Liver Disease During Pregnancy

Nancy Reau, MD, FACG[1], Santiago J. Munoz, MD, FACG[2] and Thomas Schiano, MD, FACG[3]

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INTRODUCTION

Recognizing and managing liver diseases during pregnancy is complex. Normal pregnancy physiology must be accounted for, and testing algorithms must balance the value of the information attained against the risk to both the pregnant patient and fetus. Liver disease can be preexisting, acquired during pregnancy, or can occur because of the pregnancy itself. This monograph will describe normal physiologic changes during pregnancy and the evaluation and management of common liver diseases that can occur during pregnancy and early postpartum period.

NORMAL PHYSIOLOGY OF PREGNANCY AND LIVER DISEASE

The overall blood volume increases during the second trimester because of activation of the renin-angiotensin system, which also leads to sodium and water retention (1). Cardiac output increases by up to 30%–40% with much occurring during the first trimester, and there is increased portal venous flow and increased compression of the gravid uterus on the inferior vena cava (2). This is especially important in individuals with preexisting portal hypertension, which will be exaggerated during pregnancy.

The hormonal changes that normally occur during pregnancy affect the metabolism, synthesis, and excretion of various proteins, such as increases in fibrinogen and some clotting factors (1,3). Serum aminotransferases and bilirubin remain normal during pregnancy, while the albumin typically decreases. Alkaline phosphatase is elevated and when fractionated is found to be of placental origin (3,4).

EVALUATION OF A PREGNANT PATIENT WITH ABNORMAL LIVER ENZYMES

In pregnant patients without preexisting liver disease, a new elevation of aminotransferases or bilirubin should trigger further testing (Figure 1). This includes an evaluation for viral hepatitis, autoimmune hepatitis, alcohol-related and fatty liver disease, and drug-induced liver injury, similar as in the nonpregnant patient. However, the timing of these biochemical abnormalities should be assessed in the context of liver diseases that occur uniquely to pregnancy. A careful history, physical examination, and an assessment of medications, especially herbal and alternative medicines, is essential. A nonspecific elevation in aminotransferases can be seen in many underlying systemic diseases that themselves may be affected by pregnancy. International normalized ratio and prothrombin time are normal during pregnancy; however, pregnancy by itself is a hypercoagulable state. Thrombophilias may be unmasked during pregnancy and result in the Budd-Chiari syndrome; therefore a family or personal history of clotting should be sought, and hepatic vein thrombosis should be considered in the differential, especially if ascites or tender hepatomegaly is present. Patients with known Budd-Chiari syndrome need to be counseled about the potential risks of worsening disease during pregnancy, and their anticoagulation and/or cytoreductive medications may need to be adjusted or modified. It is imperative that a hematologist be part of the multidisciplinary team managing these patients (5).

LIVER DISEASES UNIQUE TO PREGNANCY

Several liver disorders are unique to pregnancy and are best recognized by a combination of both clinical presentation and gestational age (Figure 2). Prompt identification is imperative because they can result in significant morbidity and mortality to both the pregnant patient and the fetus.

The first trimester

Hyperemesis gravidarum. Persistent vomiting and significant dehydration developing in the first trimester of pregnancy are characteristic of hyperemesis gravidarum {see chapter on hyperemesis gravidarum in this monograph}. Mild to moderate liver enzyme elevation is common and found in nearly half of patients with hyperemesis gravidarum. However, development of jaundice and/or hepatic synthetic dysfunction is uncommon, and their presence requires diligent search for other etiologies of liver injury. The abnormal liver enzymes typically resolve as the vomiting stops in the second trimester. Management is supportive, including eating smaller and more frequent meals, antiemetics in severe cases, and treatment of dehydration and hospitalization as necessary.

The second and third trimesters

Preeclampsia and eclampsia. The onset of arterial hypertension, often accompanied by new-onset proteinuria, developing after the 20th week of gestation define preeclampsia, a relatively frequent hypertension-related complication of pregnancy (6). When grand malseizures occurred, the term eclampsia was previously used, but preclampsia with severe features is now the preferred terminology. Gastroenterology consultation is typically sought when the patient develops right upper quadrant or epigastric abdominal pain in the setting of abnormal liver enzymes. The pattern of liver test abnormalities is that of a necroinflammatory process, rather than cholestatic, and consequently, other etiologies need to be excluded (viral hepatitis; ischemia; hemolysis,

[1]Section of Hepatology, Rush University Medical Center, Chicago, Illinois, USA; [2]Drexel College of Medicine and Virtua Health System Cherry Hill, New Jersey, Philadelphia, Pennsylvania, USA; [3]Recanati-Miller Transplantation Institute, the Mount Sinai Medical Center, New York, New York, USA.
Correspondence: Nancy Reau, MD, FACG. E-mail: nancy_reau@rush.edu.
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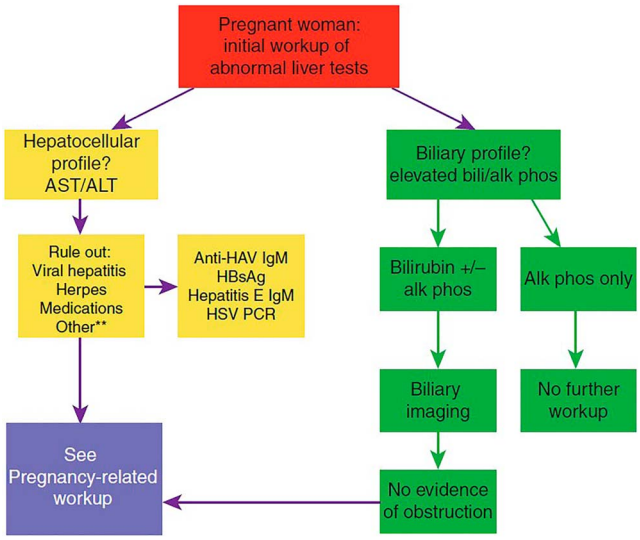

Figure 1. Evaluation of a pregnant patient with abnormal liver enzymes. Reused from Tran TT, Ahn J, Reau NS. ACG clinical guideline: Liver disease and pregnancy. Reprinted with permission from Am J Gastroenterol 2016; 111(2):176–194. doi:10.1038/ajg.2015.430. ALT, alanine transaminase; AST, aspartate transaminase; HSV, herpes simplex virus; IgM, immunoglobulin M.

elevated liver enzymes, and low platelets [HELLP]; and acute fatty liver of pregnancy [AFLP]). Hepatocyte necrosis is believed to be caused by vasoconstriction-induced ischemia and fibrin precipitation within the hepatic sinusoids. The liver involvement in preeclampsia with severe features rarely leads to acute hepatic failure, but patients may develop subcapsular and intrahepatic hematomas, rarely even hepatic rupture (7). A baseline imaging study of the liver is important, with repeat studies warranted for worsening or sudden changes in abdominal pain. If there are no severe features, delivery is recommended at 37 weeks. Delivery is considered the only intervention to resolve acute symptoms (8).

The HELLP syndrome. This third trimester complication consists of the development of hemolytic anemia, elevated liver enzymes, and low platelets (9). The HELLP syndrome is associated with advanced maternal age, nulliparity, and multiparity. At times, the syndrome may also develop in the first week postpartum and can occur in 20% of patients with preeclampsia with severe features. Genetic and environmental factors are believed to trigger a systemic angiopathic inflammatory response (10).

Patients may be asymptomatic or develop nonspecific symptoms such as nausea, vomiting, malaise, and/or upper abdominal pain. Arterial hypertension and proteinuria are observed in up to 80% of cases. The diagnosis of the HELLP syndrome is based on the typical laboratory abnormalities (hemolytic anemia, platelets $<100{,}000/mm^3$, and elevated alanine transaminase [ALT]/aspartate transaminase [AST] levels twice the upper limit of normal). Significant hyperbilirubinemia is uncommon. Intrahepatic hematomas, hemorrhages, and hepatic infarction may occur in patients with the HELLP syndrome. Hepatic ultrasound should be obtained at baseline, followed by computed tomography or magnetic resonance imaging in cases with a very high ALT level or severe abdominal pain.

Expectant management is recommended for well-encased hepatic hematomas, but for enlarging hematomas or signs of rupture (hemodynamic compromise, peritoneal signs), percutaneous embolization of the relevant branches of the hepatic artery, or surgery, should be considered (10). Severe abdominal pain, leukocytosis, or fever should raise the suspicious of hepatic infarction. Liver transplantation has been successfully used in patients with worsening liver failure despite intensive medical therapy (11). The protocol developed by the University of Mississippi is often used in the management of patients with the HELLP syndrome and consists of the use of glucocorticoids and magnesium sulfate and control of the systolic blood pressure (10).

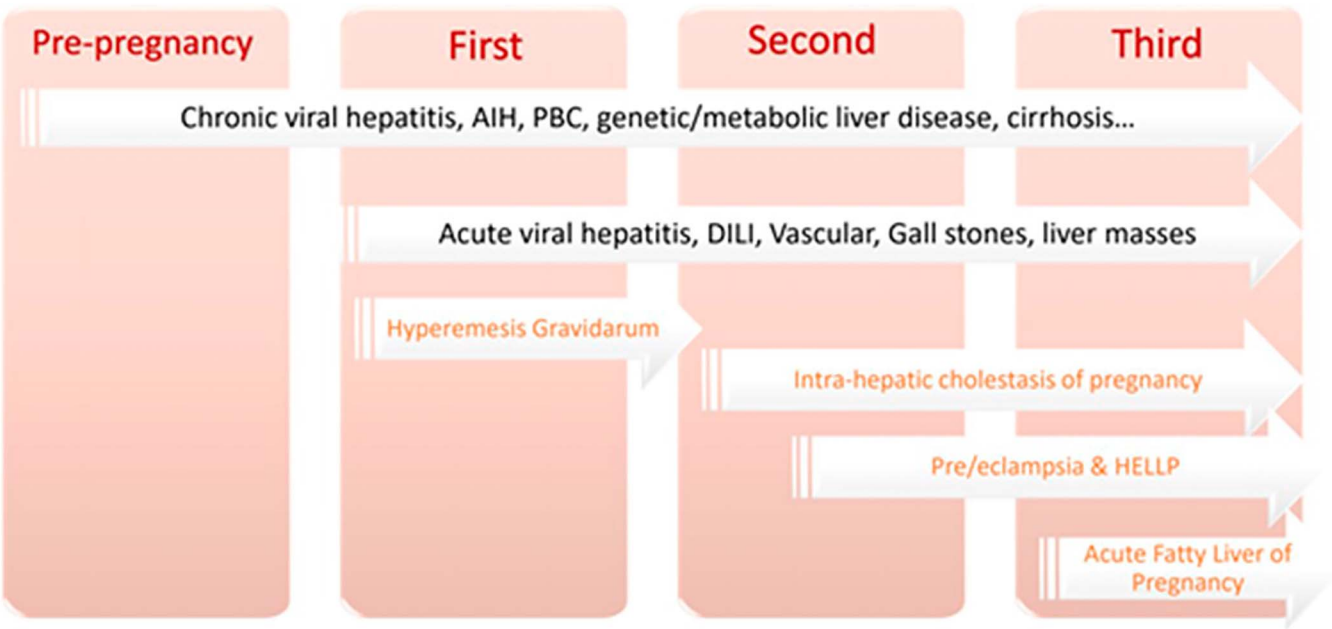

Figure 2. Liver disease unique to pregnancy—trimester-based approach. AIH, autoimmune hepatitis; DILI, drug-induced cholestasis; HELLP, hemolysis, elevated liver enzymes, and low platelets; PBC, primary biliary cirrhosis.

Table 1. Swansea criteria

Six or more criteria required in the absence of another cause	
Vomiting	
Abdominal pain	
Polydipsia/polyuria	
Encephalopathy	
Elevated bilirubin	>14 μmol/L
Hypoglycemia	<4 mmol/L
Elevated urea	>340 μmol/L
Leukocytosis	>11 × 10^6 cells/L
Ascited or bright liver on ultrasound scan	
Elevated transaminases (AST or ALT)	>42 IU/L
Elevated ammonia	>47 μmol/L
Renal impairment; creatinine	>150 μmol/L
Coagulopathy; prothrombin time	>14 s or APPT >34 s
Microvesicular steatosis on liver biopsy	

ALT, alanine transaminase; APPT, activated partial thromboplastin time; AST, aspartate transaminase.

Glucocorticoids are used to accelerate fetal lung maturation because fetal prognosis is more related to the gestational age than to the HELLP syndrome by itself. By contrast, the progression of the HELLP syndrome can be associated with maternal mortality. The thrombocytopenia of the HELLP syndrome can be severe, but there are no contraindications to platelet transfusions. If the patient requires a cesarean section, platelet transfusions are necessary for platelets less than 50,000; for vaginal delivery, platelet transfusions are required during delivery for platelets less than 30,000. There are no studies on the use of the recently available thrombopoietin receptor agonists (eltrombopag and lusutrombopag) for severe thrombocytopenia of the HELLP syndrome, but extreme caution should be exercised in view of the hypercoagulable state of pregnancy.

Acute fatty liver of pregnancy. AFLP is an uncommon form of acute liver injury typically presenting in the third trimester and associated with a high risk of progression to acute liver failure (12). The symptoms are nonspecific (abdominal pain, nausea, and vomiting) and develop in the context of marked elevation of aminotransferases (ALT/AST) and hyperammonemia. Hyperbilirubinemia can be marked, and hypoglycemia may be present, in contrast to the HELLP syndrome, but overlapping and differentiation with the coexisting HELLP syndrome can be challenging. AFLP is more common in twin pregnancies and low maternal body mass index.

The clinical diagnosis of AFLP has been facilitated by the use of the Swansea criteria (Table 1): 6 or more commonly obtained clinical and laboratory variables establish the diagnosis of AFLP with high accuracy, often obviating the need for liver biopsy.

The hallmarks of the management of AFLP include prompt diagnosis, early delivery, and symptomatic care, including intensive care unit care as necessary (13,14). The progression of AFLP to acute liver failure can be rapid and signaled by the onset of hepatic encephalopathy, coagulopathy, hypoglycemia, and renal failure. Pancreatitis can be present as well (15).

In most cases, delivery is followed by prompt clinical and liver laboratory test improvement. Evaluation for emergency liver transplantation may be required for cases of acute liver failure with poor prognostic signs or progression postpartum.

The pathogenesis of AFLP is related to accumulation in maternal blood of long-chain and medium-chain toxic fatty acids because of fetal mitochondrial homozygous deficiency of the enzyme long-chain hydroxy acyl-CoA dehydrogenase (LCHAD) (16). Neonates delivered by patients with AFLP may develop signs and symptoms of LCHAD deficiency (hypoglycemia, fatty liver, cholestasis, and hypocalcemia) and should be evaluated for phenotypic expression of LCHAD deficiency and treated accordingly.

Intrahepatic cholestasis of pregnancy. This idiopathic form of intrahepatic cholestasis is the most common liver disease associated with pregnancy. Its prevalence varies broadly according to geography and ethnicity, with highest frequencies reported in South America and Scandinavian countries. The overall prevalence in the United States is approximately 0.5% of pregnancies but can reach up to 5% of domestic Latin populations (17).

The onset of pruritus in the second or third trimester, often marked in palms and soles, without evidence of large bile duct obstruction, strongly suggests the diagnosis of intrahepatic cholestasis of pregnancy (IHCP). Jaundice may develop after pruritus, reflecting more severe cases. Main differential diagnoses include biliary obstruction and drug-induced cholestasis. Abdominal pain is uncommon in IHCP. Alkaline phosphatase elevation is the most common test abnormality, but placental origin confounds its interpretation. ALT/AST levels are normal or moderately elevated.

As in any cholestatic process, serum total bile acids are elevated in IHCP. More recently, a large meta-analysis of individual patient data showed that levels greater than 100 μmol/L indicate a high risk of intrauterine fetal death, with lower levels having stillbirth rates similar to those in pregnancy without IHCP (18).

The frequency of IHCP is increased with advanced maternal age, a history of estrogen-related cholestasis, previous episodes of IHCP, a family history of IHCP, or ethnic/national origin in countries with high rates of IHCP. IHCP does not affect maternal prognosis but is associated with prematurity, fetal distress, and stillbirth.

The pathogenesis of IHCP is complex including interactions between genetic, hormonal, environmental, and immunological factors (19). Themanagement of IHCP includes ursodiol (10–15 mg/kg/d) for symptomatic relief of pruritus and to improve serum bile acids and liver biochemistries. Cholestyramine could be added for severe pruritus, refractory to ursodiol. The acceleration of fetal lung maturation with dexamethasone may be required if delivery is planned before 37 weeks gestation. Planned fetal delivery at 36 weeks is recommended for patients with bile acids greater than 100 μmol/L and individualized delivery date for those with levels less than 100 μmol/L. Delivery leads to the resolution of IHCP and prevents fetal distress including death.

PREGNANT PATIENTS WITH PREEXISTING LIVER DISEASE

Although most chronic liver diseases are well tolerated during pregnancy, multidisciplinary comanagement by hepatology, maternal fetal medicine, and pediatrics is recommended. Discussion before pregnancy covering risk and modifications to therapy is ideal.

Viral hepatitis

Screening for hepatitis B and C in each pregnancy is recommended by the Centers for Disease Control and supported by the

US Preventative Task Force and gastroenterology, hepatology, and maternal fetal medicine societies (20). Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis C virus (HCV) antibody with reflex to polymerase chain reaction/PCR (viral load) blood tests should be used for screening. Vaccination for hepatitis B should be offered and may be given in any trimester if HBsAg and HBsAb are negative. Viral hepatitis should not affect the mode of delivery (vaginal versus cesarean section) or recommendations for breastfeeding.

Viral hepatitis B. Hepatitis B virus (HBV) is well tolerated during pregnancy with rare reports of maternal/fetal consequences (21). Pregnant patients who are found to have HBsAg present should then be tested for active replication (HBV DNA or viral load). Most individuals of childbearing age will be in the immune-tolerant phase of HBV (high viral load and normal liver enzymes), and treatment considerations are intended to decrease the risk of maternal-to-child transmission (MTCT). Still testing for standard indications for antiviral therapy (liver inflammation assessed by elevated ALT and AST levels) and the presence of cirrhosis is recommended. Although antiviral therapy could be deferred until postpartum in those who meet indications for therapy but at low risk for MTCT, it is recommended to treat all individuals with cirrhosis and active viral replication. It is important to recognize albumin will decrease with pregnancy, but bilirubin and platelet count are not affected by gravidity. Noninvasive technologies (such as elastography) have not been validated during pregnancy. MTCT of HBV approaches 90% without active/passive neonatal immunization (22). Neonates born to HBsAg-positive patients should be given HBIG and HBV vaccination within 12 hours of birth (23). High levels of HBV DNA are associated with transmission despite prophylaxis. Pregnant patients with high levels of viral replication (10^6–10^8 IU/mL) should therefore be offered antiviral therapy in the 3rd trimester to decrease this risk (22).

Some patients may be on antiviral therapy during conception. It is important to discuss the risks and benefits of remaining on antiviral treatment. Patients with advanced liver disease should not stop therapy because of the risk of decompensation with a hepatitis B flare. If treatment is continued during pregnancy, tenofovir is the preferred antiviral agent (22). If therapy is discontinued, close monitoring for a symptomatic relapse is important.

If therapy was initiated to decrease the risk for MTCT, stopping the antiviral agent is recommended either at parturition or in the first 3 months postpartum (22). A close observation is required because nearly one-third of patients will experience an ALT flare in the first 3 months postpartum or after stopping therapy; however, it is rarely clinically symptomatic (Figure 3).

Viral hepatitis C. Universal screening for hepatitis C virus (HCV) with anti-HCV during pregnancy is now recommended because the prevalence of HCV in people with the capacity for pregnancy has increased in parallel with injection drug use (20). HCV RNA (viral load) should be performed in all positive anti-HCV patients, preferably reflexive. If the viral load is positive, referring the pregnant patient to a clinician who can discuss antiviral therapy is important.

Pregnancy has no effect on hepatitis C; however, HCV is associated with higher rates of intrahepatic cholestasis of pregnancy (ICP) and preterm birth (24).

MTCT of HCV is approximately 5% (10% in HCV-HIV coinfection) (25). Although viral load has been associated with the risk of MTCT, a threshold for risk has not been established. Treatment of HCV during pregnancy solely to prevent MTCT is not recommended. Treatment to cure HCV is preferred in prepregnancy or postpartum. However, small studies have found no complications in neonates exposed to antiviral therapy, and guidelines state that the decision to embark on treatment should be individualized (26).

No specific intervention other than suppression of human immunodeficiency virus replication in human immunodeficiency virus/HCV coinfection has been shown to decrease HCV transmission. It is logical to avoid invasive procedures if possible

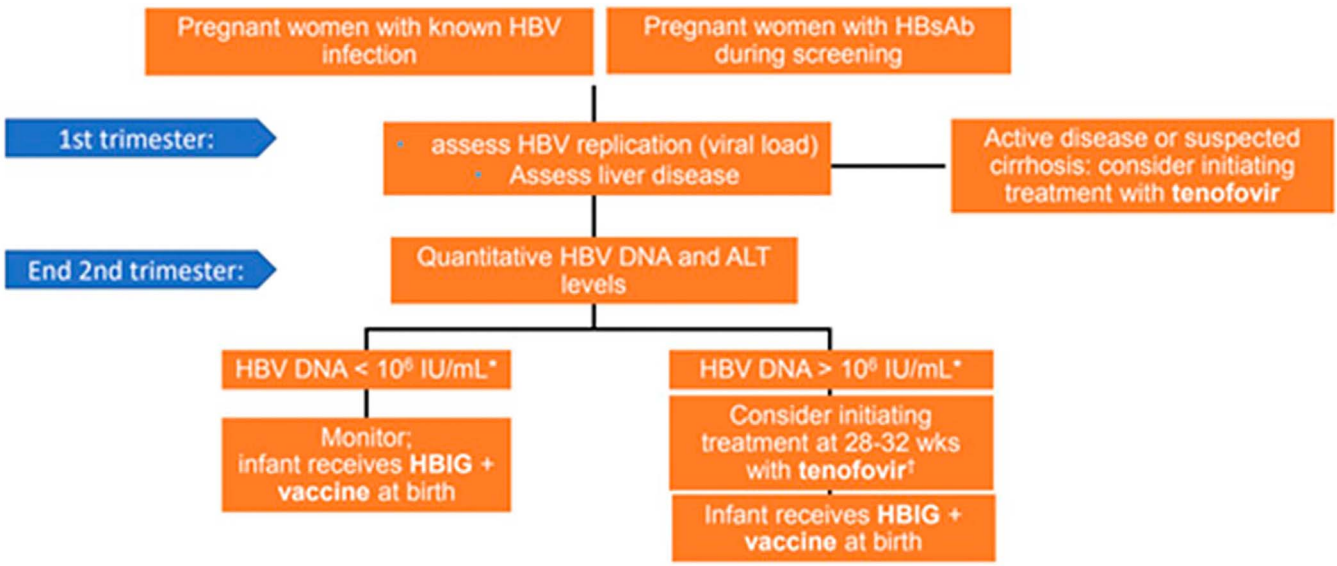

Figure 3. HBV management in patients during pregnancy. *HBV DNA from 6 to 8 $\log_{10}$ IU/mL can be considered for therapy based on physician and patient preference. †Tenofovir is preferred if treatment is expected to be >12 weeks of if treatment is expected to continue while breastfeeding. Lamivudine and Telbivudine are also safe during pregnancy but have risk of resistance with prolonged exposure. ALT, alanine transaminase; HBV, hepatitis B virus; HBsAb, hepatitis B surface antibody.

but not at the expense of maternal/fetal safety. Mode of delivery should be based only on obstetrical indications because vaginal vs cesarean section has not been linked to MTCT of HCV (26).

Chronic nonviral liver disease

Nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease (NAFLD) affects nearly one-third of Americans and is increasingly recognized in people capable of pregnancy. The prevalence of NAFLD in pregnancy has nearly tripled in the past decade and has significant clinical implications (27). Risk is especially high, affecting 42% of people with polycystic ovary syndrome (28). NAFLD is associated with gestational diabetes (28), hypertensive complications, postpartum hemorrhage, and preterm birth (27). Metabolic-associated fatty liver disease (MAFLD) has recently been proposed based on the presence of steatosis, in addition to overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation (29) (Figure 4). Patients with MAFLD are at a higher risk for adverse pregnancy outcomes such as pregnancy-associated hypertension, cesarean delivery, and preterm birth compared with those with nonmetabolic NAFLD or those with no NAFLD (30).

Autoimmune hepatitis. Well-controlled autoimmune hepatitis (AIH) usually remains in remission during pregnancy with the highest risk of flare in the first 3 months after delivery (31). Maternal risk is concentrated in those with flares and cirrhosis, where rates of decompensation are as high as 21% (31). Patients with AIH also have a higher rate of fetal loss and stillbirth (27% compared with 7%–15% for the general pregnant population) (32).

Prepregnancy immune suppression should be continued during pregnancy at the lowest dose necessary; however, mycophenolate mofetil is contraindicated because of the high risk for miscarriage and birth defects. Discontinuing all immunosuppression could result in disease relapse and maternal/fetal complications. If immunosuppression is reduced during pregnancy, it should be preemptively increased postpartum. Liver enzymes should be monitored during each trimester and then at 2- to 4-week intervals for the first 6 months after delivery (33).

Wilson disease. Wilson disease (WD) is a disorder of copper metabolism due to mutations in the copper transporting gene (*ATP7B*). Maintenance therapy for WD includes chelating agents (trientine and D-penicillamine) and zinc. Chelating agents are associated with teratogenicity in human and animals. Guidelines suggest reducing chelating agents by 25%–50% during pregnancy, though no adjustment is needed for zinc. Zinc monotherapy during pregnancy is preferred if possible. Rates of spontaneous abortion are higher in women who stop therapy, but it is also necessary to avoid overchelation because

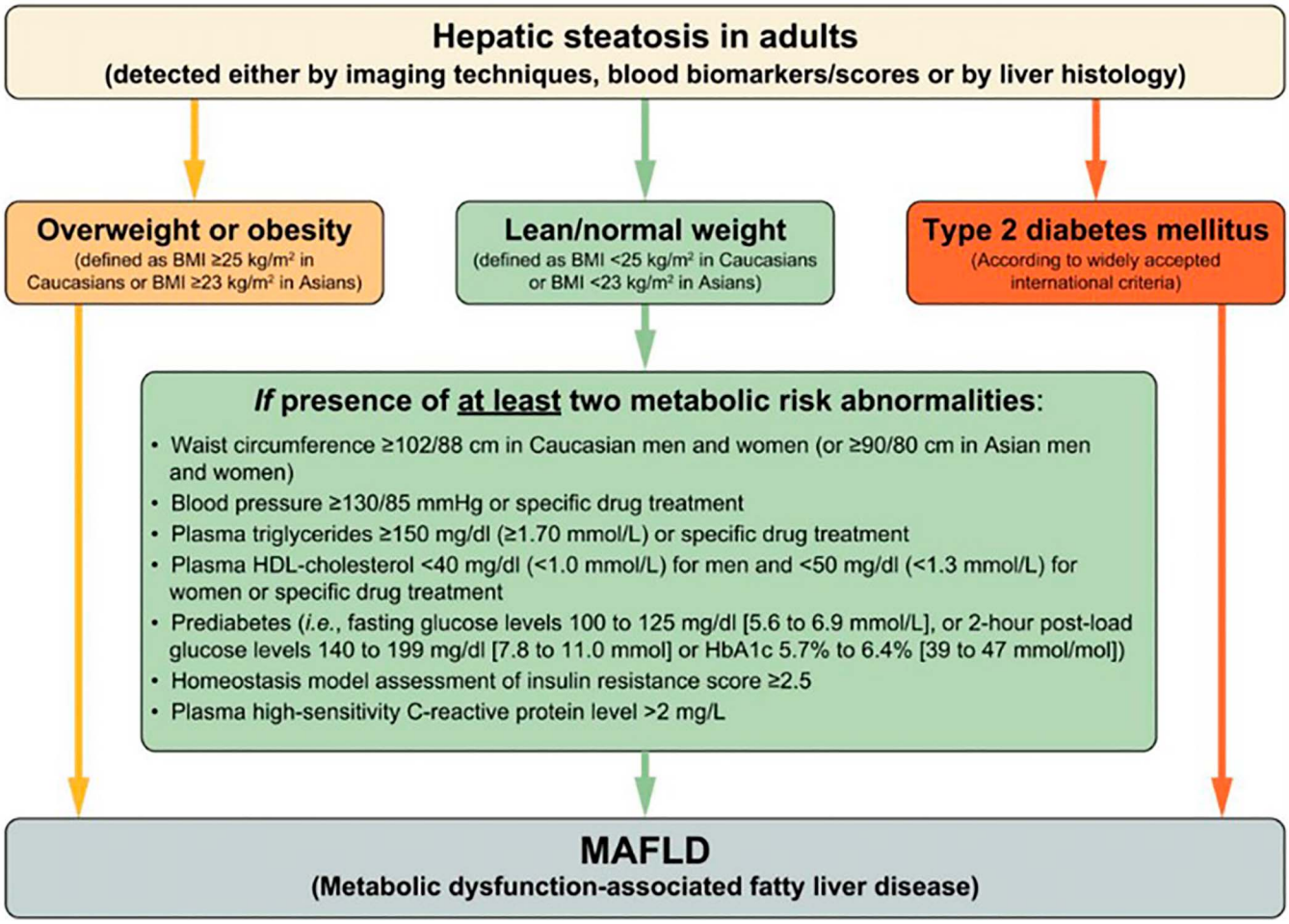

Figure 4. Diagnosis of MAFLD in those with hepatic steatosis. BMI, body mass index; MAFLD, metabolic-associated fatty liver disease. Reprinted with permission from Fouad, Y, Waked, I, Bollipo, S, et al. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int. 2020; 40: 1254–61.

copper deficiency may affect the fetus. After delivery, chelation should be adjusted.

The decision to breastfeed should be balanced between the benefit and risk to the infant because chelation medications are present in breast milk. If the mother choses to breastfeed, copper and zinc should be intermittently assessed in the infant (34).

Screening for WD is recommended in all first-degree relatives. For newborns, the measurement of ceruloplasmin in blood and urine may help with the identification of affected individuals.

Benign hepatic lesions. Hepatic cysts, hemangiomas, focal nodular hyperplasia, and adenomas are common benign liver lesions frequently occurring in reproductive-age individuals. Only adenomas are hormone sensitive and require special attention before and during pregnancy.

Tumor rupture leading to maternal and fetal death has been well described during pregnancy and is strongly related to adenoma size with lesions >5 cm being a higher risk for complications (35). The presence of an adenoma does not preclude pregnancy nor should it change the mode of delivery.

If identified before pregnancy, lesions 5 cm or larger should be considered for either resection or bland embolization. Smaller lesions do not require prophylactic management but should be monitored by ultrasound during each trimester and at 3 months postpartum. Bland embolization can be considered if the lesion increases in size to the 5 cm threshold (35).

Hypotension, abdominal pain especially with radiation into the right shoulder, and distention should lead to urgent cross-sectional imaging to exclude rupture.

PREGNANCY AND CIRRHOSIS

Patients with cirrhosis typically have decreased fecundity due to altered hypothalamic-pituitary function and impaired hepatic metabolism of sex hormones resulting in secondary amenorrhea and the development of anovulatory cycles, especially as the severity of the liver disease progresses (3,36,37). In patients seeking assistance with conception, *in vitro* fertilization may be associated with liver dysfunction itself, which could worsen underlying liver disease (1). For those who do conceive, there may be increased risks for preeclampsia, spontaneous abortion, and preterm birth along with liver decompensation (38). In data from the US Nationwide Inpatient Sample, there was increased maternal and fetal mortality with cirrhosis when compared with controls. Liver decompensation developed in 15% of pregnant women with 11% developing ascites and 5% variceal bleeding, with a 6% maternal and 12% fetal mortality rate (39,40). Cesarean delivery, placental abruption, obstetrical bleeding, and gestational hypertension were more common with cirrhosis, as were higher rates of prematurity and fetal growth restriction (39,40). Similar results have been demonstrated in a Canadian population–based cohort study and a Swedish registry study, with the latter showing no increased rate of congenital malformations or stillbirth (39,41). Flemming et al. (42) recently showed that in 2022 pregnant Canadians, cirrhosis was an independent risk factor for adverse perinatal outcomes but that liver-related complications were rare. They also showed that liver-related complications during and up to 1 year after delivery occurred in 1.2% of patients having well-compensated cirrhosis and in 13% of patients having previous liver-related complications (42). Patients with noncirrhotic portal hypertension typically have normal fertility but are at risk for similar complications from portal hypertension as those with cirrhosis and may have a predisposition for developing portal vein thrombosis (39,43).

Fetal and maternal outcomes in patients with cirrhosis have improved over time in large part due to the involvement of maternal fetal specialists as part of the multidisciplinary team. The model for end-stage liver disease score can be a helpful prognostic tool when counseling patients about their risks during pregnancy. Published data suggest that an antenatal model for end-stage liver disease score ≥10 has 83% sensitivity and specificity for predicting liver decompensation during pregnancy (39,44). Pregnant patients with cirrhosis have a similar risk (as noncirrhotic pregnant persons) for developing pregnancy-related liver complications and are at a much higher risk for liver decompensation should they occur. The incidence of NAFLD is high in the adult population, making it likely that some prepregnant patients may have subclinical chronic liver disease that could also worsen with the development of a superimposed pregnancy-related liver disorder.

The normal physiologic changes that occur during pregnancy predispose patients with cirrhosis to develop a greater degree of portal hypertension, thus leading to potentially more complications, especially an increased risk of variceal bleeding. Risk is greatest during the second trimester when intravascular volume has increased and during delivery due to compression of the inferior vena cava by the gravid uterus and repeated Valsalva maneuvers (1,38,39). Surveillance endoscopy ideally should be performed within the year before pregnancy, as recommended by the American Association for the Study of Liver Disease (39,45). If EGD is not performed before pregnancy, its performance is recommended early in the second trimester. Beta blockers are safe to use during pregnancy (Table 2) as primary prophylaxis for small varices, and their dose should be optimized for larger varices, or band ligation can be considered. The management of acute variceal bleeding is similar to that in the nonpregnant patient (39,45). Octreotide can be used although its splanchnic vasoconstriction may reduce placental perfusion. Terlipressin, which is not FDA approved or commercially available in the United States, is contraindicated because it can cause uterine contractions and decrease uterine blood flow. Cephalosporins are safe to use as antibiotic prophylaxis (39).

Although ascites rarely occur during pregnancy, there is no contraindication to the use of diuretics as medical management nor lactulose or rifaximin for hepatic encephalopathy. Spontaneous bacterial peritonitis is managed according to standard societal guidelines (46). Cross-sectional abdominal imaging should be deferred until after delivery with abdominal ultrasonography performed during pregnancy for hepatocellular carcinoma surveillance. Hepatocellular carcinoma in pregnancy may be associated with poorer obstetric outcomes with a 12.5% risk of spontaneous rupture and decreased maternal survival (1,48). Alpha-fetoprotein levels are typically elevated to some degree during pregnancy and thus are less helpful to use for surveillance. The decision of continuing medical treatment throughout pregnancy in patients with cirrhosis for chronic liver conditions such as Wilson disease, hepatitis B, and autoimmune hepatitis should be made on a case-by-case basis to prevent an acute exacerbation of the underlying liver disease that could lead to acute-on-chronic liver failure. Portal vein thrombosis may present with abdominal pain and/or liver decompensation and should it occur would require anticoagulation and interventional radiologic consultation regarding the need for transjugular intrahepatic portosystemic shunt or other radiological procedures (48). The incidence of splenic artery aneurysms and their rupture are increased during pregnancy and are even higher in the setting of portal hypertension (1,3,27).

Table 2. Safety of medications commonly used in patients with cirrhosis during pregnancy and postpartum

Medication	Category for use in pregnancy	Safety during lactation
Avatrombopag	Not assigned	Unknown
Calcineurin inhibitors	C	Unknown
Carvedilol	C	Unknown
Cefotaxime	B	Probably yes
Ciprofloxacin	C	Probably yes
Eltrombopag	C	Unknown
Furosemide	C	Unknown
Lactulose	B	Unknown
mTOR inhibitors	C	Unknown
Mycophenolate mofetil	D	Unknown
Nadolol	C	Possibly unsafe
Neomycin	D	Unknown
Octreotide	B	Unknown
Propranolol	C	Probably yes
Rifaximin	C	Unknown
Spironolactone	C	Probably yes

The decision on the mode of delivery in a pregnant patient with cirrhosis is based solely on the obstetrical determinants (39,49). The increase in intra-abdominal pressure that occurs during vaginal delivery may increase portal pressure; however, assisted vaginal delivery and truncating the second stage of labor may help in reducing this risk (3,39,48,49). Cesarean section, however, may increase the risk of abdominal wall bleeding and the development of postpartum ascites (39,50). Because of an increased risk for periprocedural and postpartum bleeding, observation in an intensive care unit may be necessary (3,37,39). There are no published data on the use of thrombopoietin analogs for the treatment of thrombocytopenia in pregnancy.

LIVER TRANSPLANT AND PREGNANCY

Most premenopausal patients undergoing liver transplantation (LT) have a normal menstrual cycle within 1 year, thus having the possibility of conception (51,52). Therefore, patients should be counseled about the possibility of pregnancy and that mycophenolate mofetil is contraindicated during pregnancy. Most medications used posttransplant are safe in both pregnancy and when lactating (Table 2). There is no specific recommendation regarding the optimal time to conceive posttransplantation. Several studies have shown a low risk of developing acute cellular rejection when conception occurs 1–2 years post-LT (36,53). Regardless of the choice of immunosuppressive agents used, post-LT pregnancies are more often complicated by the need for cesarean delivery and a higher incidence of preterm delivery but are not associated with increased congenital malformations nor worse neonatal outcomes (31,39,51–53). A recent meta-analysis examined 38 studies with 1131 pregnancies among 838 LT recipients. The live birth rate was 80.4% with a mean gestational age of 36.5 weeks (54). The rate of miscarriages (16.7%) was similar to that in the United States, and the rates of preterm birth, preeclampsia, and cesarean delivery were all higher compared with those in the general population. A multiinstitutional, survey-based retrospective cohort study of female living liver donors has shown no significant difference in pregnancy outcomes before and after donation, although 20% of patients reported some infertility (55). Calcineurin inhibitors such as cyclosporine or tacrolimus are considered safe for the developing fetus during pregnancy but are associated with an increased incidence of hypertension, preeclampsia, and eclampsia (31,53).

BEST PRACTICE RECOMMENDATIONS

- ✓ Multidisciplinary comanagement by hepatology, maternal fetal medicine, and pediatrics is recommended for any pregnant patient with liver disease.
- ✓ Any abnormalities in transaminases or bilirubin during pregnancy require further evaluation
- ✓ The key principle of management of patients with acute fatty liver of pregnancy is early delivery and treatment of acute liver failure as necessary. Newborns should be monitored for manifestations of LCHAD enzyme deficiency.
- ✓ Prompt delivery after 34–36 weeks is advised for pregnant patients with the HELLP syndrome and preeclampsia-associated liver disease.
- ✓ Patients may present with liver disease and overlapping features of preeclampsia, the HELLP syndrome, and fatty liver of pregnancy.
- ✓ Patients with ICP should have weekly bile acid testing. Total serum bile acids greater than 100 μmol/L are associated with poor fetal prognosis in cholestasis of pregnancy.
- ✓ HBsAg, HBsAb, and HCV-Ab should be tested during the first trimester for all pregnant patients. A viral load (HBV DNA or HCV RNA) should be performed in any patient who is positive for HCV-Ab or HBsAg.
- ✓ HCV during pregnancy is associated with higher rates of ICP. If pruritus occurs, bile acids should be tested.
- ✓ Invasive procedures should be deferred if possible, and mode of delivery should not be affected by viral hepatitis. Neither HBV nor HCV are contraindicated during lactation.
- ✓ Chelation therapy for WD should be reduced during pregnancy; however, there is no adjustment needed for zinc.
- ✓ AIH flares are associated with a higher risk for maternal/fetal complications. Disease flares are less common in patients who have been in remission on stable immune suppression for a year before conceptions. Immune suppression should be continued during pregnancy with the exception of mycophenolate mofetil, which is contraindicated.
- ✓ There is an increased risk of liver decompensation and portal hypertensive complications, especially variceal bleeding, in pregnant patients with cirrhosis.
- ✓ Management of liver-related complications in pregnancy follows typical societal guidelines in place for nonpregnant patients with cirrhosis.
- ✓ Although fertility rates are decreased in advanced cirrhosis, premenopausal patients should be counseled on the risks of pregnancy and for the need of involving high-risk obstetricians and maternal fetal medicine specialists as members of their multidisciplinary team.

CONFLICTS OF INTEREST

Guarantor of the article: Nancy Reau, MD, FACG.
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