Evaluation of Liver Disease in Pregnancy

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KEYWORDS

• Pregnancy • Preeclampsia • Nonalcoholic fatty liver disease • HELLP
• Hyperemesis gravidarum • Intrahepatic cholestasis of pregnancy

KEY POINTS

- The diagnostic approach to abnormal liver tests in pregnancy involves an assessment of liver injury pattern and evaluation for liver diseases unique to pregnancy.
- Liver diseases unique to pregnancy generally occur in specific pregnancy trimesters, but there are exceptions in timing of onset.
- Diagnostic criteria such as Swansea criteria for acute fatty liver disease of pregnancy and the Mississippi classification for HELLP can be helpful in the diagnostic workup of patients.
- There are specific management considerations for chronic liver disease both during pregnancy and in regards to breastfeeding in order to optimize disease and pregnancy outcomes.
- Portal hypertension in pregnant individuals can be associated with risk of variceal bleed in pregnancy; endoscopic evaluation should occur during pregnancy particularly if there is no endoscopy within a year prior to pregnancy.

Liver disease occurs in 5% to 10% of pregnancies and requires diagnostic and therapeutic considerations that may be unique to pregnancy. Liver injury in pregnancy can be broadly categorized into chronic liver disease, liver disease unique to pregnancy, and liver disease coincidental to pregnancy. Guidelines from both the American College of Gastroenterology[1] and the American Association for the Study of Liver Diseases (AASLD)[2] delineate diagnostic pathways and provide therapeutic recommendations for liver disease in pregnancy. There is ongoing clinical investigation to improve our understanding of the optimal strategies to address liver disease in

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pregnancy and to optimize maternal and fetal outcomes. This review addresses our current knowledge of the evaluation of liver disease in pregnancy.

DIAGNOSTIC APPROACH TO LIVER DISEASE IN PREGNANCY

Evaluation of a pregnant woman without known liver disease will be similar to that of a nonpregnant individual although testing needs to balance risk to the mother and fetus against the information obtained and must be interpreted in the context of gestational age. Initial evaluation starts with a history (including medications and supplements), physical examination, and laboratory assessment. The history should assess for any known personal and family history of prior liver disease, risk factors for liver disease (such as injection drug use or other bloodborne exposures for hepatitis C or hepatitis B, metabolic risk factors for nonalcoholic fatty liver disease [NAFLD]), prior pregnancy history (such as prior history of complications of pregnancy such as preeclampsia), and/or symptoms during current pregnancy (ie, nausea, emesis, pruritus). Physical examination should focus on evaluating for any evidence of chronic liver disease such as scleral icterus or jaundice, advanced liver disease such as palmar erythema, ascites, or lower extremity edema, although this can be confounded by normal physical changes of pregnancy. The pattern of liver tests elevation, hepatocellular or cholestatic, then guides further testing (**Fig. 1**). When evaluating the prevalence of liver disease subtypes among cohorts of patients, the most prevalent cause of abnormal liver chemistries is actually gallstones and biliary disease followed by liver disease unique to pregnancy.[3–5] In addition, providers should be mindful that NAFLD is the most prevalent chronic liver condition among women of reproductive age, and therefore should be considered early in evaluation. Liver diseases unique to pregnancy will increase in prevalence in the second and third trimester and must be high on the differential.

LIVER DISEASES UNIQUE TO PREGNANCY

Liver disease unique to pregnancy are diagnosed based on timing of occurrence in pregnancy (ie, which trimester of pregnancy), symptoms associated with

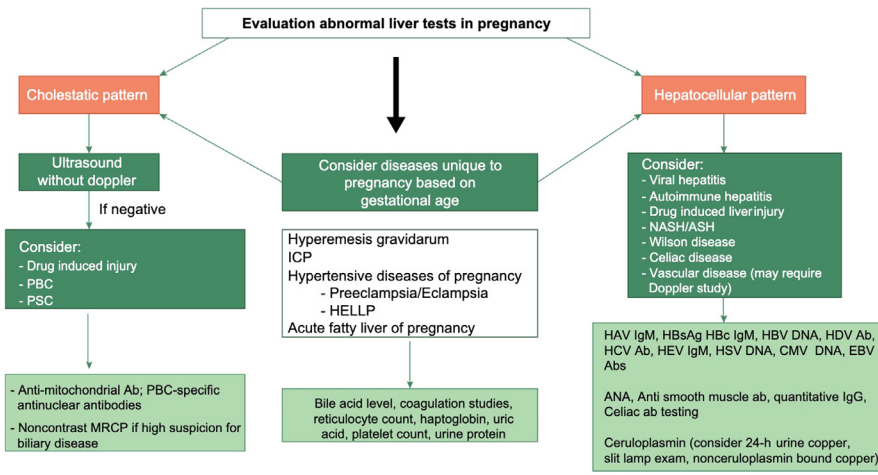

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Fig. 1. Diagnostic approach to liver disease in pregnancy.

presentations, as well as pattern of liver test abnormalities. Clinical presentation and management are summarized below. Although they are considered "unique to pregnancy," emerging data suggest that some of these conditions may be associated with chronic liver disease (**Table 1**).

Hyperemesis Gravidarum

Nausea and vomiting in pregnancy (NVP) are common health problems of early pregnancy with a reported prevalence of 75%.[6] Hyperemesis gravidarum (HG) is a severe form of NVP that is characterized by intractable nausea and vomiting, affecting 0.3% to 2% of pregnancies.[6] **Box 1** describes the diagnostic criteria for HG.

It is most common in the first trimester, usually starting at 4 or 5 weeks, and rarely persisting beyond 20 weeks.[7] Risk factors include young age, personal or family history of HG, history of psychiatric illness, nulliparity, and multiple gestations. Proposed hypotheses on the pathophysiology include metabolic and hormonal factors, GI dysmotility, *Helicobacter pylori* infection, and GDF15-GFRAL axis activation.[8–11]

Common laboratory abnormalities include electrolytes derangements, ketosis, metabolic alkalosis, polycythemia, and abnormal liver enzymes. Liver test elevation occurs in almost 50% of patients with HG.[12] Current evidence points toward a possible multifactorial interplay between starvation injury, placental release of inflammatory cytokines, and impairment of fatty acid oxidation in the pathogenesis of liver injury seen in HG.[13] Aminotransferase elevation of up to 200 U/L is the most common biochemical abnormality.[12] There is a propensity for alanine aminotransferase (ALT) to increase more than aspartate aminotransferase (AST) for unclear reasons and mild hyperbilirubinemia can be seen in some cases. The liver synthetic functions remain. Liver imaging is unremarkable but usually done to rule out other causes. Biopsy is rarely indicated except when the diagnosis is uncertain or in cases with atypical increase of liver enzymes. If performed, it is mostly normal, shows steatosis or bland cholestasis.[14]

Treatment of HG is usually supportive regardless of the presence of liver dysfunction. Patients with HG almost always require admission for the administration of intravenous fluids, thiamine, folic acid, and antiemetics. Although maternal–fetal outcomes for mild NVP are generally favorable, HG is associated with a higher incidence of preterm labor, low birth weight, and small gestational age if left untreated.[6] There are no long-term sequelae of liver dysfunction, and the biochemical abnormalities usually correct after cessation of vomiting.[12]

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy. Occurring in the second and third trimesters, the prevalence in the United States is estimated to be ranging from 0.3% to 5.6%.[15] It is characterized by intense pruritis and elevated serum bile acids with resolution of symptoms after delivery. Risk factors include advanced maternal age, previous history of ICP, multiparity, metabolic syndrome, hepatitis C virus (HCV), and family history of ICP.[16]

The cause of ICP is multifactorial and involves an interplay between genetic, hormonal, and environmental factors. Genetic predisposition likely explains the familial clustering of ICP and recurrence of ICP in future pregnancies. The presence of mutations in biliary transport proteins such as the bile salt export protein pump (BSEP/ABCB11), multidug resistance protein 3 (MDR3/ABCB4), *FIC1* gene (*ATP8B1*), and the *FXR* gene (*NR1H4*) are most cited but still uncommon.[17] ICP onset is most common in the third trimester when estrogen and progesterone serum concentrations are

Table 1
Summary of liver disease unique to pregnancy and their association with other medical conditions

			Association with Other Chronic Disease	
Trimester	**Clinical Features**	**Likely Diagnosis**	**Preexisting**	**Postpartum**
First	Vomiting, Weight loss, dehydration Laboratories: Aminotransferase—1–5×, Bilirubin <4 mg/dL, Bile acids: Normal Imaging: Mostly normal Biopsy: Mostly normal Treatment: Supportive	HG	NA	NA
Second/Third	Pruritis, Fatigue Laboratories: Aminotransferase—1–5×, Bilirubin <4 mg/dL, Bile acids: 30–100× Imaging: Mostly normal Biopsy: Hepatocellular bile and Canalicular bile plugs Treatment: Urso deoxycholic Acid. Delivery at 37 wk	ICP	Cholecystitis Choledocholithiasis	NAFLD PBC Gallstone Cholecystitis Biliary tree Cancer Liver Cancer
Second/Third/Postpartum	Hypertension, Proteinuria, headache Laboratories: Aminotransferase—1–100×, Bilirubin↑, LDH↑, Platelets↓ Imaging: hepatic infarcts, hematoma, rupture Biopsy: periportal hemorrhage and fibrin deposition Treatment: Supportive, early delivery. Hepatic artery embolization or surgery for expanding hematoma	Preeclampsia/HELLP	Hepatitis C	Heart and cerebral vascular disease
Third/Postpartum	Abdominal pain, hypertension, polydipsia, encephalopathy Laboratories: Aminotransferases—5–10×, Bilirubin↑, Uric acid↑, Platelets↓ Imaging: Steatosis, bright liver Biopsy: Microvesicular steatosis Treatment: Supportive, early delivery. Plasmapheresis	AFLP	NA	NA

Box 1
Diagnostic criteria for Hyperemesis Gravidarum

- Persistent nausea and vomiting
- Laboratory markers of starvation, such as ketonuria
- Weight loss[a]

[a]At least 5% of the prepregnancy weight.[1]

high. Some women with a history of ICP may also develop symptoms with the use of oral contraceptive pills.[18]

The classic symptom is itching, most severe in the palms and soles *without* an accompanying rash; however, some also experience epigastric pain, fatigue, and anorexia. Jaundice is very rare although reported late in the disease. Biochemical abnormalities include elevation in bile acid levels, typically greater than 10 μmol/L, with 2-fold to 10-fold increase in aminotransferases. Bilirubin is normal in most cases and alkaline phosphates level may increase but is of limited diagnostic value.[15] Cholelithiasis, cholecystitis, and choledocholithiasis are reported to occur more frequently in patients with ICP and abdominal ultrasound is usually performed to rule out these disorders. Liver biopsy is rarely required and if done shows bile plugs in hepatocytes and canaliculi, predominantly zone 3.[14]

As a rule, pruritis resolves within days after delivery and biochemical abnormalities normalize within weeks. The maternal prognosis is usually favorable. Given association with chronic liver disease[19] (see **Table 1**), genetic testing should be considered in women with severe ICP (total bile acids >100 μmol), recurrent ICP, or early-onset ICP.

Associated fetal risks include preterm births, meconium-stained amniotic fluids, neonatal respiratory depression and asphyxia, and fetal death. These risks increase with increasing bile acid levels and most commonly occur when serum bile acid level is greater than 40 μmol/L.[15] Proposed mechanisms include cardiotoxic effects of bile acids and vasoconstrictive effects of bile acids on placental veins.[18] Therefore, the American College of Obstetricians and Gynecologists recommends delivery at 36 to 37 weeks or at diagnosis if diagnosed after 37 weeks.[20]

Ursodeoxycholic acid (UDCA) is the preferred treatment and earlier studies supported its efficacy in reducing both maternal symptoms and decreasing perinatal morbidity and mortality. However, in the last 3years, 2 studies have questioned its role. A randomized controlled trial(RCT)by Chappell and colleagues, comparing UDCA 500 mg twice a day with placebo for treatment of ICP, did not reduce any perinatal outcomes.[21] There was a small, statistically significant improvement in itch score but it is unlikely to be clinically relevant. In addition, a meta-analysis did not support the efficacy of UDCA in reducing adverse fetal outcomes.[22] Given the safety profile of UDCA and lack of other therapy, UDCA remains first-line therapy. Other treatments such as rifampicin, cholestyramine, and S-adenosyl-L-methionine (SAMe) have been suggested but lack evidence.[22] Currently, an RTC is being conducted, comparing the effectiveness of UDCA to rifampin in pruritis in early-onset ICP.[23] New mechanisms of action are also being investigated for the treatment of ICP.[24]

Preeclampsia, Eclampsia and Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome

The preeclampsia spectrum of disease reflects an overlap among preeclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP), and even acute fatty liver

of pregnancy (AFLP), and therefore may pose a diagnostic challenge in its presentation. Preeclampsia is a multisystem disorder characterized by new-onset hypertension, with additional maternal organ dysfunction after 20 weeks of gestation. Signs and symptoms seen are summarized in **Box 2**. Proteinuria is often present but is not required for diagnosis in presence of other end-organ damage (renal, hepatic, neurologic, or hematologic).[25] Eclampsia is diagnosed when preeclampsia is complicated by seizures. HELLP syndrome, an acronym coined in 1982, is characterized by hemolysis, elevated liver enzymes, and low platelets. It is considered a severe manifestation of the preeclampsia/eclampsia spectrum but can occur in the absence of preexisting preeclampsia. It is estimated that preeclampsia complicates 3% to 5% of pregnancies globally.[26] HELLP syndrome can complicate up to 2% of preeclampsia cases.[12] Risk factors include personal or family history of preeclampsia/HELLP, chronic hypertension, preexisting diabetes, autoimmune disease, and multifetal gestation among others.[25]

Although preeclampsia typically occurs in the second trimester (≥20 weeks of gestation), it is recognized in about 5% of patients postpartum, usually within 48 hours of birth. HELLP, however, typically presents between 28 and 36 weeks of gestation, and almost 30% manifest symptoms in the first week postpartum.[25] The pathophysiology of preeclampsia/eclampsia/HELLP is thought to start early in pregnancy with abnormal placental implantation and decreased perfusion of the placenta as pregnancy progresses. This leads to the release of antiangiogenic factors into the maternal circulation, which interacts with endothelial grown factors and placental growth factors resulting in maternal vascular inflammation, platelet aggregation, and endothelial dysfunction. Liver involvement in hypertensive diseases of the pregnancy is hypothesized to occur secondary to fibrin deposition within the hepatic sinusoids resulting in sinusoidal obstruction and subsequent hepatic ischemia.[12] In preeclampsia, aminotransferases elevation to more than twice the upper limit of normal signifies severe features and parallels the risk of adverse maternal outcomes.[21]

In severe cases, patients can develop hematoma beneath the Glisson Capsule, which has an increased risk for rupture. In HELLP, serum aminotransferases may be elevated more than 10 times the upper limit of normal, and jaundice, if present, is due to hemolysis. Apart from elevated liver function tests (LFTs), other severe hepatic manifestations in HELLP syndrome include hepatic infarction, hemorrhage, and hematoma rupture, which can occur in up to 45% of patients.[12]

Cross-sectional imaging (computerized tomography/MRI) is recommended in preeclampsia/HELLP syndrome, especially in those with abdominal pain, shoulder pain, and hypotension to exclude hemorrhage, rupture, or infarction.[12] A liver biopsy is not required for the diagnosis but if done shows periportal hemorrhage and fibrin

Box 2
Signs and symptom of preeclampsia/HELLP syndrome

Clinical Symptoms
- Headache
- Vomiting
- Peripheral edema
- Right upper quadrant pain
- Vision abnormalities

Biochemical Abnormalities
- Thrombocytopenia
- Renal insufficiency
- Elevated liver enzymes[a]

[a] Liver enzyme elevation occurs in about 30% of cases in preeclampsia[8]

deposition.[14] Diagnostic criteria have been developed to distinguish HELLP syndrome from preeclampsia/eclampsia spectrum (**Box 3**).

Maternal–fetal complications include preterm labor, postpartum hemorrhage, intrauterine growth retardation, intrauterine death, and prematurity.[25] Studies have also shown that women with preeclampsia and eclampsia have increased risk of heart and cerebral vascular disease later in life.[27]

Management of preeclampsia/eclampsia is supportive and includes administration of antihypertensives, and steroids to improve platelet counts. The only definitive cure is delivery, which is recommended at 37 weeks for preeclampsia, 34 weeks for preeclampsia with severe features, and as soon as possible for eclampsia regardless of gestational age.[25] Studies have demonstrated prophylactic role of aspirin in reducing fetal adverse outcomes in patients with high-risk factors for preeclampsia.[28] Mississippi protocol, which involves administration of magnesium sulfate, corticosteroids, and systolic blood pressure control, has shown to inhibit HELLP syndrome progression.[29] Surgical intervention or hepatic artery embolization is warranted for increasing subcapsular hematoma or hepatic rupture.[12]

Acute Fatty Liver Disease of Pregnancy

AFLP is a rare obstetric emergency characterized by maternal hepatic dysfunction/failure, which can be fatal for both mother and the baby.[30] It usually occurs in the third trimester although 20% present postpartum.[12] It is characterized by maternal microvascular fat deposition in the hepatocytes leading to multiorgan failure. Risk factors include nulliparity, male infants, and twin pregnancies.[30]

Our current understanding of the pathophysiology for AFLP involves a defect in the mitochondrial fatty acid oxidation in the mother and the fetus. The most linked enzyme is long-chain 3-hydroxy acyl-coenzyme A dehydrogenase (LCHAD) deficiency, although other fetal fatty acid oxidation disorders are described.[31,32] A heterozygous mother for a hydroxyacyl-CoA dehydrogenase mutation carrying a fetus with homozygous or compound heterozygous mutation results in the accumulation of hepatotoxic long-chain 3-hydro-fatty acyl metabolites in the maternal circulation and liver.

Initial clinical features are nonspecific with nausea, vomiting, jaundice, and abdominal pain. It can rapidly progress to liver and multiorgan failure including encephalopathy, coagulopathy, pancreatitis, and acute kidney injury (AKI).[12] Biochemical abnormalities include elevation in serum transaminases, hyperbilirubinemia, renal dysfunction, thrombocytopenia, hyperammonemia, and lactic acidosis. The synthetic

Box 3
Mississippi classification and Tennessee classification

Mississippi Classification	Tennessee Classification
Class 1: Platelets <50,000/mm^3 AST or ALT >70 units/L Lactate dehydrogenase (LDH) >600 units	Complete syndrome: Platelets <100,000/mm^3 AST >70 units/L LDH >600 units/L
Class 2: Platelets 50,000–100,000/mm^3 AST or ALT >70 units/L LDH >600 units	Incomplete syndrome: Any one or two of the above
Class 3: Platelets >100,000/mm^3 AST or ALT >40 units/L LDH >600 units	

function of the liver is affected leading to coagulation disorders. Disseminated intravascular coagulation complicates 10% of cases.[12] The "Swansea Criteria" has been demonstrated to have 100% sensitivity and 85% positive predictive value in the diagnosis of AFLP (**Box 4**).[3] Liver imaging shows fatty infiltration and biopsy, if done, shows microvascular fat deposition in the pericentral zone with periportal sparing.[14]

The maternal mortality rate of AFLP in the past was reported to be as high as 90%; however, given our better understanding of the disease and advances in intensive care, maternal mortality now is reported to be around 7% to 18%. Early delivery has improved fetal prognosis but mortality remains substantial at 9% to 23%.[33] Most Patients recover completely; however, severe refractory cases will require liver transplantation.[34] Approximately 20% of women who develop AFLP carry LCHAD-deficient fetuses. Thus, monitoring the offspring of women who develop AFLP at birth for symptoms is recommended. Testing for the mutation can be done in symptomatic infants. Early recognition with rapid delivery is the cornerstone of management, followed by supportive therapy to the mother and fetus.[33] Therapeutic plasma exchange has also been reported to be beneficial.[35]

CHRONIC LIVER DISEASE IN PREGNANCY

Pregnancy represents a unique opportunity to identify chronic conditions and connect individuals to multidisciplinary management or outpatient follow-up. Screening for hepatitis B virus (HBV) and HCV is now recommended in every pregnancy; however, given the increasing prevalence of NAFLD and alcohol-associated liver disease, these injuries are also common in women of childbearing age. It is imperative to screen women with chronic liver disease (CLD) for fibrosis as portal hypertension (PHT) will worsen during pregnancy and significant increases maternal/fetal risk.

Hepatitis B

HBV infection acquired in adulthood is spontaneously cleared in more than 90% of healthy immunocompetent adults. However, infants who are infected via mother-to-child transmission (MTCT) have a 90% risk of developing chronic hepatitis B (CHB) infection without active/passive immunization. MTCT is responsible for about 50% of the global disease burden of CHB.[36] The peripartum period is the primary risk period for MTCT.[37]

Box 4
Swansea criteria for acute fatty liver of pregnancy

Clinical Features
- Nausea and vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy

Radiography Features
- Ascites or echogenic liver

Histologic Features
- Microvascular steatosis on liver biopsy

Laboratory Features
- Bilirubin >0.8 mg/dL
- Hypoglycemic <72 mg/dL
- Leukocytosis >11
- AST or ALT >42 units/L
- AKI or Creatinine >1.7 mg/dL
- Coagulopathy or PT > 14 s
- Ammonia >74 μmol/L
- Uric acid >340 μmol/L

Six or more of the above features are required for diagnosis in absence of another cause.*Abbreviations:* ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time.

Fig. 2 describes the approach to antiviral therapy during pregnancy. For women who meet guidelines for HBV treatment (increased ALT and high viral load or concerns for fibrosis), HBV treatment should be initiated during pregnancy.[2] For mothers who do not otherwise meet criteria for antiviral therapy who have HBV DNA is greater than 200,000 IU/mL, antiviral prophylaxis should be initiated at 28 to 32 weeks of gestation for adequate suppression of viral load and prevention of MTCT.[37] For HBV DNA levels of 7-log IU/mL or greater, there should be consideration of earlier treatment to ensure adequate time to reach HBV-DNA levels less than 200,000 IU/mL at delivery.[38]

Given low resistance, high efficacy, and safety in pregnancy, tenofovir disoproxil fumarate is preferred,[2] although there is increasing data for the use of tenofovir alafenamide for HBV in pregnancy.[39] HBV flares have been reported during pregnancy and postpartum following discontinuation of antivirals. Although most are asymptomatic, jaundice, hepatic decompensation, and pregnancy complications have been reported.[40] If antiviral therapy was used solely to prevent MTCT, treatment can be discontinued at delivery or during the first 3 months postpartum. There is a risk for postpartum flare irrespective of if treatment was given or when treatment is stopped. Monitoring is imperative during the first 6 months after birth and treatment discontinuation.[41] Cesarean delivery has not been shown to reduce the risk of MTCT and is not indicated unless required for obstetric indications. Amniocentesis may increase MTCT risk, especially in women with viral load 7-log IU/mL or greater.[2]

After delivery, infants born to hepatitis B surface antigen (HBsAg)-positive mothers should receive the hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours of birth (Fig. 3). Breastfeeding is encouraged. At age 9 to 12 months, infants should receive after vaccination serologic testing for HBsAg and anti-HBs. If HBsAg-positive, infants should be referred for appropriate follow-up.[42]

There is conflicting data regarding the influence of HBV infection on pregnancy outcomes (Table 2 for summary of association of chronic liver diseases with pregnancy outcomes and Table 3 for summary of association with fetal outcomes). Maternal outcomes including an increased risk of gestational diabetes mellitus (GDM) and antepartum hemorrhage have been reported.[43] HBV infection has been associated with a decreased risk of preeclampsia, particularly in the Asian population.[44] Preterm births, stillbirths, and spontaneous abortions have also been reported in pregnant women with HBV infection.[43] A recent systematic review and meta-analysis by Jiang and colleagues demonstrated a higher risk of ICP among HBV-positive mothers and an increased risk of HBV infection among patients with ICP. Given these findings, they suggest screening for HBV infection among pregnant women with ICP.[45]

Hepatitis C

HCV infection diagnosed during pregnancy has increased, particularly due to intravenous drug use and the opioid epidemic.[46] The rate of maternal HCV infection increased from 1.8 cases per 1000 live births to 4.7 cases per 1000 live births in the United States.[47] The AASLD recommends universal screening for HCV infection during each pregnancy with an anti-HCV antibody test, and those with positive results should be referred to a specialist for the evaluation of antiviral therapy after completion of pregnancy and breastfeeding.[2] More recently, the center for disease control and prevention (CDC), the United States preventive services task force (USPSTF), and American College of obstetricians and gynecologists (ACOG) have all also endorsed universal screening for HCV during pregnancy.

Understanding the risk of MTCT of HCV and association of HCV with pregnancy outcomes is important in counseling women. The rate of MTCT, which can occur

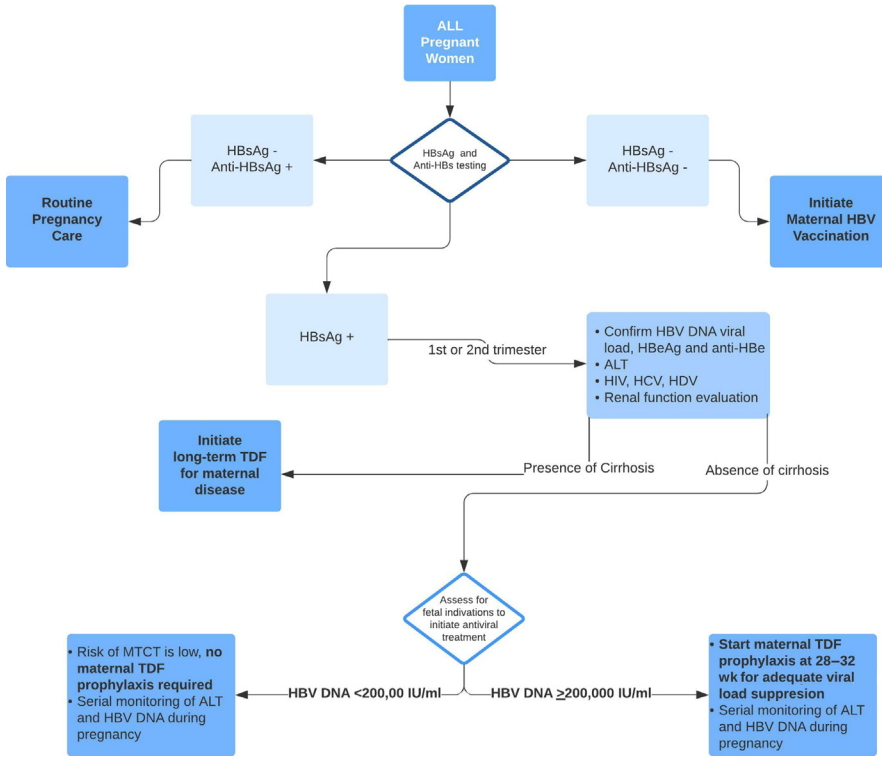

Fig. 2. Approach to antiviral therapy during pregnancy.

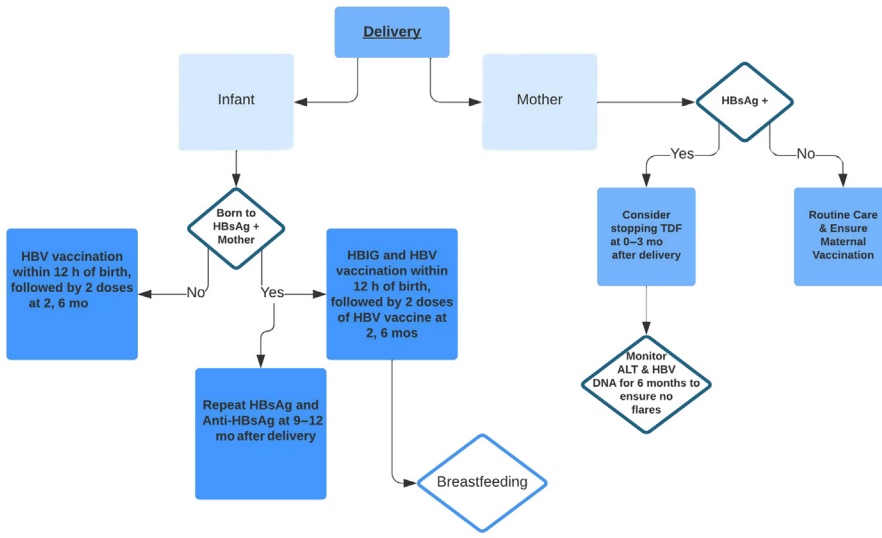

Fig. 3. Approach to infants born to HBsAg-positive mothers.

Table 2
Summary of effect of chronic liver diseases in pregnancy on the risk of maternal outcomes

Disease	Infertility	GDM	IPC	Hypertensive Disorders of Pregnancy
HBV	No change in risk	Increased	Increased	Decreased
HCV	No change in risk	Increased	Increased	No known change in risk
Cirrhosis	Increased	No change in risk	Increased	Increased
NAFLD	No change in risk[a]	Increased	No known change in risk	Increased
AIH	No known change in risk	Increased	No known change in risk	Increased
WD	Increased	No change in risk	No known change in risk	No known change in risk
PBC	No known change in risk	No known change in risk	No known change in risk	No known change in risk
PSC	No known change in risk	No known change in risk	No known change in risk	No known change in risk

[a] In the absence of concomitant PCOS.

intrapartum, peripartum, or postpartum (most common), has been estimated to be 5.8% in mothers with HCV viremia and 10.8% in mothers with HCV–human immunodeficiency virus (HIV) coinfection.[48] Other than HIV suppression in HIV/HCV-coinfected women, there are no known interventions to decrease the risk of MTCT of HCV.[46] There may be passive transfer of HCV antibody from MTCT, which can

Table 3
Summary of effect of chronic liver diseases in pregnancy on the risk of fetal outcomes

Disease	Spontaneous Abortion	Preterm Birth	Stillbirth	Risk of MTCT
HBV	Increased	Increased	Increased	HBeAg (–): 10%–40% HBeAg (+): 70%–90%
HCV	No known change in risk	Increased	No known change in risk	5.8%
Cirrhosis	Increased	Increased	Increased	N/A
NAFLD	Increased	Increased	No known change in risk	N/A
AIH	Increased	Increased	No known change in risk	N/A
WD	Increased	No known change in risk	Increased	N/A
PBC	No known change in risk	Increased	No change in risk	N/A
PSC	No known change in risk	Increased	No change in risk	N/A

Table 4
Breastfeeding recommendations in chronic liver diseases

Disease	Recommendation
HCV	Safe *unless* skin breakdown with bleeding is present or treatment with antiviral therapy is ongoing
HBV	Safe even if cracked or bleeding nipples because infants are protected by vaccination and HBIG
Cirrhosis	Safe[a]
NAFLD	Safe
AIH	Safe
WD	Not recommended
PBC	Safe only if UDCA used as treatment option
PSC	Safe only if UDCA used as treatment option

[a] Adequate protein intake is encouraged.

remain for up to 18 months, thus recommendations suggest that these children should be tested for anti-HCV after 18 months of age and subsequently with HCV-RNA to confirm viremia.[49] In order to decrease the risk of MTCT, avoiding invasive fetal monitoring, episiotomy, and prolonged rupture of the membranes is recommended. If invasive prenatal testing is required, amniocentesis is favored over chorionic villus sampling and fetal blood sampling. Neither the mode of delivery nor breastfeeding influence the risk of MTCT.[50,51] Breastfeeding is recommended, unless skin breakdown with bleeding is present or treatment with antiviral therapy is ongoing[2] (**Table 4**). **Box 5** summarizes current data on association of HCV with adverse pregnancy outcomes.

Treatment of hepatitis is generally encouraged prepregnancy or postpartum. If treatment is delayed, HCV polymerase chain reaction (PCR) testing should be performed before therapy because there are reports of spontaneous clearance after pregnancy. If treatment postpartum is desired, confirmation HCV-RNA before postpartum treatment is recommended.[2,55] The safety and efficacy of direct-acting antivirals during pregnancy is currently being evaluated.[56] Although previously recommended to avoid any treatment during pregnancy, current recommendations suggest treatment considerations on an individual basis after a risk and benefit discussion between provider and patient. Discussions should include the risk of MTCT, risk for virologic relapse, finances, patient preferences, and limited safety data.

Box 5
HCV impact on maternal and fetal outcomes

- Higher rates of preterm birth, small for gestational age, low birth weight, and intrauterine fetal death.[52]
- A 20-fold increased risk of ICP compared with non-HCV pregnant women.[53] Bile acids should be checked in HCV-positive mothers with pruritus and HCV-antibody should be checked in women with ICP.
- Reports of increased rates of antepartum hemorrhage, GDM, postpartum hemorrhage and premature rupture of membranes.[54]
- Course of HCV infection is not affected by pregnancy; no specific monitoring is required.[2]

Nonalcoholic Fatty Liver Disease

NAFLD is the most common chronic liver disease found in women of childbearing age.[57] Physiologic changes of pregnancy including increased adipose tissue, decreased insulin sensitivity, and increased lipolysis may increase the metabolic risks of women with NAFLD.[2] NAFLD has been associated with maternal complications including GDM, postpartum hemorrhage,[2,58,59] and gestational hypertension[59] (see **Table 2**). An increased risk of fetal outcomes such as preterm births and large for gestational birth has also been found in pregnant patients with NAFLD.[59] A recent systematic review found a novel association between pregnant NAFLD patients and a history of prior miscarriage or abortion, thought to be related to obesity.[59] Given the high incidence of adverse maternal and fetal outcomes in pregnant patients with NAFLD, preconception counseling should include a review of the potential risks associated with pregnancy in NAFLD in addition to counseling about the benefits of weight optimization and metabolic comorbidities before conception.[2] Breastfeeding is encouraged in NAFLD patients because lactation decreases maternal lipid, glucose, and insulin levels while improving insulin sensitivity. A longer duration of lactation has been associated with a lower rate of future NAFLD among offspring and a lower incidence of maternal metabolic complications including NAFLD, increased postpartum weight loss, and a reduction in heart disease and diabetes.[2,60,61] Although there are no NAFLD-specific medications are approved for use in or after pregnancy, management of NAFLD in pregnancy is focused on preventing excess weight gain, close monitoring of fetal growth, monitoring of liver tests similar to nonpregnant women, treatment of metabolic comorbidities, and lifestyle modifications to achieve an optimal weight.[2] Given the risk of disease progression, follow-up with a provider experienced in NAFLD management should be encouraged postpartum.

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can progress to cirrhosis if left untreated.[62] Patients with known and undertreated AIH may have an increased risk of pregnancy-related complications. The evaluation and diagnosis in the pregnant patient is similar to that of a nonpregnant patient.[2] Histology may be required in disease staging and help guide clinical management, especially in patients who lack atypical findings, negative autoantibodies, and or immunoglobulin G levels.[63] There may be a moderately increased risk of preterm birth and small for gestational age with liver biopsy, thus a discussion with the mother regarding risks weighed against the advantages of obtaining a liver biopsy is important.[64] About 20% of patients with AIH will flare during pregnancy,[65] thus AASLD recommends that conception should be delayed for at least 1 year after a stable dose of immunosuppression is maintained. Liver enzymes should be monitored during each trimester and every 2 to 4 weeks for at least 6 months postpartum due to the high rates of flares and relapse, respectively.[2,66] AIH has been associated with an increased risk of preterm birth, small for gestational age children,[67,68] spontaneous abortions,[1,66] GDM,[69] and hypertensive complications including preeclampsia, eclampsia, and/or hemolysis, elevated liver enzymes, low platelets (HELLP)[62] (see **Tables 2** and **3**). According to AASLD, patients with AIH should be counseled regarding the potential risks of treatments including azathioprine and 6-mercaptopurine (6-MP) but these drugs are safe in pregnancy and lactation.[2,62] Steroids indicated for treatment of AIH, prednisone and budesonide, are considered low risk in pregnancy and lactation. Mycophenolic acid (MPA) is contraindicated in pregnancy and lactation due to high risk of congenital

malformations and spontaneous abortions. MPA should be discontinued 6 weeks before conception attempts, and a negative pregnancy test is required within 1 week of starting treatment with MPA.[2,70] Breastfeeding is safe.[2]

Wilson Disease

Wilson disease (WD) is an autosomal recessive disorder associated with a mutation on the P-type aminophospholipid transporter synthase ATP7B transmembrane copper carrier, resulting in excess copper deposition, especially in the liver and brain.[71] Due to expression of ATP7B in the placenta, uterus and ovaries, there are effects of excess copper on pregnancy outcomes such as higher rates of infertility, stillbirth, and spontaneous abortions[2,71] (see **Tables 2** and **3**). Thus, women with WD should be enrolled in genetic counseling and medication safety regarding various treatment options needs to be discussed. AASLD recommends dose reduction of chelating agents including D-penicillamine and trientine by 25% to 50% of the prepregnancy dose due to the risk of fetal teratogenicity.[2,72] Zinc dosage can be safely maintained throughout pregnancy,[73] although a recent case series demonstrated birth defects with zinc usage in pregnancy raising the possibility that this treatment's safety profile needs to be further evaluated.[71] During pregnancy, close monitoring of copper levels is necessary to avoid over chelation during pregnancy because this may adversely affect the fetus.[2] If treatment is discontinued during pregnancy, there is a high risk of maternal liver failure, WD flares, and copper deposition in placenta with subsequent fetal damage.[1] After delivery, chelating agents require uptitration to prepregnancy doses and breastfeeding is associated with infant risks as all WD drugs are excreted in breast milk, raising potential of copper deficiency in the infant. For these reasons, breastfeeding is not recommended for mothers with WD.[2,74]

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is a chronic, autoimmune cholestatic liver disease of the intrahepatic bile ducts, predominantly affecting women. Most patients are diagnosed in the sixth decade of life but 25% of patients are of childbearing age at diagnosis,[75] and 33% of new diagnoses are made during pregnancy.[2] Pregnancy in PBC was thought to have poor outcomes[76] but recent literature reports good maternal and fetal outcomes.[75,77] Aminotransferases and total bile acid concentrations are expected to remain normal during pregnancy and an increase in these values may suggest cholestasis.[78] Thus, it is recommended to measure bile acids during pregnancy in those with known PBC, and treat if elevated, particularly in the 40 to 100 range.[2] A recent study suggested that pregnancy in women with PBC and PSC is well tolerated but linked to higher rates of preterm birth, possibly due to high levels of maternal bile acids.[77] Postpartum, 60% to 70% of patients with PBC may have an increase in disease activity,[79] thus close monitoring postpartum is recommended. Immunoglobulin M levels and M2 antibody titers may decline in pregnancy but return to baseline levels postpartum.[2,80] Pruritis is a common symptom of PBC, which may worsen in about 50% of patients with PBC during pregnancy.[79] UDCA is not associated with adverse effects and is recommended for PBC in pregnancy and during breastfeeding.[2,80] Obeticholic acid and fibrates are not recommended during pregnancy and lactation due to insufficient safety data. For the management of pruritis in pregnancy, addition of cholestyramine, rifampin, antihistamines, or SAMe to UDCA may be considered. Vitamin K deficiency may be exacerbated by cholestyramine, thus regular monitoring of prothrombin time (PT) is recommended.[2]

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a progressive autoimmune, cholestatic liver disease that affects the intrahepatic and extrahepatic bile ducts, leading to fibrosis and cirrhosis.[81] Seventy percent of patients with PSC have concurrent inflammatory bowel disease (IBD),[82] limiting data available on outcomes of pregnant patients without IBD. Although a decrease in fertility has not been linked to PSC,[83] there have been reports of increased rates of preterm births[77,84] and cesarean delivery in these patients.[84] Nonetheless, no differences were seen in small for gestational age, stillbirths, or neonatal deaths.[2,84] Although liver tests remain normal in most patients, up to one-third develop nonclinically significant increased liver tests postpartum.[84] Guidelines suggest consideration of measurement of total serum bile acids in the first trimester. In the event of new-onset or worsening pruritis in pregnancy, comparison of bile acid levels to the first trimester will aid in excluding ICP.[2] No data currently supports a therapeutic benefit of UDCA in PSC[2,85] but pregnant patients on UDCA are more likely to have stable liver enzymes than those who are not.[83] Patients who are taking UDCA before pregnancy can continue throughout their pregnancy because UDCA is considered safe in pregnancy.[77] Patients with PSC who develop new pruritus or worsening liver enzymes during pregnancy should be initially evaluated with ultrasound due to possibility of new stricture formation. Magnetic retrograde cholangiopancreatography can safely be performed in the second and third trimesters but should be avoided in the first trimester. Endoscopic retrograde cholangiopancreatography should be reserved for cases requiring endoscopic therapy.[85] Treatment of pruritus in pregnancy is similar to that of PBC.

Cirrhosis and Portal Hypertension

Fertility is not affected by compensated cirrhosis but will be reduced in those with clinically significant PHT and decompensated cirrhosis, due to hepatocyte injury leading to chronic elevation in estrogen levels and subsequent anovulation.[86] Complications of cirrhosis during pregnancy include worsening PHT and esophageal variceal bleeding.[87] Variceal bleeding is more common in the second trimester of pregnancy and during labor due to increased circulating blood volume and decreased venous return due to gravid uterus pressure on the inferior vena cava.[88] Due to improved care of pregnant women with cirrhosis, PHT and cirrhosis are no longer considered absolute contraindications to pregnancy.[2] The Model for End-Stage Liver Disease (MELD) score has been used to predict risk of significant liver-related complications during pregnancy. A MELD score of 10 or greater predicted liver-related complications with 83% sensitivity and specificity, whereas MELD scores less than 6 predicted positive outcomes with least complications.[89] Still all women with cirrhosis, especially those with MELD 10 or greater or history of prior hepatic decompensation, should be counseled on the potential risk of worsening liver disease during pregnancy.[2]

Portal Hypertension in Pregnancy

One of the most dreaded complications of PHT in pregnant women with cirrhosis is variceal bleeding. Maternal and fetal mortality is high, with a rate of 18% and 11%, respectively.[90] Current guidelines recommend preconception esophagogastroduodenoscopy (EGD) screening for varices within 12 months of conception, even in patients with noncirrhotic PHT (**Fig. 4** for approach to management). A second trimester EGD is recommended in women who do not receive a preconception EGD, have new symptoms of hepatic decompensation, or have an ongoing liver injury (active alcohol use, untreated HCV infection). Nonselective beta blockers (NSBB) are recommended for primary and

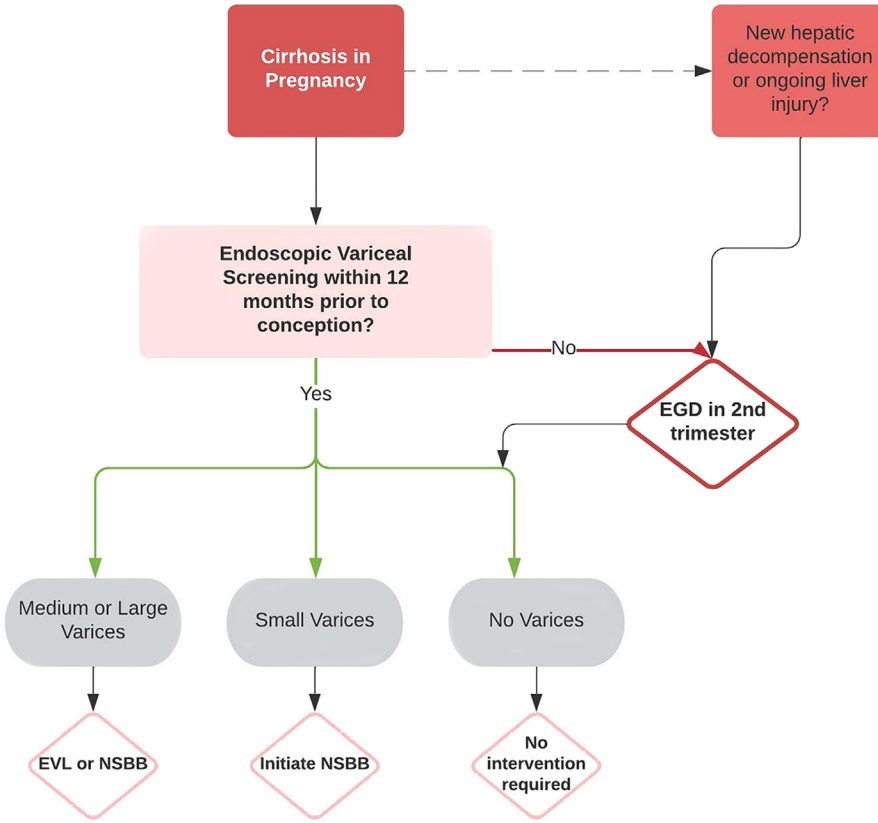

Fig. 4. Approach to PHT in pregnancy.

secondary prophylaxis of bleeding. Propanolol is the favored NSBB in pregnancy. Esophageal variceal ligation (EVL) can be performed on medium or large varices (>5 mm) or if there is evidence of high-risk bleeding stigmata such as a red whale sign or cherry red spots. During EGD in pregnancy, safe anesthetics include propofol, fentanyl, midazolam, and meperidine.[2] Endoscopy is generally safe in pregnancy but the risks and benefits must be reviewed to assess patient readiness for procedure.[1]

Complications of PHT in pregnancy include acute variceal hemorrhage and splenic artery aneurysm (**Fig. 5**). Management of acute variceal hemorrhage in pregnancy is similar to that of nonpregnant individuals.[2] In patients with refractory bleeding despite medical and endoscopic measures, rescue transjugular intrahepatic portosystemic shunt (TIPS) is not contraindicated if refractory bleeding risk is high.[91] Secondary prophylaxis for variceal bleeds include NSBB and EVL, with preference of a combination of therapy.[92] Splenic artery aneurysm rupture is a rare complication that may present as abdominal pain and syncope in the third trimester, with high mortality rates (70%–95%) in both fetus and mother. Management typically includes transcatheter embolization with ligation splenectomy for cases in which embolization fails or is unavailable.[93]

The mode of fetal delivery should only be guided by obstetric indications because there is no benefit to vaginal versus cesarean section.[1,2] Vaginal deliveries carry an increased risk of variceal bleeding because of increased intra-abdominal pressures from stress maneuvers during labor.[94] Cesarean sections are associated with

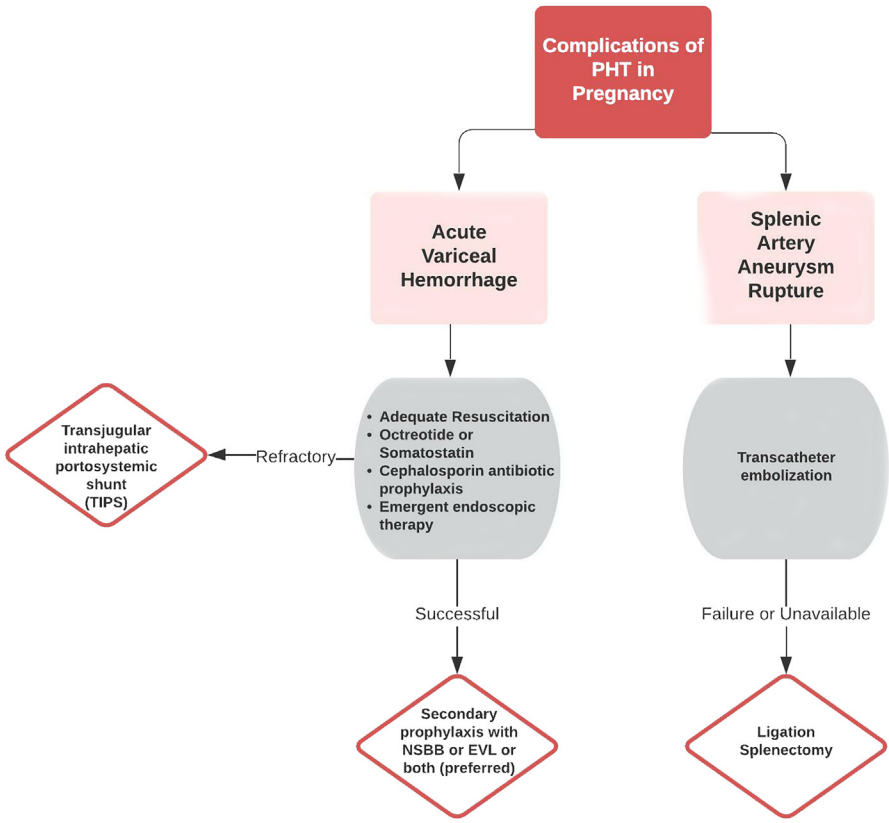

Fig. 5. Complications of PHT in pregnancy.

increased risks of postpartum ascites and bleeding from vessel injury but may be required during fetal distress.[95]

Fetal and Maternal Outcomes of Cirrhosis in Pregnancy

Close monitoring of cirrhotic patients during pregnancy is important as complications may result in high morbidity and mortality. Management in a multidisciplinary center with maternal fetal medicine and gastroenterology/hepatology is recommended.[1] Although mortality was previously thought to be high in these patients, newer studies report rates less than 2%.[96] Data from the United States Nationwide Inpatient Sample revealed hepatic decompensation in 15% of pregnant women with cirrhosis, ascites in 11% and variceal bleed in 5%.[90] A recent population-based study identified increased rates of ICP, puerperal infections, preterm births, large for gestational age infants and neonatal respiratory distress among women with cirrhosis.[96] Pregnancy in cirrhosis has also been associated with higher risks of cesarean delivery, placenta abruptae, and gestational hypertension.[90] Spontaneous abortion and stillbirth has been reported to be more common in women with cirrhosis.[97]

LIVER DISEASE COINCIDENTAL TO PREGNANCY

Evaluation of the patient with liver disease in pregnancy should also address potential liver disease "coincidental to pregnancy." This includes acute viral hepatitis (including

hepatitis A virus [HAV], hepatitis E virus [HEV], and herpes simplex virus [HSV]) that may present during pregnancy, biliary disease (ie, gallstones, which have increased incidence of complications in pregnancy), as well as liver lesions. Management of acute viral hepatitis is largely supportive although may be associated with a more severe course in pregnancy particularly with HEV. Ultrasound should be performed in the evaluation of abnormal liver tests, most notably if associated with other symptoms such as abdominal pain, to assess for gallstones, and evidence of cholecystitis should prompt surgical evaluation. Finally, although most liver lesions can be safely monitored in pregnancy, adenomas greater than 5 cm are associated with increases in size in pregnancy and potential rupture.[2] Ideally address before pregnancy with embolization or resection, large lesions require intervention and close follow-up with imaging during each trimester is recommended irrespective of size.

SUMMARY

Liver disease in pregnancy represents a broad spectrum of liver pathologic condition and liver-related conditions that require early recognition in order to guide care. Evaluation requires judicious testing to exclude chronic liver disease, coincidental liver injury, and pregnancy specific liver injury. Early recognition and management of liver disease in pregnancy is crucial in order to optimize maternal and fetal outcomes, as well as to link patients to liver specialists and possible ongoing care after delivery if indicated.

CLINICS CARE POINTS

- Evaluation of liver injury in pregnancy should include a comprehensive evaluation for underlying liver disease as well as consideration for liver disease unique to pregnancy.
- Symptoms of Hyperemesis gravidarum and ICP resolve during pregnancy and at delivery, respectively.
- Treatment of AFLP and HELLP is with urgent delivery.
- Ursodiol is the treatment of choice for ICP.
- All pregnant individuals should be screened for hepatitis B and for hepatitis.
- Treatment of hepatitis B in pregnancy is determined based on the maternal viral load and disease stage.
- Poor disease control of autoimmune hepatitis is associated with adverse pregnancy outcomes.
- Endoscopic evaluation should occur within 12 months prior to conception in patients with cirrhosis.

DISCLOSURE

G. Karim has no disclosures. D. Giri has no disclosures. T. Kushner has served in advisory role for Gilead, Abbvie. N. Reau has served in advisory role for Gilead, Abbvie.

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