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- ACG Clinical Guideline:
  - Liver Disease and Pregnancy
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# EVALUATION OF THE PREGNANT PATIENT WITH ABNORMAL LIVER ENZYMES

- A pregnant patient presenting with abnormal liver tests should undergo standard workup as with any non-pregnant individual (strong recommendation, very low level of evidence).


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- The incidence of abnormal liver tests in pregnant women is ~3–5%, even in this relatively young and healthy population. Some liver test results, which would otherwise suggest liver or biliary dysfunction in the non-pregnant individual may in fact be “normal” in the pregnant woman.


- Generally, the majority of liver tests remain in the normal range in pregnancy except those produced by the placenta (alkaline phosphatase, alphafetoprotein) or impacted as a result of hemodilution (albumin, hemoglobin). Of note, during pregnancy, cardiac output is increased by 40–45% with substantive increases to the renal, uterine, and skin systems. However, the liver blood flow shows little change during pregnancy, suggesting a relative decrease of total percent of cardiac output .


**Table 2. Normal physiologic changes in lab tests during pregnancy**

Test	Change in pregnancy
AST/ALT	↔
Bilirubin	↔
Prothrombin/INR	↔
Albumin	↓
Alkaline phosphatase	↑
Hemoglobin	↓
Alpha fetoprotein	↑
5' nucleotidase	↔
Gamma glutamyl transpeptidase	↔

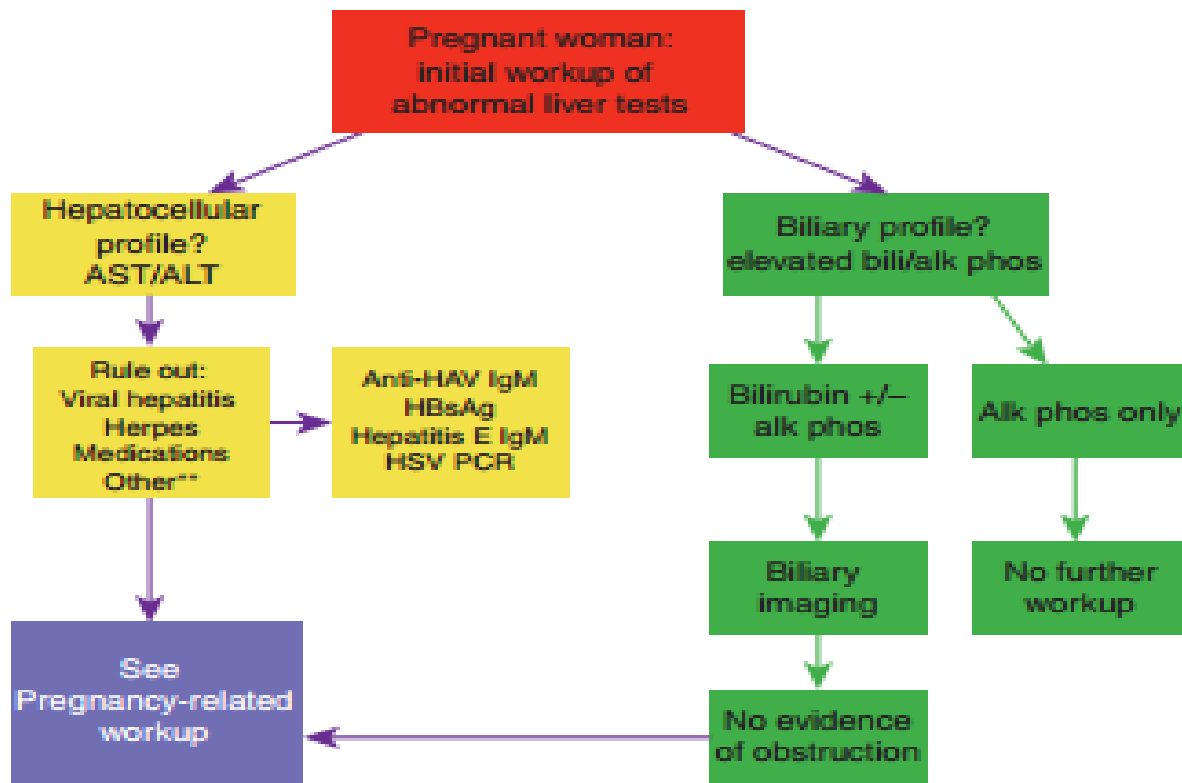
ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio.

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- Any abnormality seen in transaminases and bilirubin needs further evaluation. The first step in assessing a woman presenting at any stage of pregnancy with abnormal liver tests should be the same as with any non-pregnant patient. A complete history, physical exam, and standard serological workup should be performed as indicated by the clinical presentation.

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- Initial evaluation of these patients can be categorized into two general groups: (i) pre-existing and coincidental, not related to pregnancy, or (ii) related to the pregnancy itself.

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- **Recommendations:** 1. A pregnant patient presenting with abnormal liver tests should undergo standard workup as with any non-pregnant individual (strong recommendation, very low level of evidence).






**Figure 1.** Workup of abnormal liver test in pregnant woman. \*\*Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

# IMAGING

- Any pregnant woman presenting with abnormal aminotransferases or jaundice should first undergo an abdominal ultrasound. Ultrasound, with or without Doppler imaging, as it uses sound waves and not ionizing radiation, has never been shown to have any adverse fetal effects .Therefore, there are no contraindications to ultrasound in pregnancy and it should be used as the imaging modality of choice.

- Teratogenicity has been clearly established, with large doses of radiation  $>100$  rad, linked in humans to growth restriction and microcephaly, among other adverse effects. The greatest exposure risk is at 8–15 weeks of gestation. Fetal risks of anomalies and growth restriction appear not to be increased if the exposure is  $< 5$  rad.

- Fetal exposure for commonly used gastroenterology imaging ranges from 100 mrad, for a single abdominal film, to 2–4 rad, for a barium enema or small bowel series, to 3.5 rad for a CT scan of the abdomen. If ultrasonography is indeterminate and further imaging is necessary, judicious use of CT or MRI without gadolinium may be considered for the expeditious diagnosis of an acute presentation.

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- Oral and intravascular contrast agents used for CT contain derivatives of iodine which do not appear teratogenic in animal studies. However, neonatal hypothyroidism has been associated with iodinated contrast agent exposure during pregnancy.

- Gadolinium is not recommended as it crosses the placenta and is excreted by the fetal kidneys into the amniotic fluid where it can remain for long periods, exposing the fetal pulmonary and gastrointestinal systems to potential injury. Animal studies have also reported spontaneous abortion, skeletal abnormalities, and visceral abnormalities with high doses of gadolinium.


- Fortunately, the necessity of liver biopsy for diagnosis of disease in pregnancy is uncommon as most etiologies can be determined in this population by biochemical, serological, and clinical parameters. However, if required, percutaneous liver biopsy can be performed safely. Transjugular liver biopsy can also be performed but carries some limited radiation exposure of 0.05–0.1 rad.

- **Recommendations:** 2- Ultrasound is safe and the preferred imaging modality used in assessment of abnormal liver tests suggestive of biliary tract disease (strong recommendation, low level of evidence). \
- 3. Magnetic resonance imaging (MRI) without gadolinium can be used in the second and third trimester (conditional recommendation, low level of evidence).
- 4. Computed tomography (CT) scans carry a risk of teratogenesis and childhood hematologic malignancies but may be used judiciously with minimized radiation protocols (2–5 rads) (conditional recommendation, very low level of evidence).





# SAFETY OF ENDOSCOPY IN PREGNANCY


- Although clinical studies on the safety and effectiveness of endoscopy for the pregnant patient have been limited, endoscopy can be safe and effective if careful assessment of the risks, benefits, and clinical rationale is performed. One of the most important clinical issues in endoscopy of the pregnant patient is to ensure hemodynamic stability and oxygenation.


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- Oversedation, resulting in hypotension or hypoxia, or positioning that compresses the inferior vena cava can lead to decreased uterine blood flow and fetal hypoxia. Thus, the patient should be positioned in the left lateral position to avoid vascular compression and aggressively managed with respect to intravenous hydration .

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- The benzodiazepine class of sedatives (FDA category D) should be avoided in pregnancy owing to known congenital malformations . One of the most commonly used sedation medications during pregnancy is meperidine, an opiate analgesic, which has more recently been replaced by shorter acting agents, such as propofol, with lower risk for respiratory depression and seizures.

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- Meperidine crosses the placenta and is converted to a long-lasting normeperidine, so repeated or prolonged meperidine administration should be avoided late in pregnancy or at term, as meperidine is an FDA pregnancy category C.

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- Propofol is an FDA pregnancy category B anesthetic which is very short acting with a rapid recovery period, which is of significant benefit in the case of a pregnant patient. If propofol is used, an anesthesiologist should monitor respiratory function closely.

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- Multidisciplinary consultation with obstetrics is essential, and further anesthesia and surgical opinion may be helpful in approaching endoscopy. Deferring endoscopy until the second trimester is recommended when possible .

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- **Recommendations:** 5. Endoscopy is safe in pregnancy but should be deferred until the second trimester if possible (strong recommendation, low level of evidence).
  - 6. Meperidine and propofol can be used for endoscopic sedation (strong recommendation, moderate level of evidence).

# MANAGEMENT OF BILIARY DISEASE IN PREGNANCY

- Cholelithiasis is common in pregnancy owing to the increased estrogen levels, causing cholesterol supersaturation and increased gallstone formation. Cholecystitis is the second most common surgical condition in pregnancy and occurs in ~1 in 1,600 to 1 in 10,000 pregnancies. The incidence of cholelithiasis in pregnant women is 3.5% (10). In the setting of laboratory testing indicating a possible biliary etiology, the first step in diagnosis should be an abdominal ultrasound, which has 95% sensitivity for the diagnosis of gallstones.



- Biliary pancreatitis, symptomatic choledocholithiasis, and cholangitis may have poor fetal outcomes without intervention. ERCP safety has been reported in multiple series, with some reports of increased pancreatitis risk (16%). Reducing fetal exposure to radiation should be attempted by limiting fluoroscopy time, external fetal shielding, and adjusting the patient position.


- Symptomatic cholecystitis had been previously managed conservatively, but more recent data suggests high rates of recurrent symptoms (40–90%), increased rates of hospitalizations, preterm labor and deliveries, and spontaneous abortions when intervention is deferred. The development of gallstone pancreatitis portends a high rate (10–60%) of fetal demise. Thus, early surgical intervention with laparoscopic cholecystectomy after ERCP is preferred.

- **Recommendations:** 7. ERCP can be performed when indicated for pregnant women presenting with biliary disease that strongly necessitates intervention such as biliary pancreatitis, symptomatic choledocholithiasis, and/or cholangitis. Minimizing fetal exposure to fluoroscopy is imperative (strong recommendation, low level of evidence).
- 8. Symptomatic cholecystitis should be managed with early surgical intervention with laparoscopic cholecystectomy (strong recommendation, low level of evidence)

# LIVER MASSES IN PREGNANCY

- Fortunately, liver masses discovered during pregnancy are rare and most commonly are benign. Hemangiomas, focal nodular hyperplasia, and hepatic adenoma may be discovered on routine imaging with ultrasound. Further characterization with MRI or tagged RBC scan may be needed. Patients presenting with large hemangiomas can present asymptotically or with pain and abdominal distension.

- Spontaneous rupture of hemangiomas is exceedingly rare, even with large lesions, thus routine symptomatic follow-up and standard vaginal delivery is safe. Focal nodular hyperplasia is found in 3% of the population, and multiple case series in pregnant women reported routine pregnancies with good clinical outcomes. Hepatic adenomas have a higher risk of growth during pregnancy owing to hormonal stimulation, and ultrasound monitoring should be done during pregnancy.


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- If a diagnosis of large hepatic adenoma is made in a young woman of child-bearing age, appropriate consultation and follow-up should be performed. If a hepatic adenoma is larger than 5 cm or rapid growth is noted, surgical or radiological intervention should be recommended before pregnancy.

- **Recommendations:** 9. Asymptomatic hemangioma and focal nodular hyperplasia do not need routine imaging or surveillance during pregnancy (strong recommendation, very low level evidence).
- 10. Hepatic adenomas should be monitored with ultrasound during pregnancy for growth. Patients with large adenomas (>5 cm) should be referred for resection before pregnancy (strong recommendation, low level of evidence).

# LIVER DISEASES UNIQUE TO PREGNANCY

- Several liver injuries are unique to pregnancy and typically resolve with delivery. The gestational age of the pregnancy is an important diagnostic clue and can help tailor the diagnostic evaluation, as these insults typically occur only at certain stages of development.



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- A thorough history, including prior pregnancies, high-risk behaviors and medications, and careful physical examination is essential.

# First trimester


- **Hyperemesis gravidarum** . HG is defined by persistent vomiting, associated with loss of 5% or more of pre-pregnancy body weight, dehydration, and ketosis. HG is uncommon (0.3–2% of pregnancies), occurs early in the first trimester, and typically resolves by 20 weeks gestation. Risk factors for HG include molar pregnancy, multiple pregnancies, trophoblastic disease, prior HG, and fetal abnormalities (triploidy, trisomy 21, and hydrops fetalis).

- Liver test abnormalities are common in HG and resolve when the vomiting stops. In all, 50–60% of hospitalized women with HG will have a mild elevation in aminotransferase levels, although AST and ALT levels more than 20 times the upper limit of normal rarely have been reported.). Jaundice and hepatic synthetic dysfunction are uncommon.

- Although women with HG have increased rates of low birth weight (LBW) babies, small for gestational age babies, preterm birth, and poor 5-min Apgar scores, outcomes are generally favorable. Management of HG is supportive, however, given the risk for electrolyte abnormalities and dehydration, hospitalization is not infrequent

# Second and third trimester


- **Intrahepatic cholestasis of pregnancy** . IHCP is the most common liver disease in pregnancy with prevalence ranging between 0.3 and 5.6%. IHCP presents in the second and third trimesters as persistent pruritus, typically involving the palms and soles as well as the rest of the body, with elevated bile acid levels, and resolves with delivery.

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- Jaundice occurs in <25% of IHCP patients, always after the onset of pruritus. If jaundice is the presenting symptom, further evaluation for alternative explanations is necessary. Fat malabsorption can result in fat-soluble vitamin deficiencies requiring supplementation.

- Risk factors for IHCP include advanced maternal age, a history of cholestasis secondary to oral contraceptives, and a personal or family history of IHCP. Some studies suggest a higher prevalence in patients with hepatitis C, cholelithiasis, and nonalcoholic fatty liver disease .Evaluation for alternative etiologies should be pursued if cholestasis fails to resolve after delivery.

- In IHCP, bile acid concentrations are typically  $>10 \mu \text{ mol/l}$  with increased cholic acid levels and decreased chenodeoxycholic acid levels. Increased bile acid concentration ( $>40 \mu \text{ mol/l}$ ) is one factor that can identify higher risk, and may be the only biochemical abnormality present. Bile acid levels also correlate with fetal distress. Most complications occur when bile acid levels exceed  $40 \mu \text{ mol/l}$ . Aminotransferase levels may also be elevated, reaching values  $>1,000 \text{ U/l}$ . Ultrasonography should be performed to exclude cholelithiasis.



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- Maternal outcomes are excellent, however, there is a risk of fetal distress, preterm labor, prematurity, and intrauterine death .Early delivery at 37 weeks is encouraged, because intrauterine death is more common in the last month of pregnancy and few deaths occur before 37 weeks .


- First-line therapy for IHCP is UDCA at 10–15 mg/kg maternal body weight. It is well-tolerated and safe for both the mother and fetus. UDCA increases expression of bile salt export pumps and increases placental bile transporters. UDCA therapy normalized serum bile acid patterns in babies with minimal accumulation in amniotic fluid and cord blood.

- A recent meta-analysis also found that women who received UDCA had better outcomes with less pruritus, improved liver enzymes, and possibly improved fetal outcomes .UCDA is more effective than cholestyramine or dexamethasone in controlling pruritus. Dexamethasone may be used, if needed, to promote fetal lung maturity before delivery, as there is a higher rate of prematurity in IHCP.

- **Preeclampsia and eclampsia** . Preeclampsia is characterized by new onset hypertension (systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg) and proteinuria ( $\geq 300$  mg/24 h) after 20 weeks of gestation .Organ dysfunction defines severe preeclampsia and can include hepatomegaly and hepatocellular injury. Up to 7.5% of all pregnancies are affected, but only 25% of preeclampsia cases are severe.

- Liver involvement is not a common expression and when it does occur symptoms are generally non-specific. Eclampsia is present when grand mal seizures occur. Hepatic involvement can present with epigastric or right upper quadrant pain, likely from hepatomegaly stretching Glisson's capsule. Liver injury results as a consequence of vasoconstriction and fibrin precipitation in the liver.

- AST and ALT elevations can be striking. Complications can include hematoma below Glisson's capsule and hepatic rupture . The magnitude of the liver chemistry abnormalities parallels the risk of adverse maternal but not fetal outcomes. Liver tests cannot exclusively be used to gauge clinical decisions, as the presence of normal liver enzymes does not exclude disease.

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- An expectant approach is advised until after 34 weeks gestation to limit fetal morbidity .However, delivery is the only curative treatment and after 36–37 weeks there is no advantage in continuing the pregnancy.


- **HELLP syndrome** . The HELLP syndrome is characterized by hemolytic anemia, increased liver enzymes, and low platelets. HELLP affects a minority of pregnancies but complicates up to 20% of cases of severe preeclampsia/eclampsia. Although HELLP typically presents between 28 and 36 weeks of gestation, 30% manifest symptoms in the first week postpartum .). Risk factors include advanced maternal age, nulliparous, and multiparity.




- The hypertension-related liver diseases share similar clinical presentations. Differentiation is difficult as there is overlap in their features. The diagnosis of HELLP is most often made through recognition of typical laboratory results. Signs of hemolytic anemia and thrombocytopenia with platelets  $< 100,000$  cells/ $\mu$ l, elevations in AST, ALT, serum bilirubin, and lactate dehydrogenase are expected. There are no pathognomonic clinical signs and some women with HELLP may be asymptomatic.


- Right upper quadrant and epigastric pain, nausea, vomiting, malaise, headache, edema, and weight gain are common complaints. Hypertension and proteinuria should be expected, occurring in up to 80% of cases. Jaundice is rare, occurring in only 5% of patients. Maternal consequences can be severe with mortality rates of 1–3% .Progression can also be rapid but laboratory values typically begin to normalize 48 h postpartum.

- Fetal prognosis is most strongly linked to gestational age at delivery and birth weight. Hepatic consequences include hepatic infarction, subcapsular hematomas, and intraparenchymal hemorrhage. When the ALT or AST is  $>1,000$  U/l or abdominal pain radiates into the right shoulder, cross-sectional imaging can assist in excluding hepatic complications with more accuracy than ultrasound.

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- Hepatic infarction should be suspected with right upper quadrant pain with fever, whereas abdominal swelling or shock presentation can occur with hepatic rupture .Supportive management is appropriate for most contained hematomas. Surgery is indicated for those with enlarging hematomas or evidence of rupture with hemodynamic instability.


- Alternatively, successful percutaneous embolization of the hepatic arteries in stable women has been reported .Liver transplantation has also been an effective salvage in patients with continued decompensation despite standard interventions .Glucocorticoids are often part of the therapeutic protocol in HELLP, especially in pregnancies <34 weeks where they accelerate pulmonary maturity during expectant management..

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- The University of Mississippi developed a treatment protocol that is often applied as standard of care in the management of women with HELLP. Known as “The Mississippi Protocol”, it includes corticosteroids, magnesium sulfate, and systolic blood pressure control .


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- Thrombocytopenia can be marked. There is no contraindication to platelet transfusion, and transfusion to  $>40,000$  cells/ $\mu$ l is advised when invasive procedures are anticipated .

- **Acute fatty liver disease of pregnancy** . AFLP is a rare, life-threatening condition characterized by microvesicular fatty infiltration of the liver leading to hepatic failure. The median gestation age at the time of identification is 36 weeks. Risk factors include twin pregnancies and low body mass index



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- Early recognition, prompt delivery, and supportive care are essential to optimize maternal and fetal prognosis, as the postpartum clinical course is dependent on the interval between symptoms and termination of the pregnancy . If hepatic function does not rapidly improve, evaluation for liver transplantation offers the patient the best chance for survival.

- Presenting symptoms are non-specific: nausea, vomiting, and abdominal pain. Concomitant preeclampsia is present in roughly one half of the affected women. Striking aminotransferase elevations and hyperbilirubinemia are typical. Hepatic failure can manifest with signs of hepatic dysfunction such as encephalopathy, coagulopathy, and hypoglycemia. Renal dysfunction and pancreatitis are common

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- The diagnosis of AFLP is usually made clinically based on compatible presentation, laboratory, and imaging results. The “Swansea Criteria” combine symptoms and laboratory derangements ..

**Table 4. Swansea criteria for diagnosis of acute fatty liver of pregnancy**

Six or more criteria required in the absence of another cause

Vomiting

Abdominal pain

Polydipsia/polyuria

Encephalopathy

Elevated bilirubin >14  $\mu\text{mol/l}$

Hypoglycaemia <4 mmol/l

Elevated urea >340  $\mu\text{mol/l}$

Leucocytosis >11  $\times 10^9$  cells/l

Ascites or bright liver on ultrasound scan

Elevated transaminases (AST or ALT) >42 IU/l

Elevated ammonia >47  $\mu\text{mol/l}$

Renal impairment; creatinine >150  $\mu\text{mol/l}$

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.

- The LCHAD enzyme catalyzes the step in beta-oxidation of mitochondrial fatty acid that forms 3-ketoacyl-CoA from 3-hydroxyacyl-CoA. There is a pathophysiologic pathway between fetal deficiency of LCHAD and AFLP. Homozygous-deficient offspring spill unmetabolized long-chain fatty acids into the maternal circulation. Accumulation of fetal or placental metabolites can lead to hepatotoxicity. Some women with AFLP are heterozygous for LCHAD and carry heterozygous or homozygous infants. In addition, not all genetic defects that lead to LCHAD confer a risk for AFLP

**Table 3. Liver diseases unique to pregnancy**

Disorder	Trimester	Management
HG	First through 20 weeks	Supportive management
IHCP	Second/third	Ursodeoxycholic acid 10–15 mg/kg Early delivery at 37 weeks
AFLP	Third	Women with AFLP should be delivered promptly Infant should be monitored for manifestations of deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase including hypoketotic hypoglycemia and fatty liver
Eclampsia, preeclampsia	After 20 weeks	After 36 weeks, women with severe preeclampsia should be delivered promptly
HELLP	After 22 weeks	Delivery after 34 weeks Platelet transfusion to 40,000–50,000 cells/ $\mu$ l should be considered before delivery, especially if cesarean section is likely

AFLP, acute fatty liver disease of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets; HG, hyperemesis gravidarum; IHCP, intrahepatic cholestasis of pregnancy.

- **Recommendations:** 11. The treatment of hyperemesis gravidarum (HG) is supportive and may require hospitalization (strong recommendation, very low level of evidence).
- 12. Because of increased risk of fetal complications with intrahepatic cholestasis of pregnancy (IHCP), early delivery at 37 weeks is recommended (strong recommendation, very low level of evidence).
- 13. Ursodeoxycholic acid (UDCA) should be given at 10–15 mg/kg to women with IHCP for symptomatic improvement (strong recommendation, moderate level of evidence).

- 14. Preeclampsia with hepatic involvement elevates the diagnosis to severe preeclampsia. After 36 weeks, women with severe preeclampsia should be delivered promptly to limit maternal and fetal complications (strong recommendation, very low level of evidence).
- 15. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome should be managed by prompt delivery, especially after 34 weeks gestation (strong recommendation, very low level of evidence).





- 16. Platelet transfusion to 40,000–50,000 cells/ $\mu$ l should be considered before delivery, especially if cesarean section is likely (conditional recommendation, very low level of evidence).
- 17. Women with acute fatty liver disease of pregnancy (AFLP) should be delivered promptly; expectant management is not appropriate (strong recommendation, very low level of evidence).

- 18. All women with AFLP and their children should have molecular testing for long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD; conditional recommendation, moderate level of evidence).
- 19. The off spring of mothers affected by AFLP should be monitored carefully for manifestations of deficiency of LCHAD including hypoketotic hypoglycemia and fatty liver (conditional recommendation, very low level of evidence).

# COINCIDENT LIVER DISEASE (HAV, HEV, HSV)


- Although acute infection with HAV has been associated with preterm labor and premature rupture of membranes, this has been reported to have no significant impact on maternal or fetal outcomes .The pregnant state does not appear to alter the course of acute HAV infection. Nevertheless, pregnant women presenting with acute hepatitis should be tested for HAV-IgM as vertical transmission of HAV has been reported, even leading to outbreaks within neonatal care units .

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- In addition to careful infection control precautions, the CDC recommends HAV immunoglobulin treatment for the neonate if the maternal HAV infection occurs within 2 weeks of delivery .Treatment is otherwise supportive.


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- pregnant women presenting with acute hepatitis should be tested for HEV with HEV-IgM to make the diagnosis and to increase anticipation and preparation for possible progression to acute liver failure and need for liver transplantation evaluation. Treatment is otherwise supportive.


- Although hepatitis from HSV is very rare, HSV seroprevalence is common in women of child-bearing age in the United States at ~20% for HSV-2 and 60% for HSV-1. Clinical clues to HSV hepatitis are the presence of fever, upper respiratory infection symptoms, or an anicteric, severe hepatitis presentation on laboratory testing.

- The pathognomonic mucocutaneous lesions are present in <50% of cases, requiring a high index of suspicion for HSV in the pregnant patient with an acute hepatitis presentation. This diagnostic difficulty is compounded by limited specificity and sensitivity of routine HSV-IgM testing. HSV PCR should be performed when HSV hepatitis is suspected .

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- Empiric acyclovir is recommended if HSV hepatitis is suspected in a pregnant patient. Acyclovir should be started once HSV hepatitis is suspected, as the diagnosis is difficult to make and often delayed and as acyclovir has been shown to be safe and well-tolerated in pregnancy.



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- On the other hand, empiric acyclovir is not recommended in all pregnant patients with hepatitis when HSV infection is not suspected. Acyclovir can then be discontinued if the HSV PCR is negative.

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- Acute HBV infection or reactivation of HBV can present during pregnancy and it may be difficult to differentiate reactivation from acute HBV infection. Nevertheless, HBV testing with HBsAg and hepatitis B core IgM is recommended in pregnant patients presenting with acute hepatitis.


- **Recommendations:** 20. Pregnant women presenting with acute hepatitis should be tested for common etiologies of acute liver injury including viral hepatitis, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV), and herpes simplex virus (HSV; strong recommendation, very low level of evidence).
- 21. Pregnant women with acute hepatitis suspected from HSV should be initiated on acyclovir (strong recommendation, very low level of evidence).


# CHRONIC LIVER DISEASES, CIRRHOSIS, AND LIVER TRANSPLANTATION

- Chronic HBV infection is estimated to affect >350 million people worldwide and represents a significant source of morbidity and mortality related to cirrhosis and hepatocellular carcinoma. Mother-to-child transmission (MTCT) of HBV remains an important source of incident cases of HBV. Current barriers to eradication of incident HBV infections via MTCT include underutilization of immunoprophylaxis with hepatitis B vaccination and hepatitis B immunoglobulin in certain endemic regions as well as failure of immunoprophylaxis.

- The risk for development of chronic HBV infection is strongly linked to the age of exposure. Risk for chronic infection after exposure varies from ~90% in infants, 50% in toddlers and young children, and 5% in adults .MTCT rates also vary significantly according to the mother's HBeAg status (70–90% transmission rate for HBeAg+ mothers vs. 10–40% for HBeAg-mothers).


- Standard active–passive immunoprophylaxis with HBIG and hepatitis B vaccination administered immediately after birth (within 12 h) to infants of HBsAg-positive mothers, followed by 2 additional doses of vaccine within 6–12 months, prevents transmission in ~95%. However, recent review of published literature from 1975 to 2011 demonstrated that active–passive immunoprophylaxis fails to prevent HBV transmission in 8–30% of children born to highly viremic mothers .

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- Postulated causes of immunoprophylaxis failure include high levels of maternal viremia, intrauterine infection, or mutations of the HBV surface protein . Even in the era of immunoprophylaxis, viremia remains a strong predictor of MTCT.

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- In a study of 138 babies born to HBsAg-positive women, Wiseman et al. found the immunoprophylaxis failure rate to be 9%, all occurring with mothers who were HBeAg-positive with HBV DNA  $\geq 8 \log_{10}$  copies/ml ( $2 \times 10^7$  U/ml).




- These data suggest that HBV DNA levels of 6–6.99 log<sub>10</sub> copies/ml ( $2 \times 10^5$  IU/ml to  $1.9 \times 10^6$  IU/ml) portends a 3% risk of transmission, 7–7.99 log<sub>10</sub> copies/ml ( $2 \times 10^6$  IU/ml to  $1.9 \times 10^7$  IU/ml) a 7% risk of transmission, and >8 log<sub>10</sub> copies/ml ( $2 \times 10^7$  IU/ml) in the mother portend an 8% risk of MTCT of HBV .


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- Older data assessing MTCT rate in infants born via cesarean section vs. vaginal delivery failed to conclusively show a significant difference in neonatal HBV infection.

- Some more recent data support reconsideration of elective cesarean section to reduce MTCT including a metaanalysis that suggested a 17.5% absolute risk reduction compared with immunoprophylaxis alone. However, other studies report no benefit to elective cesarean section. Data from Beijing of 1,409 infants born to HBsAg-positive mothers from 2007 to 2011, all of whom received appropriate immunoprophylaxis at birth, reported MTCT rates of 1.4% with elective cesarean section compared with 3.4% with vaginal delivery and 4.2% with urgent cesarean section (  $P < 0.05$ ).

- When mothers in this study were stratified according to HBV DNA, in those with low HBV DNA ( $<1,000,000$  copies/ml or  $2 \times 10^5$  IU/ml), delivery modality did not impact MTCT. This suggests a potential role for elective cesarean section among women with HBV DNA  $>1,000,000$  copies/ml ( $2 \times 10^5$  IU/ml). However, before definitive recommendations can be made, validation studies are needed to determine the relative safety and efficacy of elective cesarean section and immunoprophylaxis vs. immunoprophylaxis alone in reducing MTCT without compromising fetal outcomes.

- Although some studies have suggested a favorable safety profile for antiviral therapy even in the first and second trimesters of pregnancy, when utilized purely for purposes of reducing MTCT, antiviral therapy should be initiated in the third trimester (thus minimizing the risk associated with fetal exposure to these medications). Treatment at levels lower than  $10^6$  log copies/ml ( $2 \times 10^5$  IU/ml) does not appear to be indicated unless the pregnant woman has liver disease for which viral suppression is indicated.


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- Transmission of HBV with breastfeeding is low risk in infants who receive appropriate immunoprophylaxis. Current WHO recommendations are to allow breastfeeding as there is no evidence for additional risk, even without immunization. (Protection against viral hepatitis, Recommendations of Immunization Practices Advisory Committee.

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- Breastfeeding should be avoided in the presence of breast pathology such as cracked or bleeding nipples. Oral nucleos(t)ide analogs have been shown to be excreted in breast milk, albeit at low levels, and there is limited data on the effect of these medications on infants

## □ Recommendations:


- Hepatitis B . 22. Active–passive immunoprophylaxis with hepatitis B immune globulin and the HBV vaccination series should be administered to all infants born to HBV-infected mothers to prevent perinatal transmission (strong recommendation, low level of evidence).
- 23. Women chronically infected with HBV and high viral load ( $>200,000$  U/ml or  $>10^6$  log copies/ml and higher) should be offered antiviral medication with tenofovir or telbivudine in the third trimester to reduce perinatal transmission of HBV (strong recommendation, low level of evidence).



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- 24. C-section should not be performed electively in HBV-positive mothers to prevent fetal infection (strong recommendation, very low level of evidence).
  - 25. Women chronically infected with HBV should be allowed to breastfeed as recommended for infant health (strong recommendation, very low level of evidence).


# HCV


- HCV has little impact during pregnancy with minimal risk to either the mother or infant. However, there may be a higher risk for premature rupture of membranes and gestational diabetes in women with HCV. ALT and viral loads fluctuate but these changes lack clinical significance. Pregnancy induces a state of relative immune suppression followed by immune reconstitution postpartum. The changes in liver enzymes and viral kinetics mirror a response to this immune modulation. During the second and third trimester aminotransferase levels decline, only to rebound postpartum.


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- Viral load also fluctuates, peaking during the third trimester then returning to pre-pregnancy levels after delivery . Unlike HBV, postpartum flares of HCV have not been described.

- Although HCV is transmitted through percutaneous exposure of infected blood or body fluids, screening for HCV is not part of routine perinatal testing owing to a combination of low rates of perinatal transmission and low prevalence of HCV in pregnant women. Cross-sectional studies estimate that only 0.5–8% of pregnant women have anti-HCV .

- Although there is only a 3–10% risk of transmitting HCV at the time of birth, vertical transmission remains responsible for the majority of childhood HCV infection. This risk is highest in pregnant women co-infected with HIV. Unfortunately, there is no perinatal management strategy that can clearly decrease this risk.

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- Although prolonged (>6 h) rupture of membranes may increase the risk of transmission, vaginal delivery itself does not appear to increase the risk of vertical transmission of HCV transmission compared with cesarean delivery.

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- There is no evidence of an association between breast feeding and risk for vertical transmission . Still, breastfeeding should be avoided when the potential risk for exposure is higher, such as when there are cracked nipples or skin breakdown.

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- HCV can be eradicated effectively with either all-oral- or interferon-based treatment options. HCV rarely requires urgent therapy, making it easier to defer treatment decisions until after delivery. In addition, both interferon and ribavirin are strictly contraindicated during pregnancy. There is no data at this time to guide or support the use of all-oral combination therapy during pregnancy.



## □ Hepatitis C (HCV)

- 26. All pregnant women with risk factors for HCV should be screened with anti-HCV antibody. Screening should not be performed in women without risk factors for HCV acquisition (strong recommendation, low level of evidence).
- 27. Invasive procedures (e.g., amniocentesis, invasive fetal monitoring) should be minimized in infected mothers and their fetus to prevent vertical transmission of hepatitis C (strong recommendation, very low level of evidence).

- 28. C-section should not be performed electively in HCV-positive mothers to prevent fetal infection (strong recommendation, very low level of evidence).
- 29. Women chronically infected with HCV should be allowed to breastfeed as indicated for infant health (strong recommendation, very low level of evidence).
- 30. Hepatitis C therapy should not be offered to pregnant women to either treat HCV or decrease the risk for vertical transmission (strong recommendation, very low level of evidence).

# Autoimmune hepatitis

- AIH is associated with an increased risk of fetal prematurity and loss, with worse outcomes with inadequate AIH activity control, especially in the absence of or discontinuation of AIH treatment before or during pregnancy . Although AIH was historically thought to be quiescent during pregnancy, more recent data suggest that AIH may have an initial presentation during pregnancy, an intrapartum flare risk of >20% and postpartum flare risk of up to 30–50%.

- Treatment for AIH is based on immunosuppression with corticosteroids and/or AZA, with recent practice guidelines for AIH recommending prednisone monotherapy for pregnant individuals .A systematic review of AIH treatment concluded that corticosteroids ±AZA was appropriate for induction whereas corticosteroids +AZA or AZA monotherapy was superior to corticosteroid monotherapy for maintenance management of AIH .However, there are no systematic reviews or meta-analysis on the treatment of AIH during pregnancy.

- Corticosteroids, pregnancy category C drugs, have been studied in a population-based study of >51,000 corticosteroid-exposed pregnancies, with no increase in orofacial cleft defects or other significant adverse events. Corticosteroid monotherapy has traditionally been used for the management of AIH flares during pregnancy because AZA is a pregnancy category D drug, which has limited its use.

- AZA treatment in AIH during pregnancy has not been studied systematically. However, utilization of AZA during pregnancy has been studied systematically in inflammatory bowel disease with 3,000 AZA-exposed pregnancies showing an association with preterm births but no increase in congenital abnormalities or LBWs.


- The mounting evidence of AZA's safety during pregnancy coupled with the importance of achieving and maintaining AIH disease control during pregnancy supports the mandate that treatment continuation for AIH is critical in optimizing maternal and fetal outcomes. The potential benefit of treatment with corticosteroids and AZA to keep the mother's AIH in control appears to be significantly greater than the potentially small risk of treatment-associated adverse events on the mother and fetus.

# Primary biliary cirrhosis

- Older literature suggested poor outcomes of pregnancy in patients with PBC .As patients with PBC tend to present at an older age after the usual child-bearing age, and as women with PBC were discouraged in the past from pursuing pregnancy, there is an extremely limited number of studies on PBC and pregnancy. However, more recent studies have reported good maternal and fetal outcomes .





- PBC has been associated with disease flare after delivery . UDCA is a pregnancy category B drug that is generally recommended for PBC . Studies on the use of UDCA treatment for PBC during pregnancy have been limited, especially in the first trimester . Similar to the situation with AIH, the potential risks of UDCA during pregnancy appear small compared with the potential positive effect of treatment on maternal and fetal outcomes.

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- With growing evidence that UDCA is safe during pregnancy in other diseases such as intrahepatic cholestasis of pregnancy, and the unlikely scenario that largescale studies will be performed on the efficacy and safety of UDCA during pregnancy for PBC, it appears prudent to recommend continuation of UDCA for PBC during pregnancy at this time.

# Wilson's disease

- WD is postulated to lead to reduced fertility as copper deposition in the uterus may interfere with embryo implantation leading to an increase in miscarriages and spontaneous abortions .WD and the complex nature of its management would benefit from referral to high-risk pregnancy multidisciplinary specialists in maternal–fetal medicine and liver disease. Pregnancy in general does not appear to change the course of WD progression .

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- However, treatment discontinuation or a lack of treatment has been reported to lead to disease flares with attendant risk of hepatic decompensation or liver failure .There is one recent systematic review on the treatment of WD in general, but no reports specific to treatment for WD during pregnancy.

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- Practice guidelines for WD recommends continuing treatment during pregnancy, but reducing penicillamine or trientine doses by 25–50% to promote wound healing in the event that a cesarean section is needed.


- There is inadequate data to make recommendations on a preferred treatment for WD during pregnancy, between penicillamine, trientine, or zinc. Some data on conversion to zinc therapy during pregnancy has also been reported . There are also multiple case reports of fetal myelosuppression or embryopathy associated with penicillamine treatment during pregnancy for WD

- On the other hand, treatment discontinuation or lack of treatment for WD can not only lead to maternal hepatic decompensation but can also lead to copper deposition in the placenta and fetal liver, damaging the fetus along with recognized risks of maternal hepatic decompensation. The risks of treatment discontinuation or lack of treatment for WD during pregnancy appears to outweigh the potential risks of treatment. The data to recommend dose reduction of penicillamine in anticipation of possible cesarean section appears to be very limited.

# Cirrhosis and portal hypertension


- Pregnancy in women with underlying cirrhosis has been associated with an increase in prematurity, spontaneous abortions, and maternal–fetal mortality .Non-cirrhotic portal hypertension has been reported to have better outcomes than cirrhotics with portal hypertension.



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- Variceal bleeding is the most frequent and feared complication of portal hypertension during pregnancy, with an increased risk at delivery and the second trimester, potentiated by an increase in intravascular volume, compression from the gravid uterus, and repeated Valsalva maneuvers.

- Up to 30% of cirrhotic pregnant women bleed from esophageal varices during pregnancy, and the risk of variceal bleeding increases up to 50–78% if there are pre-existing varices . Each episode of variceal bleeding leads to maternal mortality rates as high as 20–50%, with an even higher risk of fetal loss.

- Variceal bleeding during pregnancy is managed very similarly to variceal bleeding in general given the acute and life-threatening nature of the event, with a focus on endoscopic hemostasis and supportive care for the mother and fetus .Octreotide is a pregnancy category B drug and appears to be safe as an adjunct treatment in acute variceal bleeding along with antibiotics. Salvage therapy with transjugular intrahepatic systemic shunts and liver transplantation has also been described, but are not routinely advocated.

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- Timing of screening for esophageal varices appears most prudent in the second trimester, after organogenesis is complete in the first trimester and before the greatest risk of bleeding at delivery.

- Despite acceptance of band ligation and beta-blockers as firstline management of esophageal varices for non-pregnant patients, there are limited data on their efficacy and safety in pregnancy . Propranolol is a pregnancy category C drug, but has been used to treat fetal arrhythmias as well as maternal conditions such as thyrotoxicosis, arrhythmias, or hypertension.

- There are risks of intra uterine growth retardation, neonatal bradycardia, and hypoglycemia, but propranolol appears overall to be safe in pregnant patients. Nadolol is also a category C drug, but has a long half-life owing to low protein-binding and low rate of excretion, so is not preferred.

- Traditionally, vaginal delivery with a short second stage of labor has been advocated along with consideration of forceps or vacuum extraction, if needed .However, the recognition that prolonged vaginal delivery may be associated with an increased risk of variceal bleeding owing to repeated Valsalva maneuvers has led to an interest in considering cesarean sections as an alternative.


- Cesarean sections may be required for fetal distress or prematurity, but carries an increased risk of bleeding complications from the surgical site in the setting of portal hypertension. Regardless, there is no data comparing the benefits of vaginal delivery vs. cesarean section. If performed, it would be judicious to arrange for vascular surgery support in case of difficult to control collateral bleeding at the surgical site.



# Liver transplantation .


- Fertility is rapidly restored after successful liver transplantation, with reports of 80% normalization of the menstrual cycle within 1 year and as early as a few months after liver transplantation .Most experts advocate waiting at least 1 year, and some up to 2 years after liver transplantation before planning a pregnancy, citing the lower doses of immunosuppression use, lower risk of acute cellular rejection, and lower risk of opportunistic infections after the first year of liver transplantation .


- There is one published systematic review on pregnancy outcomes in liver transplant recipients . Higher rates of preterm births and cesarean sections compared with the general population were reported. The National Transplantation Pregnancy Registry, a questionnaire-based registry, has reported a higher risk of prematurity, LBW, maternal hypertension and preeclampsia, and cesarean sections compared with the general population.

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- Higher risk of acute cellular rejection and graft loss were noted if pregnancy occurred within 6 months of liver transplantation. Overall, the literature suggests that pregnancy in liver transplant recipients is safe and not uncommon, with good outcomes given careful management and monitoring .

- Overall, with the exception of mycophenolic acid, the risks of cyclosporine, tacrolimus, AZA, sirolimus, everolimus, and corticosteroids appear low compared with the risks of acute cellular rejection or graft loss with their discontinuation or attenuation. Although a higher risk of prematurity and LBW have been reported, the risks of congenital malformation do not appear to be significantly higher than the risk in the general population, without a specific pattern of malformation identified.

- Compared with tacrolimus and cyclosporine, there is less data on the use of everolimus and sirolimus during pregnancy after liver transplantation, with more of the data available for kidney transplant recipients. The potential for impaired wound healing with everolimus and sirolimus must be considered if cesarean section is performed. It is clear that mycophenolic acid should not be used during pregnancy owing to risk of congenital malformations and embryo-fetal toxicity.

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- Expert and society recommendations have traditionally opposed breastfeeding in the setting of immunosuppression medications and transplantation, given the potential for harm of these medications and a lack of safety data .

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- More recently, small series have reported safety with minimal to no adverse events for babies who are breastfed while mothers are on immunosuppression medications after liver transplantation.

- In addition, pharmacokinetic and drug safety data on breast milk concentrations have suggested minimal excretion of these immunosuppressants into breast milk . The accumulation of these data, albeit still limited, in addition to the growing recognition of the importance of breastfeeding, has led to a push to loosen these traditional dictums against breastfeeding, especially if the mother is interested in breastfeeding her baby.



- Autoimmune hepatitis 31. Pregnant women with autoimmune hepatitis (AIH) should be continued on their treatment with corticosteroids and/or azathioprine (AZA) (strong recommendation, very low level of evidence).
- 32. Pregnant women with primary biliary cirrhosis (PBC) should be continued on their treatment with UDCA (strong recommendation, very low level of evidence).
- 33. Pregnant women with Wilson's disease (WD) should be continued, with dose reduction if possible, on their treatment with penicillamine, trientine, or zinc (strong recommendation, very low level of evidence).

- 34. Pregnant women with suspected portal hypertension should undergo screening with upper endoscopy for esophageal varices in the second trimester (strong recommendation, low level of evidence).
- 35. Pregnant women who are found to have large esophageal varices should be treated with beta-blockers and/or band ligation (conditional recommendation, very low level of evidence).
- 36. Pregnant women with a history of liver transplantation should continue their immunosuppression except for mycophenolic acid (strong recommendation, moderate level of evidence).