INVITED ARTICLE

Liver Diseases in the Parturient

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Key Points

- Pregnancy-associated liver diseases are the most common causes of liver dysfunction during pregnancy affecting both maternal and fetal outcomes.
- While hyperemesis gravidarum and intrahepatic cholestasis of pregnancy are usually associated with a benign course, preeclampsia with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and acute fatty liver of pregnancy may be associated with liver failure and require specialized intensive care.
- Coexistent liver diseases, like cirrhosis with portal hypertension, hepatitis B, and hepatitis C in pregnancy require multidisciplinary care involving hepatologists, radiologists, and intensivists along with obstetricians.
- Incidental liver diseases during pregnancy include acute viral hepatitis. Hepatitis E is associated with acute liver failure in pregnancy and needs intensive care. Pregnancy is a prothrombotic state associated with vascular liver diseases, like Budd–Chiari syndrome.
- Improved care in patients having liver dysfunction during pregnancy has been associated with better outcomes for both the mother and fetus. Further research in this area may help to reduce morbidity and mortality associated with these diseases.

Introduction

Pregnancy is associated with several physiological changes, which has a bearing on multiple organ systems. While a hyperdynamic circulation is associated with increased blood flow to various organ systems, the blood flow toward the liver remains fairly constant. Biochemical changes may occur secondary to hemodilution leading to lower hemoglobin and albumin levels. Alkaline phosphatase (ALP) levels are elevated due to placental ALP. Alpha-fetoprotein levels are also elevated due to production in the fetal liver. While pregnancy represents prothrombotic state, prothrombin time (PT) and activated partial thromboplastic time (aPTT) are within normal range. Aspartate transaminase and alanine transaminase (AST and ALT), gamma-glutamyl transpeptidase (GGT), and bile acid levels are within normal range.[1] Any change in the levels of AST, ALT, GGT, bile acids, or PT warrants investigation. Liver diseases in pregnancy pose a unique challenge to clinicians, wherein there are consequences to both the mother and the unborn child. In this narrative review, we discuss liver diseases that are specific to pregnancy and coincident liver diseases in pregnancy.

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Liver Diseases Specific to Pregnancy

Hyperemesis Gravidarum

Vomiting and nausea are commonly seen during pregnancy, starting around the 4–6th week, peaking between 8th and 12th week, and resolving by 20 weeks. Hyperemesis gravidarum (HG) is associated with nausea and intractable vomiting, starting at the 4–6th week and improving by the 14–16th week, although it may last until term in 20% of patients. HG is defined by the presence of ketosis and a 5% decrease from prepregnancy weight.[2] It is commonly associated with fluid and electrolyte disturbances with nutritional deficiencies. HG is known to recur in subsequent pregnancies. Risk factors include family history of HG, past history of HG, gestational trophoblastic disease, multiple gestation, female fetus, hydrops fetalis, trisomy 21, and maternal *Helicobacter pylori* infection.[3] Dysregulation in various hormones is implicated in the pathogenesis, including estrogen, progesterone, ghrelin, leptin, and thyroxine. Abnormal thyroid function tests are seen in two-third of patients. Triggers for vomiting are usually olfactory; however, auditory and visual stimuli may also lead to symptoms. Severity of symptoms of HG can be assessed using the Pregnancy Unique Quantification of Emesis (PUQE-24) questionnaire and Nausea and Vomiting in Pregnancy-specific Quality of Life questionnaire (NVQoL).[4] Triage may help to decide which patients need admission and supportive care.

Laboratory investigations include hypokalemia, hyponatremia, and ketonuria. Increase in serum transaminases and bilirubin levels may be seen in 25–40% of patients. Hyperamylasemia is seen in patients due to vomiting leading to increased production of salivary amylase.[2] Maternal complications include

nutritional deficiencies, Mallory–Weiss tear, Boerhaave syndrome, Wernicke's encephalopathy, retinal hemorrhages, spontaneous pneumomediastinum, and central pontine myelinolysis. Infants born to mothers who gain less than 7 kg during pregnancy are at higher risk of low birth weight, prematurity, small for gestational age, and low Apgar scores.

Management involves supportive care for fluid and nutritional rehabilitation. The first-line therapy is dietary modification,[2,5] including small frequent meals, avoiding an empty stomach, and separate ingestion of solids and liquids, with a high carbohydrate diet. Vitamin supplementation with thiamine supplementation is important to avoid Wernicke's encephalopathy. Medical therapy includes anti-reflux medications, like proton pump inhibitors or histamine-2 receptor antagonists. Pyridoxine, metoclopramide, phenothiazine's like prochlorperazine, and ginger are used as antiemetics. The 5-HT3 antagonists like ondansetron are safe. Glucocorticoids are used in situations with emesis refractory to routine medical therapy. Glucocorticoids did not reduce the number of days of admission, however reduced rates of readmission. Rarely enteral tube placement or surgical feeding tube placement may be needed for maintaining maternal nutrition.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy, occurring in 0.3–5.6% of all pregnancies.[6] It has been most commonly associated with mutations in MDR3 (ABCB4) and BSEP (ABCB11). ICP usually occurs in the third trimester; however, it can occur in the first trimester as well. Patients may have significant pruritus, typically involving palms and soles, worsening at nighttime. It is associated with elevated serum bile acid levels up to 15 times the upper limit of normal. Serum aminotransferases may be elevated up to 1000 U/L. Symptoms typically resolve within 4 weeks of delivery. ICP commonly occurs in the colder months with progesterone therapy during pregnancy associated with symptoms. While the disease usually follows an uneventful course, maternal quality of life may be affected due to pruritus and fat malabsorption. Fetal outcomes may be adversely affected due to risk of premature birth and intrauterine demise. Early delivery at 37 weeks is encouraged in these patients. In addition, maternal bile acid levels of 40 µmol/L or more are associated with a higher risk of fetal complications.[7] There is also an increased risk of maternal gallstones, cholecystitis, and pancreatitis. Recurrence occurs in subsequent pregnancies in 60–70% of cases.[6]

Medical management involves the use of ursodeoxycholic acid (UDCA) in doses of up to 15 mg/kg. Higher doses of 20–25 mg/kg may be used. UDCA improves maternal symptoms, liver function tests, and fetal outcomes.[6,8] Bile acid sequestrants like cholestyramine may help relieve symptoms, however may worsen steatorrhea. S-adenosylmethionine has been shown to be of benefit in small series, especially when combined with UDCA. Oral dexamethasone up to 12 mg/day over a short course of 7 days has been shown to reduce pruritus and bile acid levels.

Preeclampsia and HELLP Syndrome

Preeclampsia is a multisystem disorder characterized by endothelial dysfunction and maternal organ dysfunction due to *de novo* hypertension. Diagnostic criteria include sustained elevation of blood pressure ≥140/90 mm Hg after 20th week of pregnancy in a previously normotensive woman and proteinuria of 300 mg/24 hours (or more than 1+ on dipstick of random urine sample).[9] Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is preeclamptic liver disease which underlies the development of hepatic hematoma, rupture, and infarction.[10,11] Most individuals (60–70%) will present after the 27th week of gestation, however 10% may present earlier. Delayed presentation of HELLP (after 37th week of gestation to up to 1 week after delivery, most often within 48 hours of delivery) may occur in up to 20–30% of patients.

Diagnostic criteria for HELLP as per the ACOG and Tennessee classification are mentioned in Tables 1 and 2, respectively.[11] Severity of thrombocytopenia is graded using the Mississippi triple class classification (Table 3).[11] Clinical features of HELLP syndrome include right upper abdominal pain, nausea or vomiting, headache, bleeding, and rarely jaundice. Some pregnant patients may present with asymptomatic fall in platelets during observation for preeclampsia and initially have no hypertension or proteinuria. Maternal complications include disseminated intravascular coagulation (DIC), abruptio placentae, acute kidney injury, hepatic subcapsular hematoma, and death. In patients having severe abdominal pain, pain radiating to the neck or shoulder, and sudden drop in blood pressure, prompt imaging with CT scan or MRI is warranted to rule out hepatic hematoma or infarction.

Management is primarily supportive, with control of blood pressure being paramount.[10–12] Intravenous labetalol and hydralazine are used for the control of blood pressure. Magnesium sulfate helps to prevent progression of preeclampsia to eclampsia. Patients should be treated in an intensive care setting prior to delivery. Patients with severe preeclampsia and HELLP syndrome may require antepartum platelet transfusions and hemodialysis. Plasmapheresis may be required to prevent postpartum thrombotic

Table 1: ACOG task force in hypertension in pregnancy: Criteria for diagnosis of HELLP syndrome

Hemolysis and at least 2 of the following: • Schistocytes and burr cells on peripheral smear • Serum bilirubin ≥1.2 mg/dL • Low serum haptoglobin • Severe anemia unrelated to blood loss
Elevated liver enzyme levels: • AST or ALT ≥twice the upper limit of normal • LDH ≥twice the upper limit of normal
Platelets <100,000/mm^3

Table 2: Tennessee classification for "true" or "complete" HELLP syndrome

Microangiopathic hemolytic anemia with abnormal blood smear, low serum haptoglobin, and ↑ serum LDH levels
Sr. LDH ≥600 IU/L or 2 × ULN and serum AST levels ≥70 IU/L or 2 × ULN, or serum bilirubin ≥1.2 mg/dL
Platelet count <100,000/µL
Incomplete HELLP—2 out of 3 criteria; Complete HELLP—3 out of 3 criteria

Table 3: Mississippi triple class classification for severity of HELLP syndrome

Class I	Platelet count ≤50,000/mm^3; AST >70 U/L; LDH >600 U/L; evidence of hemolysis on smear
Class II	50,000–100,000/mm^3; AST >70 U/L; LDH >600 U/L; evidence of hemolysis on smear
Class III	100,000–150,000/mm^3

microangiopathy. Glucocorticoid therapy may improve platelet counts and ALT levels and reduce hospital and ICU stay, however has not shown any benefit on mortality. Algorithm for the management of HELLP syndrome is mentioned in Flowchart 1.

Hepatic rupture with hematoma is a consequence of severe preeclampsia,[13] usually seen in multiparous older women. In patients with a contained hematoma, serial monitoring with imaging is needed. Interventional radiological interventions with embolization of hepatic artery may be considered in severe cases. Rarely surgical repair may be needed. While these are lifesaving interventions for the mother, rapid delivery of the fetus should be considered. DIC and hepatic failure may occur postoperatively.

Acute Fatty Liver of Pregnancy

This is a form of microvesicular fatty liver disease, presenting usually late in pregnancy (30–38th week of gestation). Rarely, it can be present earlier in the 19th or 20th week and also immediately after delivery. It occurs in 1 in 7,000–20,000 pregnancies. It is common in primigravidae and those with multiple gestations. Male fetus is also considered a risk factor.[14] Diagnosis is based on the Swansea criteria (Table 4). Acute fatty liver of pregnancy (AFLP) is known to be associated with inherited defects of beta-oxidation of fatty acids. Long-chain 3-hydroxyl-coenzyme-A dehydrogenase (LCHAD) deficiency is the most common defect followed by palmitoyltransferase-1 deficiency. Seventy-nine percent of mothers with infants having inherited defects of fatty acid oxidation develop AFLP or HELLP.[15] Surviving babies with LCHAD deficiency have nonketotic hypoglycemia and obtundation. In all cases of AFLP, mothers, fathers, and infants should be tested for G1528C LCHAD deficiency. In pregnant members of the affected families, prenatal genetic diagnosis using chorionic villus sampling is of benefit.

While diagnosis is clinically based on Swansea criteria (Table 4),[16] liver biopsy may show pathognomic changes suggestive

Flowchart 1: Approach to a the patients with HELLP syndrome

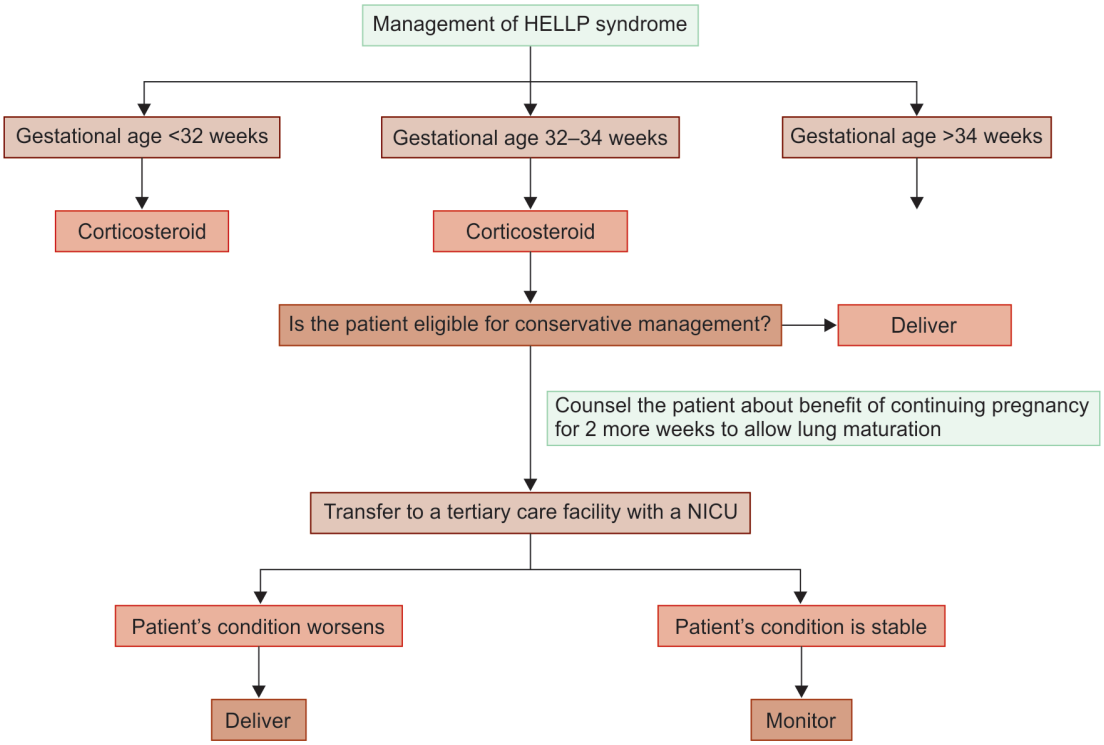


Table 4: Swansea criteria for diagnosis of acute fatty liver of pregnancy

Clinical parameters	*Investigations*
Abdominal pain	Coagulopathy (PT >14 seconds or aPTT >34 seconds)
Nausea or vomiting	Elevated serum ammonia levels (>47 µmol/L)
Ascites or bright liver on hepatic US	Elevated serum AST or ALT levels (>42 IU/L)
Polydipsia/polyuria	Elevated serum bilirubin levels (>0.8 mg/dL)
Encephalopathy	Elevated serum urate levels (>5.7 mg/dL)
	Hypoglycemia (<72 mg/dL)
	Leukocytosis (>11,000/mm^3)
	Microvesicular steatosis on liver biopsy
	Renal impairment (creatinine >1.7 mg/dL)
Diagnosis is made when ≥6 of the above present, in absence of another explanation	

of AFLP. Histologic hallmark remains small-droplet fatty infiltration of the liver which spares zone-1 of the hepatic lobule, however predominantly involves zone-3 (Fig. 1). Transjugular liver biopsy may be needed in patients with coagulopathy. Special staining techniques include the use of oil-red-O stain on the frozen specimen. Periportal hemorrhage and sinusoidal fibrin deposition are not seen in AFLP, unlike preeclampsia and HELLP.

Patients with AFLP should be managed in the ICU setting.[14,16] Early diagnosis and prompt delivery of infants reduce maternal and fetal morbidity and mortality. Supportive measures in the form of infusion of blood products, mechanical ventilation, hemodialysis, and antibiotics are needed. Glucose infusion may be needed to correct hypoglycemia. Maternal mortality is <10% with prompt recognition and delivery of the fetus. In patients with acute liver failure, liver transplantation may be required. In a previous retrospective study, the presence of hepatic encephalopathy and elevated lactate were determinants of death or need for transplant.[17] Table 5 summarizes the differences in the various liver diseases associated with pregnancy.

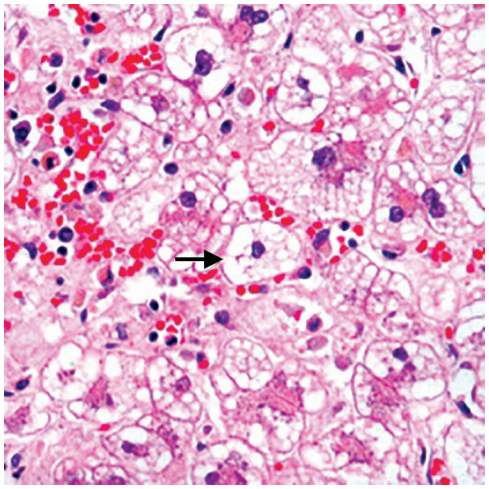


Fig. 1: Histopathologic appearance of the liver in a patient with AFLP showing microvesicular steatosis

Liver Diseases Coincidentally Occurring during Pregnancy

Acute Viral Hepatitis

Acute viral hepatitis is the commonest cause of jaundice in pregnant patients.[18] Hepatitis A virus infection is known to have a similar course in pregnant patients, as in nonpregnant individuals.[19] Fulminant hepatitis remains rare and *in utero* infection is associated with meconium peritonitis, neonatal cholestasis, and preterm labor. Supportive care with oral hydration is needed in most patients.

Hepatitis E virus (HEV) infection is associated with fulminant course in pregnant women.[20] A previous study from North India showed higher HEV RNA in pregnant as compared to nonpregnant patients. HEV RNA levels were higher in pregnant patients with acute liver failure as compared to those with only acute viral hepatitis.[21] Pregnant patients with HEV have a high risk of maternal and fetal complications, like antepartum hemorrhage, prematurity, and stillbirth. Mortality among pregnant patients with fulminant liver failure is close to 50%. Management is supportive and the use of antivirals like ribavirin is precluded by teratogenic adverse effects. Intensive care is recommended in patients with acute liver failure. Liver transplantation may be considered in patients with fulminant hepatic failure.

Herpes simplex virus may lead to hepatitis in pregnant patients. Mucocutaneous lesions are seen in up to 50% of these patients.[1,22] Significant elevation of transaminases (>1000 U/L) may be seen in these patients with jaundice and coagulopathy. Medical management with acyclovir is recommended.

Vascular Disorders of the Liver

Pregnancy is a procoagulant state with an increased risk of budd–chiari syndrome (BCS). The pooled prevalence of pregnancy-related BCS was 6.8% in a recent systematic review.[23] Diagnosis is based on Doppler ultrasound showing thrombosis of hepatic veins and inferior vena cava or MRI venography. Workup for additional prothrombotic factors is required. Acute exacerbation of chronic BCS may occur. Anticoagulation with low molecular weight heparin remains safe; however, the use of anticoagulants like warfarin is not safe due to teratogenic side effects. Radiological interventions like

Table 5: Comparison of different pregnancy-associated liver diseases

Features	*ICP*	*HELLP*	*AFLP*
% of pregnancies	0.1	0.2–0.6	0.005–0.01
Onset–weeks	25–32	Third trimester/postpartum	Third trimester/postpartum
Family history	Often	No	Occasionally
Preeclampsia	No	Yes	50%
Clinical features	Pruritus, mild jaundice, increased bile acids	Headache, weakness, hemolysis, low platelet	Liver failure coagulopathy, HE, DIC
Aminotransferases	Mild—10–20 times	Mild—10–20 times	300–500, variable
Bilirubin	<5	<5 (unless massive necrosis)	<5
Imaging	Normal	Infarcts, hematoma, rupture	Fatty infiltration
Histology	Normal to mild cholestasis	Patchy necrosis and hemorrhage	Microvesicular fat in zone 3
Maternal mortality	0%	1–25%	7–18%
Perinatal mortality	0.4–1.4%	11%	9–23%
Recurrence in subsequent pregnancies	45–70%	4–19%	LCHAD defect—yes

transjugular intrahepatic portosystemic shunt during pregnancy have been reported in case series before.[24]

Pregnancy in Patients with Preexisting Liver Disease

Cirrhosis and Portal Hypertension

While cirrhosis is associated with reduced fertility, conception is associated with high rates of preterm births, spontaneous fetal losses, and perinatal death.[25] Mortality during pregnancy is seen in 1.6% with decompensation rates being approximately 10%. Model for end-stage liver disease (MELD) sore can predict maternal decompensation during pregnancy.[1] Variceal bleeding due to portal hypertension is the leading cause of mortality in these patients. The risk of bleeding is approximately 35%, most often in the second trimester due to increased circulating volume and direct pressure of gravid uterus over the inferior vena cava impairing blood flow. Optimal management of portal hypertension remains challenging with absolute need for endoscopy in the second trimester for variceal screening, with primary prophylaxis against variceal hemorrhage and treatment of variceal hemorrhage having no clear consensus. With regard to the mode of delivery, reducing straining by augmenting the second stage of labor is recommended, with use of forceps or ventouse, as appropriate.[26] Caesarean section is preferred for obstetric indications. In patients with acute variceal bleed, endoscopic hemostasis using bands is recommended. The use of vasopressin and its analogues is avoided for risk of uterine ischemia and adverse fetal effects. Octreotide and somatostatin are preferred agents in pregnant patients.[27]

Hepatitis B Infection

All pregnant women should be screened for hepatitis B. Pregnant patients with hepatitis B are at risk of flare of disease.[28] Hence close monitoring is required during pregnancy and postpartum for derangement in liver function tests. Fetuses are at risk of mother-to-child transmission of hepatitis B. To reduce the risk of transmission, children born to hepatitis B–positive mothers should receive active vaccination and passive vaccination using immunoglobulin. Hepatitis B-positive mothers should be tested for HBV DNA at the start of the third trimester. Mothers with high viral load (>2 × 10^5 IU/mL) should receive antivirals (tenofovir or telbivudine—both category B drugs) to reduce the risk of parent-to-child transmission.[29] Mode of delivery is not associated with an increased risk of transmission. Breastfeeding is continued after immunoprophylaxis at birth.

Hepatitis C Infection

No clear guideline exists for screening for hepatitis C during pregnancy. The safety of directly acting antivirals is yet to be established during pregnancy.[30] The risk of transmission to the child is 3–5% with higher risk in the presence of HIV coinfection. Mode of delivery does not impact transmission and breastfeeding which is not contraindicated.

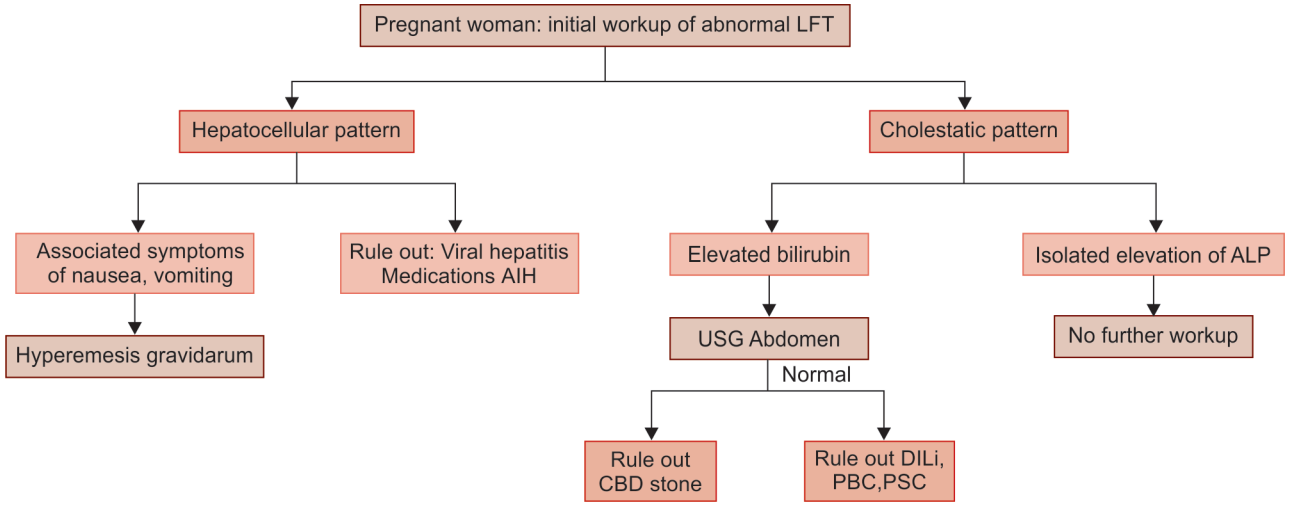
Autoimmune Hepatitis

In patients with AIH, the risk of maternal disease flare is higher in the postpartum period (11–81%) than the gestational period (7–12%).[1,31,32] Disease flares may lead to decompensation of chronic liver disease, leading to adverse fetal and maternal outcomes. Patients on azathioprine may be continued, as its safety in pregnancy and lactation has been established with experience.[28] Decompensated liver disease secondary to autoimmune hepatitis requires care in a specialized liver intensive care or high dependency unit.

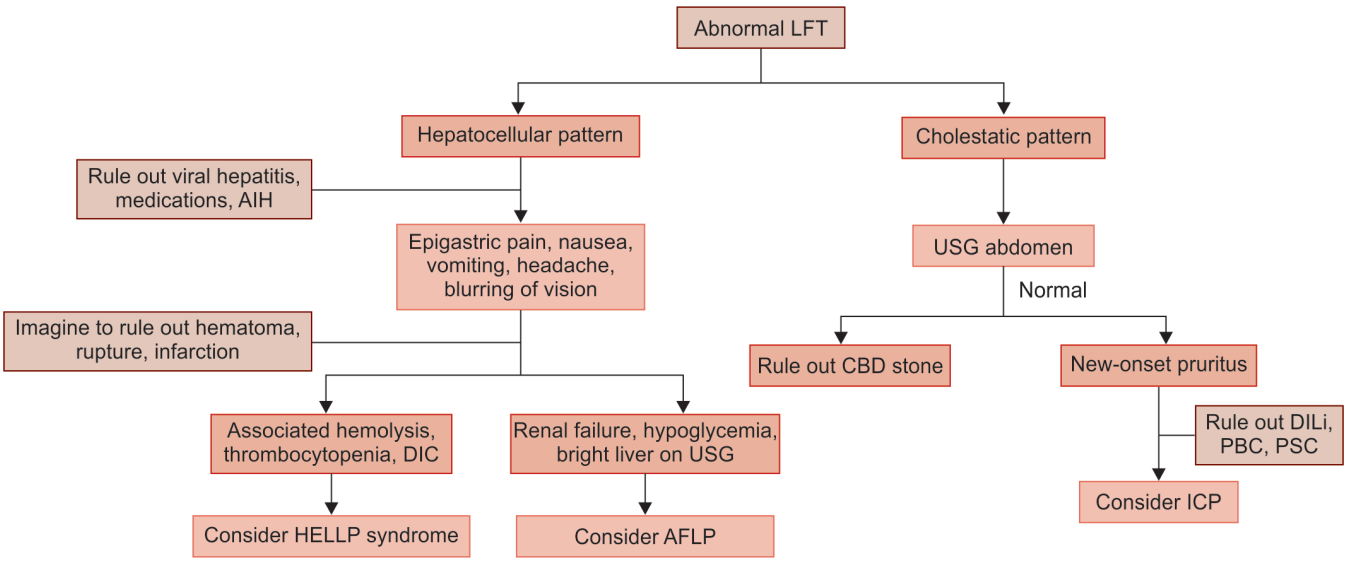
Conclusion

Liver diseases in the parturient remain a challenging area of work for hepatologists, intensivists, and obstetricians. Using an algorithmic approach to liver function derangement may help to simplify management (Flowcharts 2 and 3). Patients with preexisting liver disease who become pregnant need referral to specialized centers with multidisciplinary units caring for these patients. Preconception management of underlying liver disease has a significant bearing on pregnancy outcomes. Hence, women of childbearing age with liver disease remain a vulnerable group with a need for specialized care. Increasing research has improved maternal and fetal outcomes for patients who develop liver diseases during pregnancy and also patients with preexisting liver disease. Concerted care among various specialties may further improve both maternal and fetal outcomes.

Flowchart 2: Approach to the patients with derangement in liver function tests in the first trimester



Flowchart 3: Approach to the patients with derangement in liver function tests in the second/third trimester



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References

1. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol 2016;64(4):933–945. DOI: 10.1016/j.jhep.2015.11.030.
2. Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. J Clin Exp Hepatol 2014;4(2):151–162. DOI: 10.1016/j.jceh.2013.03.220.
3. Fell DB, Dodds L, Joseph KS, Allen VM, Butler B. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. Obstet Gynecol 2006;107(2 Pt 1):277–284. DOI: 10.1097/01.AOG.0000195059.82029.74.
4. Koot MH, Grooten IJ, van der Post JAM, Bais JMJ, Ris-Stalpers C, Leeflang MMG, et al. Determinants of disease course and severity in hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 2020;245:162–167. DOI: 10.1016/j.ejogrb.2019.12.021.
5. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-analysis. J Matern Fetal Neonatal Med 2018;31(18):2492–2505. DOI: 10.1080/14767058.2017.1342805.
6. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009;15(17):2049–2066. DOI: 10.3748/wjg.15.2049.
7. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology 2004;40(2):467–474. DOI: 10.1002/hep.20336.
8. Kong X, Kong Y, Zhang F, Wang T, Yan J. Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study) [published correction appears in Medicine (Baltimore) 2017;96(3):e6031]. Medicine (Baltimore) 2016;95(40):e4949. DOI: 10.1097/MD.0000000000004949.
9. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014;4(2):97–104. DOI: 10.1016/j.preghy.2014.02.001.
10. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004;103(5 Pt 1):981–991. DOI: 10.1097/01.AOG.0000126245.35811.2a.
11. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. BMC Pregnancy Childbirth 2009;9:8. DOI: 10.1186/1471-2393-9-8.
12. Martin JN Jr, Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol 2006;195(4):914–934. DOI: 10.1016/j.ajog.2005.08.044.
13. Greenstein D, Henderson JM, Boyer TD. Liver hemorrhage: recurrent episodes during pregnancy complicated by preeclampsia. Gastroenterology 1994;106(6):1668–1671. DOI: 10.1016/0016-5085(94)90425-1.
14. Naoum EE, Leffert LR, Chitilian HV, Gray KJ, Bateman BT. Acute fatty liver of pregnancy: pathophysiology, anesthetic implications, and obstetrical management. Anesthesiology 2019;130(3):446–461. DOI: 10.1097/ALN.0000000000002597.
15. Browning MF, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. Obstet Gynecol 2006;107(1):115–120. DOI: 10.1097/01.AOG.0000191297.47183.bd.
16. Morton A, Laurie J. Physiological changes of pregnancy and the Swansea criteria in diagnosing acute fatty liver of pregnancy. Obstet Med 2018;11(3):126–131. DOI: 10.1177/1753495X18759353.
17. Westbrook RH, Yeoman AD, Joshi D, Heaton ND, Quaglia A, O'Grady JG, et al. Outcomes of severe pregnancy-related liver disease: refining the role of transplantation. Am J Transplant 2010;10(11):2520–2526. DOI: 10.1111/j.1600-6143.2010.03301.x.
18. Licata A, Ingrassia D, Serruto A, Soresi M, Giannitrapani L, Montalto G, et al. Clinical course and management of acute and chronic viral hepatitis during pregnancy. J Viral Hepat 2015;22(6):515–523. DOI: 10.1111/jvh.12335.
19. Chaudhry SA, Koren G. Hepatitis A infection during pregnancy. Can Fam Physician 2015;61(11):963–964. PMID: 26881283.
20. Singh S, Mohanty A, Joshi YK, Dwivedi SN, Deka D. Outcome of hepatitis E virus infection in Indian pregnant women admitted to a tertiary care hospital. Indian J Med Res 2001;113:35–39. PMID: 21910283.
21. Kar P, Jilani N, Husain SA, Pasha ST, Anand R, Rai A, et al. Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy?Am J Gastroenterol 2008;103(10):2495–2501. DOI: 10.1111/j.1572-0241.2008.02032.x.
22. Mortele KJ, Barish MA, Yucel KE. Fulminant herpes hepatitis in an immunocompetent pregnant woman: CT imaging features. Abdom Imaging 2004;29(6):682–684. DOI: 10.1007/s00261-004-0199-y.

23. Ren W, Li X, Jia J, Xia Y, Hu F, Xu Z. Prevalence of Budd-Chiari syndrome during pregnancy or puerperium: a systematic review and meta-analysis. Gastroenterol Res Pract 2015;2015:839875. DOI: 10.1155/2015/839875.
24. Ingraham CR, Padia SA, Johnson GE, Easterling TR, Liou IW, Kanal KM, et al. Transjugular intrahepatic portosystemic shunt placement during pregnancy: a case series of five patients. Cardiovasc Intervent Radiol 2015;38(5):1205–1210. DOI: 10.1007/s00270-015-1053-z.
25. Tan J, Surti B, Saab S. Pregnancy and cirrhosis. Liver Transpl 2008;14(8):1081–1091. DOI: 10.1002/lt.21572.
26. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–752. DOI: 10.1016/j.jhep.2015.05.022.
27. Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60(3):954–963. DOI: 10.1002/hep.27006.
28. Giles M, Visvanathan K, Lewin S, Bowden S, Locarnini S, Spelman T, et al. Clinical and virological predictors of hepatic flares in pregnant women with chronic hepatitis B. Gut 2014;64(11):1810–1815. DOI: 10.1136/gutjnl-2014-308211.
29. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560–1599. DOI: 10.1002/hep.29800.
30. Snijdewind IJ, Smit C, Schutten M, Nellen FJ, Kroon FP, Reiss P, et al. Low mother-to-child-transmission rate of Hepatitis C virus in cART treated HIV-1 infected mothers. J Clin Virol 2015;68:11–15. DOI: 10.1016/j.jcv.2015.04.002.
31. Westbrook RH, Yeoman AD, Kriese S, Heneghan MA. Outcomes of pregnancy in women with autoimmune hepatitis. J Autoimmun 2012;38(2–3):J239–J244. DOI: 10.1016/j.jaut.2011.12.002.
32. Schramm C, Herkel J, Beuers U, Kanzler S, Galle PR, Lohse AW. Pregnancy in autoimmune hepatitis: outcome and risk factors. Am J Gastroenterol 2006;101(3):556–560. DOI: 10.1111/j.1572-0241.2006.00479.x.