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 thromboplastin 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. 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.

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...
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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. 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 night. 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. There is also an increased risk of maternal gallstones, cholecystitis, and pancreatitis. Recurrence occurs in subsequent pregnancies in 60%–70% of cases.

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. 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). Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is preeclamptic liver disease which underlies the development of hepatic hematoma, rupture, and infarction. 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. Severity of thrombocytopenia is graded using the Mississippi triple class classification (Table 3). 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. 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 tendencies.

### 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 burst 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 | Criteria |
|-------|----------|
| 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$^3$ |

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Liver Diseases in the Parturient 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. 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.

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), liver biopsy may show pathognomic changes suggestive of the condition. 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, 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. Diagnosis is made when ≥6 of the above present, in absence of another explanation.

### 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/mm³) |
|                     | 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.
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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 |

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

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

Abnormal LFT

Hepatocellular pattern

Epigastric pain, nausea, vomiting, headache, blurring of vision

Rule out viral hepatitis, medications, AIH

Imagine to rule out hematoma, rupture, infarction

Associated hemolysis, thrombocytopenia, DIC

Consider HELLP syndrome

Cholestatic pattern

USG abdomen

Normal

Rule out CBD stone

New-onset pruritus

Rule out DILI, PBC, PSC

Consider AFLP

Consider HELLP syndrome

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