ACG Clinical Guideline: Liver Disease in the Pregnant Patient

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Abstract

Consultation for liver disease in pregnant women is a common and oftentimes vexing clinical consultation for the gastroenterologist. The challenge lies in the need to consider the safety of both the expectant mother and the unborn fetus in the clinical management decisions. This practice guideline provides an evidence-based approach to common diagnostic and treatment challenges of liver disease in pregnant women.

Introduction

Management of pregnant women with liver disease is a common clinical scenario, and one that can be challenging given the need to consider not only the expectant mother, but also the unborn fetus in treatment decisions. The purpose of this guideline is to provide a review of the diagnostic and treatment challenges of managing liver disease in pregnant women. The evidence behind approaches to diagnosis and treatment of liver disease in pregnant women are assessed to provide management recommendations.

These recommendations are based on the following: (i) a search and review with analysis of the recently published world literature on the topic using Medline search from 1946 to present, EMBASE 1988 to present, and SCOPUS from 1980 to present using the search terms listed in the Appendix. (ii) Guideline policies of the ACG. Intended for use by physicians and allied health professionals, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. These are intended to be flexible and adjustable for individual patients (1).

To best characterize the evidence cited in support of the recommendations, the ACG practice guidelines have implemented the use of the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system. The strength of recommendations in the GRADE system is classified as strong (when the positive effects of an intervention or recommendation clearly are greater than the negative effects) or conditional (when there is uncertainty regarding the positive vs. negative aspects of the recommendation) (2). The quality of evidence supporting strong or conditional recommendations is designated by one of four levels: high (suggesting that further research is unlikely to change the authors' confidence in the estimate of effect), moderate (further research would be anticipated to have an impact on the confidence in the estimate of effect), low quality (further research would be anticipated to have an important impact on the confidence in the estimate of the effect and also likely change the estimate), or very low quality (the estimate of effect is uncertain) (2). To determine the level of evidence, the results from the selected papers with the greatest level of evidence were extrapolated and utilized in the GRADE program (http://www.gradepro.org). A summary of the recommendations are outlined in Table 1.

Table 1. Recommendation statements	
Initial evaluation of pregnant patient	
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).
Imaging in pregnancy	
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 without gadolinium can be used in the second and third trimester (conditional recommendation, low level of evidence).
4.	Computed tomography 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).
Endoscopy in pregnancy	
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	
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	
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 prior to pregnancy (strong recommendation, low level of evidence).
Hepatitis B in pregnancy	
11.	Active–passive immunoprophylaxis with hepatitis B immunoglobulin 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).
12.	Women chronically infected with HBV and high viral load (>10^6 log copies/ml (200,000 IU/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).
13.	C-section should not be performed electively in HBV-positive mothers to prevent fetal infection (strong recommendation, very low level of evidence).

14.	Women chronically infected with HBV should be allowed to breastfeed as recommended for infant health (strong recommendation, very low level of evidence).
Hepatitis C in pregnancy	
15	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).
16	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).
17	C-section should not be performed electively in HCV-positive mothers to prevent fetal infection (strong recommendation, very low level of evidence).
18	Women chronically infected with HCV should be allowed to breastfeed as indicated for infant health (strong recommendation, very low level of evidence).
19	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).
Liver disease unique to pregnancy	
20	The treatment of hyperemesis gravidarum is supportive and may require hospitalization (strong recommendation, very low level of evidence).
Intrahepatic cholestasis of pregnancy	
21	Owing to increased risk of fetal complications with IHCP, early delivery at 37 weeks is recommended (strong recommendation, very low level of evidence).
22	Ursodeoxycholic acid, should be given at 10–15 mg/kg, to women with IHCP for symptomatic improvement (strong recommendation, moderate level of evidence).
Preeclampsia and eclampsia	
23	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).
HELLP syndrome	
24	HELLP syndrome should be managed by prompt delivery, especially after 34 weeks gestation (strong recommendation, very low level of evidence).
25	Platelet transfusion to 40,000–50,000 cells/μl should be considered before delivery, especially if cesarean section is likely (conditional recommendation, very low level of evidence).
Acute fatty liver disease of pregnancy	
26.	Women with AFLP should be delivered promptly; expectant management is not appropriate (strong recommendation, very low level of evidence).
27.	All women with AFLP and their children should have molecular testing for long-chain 3-hydroxyacyl-CoA dehydrogenase (conditional recommendation, moderate level of evidence).
28.	The offspring of mothers affected by AFLP should be monitored carefully for manifestations of deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase including hypoketotic hypoglycemia and fatty liver (conditional recommendation, very low level of evidence).

Hepatitis A, hepatitis E, herpes simplex virus	
29.	Pregnant women presenting with acute hepatitis should be tested for common etiologies of acute liver injury including viral hepatitis HAV, HBV, HEV, and HSV (strong recommendation, very low level of evidence).
30.	Pregnant women with acute hepatitis suspected from HSV should be initiated on acyclovir (strong recommendation, very low level of evidence).
Other chronic liver disease	
31.	Pregnant women with AIH should be continued on their treatment with corticosteroids and/or AZA (strong recommendation, very low level of evidence).
32.	Pregnant women with PBC should be continued on their treatment with UDCA (strong recommendation, very low level of evidence).
33.	Pregnant women with 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).

AFLP, acute fatty liver disease of pregnancy; AIH, autoimmune hepatitis; AZA, azathioprine; ERCP, endoscopic retrograde cholangiopancreatography; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HEV, hepatitis E virus; HSV, herpes simplex virus; IHCP, intrahepatic cholestasis of pregnancy; PBC, primary biliary cirrhosis; WD, Wilson's disease.

EVALUATION OF THE PREGNANT PATIENT WITH ABNORMAL LIVER ENZYMES

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.	

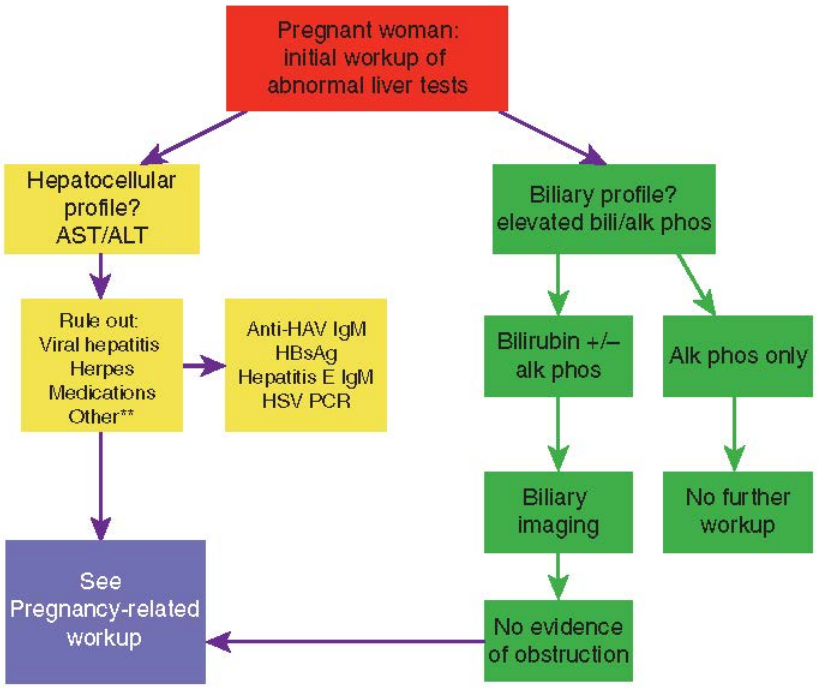

Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

LIVER DISEASES UNIQUE TO PREGNANCY

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/μl 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.

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 μmol/l
Hypoglycaemia	<4 mmol/l
Elevated urea	>340 μmol/l
Leucocytosis	>11×106 cells/l
Ascites 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.

Conclusion

Clinical evaluation of the pregnant woman who presents with liver test abnormalities relies on the accurate determination of intrinsic liver disease or liver disease related specific to pregnancy. Judicious and timely evidence-based management most often results in good maternal and fetal outcomes.