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Liver and Biliary Disease of Pregnancy and Anesthetic Implications: A Review

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Abstract

Liver and biliary disease complicates pregnancy in varying degrees of severity to the mother and fetus, and anesthesiologists may be asked to assist in caring for these patients before, during and after birth of the fetus. Therefore, it is important to be familiar with how different liver diseases impact the pregnancy state. In addition, knowing symptoms, signs, and laboratory markers in the context of a pregnant patient will lead to faster diagnosis and treatment of such patients. This review article discusses changes in physiology of parturients, patients with liver disease, and parturients with liver disease. Next, general treatment of parturients with acute and chronic liver dysfunction is presented. The article progresses to specific liver diseases with treatments as they relate to pregnancy. And finally, important aspects to consider when anesthetizing parturients with liver disease are discussed.

Keywords

general anesthesia; hepatic; neuraxial anesthesia; regional anesthesia

Introduction

Liver disease in pregnancy has a wide spectrum of severity and ranges from mild to severe liver dysfunction complicating 3% of pregnancies.[1] Liver and biliary diseases impact anesthesia care, regardless if pregnancy-specific or coincidentally found in pregnancy.[2] While some liver diseases have effective treatments, unfortunately, some treatments are not

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curative and aim at treating symptoms while awaiting liver recovery. In rare situations, the only option is a liver transplantation.

The purpose of this review is three-fold: i) help clinicians recognize liver dysfunction and assist in treatment of the parturient; ii) review disease processes specific to and coincidentally found in pregnancy and their differential diagnoses; iii) raise attention to the anesthetic implications surrounding care of a parturient with liver and biliary disease.

Symptoms, Signs, and Laboratory Markers for Liver and Biliary Dysfunction

The physiology of pregnancy and liver disease have overlapping features and may be difficult to distinguish in parturients with liver dysfunction. Similarities and key differences are reviewed below. Although cardiac output is increased in the parturient, blood flow to and size of the liver are unchanged throughout pregnancy.[3,4] The liver may be pushed cephalad by the uterus, but enlargement should prompt an investigation.[5] Spleen size is not a unique feature, as it is enlarges with liver disease and pregnancy progression.[6] Table 1 reviews laboratory abnormalities, signs, and symptoms of liver dysfunction.

Gluconeogenesis is an essential function of the liver; accordingly, severe dysfunction leads to hypoglycemia and elevated lactate.[7] A hallmark of liver dysfunction is elevated transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), a consequence of altered amino acid metabolism and release of hepatic enzymes from hepatocytes damaged by inflammation.[4] In comparison, transaminase levels are normal during uncomplicated pregnancy.[8]

Alkaline phosphatase (ALP) elevation up to 1.5 times is normal due to fetal ALP production, but if ALP and gamma glutamyl transferase (GGT) rise together, they point toward biliary tract obstruction.[4,7] Hyperbilirubinemia is seen clinically as jaundice and is due to biliary tract obstruction or the liver's inability to metabolize and excrete the metabolic byproducts of heme.

Liver dysfunction and pregnancy are both associated with elevated estrogen and progesterone.[7] Hyperventilation is seen in both processes due to high progesterone. Additionally, elevated estrogen levels in both normal pregnancy and liver dysfunction can be seen clinically as palmar erythema.[9] Spider telangiectasias are more commonly seen in chronic liver dysfunction than in pregnancy.[7]

An important liver function relevant to anesthetic care is protein production, especially albumin and coagulation factors.[7] It is common for parturients to have low serum albumin levels, but if combined with liver dysfunction, these can become critically low. The albumin level in a non-pregnant female is 4.1–5.3 g dl^{-1} and drops to 2.3–4.2 g dl^{-1} during the third trimester.[10] Albumin is essential for oncotic pressure in the circulatory system as well as drug binding vs "free" levels of administered drugs. Unique to liver disease is the decreased ability to produce coagulation factors.[11] Decreased production of coagulation factors leads to prolonged prothrombin time (PT) and partial thromboplastin time (PTT).[11]

Liver dysfunction results in reduced factors that contribute to both clot formation as well as prevention; therefore, prolonged PT and PTT do not accurately predict coagulation status in this setting. Antithrombin III is a protease that inhibits thrombin, factor IXa, and Xa, and at low levels, can increase clotting.[12] It is decreased in pregnancy and liver dysfunction.[13,14] Antithrombin III levels continue to decrease with advancement of liver disease.[15] In addition, pregnancy alone is hypercoagulable in nature due to increased production of factors VII, X, VIII, fibrinogen and von Willebrand factor.[16] Pregnancy increases risk of venous thrombosis 4–5-fold.[17]

Acute and Chronic Liver Dysfunction Treatment

Chronic liver dysfunction is rare in pregnancy because many pathophysiologic changes secondary to significant liver disease lead to infertility.[6,18,19] Unlike acute liver dysfunction, chronic liver dysfunction develops slowly.[20] Familiarity with the physiologic processes of the liver is useful to better treat the deteriorating patient; table 2 shows a list of common manifestations.

The liver's inability to convert ammonia to urea can manifest clinically as encephalopathy.[7,21] Accumulation of ammonia and other neurotoxins including glutamate, manganese, short fatty acids, and mercaptans in the setting of acute liver dysfunction is associated with increased intracranial pressure (ICP) due to osmotic forces. The accumulation of these toxins leads to cerebral edema with astrocyte swelling. This complication is much more common in acute than chronic liver dysfunction as chronic liver disease results in compensatory mechanisms to prevent cerebral edema.[22,23] Initial treatment of increased ICP includes head elevation and administration of mannitol or hypertonic saline to increase serum osmolality.[21,24] Anesthesiologists need to consider intubation for airway protection or to hyperventilate the patient to lower ICP.[22,24] Encephalopathy begins with mild confusion, but can progress to coma.[24] Patients with encephalopathy are sensitive to sedatives; these should be administered cautiously.[24] Chronic management of liver dysfunction complicated by encephalopathy aims at decreasing the colonic absorption of nitrogen with lactulose and oral administration of unabsorbed antibiotics, such as rifaximin.[25]

Low coagulation factors and thrombocytopenia are common in people with both acute and chronic liver dysfunction,[11] while healthy parturients tend to be within normal limits to hypercoagulable.[7] Thrombocytopenia in liver disease is secondary to splenic sequestration and decreased production of thrombopoietin.[11] Patients with severe liver dysfunction are predisposed to gastrointestinal, muco-cutaneous and bleeding from medical interventions.[11] Despite an increased risk of spontaneous bleeding, it is not recommended to replace platelets and coagulation factors unless there is active bleeding or until an invasive procedure is planned.[24] Twenty-five percent of patients have an underlying vitamin K deficiency, and it is acceptable to prescribe one dose of intravenous vitamin K 10 mg for spontaneous bleeding.[21] Treatment can be challenging because liver dysfunction patients can be hypo- and hypercoagulable at the same time, as decreased hepatic production of procoagulant proteins can coexist with reduced synthesis of natural anticoagulants such as of protein C, protein S, and Antithrombin III.[11,22] Although these patients are at increased risk for

bleeding, there can also be risk of deep venous thrombosis and pulmonary embolism. Due to the unpredictable relationship of procoagulant and anticoagulant factors in chronic liver disease, indiscriminate use of fresh frozen plasma is not beneficial in correcting perceived coagulation defects in these patients.[26]

Patients with liver disease commonly have low systemic vascular resistance (SVR) and high cardiac output.[7,21,22,24] They often have low blood pressure, and initial treatment aims at fluid resuscitation while avoiding lung injury and worsening cerebral edema.[22,24] Patients with liver dysfunction often appear hypervolemic with edema as well as ascites, but may be intravascularly depleted, making it difficult to know when euvolemia is reached.[27] Under specific circumstances (sinus rhythm, mechanical ventilation), pulse pressure variation or stroke volume variation can aid in determining the patient's fluid status. This practice, though, has not been studied specifically in the liver disease population.[28]

No difference was found between crystalloid and albumin when resuscitating critically ill patients, but due to cost and lack of superiority of albumin, crystalloids are preferred.[29] There are a few instances in patients with decompensated liver dysfunction where albumin would be preferred. One instance is volume expansion in patients with hypervolemic hyponatremia.[29] In addition, after large-volume paracentesis (>5 l) in the setting of cirrhosis and portal hypertension, albumin administration of 6–8 g l^{-1} ascites removed can help alleviate the risk of renal dysfunction.[30] Other instances are treatment and prevention of hepatorenal syndromes and to improve survival from spontaneous bacterial peritonitis.[29] Due to the rarity of encountering decompensated cirrhosis in pregnancy, not all research includes pregnant patients; nonetheless, albumin administration is still expected to be beneficial in these settings, including increased survival.[31]

After adequate fluid resuscitation, the vasopressor of choice in patients with liver dysfunction is norepinephrine because it affects circulation through the splanchnic organs the least compared to vasopressin and epinephrine.[22,24] When blood pressure is unresponsive to fluid and vasopressor therapy, steroid insufficiency or a source of infection should be investigated.[32] It can be difficult to discern the cause of hypotension due to overlapping symptoms being either from peripheral vasodilatation due to nitric oxide or due to sepsis.[29] Treatment for spontaneous bacterial peritonitis should be promptly initiated if ascites has a ≥250 cells μl^{-1} polymorphonuclear cell count because prognosis of spontaneous bacterial peritonitis is poor in cirrhotic patients.[33] The role of empiric antibiotics in managing liver failure is controversial. The risk of infection is high; thus, a high index of suspicion should exist.[34]

Portopulmonary hypertension should be considered when caring for patients with chronic liver dysfunction[35,36] and is due to high resistance in the pulmonary arterial bed.[37] Causes of high resistance can be from smooth muscle and/or endothelial proliferation, vasoconstrictors, and platelet aggregation.[37] Typical symptoms of portopulmonary hypertension are dyspnea with exertion and features of right heart failure. High pulmonary pressure in the absence of other causes and in the setting of portal hypertension is diagnostic.[37] Though rare in pregnancy, the anesthesiologist should consider the impact

of portopulmonary hypertension on right ventricular function when designing the anesthetic plan.[36]

In addition, hepatopulmonary syndrome is another manifestation of chronic liver dysfunction.[35] It is thought to be secondary to changes in the pulmonary microvascular bed leading to diffusion limitations and shunting by intrapulmonary vascular dilation predominantly in the lung bases, resulting in complaints of platypnea (increased shortness of breath when moving from supine to upright) and orthodeoxia (decrease in arterial blood oxygen by more than 5% or 4 mmHg when assuming upright posture).[37] An increase of oxygen saturation is noted when patients are supine, due to a relative increase in perfusion of the less-affected upper lung fields. The diagnosis of hepatopulmonary syndrome includes confirming the presence of portal hypertension, an alveolar-arterial oxygen gradient greater than 15 mmHg in the setting of hypoxia, and pulmonary vasodilation.[38] Pulmonary vasodilation is shown by the appearance of microbubbles in the left side of the heart in a delayed fashion (3–6 beats) during contrast echocardiography or greater than 6% uptake of technetium 99m-labelled macro-aggregated albumin in a lung perfusion scan.[38]

Finally, hepatic fibrosis leads to portal hypertension from increased resistance to portal flow through scarred liver tissue. Significant hepatic inflammation as seen in alcohol-related hepatitis can also cause narrowing of hepatic sinusoids and increased hepatic resistance.[39] These cause diversion of blood flow through esophageal, hemorrhoidal, and intra-abdominal veins.[6] Mortality for pregnant women with cirrhosis complicated by portal hypertension has been found to be as high as 10.5%,[9] while a more recent cohort of 103 women from Sweden suggests no increased risk.[40] This diversion of blood puts patients at increased risk for spontaneous bleeding. Although the preferred mode of delivery is controversial,[41,42] patients with known varices are advised to undergo elective cesarean delivery or assisted vaginal delivery because increased intra-abdominal pressure during labor and already increased blood volume during pregnancy can precipitate variceal hemorrhage.[6,42,43] Beta-blockers are prescribed prophylactically to decrease risk of spontaneous esophageal bleeding in the setting of large varices.[6,44] Propranolol is typically chosen over nadolol because of its shorter half-life.[7] Octreotide can cause arteriolar vasospasm affecting placental perfusion, but should be considered in the setting of variceal bleeding.[6,25,45] Immediate intubation for airway protection is indicated. A gastroenterology consultation should be requested promptly for band ligation of bleeding varices.[6]

Liver and Biliary Diseases Unique to Pregnancy

There are several liver and biliary diseases unique to pregnancy; table 3 shows differences and similarities between them. Intrahepatic cholestasis of pregnancy typically presents with intense itching during the second and third trimester; in a minority, clinical jaundice is seen.[1] The exact cause is unknown, but it is thought to be due to abnormal transport of bile acids.[46] This is a serious condition due to increased fetal mortality in the untreated parturient.[1] It is most common with previous history of intrahepatic cholestasis of pregnancy, and with multiple gestations.[47] It is associated with meconium, asphyxia events, and preterm delivery.[48] There was a positive correlation between maternal bile acids and adverse fetal outcome in one large prospective study.[49] Hepatic aminotransferase levels can be elevated

up to five times normal, and patients are prone to malabsorption of vitamin K.[50] Due to increased fetal mortality, delivery is recommended at 37 weeks.[49] Ursodeoxycholic acid is the treatment of choice for pruritus in the pregnant woman, when itching is related to bile acids.[1,48] A small retrospective study found that neuraxial anesthetic is safe, and there is no need to delay for results of coagulation studies to return.[50]

Hyperemesis gravidarum typically presents during the first trimester and usually resolves by 20 weeks of pregnancy.[51] Patients present with severe nausea and vomiting associated with electrolyte abnormalities, dehydration, and weight loss of up to 5%.[7,9,52] With prolonged emesis, a parturient can develop mild jaundice, mild elevation of hepatic transaminases, and transient hyperthyroidism.[9] Bilirubin can be mildly elevated and cause jaundice. Persistent jaundice should prompt an evaluation for other causes.[53] The exact mechanism is unknown, but prior hyperemesis gravidarum, fetal abnormalities, multiple gestations, and molar pregnancies increase the risk.[51] Hormonal, infectious, mechanical, or psychogenic origins of hyperemesis gravidarum have been considered.[51] Treatment is supportive and includes vitamin supplementation, hydration, and anti-nausea medication.[51] The abnormal laboratory findings resolve once the emesis resolves.[54] Severe cases of unremitting hyperemesis may require parental nutrition.[52]

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), which is part of the preeclampsia spectrum, develops during the second and third trimester.[3] HELLP is seen in 10–20% of preeclampsia cases.[55] Increased maternal mortality is associated with oliguria and increased bilirubin and complicates 1% of pregnancies.[56] Fetal outcomes are more closely related to gestational age as opposed to maternal severity of HELLP syndrome.[57] Infants born to mothers with HELLP have morbidity and mortality between 10% and 60% with morbidity related to respiratory distress syndrome and intrauterine growth retardation.[56] Prior history of preeclampsia or HELLP, multiple gestations, multiparous women, advanced maternal age, very young age, or Caucasian race are risk factors for HELLP.[7] Symptoms and laboratory abnormalities of HELLP are hypertension, abdominal pain, low platelets, hemolytic anemia, elevated hepatic transaminases, headache, and nausea.[58] Severe cases of HELLP syndrome can develop liver infarction with possible hepatic rupture, kidney dysfunction, pulmonary edema, and placental abruption. Disseminated intravascular coagulation has been found in up to 20% of HELLP patients.[43] If a patient with HELLP complains of right upper quadrant abdominal pain, imaging for rapid diagnosis of subcapsular hepatic hematoma or hepatic rupture should be performed.[59] Mortality of hepatic rupture and hepatic hematoma is seen in 16–60% of parturients.[43] It is imperative that anesthesiologists review current laboratory information determining coagulation status prior to placement of a neuraxial anesthetic. Treatment of HELLP is immediate delivery, seizure prophylaxis, and blood pressure control.[3,58,60] In the event of an indwelling epidural catheter, removal should wait until after normalization of coagulation. Normalization typically takes 48 hours after delivery, but can take up to 8 days.[57] If the epidural catheter needs to be removed prior to normalization of platelets and clotting factors, to mitigate risk of epidural hematoma, transfusion of platelets and/or clotting factors may be indicated.

Finally, acute fatty liver of pregnancy (AFLP) is rare, but possibly deadly to both the mother and fetus. It presents during the third trimester and rarely in the early postpartum period.[61,62] Maternal mortality ranges from 12.5 to 18%, while fetal mortality is estimated between 7 and 66%; better outcomes are found with early recognition.[62–65] AFLP is associated with multiple gestations as well as first-time pregnancies.[66,67] The etiology is thought to be related to deficiency in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) in fetal mitochondria resulting in microvesicular fatty infiltration of the mother's liver.[66] Women with heterozygous LCHAD deficiency combined with preeclampsia have a higher risk of AFLP compared to heterozygous LCHAD alone.[68]

Anorexia, nausea, malaise, fatigue, and headache are the typical early nonspecific signs of the disease.[1,69] As early recognition is important, Swansea's criteria have been developed, and six out of 14 features must be present for a diagnosis without alternative explanations for the symptoms.[43,69,70] These 14 features are: vomiting, leukocytosis, abdominal pain, ascites, polydipsia or polyuria, elevated liver enzymes, encephalopathy, elevated ammonia, elevated bilirubin, renal impairment, low glucose, prolonged PT/PTT, elevated urate, or microvesicular steatosis from liver biopsy.[43,69,70] If delivery is not expedited, the disease may worsen with progression of jaundice, encephalopathy, peripheral edema, hypertension, renal failure, hypoglycemia, and other signs of acute liver failure.[9,69] Hepatic transaminases are typically elevated to ten times the upper normal range.[69] Lactate dehydrogenase, uric acid, and white blood cell count often increase as the disease progresses.[69] Rapid delivery, blood pressure control, preparation for massive transfusion, monitoring coagulation status, prevention of hypoglycemia, and seizure prophylaxis are key treatments of this disease process.[1,69]

Many parturients prefer neuraxial anesthesia, but the concern for coagulopathy during the spinal anesthetic or placement and removal of the epidural catheter puts patients at increased risk of epidural hematoma. In a retrospective case series of 28 women with AFLP, 13 patients had neuraxial anesthesia. Two patients that underwent neuraxial anesthesia had an international normalized ratio (INR) greater than 2, but did not experience complications.[71] Expert opinions continue to recommend a neuraxial anesthetic with INR less than 1.5.[71,72] Once the fetus is delivered, the mother's indices of liver function are expected to return to normal within several weeks.[61] If the liver does not adequately recover, the clinician should consider sepsis, hypoxic-ischemic liver injury, or alternative etiologies.[61] Rarely, patients with AFLP will require liver transplantation.[61] The slow return of liver function and production of coagulation factors is part of the complex judgement when deciding to place an epidural because of risk of epidural hematoma during catheter removal in AFLP patients.

Liver and Biliary Diseases Incidental to Pregnancy

The differential diagnosis of liver disease is long, and anesthesiologists should be familiar with the more common causes of chronic liver disease because they may be asked to help care for a parturient with liver disease of unknown etiology. Anesthesiologists must consider both pregnancy-specific as well as coincidental liver diseases affecting the general population.

Infectious etiologies should be considered in women presenting with an unknown cause of liver dysfunction. Hepatitis A and E are spread through the fecal oral route and are more often seen outside the United States.[73,74] Hepatitis E is asymptomatic or mildly symptomatic in the general population, but may become more severe in the pregnant and immunosuppressed person.[73,75]

In contrast, hepatitis B and D are transmitted through exposure to body fluids and blood. Infants often contract hepatitis B perinatally in areas endemic with the disease.[76] In areas of low hepatitis B prevalence, the virus is mostly contracted by sexual contact, intravenous drug abuse, and healthcare-associated transmission.[77,78] The decreased incidence and prevalence of hepatitis B in the United States is largely due to vaccination.[77] The vaccine is offered to all infants, and hepatitis B immunoglobulin is available to infants born to mothers with known hepatitis B. Immunoglobulin has been found to decrease virus transmission to the infant by 90%.[78,79] Tenofovir, or less commonly, telbivudine or lamivudine should be provided to pregnant women at the beginning of their third trimester if their hepatitis B virus level is >200,000 IU ml^{-1}, because decreases in circulating virus levels will also reduce transmission to the newborn.[25,78–81] Hepatitis D is only found in patients that also have coexisting hepatitis B, and both infections together may be more severe than hepatitis B alone.[82] Antiviral therapies for hepatitis D do not exist.

Hepatitis C virus (HCV) transmission occurs most commonly parenterally from needle sharing, transfusion of contaminated blood products, and unsafe medical practices.[83] HCV is also transmitted sexually.[83] Maternal-to-fetal HCV transmission is recognized in approximately 5% of pregnancies.[25,84,85] Chronic treatment is dependent on the patient's HCV genotype.[86] The medications now used are direct-acting antivirals which are tolerated well and very effective.[86] The safety of direct-acting antiviral treatment for hepatitis C during pregnancy is currently unknown, and treatment is typically deferred until after pregnancy.[87]

Herpes simplex virus (HSV) hepatitis is rare, but should remain in the differential of at-risk populations.[88] HSV hepatitis presents as an acute, severe hepatitis with hepatic transaminases often greater than 1,000 IU ml^{-1}. Due to the presence of T cell dysfunction, HSV hepatitis is more common in immunocompromised or pregnant patients.[89] In severe acute liver disease of unknown etiology, the empiric administration of acyclovir should be considered while awaiting return of polymerase chain reaction tests for HSV.[88,90] This practice can be lifesaving because fetal herpes has an approximate 39% mortality rate, and treatment with acyclovir is safe and well tolerated.[88,90]

The most common cause of right upper quadrant pain in pregnancy is cholecystitis.[91] The hormonal changes during pregnancy contribute to gallstone formation.[92] Ultrasound together with clinical evaluation is used to confirm the diagnosis.[93,94] Gallstones complicate 3% of pregnancies, but only 0.1% of patients develop acute cholecystitis. Acute cholecystitis is associated with not only right upper quadrant pain, but also fever and increased white blood cell count.[7] A gallstone obstructing the common bile duct will result in elevation of hepatic transaminases, alkaline phosphatase, and bilirubin. Antibiotic therapy is indicated initially for cholecystitis as well as cholangitis. Cholecystectomy is recommended over

conservative treatment of cholecystitis because worse outcomes for the fetus were found with conservative management of acute cholecystitis.[91,95] Endoscopic retrograde cholangio-pancreatography (ERCP) may be necessary to relieve bile duct obstruction, but radiation to the fetus should be minimized.[91,96] If left untreated, parturients can develop gangrenous cholecystitis. Common bile duct stones can lead to cholangitis and pancreatitis.

Liver and biliary tract autoimmune diseases can complicate pregnancy.[9] The most common autoimmune diseases are autoimmune hepatitis, primary biliary cholangitis (PBC, previously called primary biliary cirrhosis), and primary sclerosing cholangitis. These diseases are summarized in table 4 with their respective treatments. Immunosuppression is the treatment goal of these diseases with specific immunosuppressive medications and corticosteroids,[97] some of which have been deemed safe during pregnancy.[98] Flares associated with these diseases during pregnancy can occur, and are associated with worse maternal-fetal outcomes.[98,99] Autoimmune hepatitis during pregnancy may demonstrate a flare of liver inflammation in 25%, although this occurs most commonly post-partum.[100] Immunosuppressive therapy during pregnancy to prevent a flare of autoimmune hepatitis, as well as augmentation of immunosuppression are indicated as the risks of significant inflammation exceed the risks of medications to the fetus.[98,99] Azathioprine and prednisone are commonly used for treatment of autoimmune hepatitis and should be continued during pregnancy.[43,101] Azathioprine was found to be teratogenic in animals, but not in humans.[9] Mycophenolate mofetil is contraindicated due to associated congenital malformations.[100–104] Ursodeoxycholic acid is used for treatment of PBC and deemed safe during pregnancy, but studies are limited for fetal outcomes.[105,106] Significant worsening of PBC is not commonly seen during pregnancy.[106] Primary sclerosing cholangitis can present with biliary obstruction; treatment with ERCP is preferably deferred to the post-partum period.[107]

Systemic metabolic diseases can lead to hepatic destruction, fibrosis and cirrhosis.[7] Wilson's disease is associated with neurologic and ophthalmologic findings, infertility, renal dysfunction, and liver dysfunction due to copper depositions.[108] Copper chelators and zinc are the treatments of choice and have not shown harm to the fetus during pregnancy.[108,109,110] Clinically significant hemochromatosis is rarely identified in a woman of child-bearing age.

Pregnancy is associated with hypercoagulability, and hypercoagulable patients are predisposed to thrombosis, including hepatic or portal vein thrombosis.[9,111,112] Budd-Chiari results from hepatic vein thrombosis and impedes drainage of the liver, leading to portal hypertension and eventual liver fibrosis and dysfunction.[9,112] Portal vein thrombosis impairs blood flow to the liver and contributes to the development of splenomegaly and gastroesophageal varices. If it progresses to involve the superior mesenteric veins, intestinal ischemia can result. Treatment includes decompressive therapy or anticoagulation with low-molecular-weight heparin (LMWH) because warfarin is rarely prescribed as it readily crosses the placenta and can lead to congenital abnormalities, especially when taken in the first trimester.[112–115] Please note, according to American College of Obstetricians and Gynecologists guidelines, warfarin is only considered for women with mechanical heart valves because of the high thrombosis risk even with LMWH therapy. Following LMWH

therapy in the first trimester, vitamin K antagonists are given until close to delivery when LMWH is resumed because of the risk of fetal hemorrhage in women on warfarin and to facilitate neuraxial anesthesia.[115]

Finally, clinicians must consider intentional or accidental drug toxicity in their differential diagnosis of a patient with new liver dysfunction.[7] Acetaminophen is the most common drug overdose during pregnancy.[116] Glutathione binds reactive oxide metabolites of acetaminophen in patients with normal liver function and safe doses of acetaminophen.[116] High doses of acetaminophen result in production of toxic metabolites that are injurious to the liver and kidneys.[116] The antidote to acetaminophen overdose is N-acetyl cysteine which results in better outcomes for the mother and fetus if administered within 16 hours of ingestion.[116] Alcoholic hepatitis is an additional cause that should be considered in the differential diagnosis of liver dysfunction if large amounts of alcohol have been ingested.[117] Finally, it is always important to obtain a full list of prescribed, over-the-counter and herbal medications from patients who present with evidence of liver inflammation due to the unpredictable hepatotoxicity of some of these agents.[118,119]

Anesthetic Implications

Maternal and fetal hemodynamic stability are critically important, and anticipating effects of drugs and interventions performed for a parturient will aid in maintaining hemodynamic stability. Highly protein-bound drugs may have an increased duration of effect in parturients and patients with liver dysfunction due to decreased levels of albumin and other proteins in the circulation for the drug to bind. Therefore, anesthesiologists should anticipate the potential for increased “free” drug and a possible increased drug effect compared to administration of the same drug to a non-obstetric patient with normal liver function.[120] Additionally, there is potential for a prolonged drug effect when administering drugs reliant on liver metabolism as these may have variably increased half-lives.[120] The anesthesiologist may consider medications that rely less on hepatic metabolism, resulting in more predictable drug clearance. Both patients with liver disease and parturients have larger volumes of distribution; therefore, patients may need a larger initial dose.[7] However, dosing intervals and maintenance doses may require alteration due to decreased elimination secondary to altered liver metabolism. Patients with significant liver dysfunction may have coexisting renal dysfunction, an important consideration when prescribing medications metabolized and cleared by the kidney.[121] Table 5 lists medications commonly used in anesthesia and their implications in patients with liver dysfunction and pregnancy.

Intravenous medications such as propofol and ketamine maintain hepatic blood flow, while inhaled volatile anesthetics and nitrous oxide decrease hepatic blood flow.[122,123] Neuraxial anesthesia dose-dependently decreases SVR from sympathetic blockade, and therefore reduces mean arterial blood pressure and portal venous hepatic blood flow, while hepatic artery flow is maintained due to a reduction in hepatic artery resistance.[124,125] Hepatic oxygen delivery is maintained, as long as care is taken to maintain cardiac output and perfusion pressure.

The choice of vasopressor to maintain cardiac output and perfusion pressure in the patient with liver disease in the setting of a further decreased SVR from neuraxial blockade depends on the extent of the sympathetic blockade and a variety of other considerations (extent of liver dysfunction, pulmonary hypertension, effect of the sympathetic blockade on the cardiac accelerator nerves, etc.) and needs to be decided on a case-by-case basis.

Fentanyl and sufentanil do not have an increased effect compared to other opioids such as meperidine, morphine, and alfentanil.[126–129] Neuraxial morphine behaves similarly in healthy patients and those with liver dysfunction.[7] Remifentanil was not found to have any clinical change in metabolism after a 4-hour infusion in patients with liver impairment, except for increased respiratory depression.[130] Liver dysfunction patients have prolonged effects from benzodiazepines such as diazepam and midazolam.[131]

Non-depolarizing tetrahydroisoquinolinium muscle relaxants like cisatracurium or atracurium should be considered because aminosteroid relaxants like vecuronium and rocuronium can have prolonged effects.[132–134] If an aminosteroid is chosen, the anesthesiologist should monitor relaxation depth closely and should consider reversal with sugammadex on a case by case basis. The liver produces pseudocholinesterase, and, therefore, succinylcholine and ester local anesthetics may have a longer duration of action.[134]

Liver dysfunction also predisposes to local anesthetic toxicity because of decreased clearance of amide local anesthetics by the liver and decreased metabolism of ester local anesthetics by pseudocholinesterase.[135–137] Furthermore, liver dysfunction patients and parturients have low protein concentrations and are particularly susceptible to bupivacaine toxicity because it is 95% protein-bound.[138]

Non-steroidal anti-inflammatory medications for pain control should be avoided because many patients with liver dysfunction have increased risk for gastrointestinal bleeding and kidney dysfunction.[43,134] Up to 2–3 g daily of acetaminophen are safe to use, though.[139]

For uterine hemorrhage, standard doses of oxytocin, ergonovine and carboprost should be administered even though they are metabolized in the liver.[43] The anesthesiologist should avoid ergonovine in the setting of pre-eclampsia and carboprost in the setting of portopulmonary hypertension.

Neuraxial anesthesia is preferred for labor and cesarean delivery if there are no contraindications (listed in table 6).[7] Intravascular hypovolemia, thrombocytopenia, and decreased coagulation factors are more common contraindications for neuraxial anesthesia in patients with liver disease. Knowing which diseases are more likely to have abnormalities leading to contraindications for a neuraxial technique will lead to less delay in the placement of a neuraxial anesthetic or performing an unnecessary general anesthetic. Some of the diseases to consider further testing are HELLP, AFLP, acute liver dysfunction, and chronic liver disease with unknown severity.

Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) might be considered with abnormal coagulation studies to help determine if a neuraxial anesthetic

is appropriate, but using viscoelastic hemostatic assays for this purpose has not been studied extensively.[140,141] Both normal pregnancy and some liver diseases can be associated with hypercoagulability.[134] Conversely, patients with thrombocytopenia or platelet dysfunction will have a decreased maximum amplitude (MA) in the TEG or maximum clot firmness (MCF) in the ROTEM; parturients with clotting factor deficiencies will have a prolonged R and K with a decreased MA and angle in the TEG or a prolonged clotting time (CT) and clot formation time (CFT) with a decreased MCF and angle in the ROTEM; hypercoagulability results in decreased R and K with an increased MA and angle in the TEG or a decreased CT with an increased MCF and angle in the ROTEM, respectively.[142] Fibrinolysis is often described as tear drop shaped.[142] It is important to have an extensive benefit-to-risk discussion with the patient prior to placement of neuraxial anesthesia if coagulation studies are abnormal.

When neuraxial anesthesia is not clinically appropriate, general anesthesia may be needed.[7] Patients should be treated as a full stomach and intubated via rapid sequence induction.[143] They should receive a non-particulate antacid to neutralize stomach contents prior to anesthesia induction.[144] The muscle relaxant of choice is succinylcholine for intubation. Although it has no clinically relevant difference in duration of action between healthy patients and those with liver dysfunction,[120] both conditions decrease pseudocholinesterase concentrations so that neuromuscular monitoring is indicated, even in the absence of another paralytic, to verify full of neuromuscular recovery.

If placement of a gastric tube is subsequently indicated, it should be passed gently because of possibly unknown esophageal varices.[145] An arterial line might be indicated for close blood pressure monitoring or repeated blood samples. Central access should be considered if the patient has inadequate peripheral intravenous access or requires large volume resuscitation, vasopressors, or inotropes.

General anesthesia is best maintained using medications with limited hepatic metabolism.[7] Volatile anesthetics are often used for emergency cesarean deliveries, but dose-dependent uterine relaxation[146] can increase bleeding. Despite also exhibiting a dose-dependent effect on uterine tone in experimental settings,[147] propofol is a better choice because it barely alters uterine tonicity at clinical concentrations[148] and does not decrease blood flow to the liver.[123] Nitrous oxide should be considered as an adjunct, in the absence of pulmonary hypertension, as it does not alter uterine tonicity and allows a reduction of the volatile anesthetic and/or propofol dose. Although rarely needed after an induction dose of succinylcholine, cisatracurium or atracurium should be considered for longer neuromuscular blockade because their metabolism is not reliant on the liver.[134] Their metabolite laudanosine is cleared at the same rate in healthy and cirrhotic patients.[149] Aminosteroid neuromuscular blockers may be used, but close neuromuscular monitoring and reversal must be ensured prior to extubation.[120] Also, the parturient may be receiving magnesium which can prolong muscle relaxation.[56] Sugammadex to reverse aminosteroid neuromuscular blockers has been safely used after cesarean delivery with residual weakness found only in patients with chronic renal failure.[150] It is deemed safe in patients with liver dysfunction, but more studies are needed.[151]

Summary

In conclusion, liver dysfunction can present with multiple systemic derangements. Acute and chronic liver dysfunction have overlapping features, but also key differences, particularly regarding the increased risk of hyperammonemia and cerebral edema in patients with acute liver failure. The presence of portal hypertension in patients with cirrhosis is a further important difference. Knowing the differences in these disease states will aid in determining the rapidity of progression and the likelihood of other organ systems being affected. Neuraxial anesthesia is preferred in obstetrics because it provides excellent pain control and avoids the need to secure a potentially difficult airway. Although some manifestations of liver dysfunction preclude neuraxial anesthesia, knowing contraindications to provide safe and efficient care is of utmost importance.

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Glossary of Terms

AFLP	acute fatty liver of pregnancy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFT	clot formation time in ROTEM
CT	clotting time in ROTEM
ERCP	endoscopic retrograde cholangio-pancreatography
GGT	gamma glutamyl transferase
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelets
HSV	herpes simplex virus
ICP	intracranial pressure
INR	international normalized ratio
LCHAD	long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency
LMWH	low-molecular-weight heparin
MA	maximum amplitude in TEG

MCF	maximum clot firmness in ROTEM
PBC	primary biliary cholangitis
PT	prothrombin time
PTT	partial thromboplastin time
ROTEM	rotating thromboelastometry
SVR	systemic vascular resistance
TEG	thromboelastogram

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Table 1:

Laboratory abnormalities, signs, and symptoms of pregnancy and/or liver dysfunction

Sign, symptom, laboratory abnormality	Normal pregnancy	Liver dysfunction	Parturient with liver dysfunction
Glucose	−	−, then ↓	−, then ↓
Lactate	−	↑	↑
AST	− to ↓	↑	↑
ALT	− to ↓	↑	↑
ALP	− to ↓	↑	↑
GGT	−	↑	↑
Bilirubin and jaundice	−	↑	↑
Estrogen	↑	↑	↑↑
Progesterone	↑	↑	↑↑
Albumin	↓	↓	↓↓
Coagulation factors	− to ↑	↓/↑	↑/↓
CO_2	↓	↓	↓

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CO_2: carbon dioxide; GGT: gamma glutamyl transferase; − normal; ↓ decreased; ↑ increased; ↑/↓ mixed.

Table 2:

Common manifestations of liver dysfunction

Organ	Manifestation
Brain	Encephalopathy Increased ICP
Heart	Increased cardiac output from low SVR Low SVR Increased heart rate Low cardiac output if complicated by pulmonary hypertension resulting in right ventricle dysfunction
Lungs	Portopulmonary hypertension Hepatopulmonary syndrome Hydrothorax
GI	Esophageal varices Portal hypertension Ascites
Kidney	Kidney dysfunction Hepatorenal syndrome type 1 (two-fold increase in creatinine with decreased urine output over two weeks and is associated with multi-organ dysfunction in absence of renal pathology)[152] Hepatorenal syndrome type 2 (slower decrease in renal function in the absence of other renal pathology)
Hematologic	Thrombocytopenia Prolonged PT/PTT Decreased Antithrombin III

GI: gastro-intestinal; ICP: intracranial pressure; PT: prothrombin time; PTT: partial thromboplastin time; SVR: systemic vascular resistance.

Table 3:

Laboratory abnormalities and symptoms of different liver and biliary diseases unique to pregnancy

Disease	Trimester	Laboratory Abnormalities	Symptoms
Intrahepatic cholestasis of pregnancy	2nd or 3rd	Increased bile acids Increased bilirubin Increased GGT and ALP	Jaundice and itching
Hyperemesis gravidarum	1st	Increased AST and ALT Increased bilirubin Electrolyte abnormalities associated with vomiting Increased thyroid function	Severe nausea and vomiting Jaundice
HELLP	2nd or 3rd	Low hemoglobin Low platelets Increased AST and ALT Increased creatinine Increased uric acid Increased LDH	Hypertension Abdominal pain Headache Nausea Edema
AFLP	3rd	Increased AST and ALT Increased creatinine Hypoglycemia Increased bilirubin Increased ammonia Increased LDH Increased uric acid Prolonged PT and PTT Low fibrinogen	Anorexia Nausea Malaise Fatigue Headache Jaundice Encephalopathy Edema

AFLP: acute fatty liver of pregnancy; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; HELLP: hemolysis, elevated liver enzymes, and low platelets; LDH: lactate dehydrogenase; PT: prothrombin time; PTT: partial thromboplastin time.

Table 4:

Common hepatobiliary autoimmune diseases in pregnancy and their treatment

Disease	Treatment	Continue during pregnancy	Pathophysiology
Primary sclerosing cholangitis	Ursodeoxycholic acid Steroids	Yes Yes	Fibrous stenosis of the intra- and extra-hepatic bile ducts
Primary biliary cholangitis	Ursodeoxycholic acid Azathioprine Steroids	Yes Yes Yes	Autoimmune liver injury related to anti-mitochondrial antibodies leading to destruction of small bile ducts and cholestasis
Autoimmune hepatitis	Mycophenolate mofetil Azathioprine	No Yes	Unknown, but it is felt to be a T-cell mediated immune intolerance to the liver parenchyma; it is thought to be triggered by the environment

For more details, please refer to[153–155].

Table 5:

Medications commonly used in anesthesia and their implications in liver dysfunction

Medication	Implications in liver dysfunction
Volatile anesthetic	Decreased hepatic blood flow
Nitrous oxide	Decreased hepatic blood flow Exacerbates pulmonary hypertension
Benzodiazepines	Highly protein bound Metabolized by the liver
Vecuronium and Rocuronium	Metabolized by the liver
Succinylcholine	Decreased pseudocholinesterase production (clinically only relevant in severe liver disease)
Sugammadex	Safely used in liver failure patients and obstetrics Renal failure patients may require higher doses[156]
Amide local anesthetics	Metabolized by the liver Highly protein bound and may lead to supratherapeutic plasma levels
Ester local anesthetics	Decreased pseudocholinesterase production

For pharmacokinetic and pharmacodynamic changes of commonly used drugs in pregnancy and child birth, please refer to Ansari et al.[157]

Table 6:

Contraindications to consider for neuraxial anesthesia

Absolute Contraindications	Relative Contraindications
• Patient Refusal	• Coagulopathy
• Infection at the site of needle insertion	• Sepsis
• Uncorrected hypovolemia	• Fixed cardiac output state
• Increased ICP	• Indeterminate neurological disease
	• Thrombocytopenia

Relative contraindications depend on the severity of the particular conditions. If the patient is allergic to a specific drug, consider alternative compound. For more details, please refer to[158–160].