitis C in pregnancy with ongoing trials not yet completed.[32–34] The risk of MTCT is approximately 5%–6%[35] among HCV RNA-positive women, and it increases if the mother is also HIV-positive. Cesarean delivery is not routinely recommended in cases of isolated HCV infection because it does not reduce MTCT; however, in those co-infected with HIV or in whom there is high-level HCV RNA, consideration of delivery mode should be individualized. Breastfeeding is not contraindicated.

Hepatitis D virus

Hepatitis D virus (HDV) is a viral co-infection that occurs in approximately 5% of people with chronic HBV infection. Maternal testing for serum hepatitis D antigen can be performed and confirmatory testing with HDV DNA polymerase chain reaction. Management and measures to prevent perinatal infection with HBV should be implemented in cases of HDV.[4]

Hepatitis E virus

Hepatitis E virus (HEV) is an RNA virus transmitted via the fecal-oral route, often via contaminated water or uncooked food. Infection in pregnancy can result in acute hepatitis and liver failure, maternal or fetal death. Diagnosis can be made using serologic testing for HEV immunoglobulin M antibodies. Acute liver failure following acute infection is more common when women are infected in the third trimester and in those infected with HEV genotype 1. Management is supportive. In severe cases of acute HEV infection and grade 1–3 encephalopathy, delivery of the fetus or therapeutic termination of pregnancy should be considered on an individualized basis as a mechanism to reduce maternal morbidity and mortality.[4]

3.2 | Cirrhosis and portal hypertension (including common causes e.g. MASLD/autoimmune hepatitis) (Figure 5)

The number of pregnant women with cirrhosis, with or without portal hypertension, is rising, as is the proportion managing to conceive naturally.[36,37] The etiology of cirrhosis differs by population.[38,39] In a meta-analysis, cirrhosis had a higher risk of preterm delivery (odds ratio [OR] 6.7, 95% confidence interval [CI]5.1–9.1), cesarean section (OR 2.6, 95% CI 1.7–3.9), pre-eclampsia (OR 3.8, 95% CI 2.2–6.5),

TABLE 5 Differential diagnoses of acute fatty liver of pregnancy.

	AFLP	HELLP	TTP	HUS
Most common time of presentation	Usually after 30 weeks of gestation; typically 35–36 weeks	Third trimester	Mid-trimester to postpartum	Postpartum
Epigastric pain	May be present	May be present and can be severe[a]	May be present	Rare
Vomiting	Common	May be present	May be present	May be present
CNS signs	Encephalopathy poor prognostic marker	May be associated with headache or visual disturbance	Dominate clinical picture and include headache, focal neurologic deficit, seizures, and confusion	Rare
Fever	Absent	Absent	Common	Absent
Purpura	Absent	May be present	May be present	May be present
Hypertension	May be present	Common	Uncommon	May be present
Proteinuria	May be present	Common	Common and often associated with hematuria	Common and often associated with hematuria
Elevated liver enzymes	Yes	Yes	Nil	Nil
Raised creatinine	Yes	May be present	May be present	Severe AKI
LDH	Normal	Increased	Very high	Very high
Thrombocytopenia	May be present	Yes	Yes	Yes
Hypoglycemia	Common	May be present	Uncommon	Uncommon
ADAMTS-13 activity	Normal	Normal	<10%	>30%
Complement pathway abnormalities	No	May be present	No	Yes
Other	Elevated lactate and absence of ketones Elevated ammonia	May be associated with fetal growth restriction		

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with thrombospondin motifs 13; AKI, acute kidney injury; ALP, acute fatty liver disease of pregnancy; CNS, central nervous system; HELLP, syndrome of hemolysis, elevated liver enzmes, and low platelets; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

[a]If abdominal pain present consider liver imaging to exclude hematoma.

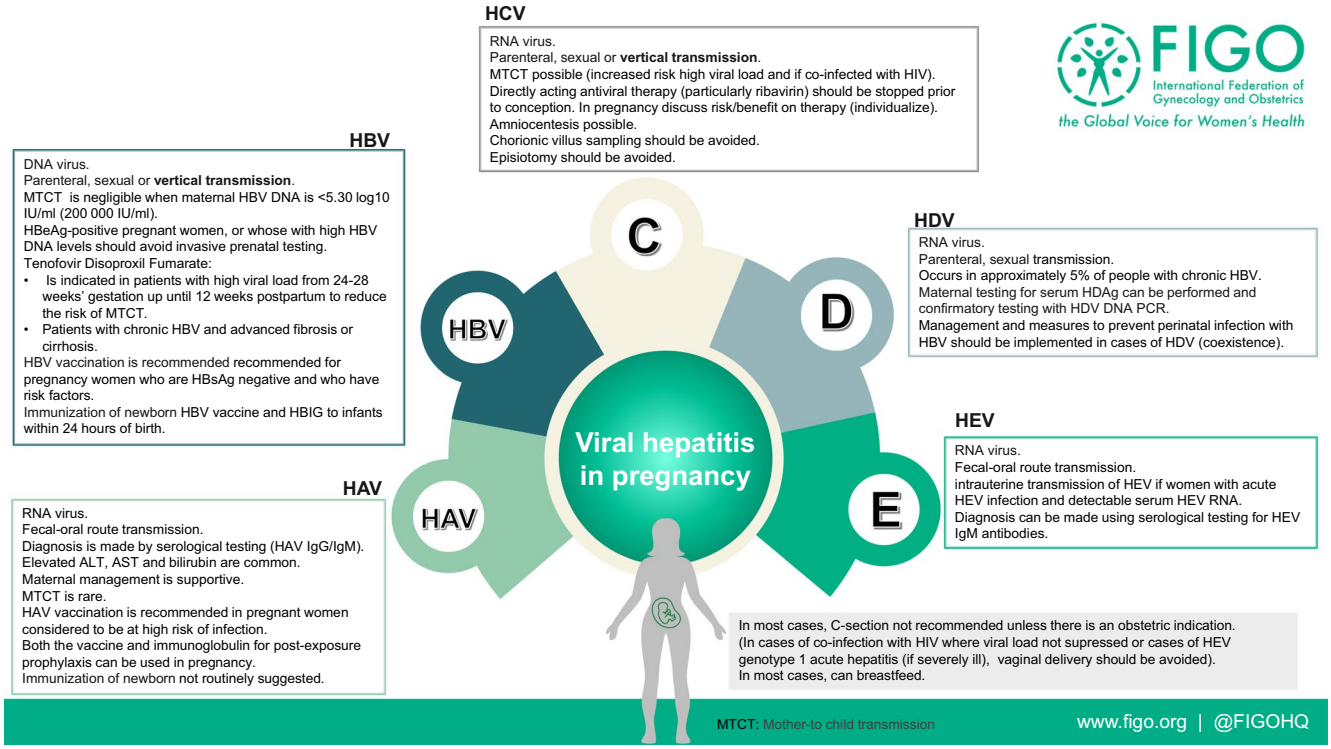

FIGURE 4 Summary of viral disorders.

and small-for-gestational-age neonates (OR 2.6, 95% CI 1.6–4.2) when compared with pregnant women without cirrhosis.[40] Affected women are at increased risk of hepatic decompensation in pregnancy (including the development of ascites, variceal bleeding and encephalopathy),[41,42] cholestasis,[38] and intensive care unit admission. In certain populations, but not all, rates of pre-eclampsia[40] are reported to be increased. Prognostic scoring systems can facilitate risk prediction in both the pre-pregnancy and pregnancy periods (Box 1).

Maternal mortality for pregnant women with cirrhosis is falling with rates of 0.89% reported in a recent meta-analysis.[40] Variceal bleeding is a leading cause of maternal mortality and those at risk of varices need careful management in pregnancy.

Diagnosis

Many women with cirrhosis will have a diagnosis before pregnancy. Determining the underlying cause of the cirrhosis is important as this will enable consideration of potential associated complications (e.g. women with MASLD have increased rates of gestational diabetes mellitus).[38]

BOX 1 Prognostic scoring systems used to facilitate risk prediction

- A pre-pregnancy Model for End-stage Liver Disease (MELD) score of <6 predicts a favorable outcome, whereas a MELD score >10 predicts decompensation in pregnancy.[42]
- A pre-pregnancy albumin-bilirubin (ALBI) score ≤2.7 is predictive of an increased likelihood of live birth.[36] Higher ALBI scores are associated with shorter gestation and preterm birth.[36]
- A pre-pregnancy aspartate aminotransferase (AST) to platelet ratio index (APRI) of <0.84 predicts pregnancies that will continue to term.[36]

Footnote: MELD is calculated as $3.78\times\ln[\text{serum bilirubin (mg/dL)}]+11.2\times\ln[\text{INR}]+9.57\times\ln[\text{serum creatinine (mg/dL)}]+6.43$. ALBI is calculated as $(\log_{10}\text{bilirubin [μmol/L]}\times 0.66)+(\text{albumin [g/L]}\times -0.0852)$. APRI is calculated using (AST/upper limit of normal)×100/platelet count.

Management

Women with established cirrhosis or known portal hypertension should preferably undergo a screening endoscopy within 1 year before conception to assess for clinically significant varices and to allow for primary prophylaxis to be initiated. Beta-blockers, such as carvedilol or propranolol, can safely be used in pregnancy (benefit outweighs risk of fetal growth restriction/hypoglycemia). If an endoscopy has not been performed within 1 year it can be safely performed in pregnancy (preferably in the second trimester), in

TABLE 6 Summary of birth, breastfeeding, and other considerations for the management of hepatitis in pregnancy.

	HAV	HBV	HCV	HDV	HEV
MTCT	Extremely rare	Low when maternal levels of HBV DNA <5.30 $\log_{10}$ IU/mL (200000 IU/mL) and infant immunoprophylaxis with HBIG and vaccine initiated post delivery; increases above this threshold regardless of infant immunoprophylaxis. In patients with high viral load, TDF is indicated from 24 to 28 weeks of gestation up until 12 weeks postpartum to reduce the risk of MTCT	MTCT possible, approximately 5%–6%; increased risk in cases of high viral load and if co-infected with HIV	Extremely rare	Vertical transmission does not occur in HEV RNA-negative mothers, but intrauterine transmission of HEV infection can occur in newborns if women have acute HEV infection and detectable serum HEV RNA
Delivery[a]	Cesarean delivery not recommended unless there is an obstetric indication	Cesarean delivery not routinely recommended to reduce the risk of HBV in HBsAg-positive women but may be considered in Asian HBeAg-positive women with high HBV DNA titers who have not received antiviral therapy during pregnancy	Cesarean delivery not recommended unless there is an obstetric indication	Cesarean delivery not recommended unless there is an obstetric indication	Cesarean delivery not routinely recommended except in cases of HEV genotype 1 acute hepatitis (if severely ill)
Breastfeeding	Can breastfeed	Breastfeeding is safe for infants who receive active/passive immunization, exercise caution in mothers with high serum HBV DNA load if cracked nipples or infant oral ulcers	Can breastfeed, exercise caution in cracked nipples or bleeding	Can breastfeed	Asymptomatic mothers can breastfeed
Immunization of newborn	Not routinely suggested but passive IgG immunization to the neonate can be considered if mother has acute hepatitis A just before delivery	Rate of MTCT from high-titer HBV DNA and HBeAg-positive mothers can be reduced from >90% to 5%–10% with administration of HBV vaccine and HBIG to infants within 24 h of birth.	N/A	Measures to prevent perinatal infection with HBV are uniformly effective in preventing HDV infection	N/A
Other considerations		HBeAg-positive pregnant women or those with high HBV DNA levels should be counseled to avoid amniocentesis and that non-invasive prenatal testing is preferred	Amniocentesis possible Chorionic villus sampling should be avoided Episiotomy should be avoided where possible in HCV RNA-positive women		

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HBIG, hepatitis B immunoglobulin; MTCT, mother-to-child-transmission; N/A, not applicable; TDF, tenofovir disoproxil fumarate.

[a]In cases of co-infection with HIV where viral load not supressed, vaginal birth should be avoided.

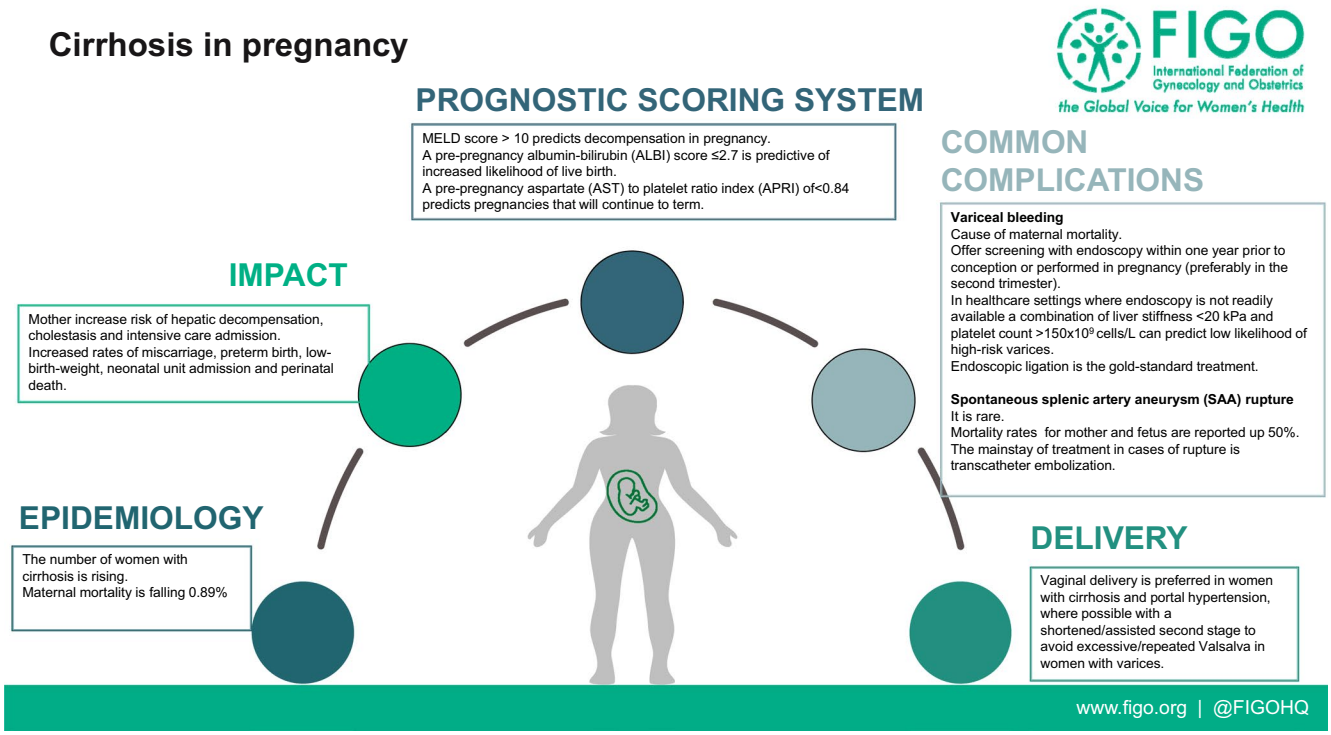

FIGURE 5 Summary of cirrhosis in pregnancy.

the left lateral position. Sedation using benzodiazepines can be used with caution. Where endoscopy is not readily available within healthcare settings, a combination of liver stiffness on ultrasound less than 20 kPa and platelet count greater than 150×10^9 cells/L can predict low likelihood of high-risk varices and can assist with decisions about beta-blocker treatment. In a single-center study, a platelet count less than 110×10^9 cells/L predicted the presence of varices in the second trimester with 78% sensitivity and 89% specificity.[42] The management of acute variceal bleeding in pregnancy is the same as for non-pregnant people. The priority should be to resuscitate and stabilize the mother and proceed without delay to endoscopic ligation once hemodynamically stable (reference standard treatment). Octreotide, broad-spectrum antibiotics, cyanoacrylate, and transjugular intrahepatic portosystemic shunts can be used in pregnancy;[4] octreotide is the first-line medical treatment in pregnancy. Where possible, Terlipressin should be avoided as it may induce uterine contraction, miscarriage, or placental abruption. Injection sclerotherapy has been used successfully in pregnancy in a small number of cases.[43]

An important risk to consider is spontaneous splenic artery aneurysm (SAA) rupture. Although SAA is rare, it is more common in the third trimester[44,45] and mortality rates for mother and fetus are reported up to 50%.[45,46] Women may have "double-rupture" phenomenon as the result of an initial self-contained bleed, so they should attend for medical review if they experience new abdominal pain. The mainstay of treatment in cases of rupture is transcatheter embolization. Pre-pregnancy prophylactic intervention is appropriate if a known SAA is 2 cm or larger, and European and American guidelines recommend considering treatment in pregnant women, regardless of size.[4,47,48] SAA identified in pregnancy should be discussed in a multidisciplinary team meeting; the risk of rupture is higher than in non-pregnant individuals. Expectant management is often most appropriate with planned postnatal transcatheter embolization.

Vaginal delivery is preferred in women with cirrhosis and portal hypertension, where possible with a shortened/assisted second stage to avoid excessive/repeated Valsalva in women with varices. Cesarean delivery should be reserved for those with obstetric indications; coagulopathy and thrombocytopenia should be corrected before the procedure. Where possible, magnetic resonance imaging or ultrasound should be performed to map the presence or absence of intra-abdominal or pelvic varices.[4] Women with cirrhosis are at increased risk of postpartum hemorrhage; standard management should be implemented if bleeding occurs.

Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver diseaseis now a leading cause of cirrhosis in the pregnant and non-pregnant populations worldwide.[38,49] In women with MASLD who are planning pregnancy, co-existing metabolic diseases, for example obesity, diabetes mellitus, and hypertension, should be optimized with the support of a multidisciplinary team, and the risks in pregnancy should be discussed. Women should also be informed of, and screened for, the

increased risk of developing gestational diabetes mellitus (three-fold), hypertensive disorders of pregnancy (two-fold), small-for-gestational-age babies, preterm birth and cesarean delivery.[50] It is reasonable to consider prophylaxis for preterm pre-eclampsia with low-dose aspirin (up to 150 mg) from early pregnancy to 34 weeks of pregnancy. Breastfeeding should be encouraged as it has been associated with lower rates of long-term metabolic syndrome in the mother and child.[51–55]

Autoimmune hepatitis

Women may enter pregnancy with a known history of autoimmune hepatitis or can present de novo in pregnancy. Diagnostic criteria in pregnancy are the same as in the non-pregnant population and liver biopsy can be performed where indicated. Treatment with prednisolone, budesonide, and thiopurines should be continued or started in pregnancy as disease stability is associated with improved maternal and fetal outcomes. It should be noted that thiopurine treatment may be associated with markedly raised serum bile acids, and associated risk of preterm birth and stillbirth, in a small number of pregnant women.[56] If this occurs, the risks and benefits of continuation of treatment should be considered on a case-by-case basis. Women should also be counseled regarding increased rates of gestational diabetes, cholestasis, hypertensive disorders of pregnancy, preterm birth, and fetal growth restriction, which require appropriate screening and close surveillance in pregnancy.[57–59] These risks may be ameliorated with low-dose aspirin prophylaxis.[60] There is an increased risk of flare postpartum and a pre-emptive increase in dose of immunosuppressants may be considered.

Liver cirrhosis

Best practice guidance

1. Pre-pregnancy counseling should focus on issues of relevance to cirrhosis and the underlying disorder.
2. A screening endoscopy should be performed before or during pregnancy in women at risk of clinically significant varices or bleeding to establish whether intervention is needed. This may not be required if an endoscopy has been performed within a year before conception and was reassuring.
3. In the absence of contraindications, beta-blockers should be given to women with portal hypertension for prophylaxis of variceal bleeding.

Pragmatic guidance

1. Scoring systems such as those described in Box 1 enable risk stratification for maternal complications and adverse pregnancy outcomes.

4 | PREGNANCY AFTER LIVER TRANSPLANT

Delaying pregnancy at least until 1 year is advised as it is associated with improved maternal and fetal outcomes including more stable graft function, reduced susceptibility to acute cellular rejection, reduced burden of immunosuppression and risk of infection, reduced rates of prematurity, and low birth weight.[61–65]

Pregnancy-compatible drugs include azathioprine, cyclosporine, tacrolimus, and prednisolone. Mycophenolate mofetil is teratogenic and should be stopped at least 12 weeks before conception.[4] De novo renal impairment occurs in up to one-quarter of pregnant liver transplant patients and this should be monitored to enable decisions around management and the possibility of expedited delivery.[64–66]

Women are at increased risk of gestational hypertension, pre-eclampsia, cholestasis, gestational diabetes, and acute kidney injury and clinicians should ensure screening for these conditions and initiation of low-dose aspirin in the first trimester for pre-eclampsia prophylaxis.[66–73] Live-birth rates in women with liver transplant have increased over time with rates up to 84% now reported.[66] Miscarriage rates reflect that of the background population and stillbirth rates of around 1% are reported. Rates of preterm birth and fetal growth restriction are increased compared with the background pregnant non-transplant population.[64,74–77] Mode of delivery should be related to obstetric indication, routine cesarean birth is not indicated.[78]

Pregnancy after liver transplant

Best practice guidance

1. Women with liver transplant should be counseled to delay pregnancy for 1 year post transplant.
2. Pre-pregnancy counseling should include discussion around the safety of medications, need for monitoring of blood markers of rejection, and increased rates of maternal gestational disorders including the appropriate screening.
3. Give low-dose aspirin for pre-eclampsia prophylaxis unless contradicated.

4.1 | Delivery considerations

Decisions around management of delivery will vary depending on the underlying disorder and should involve the woman and the multidisciplinary team, with plans for birth clearly documented in the patient notes. Complications that may occur at the time of birth in pregnancies affected by liver disease include thrombocytopenia, hypoglycemia, hypertension, vascular abnormalities (e.g. varices), and the possibility of urgent, and potentially preterm, birth.

TABLE 7 Delivery considerations for women with pre-existing and gestational liver disorders.[a]

			Mode of delivery				
			Vaginal delivery precautions				
Condition	Timing of delivery	Neuroaxial anesthesia	Induction of labur	Instrumental delivery	Normal vaginal delivery	Cesarean section precautions	Immediate postpartum care
Pre-existing liver disorders							
Autoimmune hepatitis	Planned	Yes	Yes	Yes	Yes	No	May worsen in postpartum period
Cirrhosis, portal hypertension, vascular liver disease	Planned	Yes	Yes	Yes	Yes, aim for short second stage	Hemorrhage precautions Consider pelvic varices	Caution with thromboprophylaxis
Viral disorders in pregnancy	Usually term	Yes	Yes	Yes	Indicated in all women with viral infections apart from those where viral load is not sufficiently suppressed, HIV co-infected women and those with HEV genotype 1 acute hepatitis (if severely ill)	Yes	HBV: Neonatal immunoprophylaxis with HBIG and vaccine administration within 24 h
MASLD	Normal	Yes	Yes	Yes	Yes	No	No
Gestational liver disorders							
AFLP	Planned	Yes	Yes	Yes	Yes	Yes	May worsen in 20% 2–5 days postpartum
ICP	Planned between 35 and 36 weeks if serum bile acids ≥100 μmol/L	Yes	Yes	Yes	Yes	No	Ensure liver tests and serum bile acid concentrations return to normal by 3 months postpartum

Abbreviations: AFLP, acute fatty liver of pregnancy; HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin; HEV, hepatitis E virus; HIV, human immunodeficiency virus; ICP, intrahepatic cholestasis of pregnancy; MAFLD, metabolic-associated fatty liver disease.

[a]This table has been adapted from the EASL Liver Disease and Pregnancy Clinical Practice Guideline.[4]

Women with stable pre-existing liver disease usually deliver at term. Some liver disorders may co-exist with other conditions that can influence decisions relating to mode of birth, e.g. substance use or HIV infection. Other pregnancy-associated liver disease may require iatrogenic delivery at preterm gestations, e.g. ICP, AFLP, or HELLP syndrome. Maternal stabilization and access to equipment and resources (intensive care, interventional radiology, endoscopy, transplant team, platelet and blood products) should be considered. Transfer to a tertiary center may be required. Table 7 summarizes the delivery considerations for women with pre-existing and gestational liver disorders.

Other birth considerations include stress dose steroids for women on long-term glucocorticoid therapy (e.g. ≥5 mg prednisolone for >3 weeks or equivalent) and the use of blunt needles to reduce the incidence of needle stick injury in healthcare workers, especially in serology-positive patients.[79,80]

Many liver disorders are associated with an increased risk of bleeding. Obstetric anesthesia input should be sought from an early stage. Optimization of hematologic markers, availability of blood products, and large-bore intravenous access should be considered. Postpartum hemorrhage prophylaxis should be initiated as per local/national guidelines with acknowledgment of the potential effect of abnormal liver metabolism on drugs. Pharmacy consultation regarding the dosing of routinely used medications peripartum that are metabolized by the liver can be helpful in delivery planning (for example, misoprostol is metabolized by the liver).

Breastfeeding initiation in the first hour of life is recommended by the WHO and FIGO.[81] Women with MASLD and their offspring have additional benefits with breastfeeding (lower incidence of the metabolic syndrome for the mother and for the offspring reduced incidence of MASLD) and should be supported to do so.[4,54] Viral hepatitis is not a contraindication to breastfeeding.[4]

Particular care should be paid to postpartum wound care in women at risk of impaired healing, e.g. post-transplant patients on immunosuppression. A venous thromboembolism risk stratification should be performed as per local guidelines and thromboprophylaxis should be initiated where appropriate.

Delivery planning for liver disease

Best practice advice

1. Multidisciplinary team input should be sought for delivery planning in women with liver disease in pregnancy.
2. Women with liver disease are at increased risk of bleeding. Blood products should be available peripartum.
3. Breastfeeding should be encouraged, especially in women with metabolic dysfunction-associated steatotic liver disease.

4.2 | Pre-pregnancy counseling

Women with a history of chronic liver disease (CLD) or liver transplant who become pregnant are at increased risk of destabilization of their underlying condition, preterm birth, low birth weight, intrauterine growth restriction, and neonatal respiratory distress syndrome.[38,82,83] Pre-pregnancy counseling offers the opportunity to discuss these risks, optimize the woman's health before pregnancy, and discuss the safety of/ adjust any medications that the woman may be taking. All women with CLD or liver transplant should therefore be offered pre-pregnancy counseling from a multidisciplinary team with expertise in the management of liver disorders in pregnancy.[4] Many women with a previous history of a gestational liver disorder will also benefit from pre-pregnancy counseling.

When considering pregnancy, women with CLD report concerns regarding risk to their own health; such as deterioration of their underlying disease in pregnancy and death.[84] They also report concerns regarding the outcome of their pregnancy such as pregnancy loss, effect of medications on their unborn child and risk of inheritance.[84] In a study that reported the benefits of pre-pregnancy counseling in this group, 98% of these women felt better informed after attending. Positive experience and reported benefits of attending pre-pregnancy counseling have also been reported for other chronic diseases.[85,86] In a small sub-group of 24 patients in the study of women with CLD recieving pre-pregnancy counseling, when compared with controls who did not receive pre-pregnancy counseling, there were no differences in pregnancy-related outcomes. There were no major differences in incidence of gestational diabetes/hypertension, pre-eclampsia, fetal growth restriction (<10th centile for gestational age), preterm birth (<37 weeks of gestation), and intrauterine death (>24 weeks of gestation), albeit the numbers in this study were small.[84] Differences in outcomes for other chronic diseases, however, have been reported.[87,88] In a study of women with inflammatory bowel disease, those who received pre-pregnancy counseling were more adherent to medication during pregnancy, folic acid use, and smoking cessation. Their disease was demonstrated to be more quiescent during pregnancy (even when matched for parity and disease activity before conception). These women were less likely to deliver babies of low birth weight.[89]

Pre-pregnancy counseling

Best practice advice

1. All women with pre-existing liver disease should be offered pre-pregnancy counseling to enable discussions around optimizing the woman's health before pregnancy and discussion regarding safety of/adjustment of medications.
2. Women with a history of gestational liver disorders may benefit from pre-pregnancy counseling.

Pragmatic guidance

1. In healthcare settings in which pre-pregnancy counseling is not routine, opportunities to offer guidance should be taken if/when a woman of childbearing age presents to any healthcare professional.

5 | SUMMARY

The prevalence of women entering pregnancy with or developing de novo liver disorders is increasing. In addition, more women are entering pregnancy with risk factors for developing gestational liver disorders in pregnancy. Both pre-existing and gestational liver disorders can be associated with maternal and fetal morbidity. This guideline aims to provide both best practice and pragmatic guidance for the management of such patients within the multidisciplinary team.

AUTHOR CONTRIBUTIONS

FM conceieved the idea for the guideline. MN, CM, UB, CM, and CW wrote the first draft of the manuscript. The remaining authors commented on the draft. MN and CW addressed the authors, comments and finalized the paper.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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APPENDIX A

Drug safety table

Acknowledgement European Association for the Study of the Liver, table reproduced from the Clinical Practice Guideline on the management of liver disease in pregnancy with permission.

Drug	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Antibiotics					
Rifampicin	Limited data	Limited data	Limited data[a]	Limited data	Yes
Antihypertensives					
Labetalol	Yes	Yes	Yes[b]	Yes	Yes
Nifedipine	Yes	Yes	Yes	Yes	Yes
Mathyldopa	Yes	Yes	Yes	Yes	Yes
Hydralazine	Yes	Yes	Yes	Yes	Yes
Magnesium sulphate	Yes	Yes	Yes	Yes	Yes
Antivirals					
Tenofovir disoproxil fumarate	Yes	Yes	Yes	Yes	Yes
Tenofovir alafenamide	Yes	Yes	Yes	Yes	Yes
Lamivudine	Yes	Yes	Yes	Yes	Yes
Telbivudine	Yes	Yes	Yes	Yes	Yes
Ledipasvir-sofosbuvir	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Sofosbuvir-velpatasvir	No data	No data	No data	No data	Yes
Glecaprevir-pibrentasvir	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Ribavirin	No	No	No	No	No
Benzodiazepines					
Diazepam	Limited data[c]	Limited data[c]	Limited data[c,d]	Limited data[c]	Yes
Carbamate derivatives					
Disulfiram	No	No	No	No	Yes
Corticosteroids					
Dexamethasone	Yes	No[e]	No[e]	Yes	Yes
Betamethasone	Yes	No[e]	No[e]	Yes	Yes
Prednisolone	Yes	Yes	Yes	Yes	Yes
Budesonide	Yes	Yes	Yes	Yes	Yes
Fibrates					
Bezafibrate	No	No	Very limited data[r]	No	Yes
GABA-B receptor agonists					
Baclofen	Limited data	Limited data	Limited data	No	Yes
Ileal bile acid transporter inhibitors/bile acid sequestrants					
IBAT inhibitors	Limited data	Limited data	Limited data	Limited data	Yes
Cholestyramine	Yes[f]	Yes[f]	Yes[f]	Yes	Yes
Colestipol	Limited data[f]	Limited data[f]	Limited data[f]	Limited data	Yes
Immunomodulators					
Interferon	Limited data[g]	Limited data[g]	Limited data[g]	Limited data[g]	yes
Immunosuppressants					
Tacrolimus	Yes	Yes[h]	Yes[h]	Yes	Yes
Mycophenolate mofetil	Stop 12 weeks in advance	No	No	No	Yes

APPENDIX A (Continued)

Drug	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Sirolimus	Limited data[i]	Limited data[i]	Limited data[i]	Limited data[i]	Yes
Everolimus	Limited data[i]	Limited data[i]	Limited data[i]	Limited data[i]	Yes
Cyclosporin	Yes	Yes[j]	Yes[j]	Yes	Yes
Infusions					
Plasma exchange	Yes	Yes	Yes	Yes	Yes
N-acetylcysteine	Yes	Yes	Yes	Yes	Yes
FFP	Yes	Yes	Yes	Yes	Yes
Platelets	Yes	Yes	Yes	Yes	Yes
Blood	Yes	Yes	Yes	Yes	Yes
Immunoglobulin	Yes	Yes	Yes	Yes	Yes
Opioid agonists					
Naltrexone or nalmefene	Limited data[k]	Limited data[k]	Limited data[k]	Limited data[k]	Yes
N-methyl-D-aspartate agonists					
Acamprosate	Limited data[l]	Limited data[l]	Limited data[l]	Limited data[l]	Yes
Nutrient replacements					
Calcium supplements	Yes	Yes	Yes	Yes	Yes
Pabrinex	Yes	Yes	Yes	Yes	Yes
Vitamin K	Yes	Yes	Yes	Yes	Yes
Salicylates					
Aspirin	Yes	Yes	Yes	Yes	Yes
Thiopurines					
Azathioprine	Yes	Yes	Yes	Yes	Yes
Mercaptopruine	Yes	Yes	Yes	Yes	Yes
ICP drugs					
Ursodeoxycholic acid (UDCA)	Yes	Yes	Yes	Yes	Yes
S-adenosyl methionine (SAMe)	Limited data[m]	Limited data[m]	Limited data[m]	Limited data[m]	Yes
Guar gum	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Activated charcoal	Limited data	Limited data	Limited data	Limited data	Yes
Semisynthetic bile acid obeticholic acid	Very limited data[n]	Very limited data[n]	Very limited data[n]	Very limited data[n]	Yes
Portal hypertension					
Carvedilol	Limited data[s]	Limited data[s]	Limited data[b,s]	Yes	Yes
Propanolol	Yes	Yes	Yes	Yes	Yes
Anti-emetics					
First-line recommended treatments for management of Hyperemesis Gravidarum					
Chlorpramazine	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Cyclizine	Yes	Yes	Yes	Yes	Yes
Doxylamine/pyridoxine	Yes	Yes	Yes	Yes	Yes
Prochlorperazine	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Promethazine	Yes	Yes	Yes	Yes	Yes
Second line recommended treatments for management of Hyperemesis Gravidarum					
Domperidone	Yes	Yes	Yes	Yes	Yes
Metoclopramide	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Ondansetron	Yes[p]	Yes[p]	Yes[p]	Yes[p]	Yes[p]

APPENDIX A (Continued)

Drug	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Third line recommended treatments for management of Hyperemesis Gravidarum					
Corticosteroids	Yes[q]	Yes[q]	Yes[q]	Yes[q]	Yes[q]

Abbreviation: UKTIS, UK Teratology Information Service.

[a] Limited data, however, available data do not suggest increased risk, therefore should not be withheld where indicated. Neonatal hemorrhage has been reported following exposure in late pregnancy, therefore both maternal supplementation with vitamin K and neonatal intramuscular vitamin K at birth is recommended when rifampicin is administered in the weeks preceding delivery (UKTIS).

[b] Monitor for rare risk of neonatal bradycardia, hypotension and hypoglycaemia post-delivery.

[c] Limited data. Recent, well-designed studies do not report fetal risk therefore where clinically justifiable can be used in pregnancy, ideally with lowest effective dose. Abrupt withdrawal should be avoided (UKTIS).

[d] Prolonged use near term, particularly in large doses, is associated with risk of neonatal withdrawal syndrome and/or 'floppy infant syndrome' therefore monitoring for neonatal respiratory depression is advised (UKTIS).

[e] Both dexamethasone and betamethasone are fluorinated corticosteroids thus readily cross the placenta. Repeated doses in pregnancy have been associated with neurocognitive and neurosensory disorders in the offspring during childhood.[2] Their use should be avoided where possible in pregnancy where the indication is for treatment of the mother; their use should be reserved for fetal lung maturity in the context of preterm birth.

[f] Cholestyramine and colestipol may cause maternal deficiencies of fat-soluble vitamins which may lead to adverse effects (particular vitamin K deficiency) therefore assessment of maternal prothrombin time, appropriate maternal vitamin K supplementation and administration of vitamin K to the neonate should be considered if given during pregnancy (UKTIS).

[g] Interferon administration is usually not recommended for viral hepatitis.

[h] Monitoring of maternal blood pressure, renal function, blood glucose and drug levels recommended.

[i] Limited data, not routinely recommended.

[j] Monitoring of maternal blood pressure recommended.

[k] Limited published data do not report fetal anomaly. Use in pregnancy should be weighed up against the risk of fetal alcohol syndrome on a case-by-case basis.

[l] Limited published data do not report fetal anomaly. Unpublished data ($n = 32$) include cases of miscarriage, congenital malformation and adverse neurodevelopmental effects (however, number of exposed pregnancies small and data likely confounded by maternal alcohol use) (UKTIS). Use in pregnancy should be weighed up against the risk of fetal alcohol syndrome on a case-by-case basis.

[m] Data are limited but reassuring.

[n] Too few data to make recommendation; animal data reassuring.

[o] Drug-induced extrapyramidal symptoms and oculogyric crises can occur with the use of phenothiazines and metoclopramide, patients reporting relevant symptoms should have the drug withdrawn and appropriate treatment initiated.

[p] Ondansetron use in pregnancy has been associated with an increased rate of orofacial clefting. However, the absolute risk increases from a background risk of 11 cases per 10, 000 births to 14 cases per 10, 000 births, this risk should be put into context when advising women regarding this medication versus the risk of untreated disease.

[q] Typical dosing regimen includes intravenous hydrocortisone 100 mg twice daily and following clinical improvement conversion to oral prednisolone 40-50 mg daily with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached.

[r] For women with severe pre-existing cholestasis fibrates may be considered after the first trimester if benefits are likely to exceed perceived risks.

[s] Data is highly limited, however, studies of beta-blockers as a class are reassuring and therefore carvedilol should be initiated or continued as primary prophylaxis for variceal hemorrhage based on a benefit versus theoretical risk basis.