

Acute Fatty Liver of Pregnancy

Pathophysiology, Anesthetic Implications, and Obstetrical Management

Emily E. Naoum, M.D., Lisa R. Leffert, M.D., Hovig V. Chitilian, M.D., Kathryn J. Gray, M.D., Ph.D., Brian T. Bateman, M.D., M.Sc.

Acute fatty liver of pregnancy is a potentially morbid obstetric complication characterized by acute hepatic failure secondary to fatty infiltration of the liver. The resultant effects include coagulopathy, electrolyte abnormalities, and multisystem organ dysfunction. Management of this condition requires an anesthesiologist's understanding of both its pathophysiology and its obstetric impact for appropriate recognition and management.

Epidemiology

Acute fatty liver of pregnancy was once considered to be extremely rare; however, with increased awareness and improved prenatal care and testing, the diagnosis is made earlier, and milder cases are recognized. The prevalence is now estimated to be 1 to 3 cases per 10,000 deliveries.¹⁻⁴ Estimates of the mortality rate for acute fatty liver of pregnancy range widely. Data from publications in the 1980s suggested mortality rates in excess of 70%,⁵ but more recent estimates are dramatically lower—around 2%.^{1,6,7} The recognition of milder presentations, early intervention and delivery, and aggressive management of complications have likely contributed to a decreased mortality rate.

Perinatal mortality for infants born to affected mothers is also highly variable,^{8,9} with recent estimates reporting perinatal mortality of approximately 10 to 20%^{1,7,8,10-13} with the majority of reported cases caused by stillbirth. Perinatal morbidity related to fetal acidosis and prematurity has also been described.^{14,15} Although the reason is not clear, the severity of maternal illness is not well correlated with the incidence or severity of fetal complications.¹¹

Risk factors for acute fatty liver of pregnancy include multiple gestations, male fetuses, fatty acid oxidation disorders in the fetus, and previous episodes of acute fatty liver of pregnancy.^{1,4-10,16-18} There may be an increased risk in patients with a body mass index less than 20; however, given the rarity of the disease, the study in which this was noted was underpowered to determine whether this is a causal effect or just a chance finding.⁶ The majority of cases present during the third trimester, although there are reports of second trimester cases as well.¹⁹

Pathophysiology

Hormonal changes during normal pregnancy are associated with a physiologic decrease in the oxidation of long- and medium-chain fatty acids, resulting in an increased maternal serum level of fatty acids over the course of gestation.¹² This may increase maternal susceptibility to an overwhelming burden of free fatty acids that act as hepatotoxins in at-risk patients.^{12,20,21} One of the hallmark findings in patients with acute fatty liver of pregnancy is multiorgan fatty infiltration. Widespread microvesicular fatty steatosis of the liver impairs hepatic production of cholesterol, fibrinogen, and coagulation factors and decreases bilirubin conjugation and clearance.⁴ Direct fatty infiltration of the kidney likely contributes to acute renal impairment, although in most cases of acute fatty liver of pregnancy, kidney dysfunction is multifactorial related to hypoperfusion, and in some advanced cases, hepatorenal syndrome has been implicated.^{9,12} Fatty acid metabolites are toxic to pancreatic tissue and likely play a role in the etiology of acute fatty liver of pregnancy-associated pancreatitis.^{5,22} Placental dysfunction may stem from increased fatty acids within the placenta itself, resulting in impaired oxygen delivery to the fetus.²³ Fibrin deposition in the chorionic villi may also result in placental hypoperfusion and hypoxic damage to the fetus.²⁴ Endothelial cell dysfunction contributes to consumption coagulopathy with enhanced fibrinolysis and increased vascular permeability.²⁵

One of the breakthroughs in understanding acute fatty liver of pregnancy pathophysiology was the discovery that fetal fatty acid oxidation disorders are linked to acute fatty liver in the mother.²⁶⁻²⁹ Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase is a part of a complex mitochondrial enzyme involved in the β -oxidation of fatty acids in mitochondria.³⁰ Deficiencies in this enzyme result in an accumulation of hepatotoxic long-chain fatty acid metabolites in the fetus that can cross into the maternal circulation, leading to maternal hepatotoxicity and mitochondrial dysfunction (fig. 1).^{23,31-33} Impaired antioxidant function and cytotoxic lipid peroxidation products can also depress cellular metabolism and activate proinflammatory pathways.³⁴ Increased levels of free fatty acids such as arachidonic acid,

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serum nitrates, and malondialdehyde are associated with both oxidative and nitrosative stress within the peroxisomes and mitochondria in acute fatty liver of pregnancy.^{23,32} High levels of free fatty acids increase reactive oxygen species production and caspase activity and induce apoptosis.²³

Mutations in the genes encoding long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, mitochondrial trifunctional protein, and other enzymes involved in fetal fatty acid oxidation have been associated with an increased incidence of maternal liver disease.^{1,26–29} Specifically, fetal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency is associated with acute fatty liver of pregnancy, and the incidence of liver disease is as high as 75% in mothers carrying fetuses affected by long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency.^{25,27,28,35,36} In known cases of fetal fatty acid oxidation defects, there is a 20-fold increase in maternal liver disease.²⁸ Fatty acid oxidation disorders have autosomal recessive inheritance, so when present in the fetus, the mother is usually a carrier for the disorder and is therefore more susceptible to an overwhelming burden of toxic free fatty acids.³⁷ The majority of reported acute fatty liver of pregnancy cases, however, are not conclusively associated with fatty acid oxidation disorders in the infant.³¹

The offspring of mothers affected by acute fatty liver of pregnancy should also undergo screening and be monitored for signs and symptoms of fatty acid oxidation disorders.³⁸ Obstetricians must clearly communicate to neonatologists the presence of maternal acute fatty liver of pregnancy to ensure that the newborn is appropriately screened and monitored for complications of hypoglycemia and metabolic derangements.^{28,39} This is important because a normal newborn screen (which includes screening for fatty acid oxidation disorders) does not entirely exclude the possibility of a fatty acid oxidation disorder. In couples with prior pregnancies affected by acute fatty liver, preconception carrier screening for fatty acid oxidation defects is recommended to provide counseling on the risk of recurrence in future pregnancies.^{6,17,36,38,40–42}

Clinical Presentation

The prodromal maternal symptoms of acute fatty liver of pregnancy are often vague and include malaise, anorexia, and fatigue over several days to weeks. These symptoms progress to include nausea, vomiting, abdominal pain, jaundice, icterus, headache, polydipsia, pruritis, edema, ascites, encephalopathy, asterixis, hypertension, and bleeding diatheses.^{1,4,6,9,15,17}

Initial laboratory findings in acute fatty liver of pregnancy are the classic abnormalities seen in acute liver failure including transaminitis, hyperbilirubinemia, elevated γ -glutamyl transpeptidase, elevated ammonia, elevated alkaline phosphatase, hyperuricemia, elevated creatinine and blood urea nitrogen, leukocytosis with neutrophilia and toxic granulation, hypocholesterolemia, elevated international normalized ratio, prolonged prothrombin time,

hypofibrinogenemia, thrombocytopenia, hypoglycemia, and elevated lipase.^{1,4,5,13,43} Hemolysis with reticulocytosis, nucleated red blood cells, and echinocytes, as well as low fibrinogen and elevated fibrin–fibrinogen split products, may be seen as the disease course progresses.⁴ Hypoglycemia and coagulopathy are the defining clinical features that can distinguish acute fatty liver of pregnancy from hemolysis, elevated liver enzymes, low platelet count syndrome.^{24,44,45}

Antithrombin III level can be decreased in the setting of acute liver failure⁴⁶ and is often depressed in acute fatty liver of pregnancy.² This may be due to decreased hepatic production of antithrombin III or its consumption in the setting of disseminated intravascular coagulation. Acquiring a third trimester value of antithrombin III level in patients with known risk factors for acute fatty liver of pregnancy may help predict and potentially prevent acute hepatic failure by detecting subclinical illness before the full presentation.² Unfortunately, most patients affected by acute fatty liver of pregnancy have no known risk factors, and routine antithrombin III screening would not be appropriate for all pregnant patients.²

Diagnosis

The Swansea criteria have been prospectively validated for the diagnosis of acute fatty liver of pregnancy (table 1) when identifying six or more of the following features in the absence of another explanation: vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, elevated bilirubin, hypoglycemia, elevated urate, leukocytosis, ascites or bright liver on ultrasound, elevated transaminases, elevated

Table 1. Swansea Criteria for Diagnosis of Acute Fatty Liver of Pregnancy

Six or More of the Following Features Present in the Absence of Another Explanation	
Symptoms	Vomiting Abdominal pain Polydipsia/polyuria Encephalopathy
Laboratory	Leukocytosis Elevated transaminases Elevated ammonia Elevated bilirubin Elevated urate Hypoglycemia Coagulopathy Renal impairment
Imaging Pathology	Ascites/bright liver on ultrasound Microvesicular steatosis on liver biopsy

Adapted from Ch'ng CL, Morgan M, Hainsworth I, Kingham JG: Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut* 2002; 51(6):876–80 and NHS Guidelines: Acute fatty liver of pregnancy guideline (GL780), March 2016. Available at: http://www.royalberkshire.nhs.uk/Downloads/GPs/GP%20protocols%20and%20guidelines/Maternity%20Guidelines%20and%20Policies/Medical%20conditions%20and%20complications/Acute%20fatty%20liver%20of%20pregnancy_V2.1_GL780.pdf. Accessed February 9, 2018.

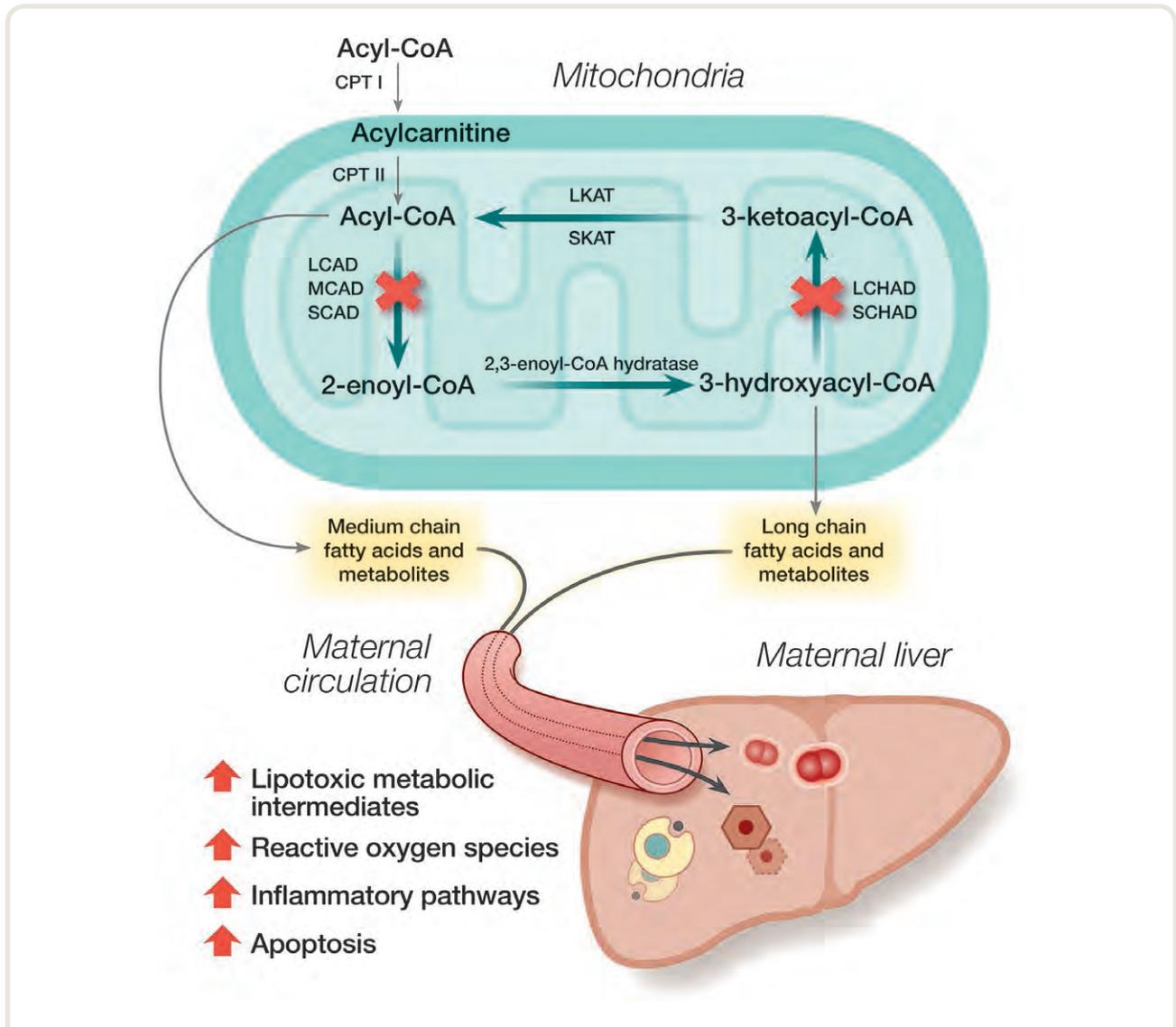


Fig. 1. Pathophysiology of acute fatty liver of pregnancy. Impaired mitochondrial β -oxidation of fatty acids caused by enzyme deficiencies has been implicated in the pathogenesis of acute fatty liver of pregnancy. Homozygous fetal enzymatic deficiencies result in increased levels of free fatty acid metabolites that cross into the maternal circulation. Pregnant women who are heterozygous for fatty acid oxidation enzyme defects may be more susceptible to the increased metabolic demands of pregnancy and more susceptible to liver injury from lipotoxic metabolites, inflammatory pathway activation, reactive oxygen species, and apoptosis. The fetal fatty acid oxidation defects that have been associated with acute fatty liver of pregnancy are deficiencies in long-chain acyl-coenzyme A (CoA) dehydrogenases (LCHAD) and mitochondrial trifunctional protein (most common), as well as deficiencies in short-chain acyl-coenzyme A dehydrogenases (SCAD) and medium-chain acyl-coenzyme A dehydrogenases (MCAD).^{1,33} CPT, carnitine palmitoyltransferase; LCAD, long-chain acyl-coenzyme A dehydrogenase; LKAT, long-chain 3-ketoacyl-coenzyme A thiolase; SCHAD, short-chain 3-hydroxyacyl-coenzyme A dehydrogenase; SKAT, short-chain 3-ketoacyl-coenzyme A thiolase. Figure adapted from Liu J, Ghaziani TT, Wolf JL: Acute fatty liver disease of pregnancy: Updates in pathogenesis, diagnosis, and management. *Am J Gastroenterol* 2017; 112:838–46 and Treem WR, Rinaldo P, Hale DE, Stanley CA, Millington DS, Hyams JS, Jackson S, Turnbull DM: Acute fatty liver of pregnancy and long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Hepatology* 1994; 19:339–45.

ammonia, renal impairment, coagulopathy, and/or microvesicular steatosis on liver biopsy.⁴³

The differential diagnosis of liver disease and elevated liver enzymes during pregnancy is quite broad (fig. 2).^{43–45,47,48} Providers must consider acute pregnancy-related liver conditions, acute onset primary liver disease, and

acute-on-chronic liver dysfunction. Chronic liver disease may not have been previously diagnosed in an asymptomatic woman, and an acute worsening of hepatic function in the setting of chronic liver disease is always a possibility.^{10,43,44,47,49} Other conditions, including hepatic hematoma and/or infarct, may occur as sequelae to the primary liver condition.

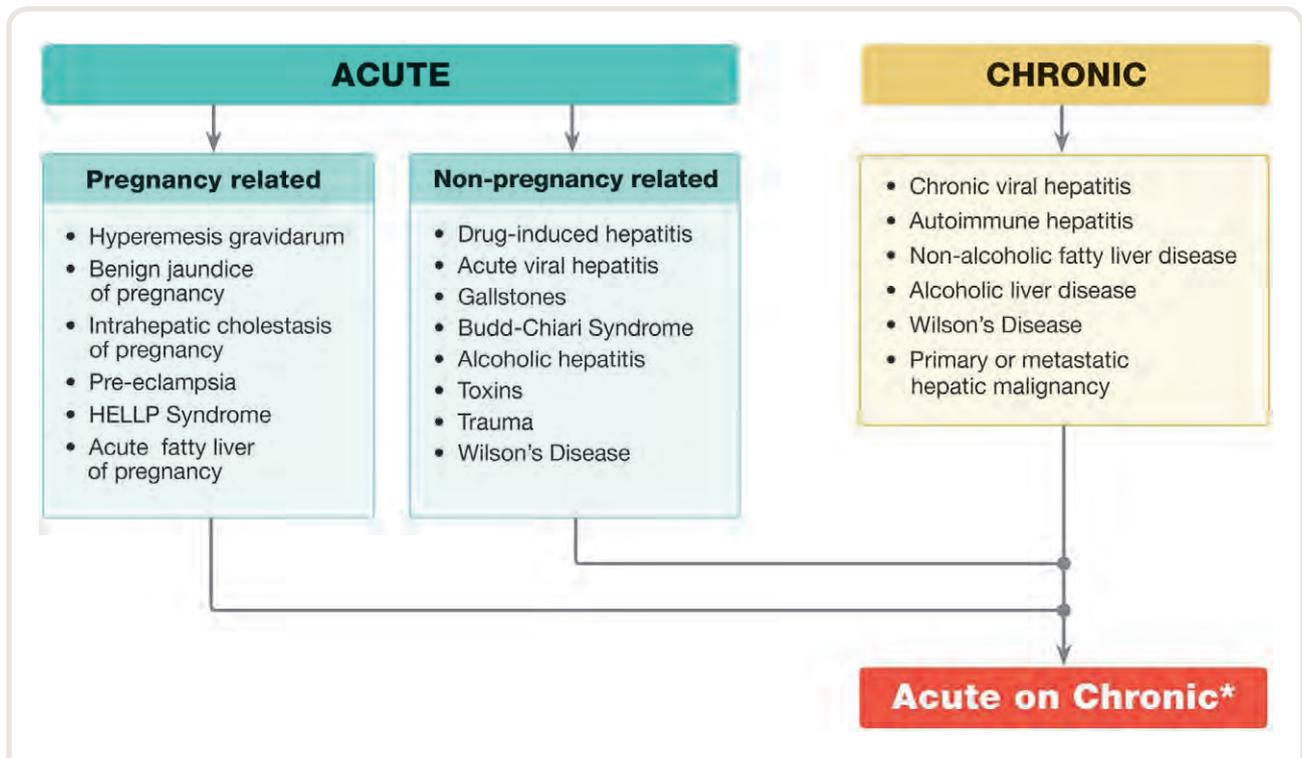


Fig. 2. Differential diagnosis of liver failure in pregnancy. HELLP, hemolysis, elevated liver enzymes, low platelet count.

Pregnant women who present with abnormal liver enzymes should have an extensive workup that includes viral and autoimmune serology testing, coagulation studies, and consideration of imaging to determine the etiology of liver dysfunction.³⁸ A detailed history including medical comorbidities, presenting signs and symptoms, physical exam, and investigational studies helps to differentiate between these etiologies. In patients who present with new-onset pregnancy-associated liver disease, a definitive diagnosis can be challenging to make, and there are some experts who propose a spectrum of maternal liver disease rather than defined illnesses.¹⁵

Hemolysis, elevated liver enzymes, low platelet count syndrome is a significantly more common entity than acute fatty liver of pregnancy, and differentiating the two conditions can be particularly challenging. Hemolysis, elevated liver enzymes, low platelet count syndrome, and acute fatty liver of pregnancy share overlapping risk factors including multifetal pregnancies, and both can result in liver dysfunction. There is a relatively high concurrence of acute fatty liver of pregnancy and preeclampsia, supporting the theory of overlap, and a diagnosis of one does not exclude the diagnosis the other.^{1,15} Severe hemolysis, elevated liver enzymes, low platelet count syndrome, and acute fatty liver of pregnancy may be indistinguishable in some cases, even with a liver biopsy, and it may be impossible to differentiate because histologic findings are diverse and can be challenging to interpret.^{1,37} However, the typical liver histology associated

with hemolysis, elevated liver enzymes, low platelet count syndrome is periportal hemorrhage and necrosis, *versus* that of acute fatty liver of pregnancy, which is associated with zone 3 microvesicular steatosis.^{30,37,41,50,51} The liver damage in hemolysis, elevated liver enzymes, low platelet count syndrome is thought to be cytokine and immune-mediated *versus* reactive oxygen species-mediated, resulting in mitochondrial-mediated apoptosis in acute fatty liver.

Hypertension is common in both hemolysis, elevated liver enzymes, low platelet count syndrome and acute fatty liver of pregnancy; however, severe comorbidities, such as profound hypoglycemia, renal failure, coagulopathy, disseminated intravascular coagulation, and encephalopathy, are more commonly associated with acute fatty liver of pregnancy.^{25,30} Hemolysis, elevated liver enzymes, low platelet count syndrome is always associated with thrombocytopenia but not necessarily coagulopathy, whereas acute fatty liver can present with variable platelet counts including normal range. Antithrombin activity is often severely depressed in acute fatty liver; however, antithrombin activity can also be reduced in hemolysis, elevated liver enzymes, low platelet count syndrome, further complicating the ability to distinguish it from acute fatty liver of pregnancy. Testing for antithrombin activity requires time, and results may not be available at the time of clinical diagnosis; therefore, given the need to act expeditiously, waiting for the result is often not appropriate. Antithrombin activity may be reduced before clinical evidence of hepatic impairment in some women with pregnancy-related liver dysfunction.²⁵

Incorporation of antithrombin activity into the diagnostic criteria for acute fatty liver of pregnancy may facilitate more prompt diagnosis and improve the investigation of liver dysfunction. Pregnancy-induced antithrombin deficiency (less than 65% of antenatal levels) dramatically increases the risk of liver dysfunction.⁵² Combining antithrombin activity and platelet count improves the sensitivity and positive predictive value of these tests for perinatal liver dysfunction (proposed cutoffs of less than 77% and platelets less than $139 \times 10^9/\text{ml}$) to 73 and 9.2%, respectively⁵²; currently, antithrombin activity is not used as a diagnostic clinical tool.

Treatment of both conditions centers on the delivery of the fetus, because this is the only established treatment for acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, low platelet count syndrome. Therefore, when either diagnosis is suspected, management is aimed at a prompt, safe delivery for the mother and infant. Mothers who carry a diagnosis of preterm hemolysis, elevated liver enzymes, low platelet count syndrome may have delivery delayed to complete a course of betamethasone for fetal lung maturity; however, delayed delivery is not appropriate in acute fatty liver even in the preterm setting given the maternal and fetal risk.

Liver biopsies are rarely performed during pregnancy given the risks of the procedure. In hemolysis, elevated liver enzymes, low platelet count syndrome, liver biopsies are particularly controversial because they are not necessary for management if the diagnosis is strongly suspected, and they carry a significant risk of bleeding caused by the liver failure and coagulopathy associated with acute fatty liver.¹ Characteristic pathologic findings include swollen, pale hepatocytes and intracytoplasmic fat lobules.^{9,16,41} Electron microscopy of the liver may show non-membrane-bound fat and pleomorphic mitochondria.^{17,41,50} Current published guidelines recommend diagnosis based on the Swansea criteria to obviate the need for a liver biopsy in the clinical management of patients with acute fatty liver of pregnancy.³⁸

Radiologic Findings

Radiologic studies in acute fatty liver of pregnancy have limited diagnostic value with a low sensitivity and specificity for a variety of imaging techniques. Abdominal ultrasound may demonstrate ascites or a bright liver with increased echogenicity^{4,12,53}; however, the sensitivity is low (less than 50%) for detection of abnormalities in acute fatty liver.^{4,6,12} In a small study of patients with acute fatty liver of pregnancy, serial ultrasounds were done, and at least one sonogram in each patient was abnormal with increased echogenicity and/or ascites.⁵⁴ These findings also suggested that duration of ultrasound abnormalities might be related to the severity of disease and could be considered for monitoring given that it is a low-risk and noninvasive imaging method.⁵⁴ Ultrasound for diffuse liver parenchymal disease has a high false-negative rate but may be useful in supporting the diagnosis in a patient with suspected liver disease.⁵⁵

Computerized tomography has a low sensitivity for detecting acute fatty liver of pregnancy but may demonstrate fatty infiltration of the liver, prominent intrahepatic blood vessels, or decreased attenuation of the liver.^{2,19} One study showed magnetic resonance imaging–detectable excess fat in the liver of a small group of women clinically diagnosed with acute fatty liver of pregnancy, and it is proposed as a tool to support the diagnosis and avoid performing a liver biopsy.⁵⁶ Despite this promising finding, larger-scale investigations of the efficacy and safety of magnetic resonance imaging in the diagnosis of acute fatty liver remain to be performed. One of the considerations must include the risk of being physically away from a labor and delivery floor to perform the imaging should the patient decompensate or should the need for delivery become imminent. Although imaging techniques typically do not currently contribute to the diagnosis or direct management of acute fatty liver of pregnancy,^{1,2} they do have a role in the investigation of associated complications including pulmonary, pancreatic, and vascular pathology⁵⁷ in the peri- and postpartum periods.

Complications

Complications are secondary to hepatic dysfunction and can affect multiple organ systems. Blood dyscrasias including coagulopathy, thrombocytopenia, disseminated intravascular coagulation, and hemolysis are frequently present.^{4,5,7,10,12,15,16,57} Acute liver failure from any cause is associated with the decreased production of coagulation factors as well as a decrease in procoagulant proteins, leading to coagulopathy in coexistence with hypercoagulability.⁵⁸ A functional platelet defect may also occur in liver failure because of coexisting uremia and endothelial abnormalities and is related to the degree of liver dysfunction.⁵⁸ Decreased production of fibrinogen, reduced levels of antifibrinolytic pathway components, and upregulation of tissue plasminogen activator are observed, all of which promote hyperfibrinolysis and disseminated intravascular coagulation.⁵⁸ Some centers perform viscoelastic testing with thromboelastography or rotational thromboelastometry to guide prompt resuscitation and therapy. However, large-scale prospective studies comparing viscoelastic testing with conventional tests of hemostasis are lacking; thus, the clinical applicability has not been firmly established.⁵⁸

Hemorrhage is common, because the coagulopathy of acute fatty liver of pregnancy can exacerbate common causes of hemorrhage including uterine atony, bleeding from surgical sites, and bleeding from perineal or cervical lacerations.^{4,8,10–12} Intraabdominal hemorrhage is a major negative prognostic factor in pregnancy-related liver disease and is common regardless of delivery method.^{4,8,10} Patients with acute fatty liver of pregnancy are more likely to require blood product transfusion than are patients with uncomplicated deliveries, with up to 65% of patients requiring transfusion during their hospitalization.^{4,10} Surgical and obstetric hemorrhagic complications occur more frequently and

may require surgical reexploration to control bleeding.^{4,8,10} Nonobstetric hemorrhage, most commonly caused by upper gastrointestinal bleeding, has also been reported. Typical causes include Mallory–Weiss tears, esophagitis, and ulcers. Interventional therapies may be required.^{1,5,16,17}

Renal complications range from mild acute kidney injury to renal failure requiring hemodialysis.^{3–6,10,12,15,17,53,57,59,60} In the setting of acute liver failure, hepatorenal syndrome has been implicated in some cases of renal dysfunction.¹² Transient diabetes insipidus has also been reported.^{4,15,53} It may be the result of elevated levels of vasopressinase, a hepatically cleared enzyme that metabolizes arginine vasopressin.⁶¹

Encephalopathy may be the presenting symptom. In the setting of significant acute liver injury (elevated transaminases) and impaired synthetic function (jaundice and international normalized ratio greater than 1.5), it is the defining feature of acute liver failure and has the potential to rapidly progress to convulsions and coma.^{3–6,9,12,15,53,57} The development of cerebral edema and intracranial hypertension confers a high risk of mortality and morbidity.⁶² As discussed below, worsening encephalopathy and elevated intracranial pressure (ICP) may require pharmacologic therapy and invasive monitoring.^{63,64}

Pancreatitis may be present and can be complicated by pseudocysts with secondary infections, hemorrhagic pancreatitis, and necrotizing pancreatitis.^{5,11,16,22,57} Pancreatitis typically develops after the onset of renal and hepatic dysfunction. Some experts suggest following serum markers including lipase and amylase for several days after the onset of illness and maintaining a low threshold to perform imaging if abnormal.⁵⁷ Pancreatitis has been suggested as a poor prognostic indicator because it is associated with more adverse outcomes.¹¹

Beyond the acute fatty liver damage, worsening liver injury is possible and can include hepatic hematoma, infarction, and/or rupture.^{43,47} Acute portal hypertension may further compromise hemodynamics and contribute to multiorgan dysfunction.⁶⁵

Infection may develop in patients with acute fatty liver of pregnancy and can include sepsis, pneumonia, urinary tract infections, *Clostridium difficile*, and peritonitis.^{6,8,9,17,53,59} Poor healing is also frequently reported with wound seroma, infection, and breakdown in the setting of critical illness and weakened immunologic function.¹² Acute respiratory distress syndrome and pulmonary edema may require intubation and mechanical ventilation.^{6,7,15,53}

Obstetric Management

The definitive management for acute fatty liver of pregnancy is delivery of the fetus, but consideration should be given to each individual case as to the timing and method of delivery. Although there is not a consensus on the best method of delivery, once the diagnosis of acute fatty liver of pregnancy has been made, clinical guidelines from the National Health Service and American College of

Gastroenterologists recommend that it is prudent to deliver the fetus promptly and safely.^{38,63,66} There are no reports of mothers recovering from acute fatty liver of pregnancy with expectant management, and delivery generally correlates temporally with the resolution of disease.^{67,68}

Prompt induction of labor and delivery after a suspected diagnosis of acute fatty liver is associated with a decreased risk of maternal and fetal mortality.⁹ Thus, if a spontaneous delivery is not imminent, induction of vaginal delivery should be pursued in appropriate candidates, and if this is not successful, a cesarean section should be performed.^{66,68} Recent literature describes cesarean delivery in approximately 65% of cases.^{4,6,10,13,60}

There is insufficient evidence as to whether the method of delivery impacts the site or occurrence of bleeding in patients with pregnancy-related acute liver failure.¹¹ In an emergency setting, cesarean delivery may result in a higher incidence of intraabdominal bleeding than vaginal delivery in these patients.⁸ There are reports of higher mortality with cesarean delivery than with vaginal; however, it is challenging to draw conclusions from the current literature given the high risk of confounding by illness severity.¹³ Pregnant women who present with more severe disease are more likely to undergo a cesarean section to expedite delivery. There are no randomized controlled trials comparing vaginal and cesarean delivery and many confounding factors that contribute to decision-making, including the acuity of the situation, maternal disease severity, fetal status, and provider experience. For these reasons, an individualized delivery plan for each patient is imperative. The fetal heart rate should be monitored closely because changes secondary to intrapartum fetal hypoxia and acidosis can be abrupt.²⁴

Major hemorrhagic complications related to surgical trauma are common in the setting of liver failure and coagulopathy, so episiotomy should be avoided if possible.²⁴ Some authors suggest delayed secondary closure after cesarean section because of the high rate of wound complications and infection; however, this has not been formally studied.²⁴

It is unlikely that formal guidelines for the obstetric management in cases of acute fatty liver of pregnancy will be developed given the rarity of the condition and the wide spectrum of presentation. Factors to consider when developing an obstetric management plan include the severity of maternal illness and coexisting conditions, fetal status, laboratory abnormalities, maternal obstetric history, patient preference, progression of labor, and provider experience. Clinical judgment based on the current literature and the interdisciplinary input of obstetric, anesthesia, critical care, hepatology, and neonatal experts has the greatest potential to lead to a safe and appropriate plan for any given patient.

Anesthetic Management

The preoperative assessment and planning should be conducted in conjunction with the obstetric team. Anesthetic

management for delivery must be tailored to the condition of the patient, taking into consideration the complications associated with acute liver failure: intracranial hypertension, coagulopathy, renal insufficiency, electrolyte abnormalities, hemodynamic instability, multiorgan dysfunction, and unpredictable drug metabolism (table 2).⁶⁹ As such, expertise in the anesthetic management of both parturients and patients with acute liver failure is required. Maternal status should be optimized before delivery: this may require ICP management, blood product transfusion, volume replacement, electrolyte repletion, and vasopressor support.

There is scant guidance in the literature regarding the preferred anesthetic technique in acute fatty liver of pregnancy patients; however, the principles used to guide the perioperative management of acute liver failure patients can be applied. Anesthetic management must be tailored to the degree of hepatic dysfunction of the patient, taking into account the coagulation status and the degree of cerebral edema and intracranial hypertension of the patient. Clinical deterioration can proceed rapidly in acute liver failure patients, and the involvement of liver transplant anesthesiologists is advised. Invasive blood pressure monitoring with an arterial line is warranted, and large-bore IV access is advised if coagulopathy is present with a high risk of large-volume blood loss. Central venous access may be required in critically ill patients. Additional monitoring with pulmonary artery catheters and transesophageal echocardiography is rarely used but may be considered in select patients. In patients with acute liver failure, both neuraxial and general anesthesia present increased risks. Although neuraxial anesthesia is typically favored in the parturient, the coagulopathy and intracranial hypertension that are associated with acute liver failure increase the risks of this approach. Conversely, general anesthesia carries the risk of further exacerbating hepatic dysfunction and intracranial

hypertension, in addition to the increased risk associated with securing the airway in a parturient. In a case series of 28 acute fatty liver of pregnancy patients undergoing cesarean delivery, neuraxial anesthesia was used in 16 cases, and general anesthesia was used in 12. The decision was driven based on the coagulation status of each patient. All patients who received general anesthesia had a prothrombin time of more than 20s, whereas all but two of the patients who received neuraxial anesthesia had a prothrombin time of less than 20s.¹⁸

The use of neuraxial anesthesia for labor, as well as for cesarean delivery, has been reported in patients with acute fatty liver of pregnancy with a low complication rate; however, it is widely debated given the high frequency of coagulopathy and the potential risk of spinal and/or epidural hematoma.^{6,18,70,71} Some reported series include patients who received spinal or epidural anesthesia despite documented coagulopathy. None of the patients in these reports developed neurologic compromise, but the numbers of patients were small, and in many cases fresh frozen plasma and platelets were transfused before neuraxial blockade.^{18,71,72} Correction of coagulopathy with blood products is inexact when the patient's condition is evolving, and any improvement in lab abnormalities may be temporary.⁷¹ The use of neuraxial anesthesia in the presence of an international normalized ratio of more than 1.5 is not recommended. If coagulopathy develops after neuraxial anesthesia has been administered, the patient should be monitored closely for evidence of neuraxial hematoma, and the threshold to obtain neuraxial imaging should be low. Under these circumstances, some recommend leaving the epidural catheter *in situ* until the coagulopathy is corrected.⁷² The benefit of this approach must be weighed against the risk of infection given the variable time frame for improvement of hematologic values in acute fatty liver of pregnancy

Table 2. Summary of Anesthetic Concerns in Acute Fatty Liver of Pregnancy

Predelivery concerns	<ul style="list-style-type: none"> ○ Fluid status: volume replacement with crystalloid, colloid, and/or blood products ○ Laboratory studies: electrolyte derangements, anemia, and/or coagulopathy ○ Volume replacement and electrolyte repletion if possible before pursuing delivery to optimize hemodynamic stability ○ Maintain active blood bank sample and have adequate cross-matched blood products for transfusion ○ Monitoring required: quantity and caliber of intravenous access, arterial line, central line, and/or central venous pressure ○ Continuous neurologic monitoring and assessment for progression of hepatic encephalopathy
Peripartum management	<ul style="list-style-type: none"> ○ Labor analgesia: safety to pursue neuraxial analgesia dependent on hematologic values and trajectory of illness ○ Cesarean delivery: general <i>versus</i> neuraxial anesthesia dependent on hematologic values and trajectory of illness ○ Hemodynamic management with vasopressors as needed ○ Ongoing fluid replacement with crystalloid and/or colloid ○ Correction of coagulopathy with blood products ○ Consider administration of adjunct agents such as tranexamic acid ○ Administration of uterotonic agents as needed
Postpartum care	<ul style="list-style-type: none"> ○ Avoidance of cerebral vasodilators ○ Disposition: labor and delivery floor <i>versus</i> intensive care unit ○ Pain control: local anesthetics, short-acting opioids ○ Management of complications: encephalopathy, ongoing coagulopathy, renal failure, respiratory failure, circulatory failure, worsening hepatic failure, sepsis, pancreatitis ○ Ongoing neurologic, hemodynamic, and laboratory monitoring

and the increased risk for sepsis in these patients.⁷⁰ Platelet dysfunction may also be present even in the presence of normal platelet counts. Platelet transfusion to 40,000 to 50,000/ μ l should be considered before delivery.³⁸ In the setting of encephalopathy, the decision to pursue neuraxial anesthesia should also balance the risk of elevated ICP and herniation.⁷³

In the setting of coagulopathy and platelet dysfunction, general anesthesia is preferred for cesarean delivery with acute fatty liver of pregnancy. However, the administration of general anesthesia presents significant risks to parturient with acute liver failure because of the potential for worsening ICP and hepatic dysfunction, in addition to the higher risk associated with airway management in the parturient.⁷⁴ In patients with intracranial hypertension, every effort must be made to maintain cerebral perfusion pressure and avoid increasing ICP. The use of an ICP monitor can guide intraoperative management; however, ICP monitoring in acute liver failure patients is institution-dependent.⁷⁵ Hypotension, hypertension, and hypercapnia must be avoided. The patient should be positioned with the head elevated 30°. If the patient is not intubated, rapid sequence induction with succinylcholine should be carried out to secure the airway quickly and minimize the risk of coughing, aspiration, and hypercapnia. Remifentanyl may be considered as an alternative to succinylcholine; however, there is the potential for placental transfer and fetal depression.⁷⁰ Gentle laryngoscopy is critical in all pregnant patients given the increased potential for airway edema and/or difficult airway, and this is compounded by the risk of bleeding in the setting of coagulopathy.⁷⁶

Effects of neuromuscular blocking agents that are hepatically metabolized may be prolonged, and dosing should be guided by train-of-four monitoring. Induction agents that have negative inotropic and vasodilatory effects can cause significant hemodynamic instability in patients with relative intravascular hypovolemia and may require concurrent vasopressors.⁶⁹ Care must be taken with the use of volatile anesthetic agents because they can decrease hepatic blood flow and oxygen delivery to the liver and theoretically exacerbate the hepatic metabolic insult. Furthermore, they can raise ICP by increasing cerebral blood flow. In acute liver failure patients, volatile anesthetics are relatively contraindicated given their cerebral vasodilatory effects. Although their use in acute liver failure of pregnancy patients has been described in the literature, they should be administered at doses less than one minimum alveolar concentration.^{69–71,77} Propofol infusion can be used as an alternative. Patients should be ventilated to maintain PACO₂ in the range of 30 to 40 mmHg. Although no relationship between positive end-expiratory pressure and ICP has been demonstrated in intensive care unit patients with severe acute brain injury and normal lung function, expert recommendation for the intraoperative

management of patients with acute liver failure is to maintain a positive end-expiratory pressure less than 12 cm H₂O.^{77,78} Acute elevations in ICP intraoperatively should be managed with hyperventilation and the administration of hypertonic saline (200 ml of 2.7% NaCl or 30 ml of 20% NaCl) or mannitol.⁷⁷ The maintenance of intravascular volume and normotension is imperative to preserve cerebral perfusion pressure and hepatic blood flow. The metabolic insult to the compromised liver may be exacerbated when corrected because of reperfusion injury with endothelial dysfunction, apoptotic cell death, and immune activation.⁷⁹

Postoperative pain management may be challenging because of the altered metabolism of opioids and the risk of hypercapnia. In patients undergoing elective cesarean delivery, transversus abdominus plane blocks have been shown to decrease sedation, pain scores, and opioid consumption in the absence of neuraxial opioids. They may improve the ability to monitor the progression of neurologic symptoms in patients with acute fatty liver of pregnancy by reducing confounding drug-related factors.⁸⁰ An important consideration is that pregnancy decreases drug binding to local anesthetics,⁸¹ and pharmacokinetics may be difficult to predict in an evolving picture of acute liver failure. One report of suspected local anesthetic systemic toxicity in a patient with acute fatty liver of pregnancy who received transversus abdominus plane blocks with bupivacaine⁸² emphasizes the need to consider pregnancy-related decreases in α 1-glycoprotein and albumin, as well as impaired renal and hepatic clearance, in these patients when selecting drug doses and intervals of administration. Transversus abdominus plane blocks and/or catheters may also be relatively contraindicated in the setting of coagulopathy, although no defined threshold for safety has been established.

Alternative pain management strategies are limited because acetaminophen and nonsteroidal antiinflammatory drugs are relatively contraindicated in acute liver failure, renal insufficiency, and conditions that increase the risk of gastrointestinal bleeding. If an opioid is required for pain control, dosing should be conservative, anticipating impaired hepatic and renal metabolism. Appropriate reversal agents should be available in the case of an unintended overdose.⁷²

Management of Hemorrhage

Coagulopathy is one of the most prevalent and devastating complications in acute fatty liver of pregnancy patients and can be difficult to manage with blood product transfusion alone. Antithrombin concentrate infusion may increase the level of antithrombin and improve disseminated intravascular coagulation lab parameters in patients with acute fatty liver of pregnancy, but it has not been shown to have any significant impact on clinical outcomes.¹²

Recombinant factor VIIa has been studied in a number of clinical bleeding scenarios; however, the outcomes have

been mixed and criticized for heterogeneity and a significant potential for bias.^{83,84} In obstetric hemorrhage, there may be a decreased requirement for blood product transfusion with recombinant factor VIIa administration, but the risk of thromboembolic complications is of concern in the hypercoagulable pregnant population.⁸⁴ There are very limited data to support the use of recombinant factor VIIa in patients with severe acute fatty liver of pregnancy and coagulopathy with persistent postoperative bleeding, and larger studies of safety and efficacy have not been performed.⁸⁵

Antifibrinolytic agents such as tranexamic acid that stabilize blood clots may have a role in high-risk patients with coagulopathy and an elevated risk for development of disseminated intravascular coagulation including patients with acute fatty liver of pregnancy.⁸⁶ Although low-risk patients do not benefit from prophylactic use of tranexamic acid,⁸⁶ a recent clinical trial comparing tranexamic acid administration in high-risk patients to placebo demonstrated the safety of its use (including no increased risk of thromboembolism) and a reduction in death caused by bleeding in patients with diagnosed postpartum hemorrhage.⁸⁷ These findings, albeit in a different clinical setting, suggest that earlier administration may result in improved outcomes.

Additional Intensive Care Management

Plasma exchange is an area of interest within the critical care community for the management of acute fatty liver of pregnancy. The proposed beneficial mechanisms are removal of endotoxins, support of coagulation factors, intravascular volume and proteins, electrolyte management, and acid–base balance.⁸⁸ Plasma exchange may result in improvements in oxidative stress markers and apoptotic indicators, as well as hasten hepatic recovery and decrease intensive care unit stay and hospitalization, but it has not been shown to have a mortality benefit.³² The addition of plasma exchange and plasma perfusion may increase survival compared to conventional treatment alone, but small study sizes and retrospective study designs make it challenging to draw conclusions from current literature.⁸⁹ Combining plasma exchange with continuous renal replacement therapy in patients with severe acute fatty liver of pregnancy and multiorgan dysfunction may improve clinical symptoms and laboratory results.⁸⁸

Molecular adsorbent recirculating system therapy has been used for acute fatty liver of pregnancy as a nonbiologic albumin dialysis technique.⁹⁰ In patients with acute liver injury, treatment with molecular adsorbent recirculating system results in improvement in hyperbilirubinemia and stabilization of liver function; however, there is no strong evidence of a mortality benefit.^{91,92} Treatment with molecular adsorbent recirculating system may be considered in patients with acute fatty liver of pregnancy who have a worsening clinical status despite maximal medical therapy and who may require an urgent liver transplantation.⁹²

Molecular adsorbent recirculating system therapy may be continued until there is laboratory evidence of native liver recovery, liver transplantation, or irreversible systemic complications.⁹² Indications and use of adjunct agents and advanced therapies for acute fatty liver of pregnancy are at the discretion of the multidisciplinary team and treatment center experience and are subject to consideration on an individual patient basis.

Liver Failure Management

Left untreated, acute fatty liver of pregnancy can lead to acute liver failure. Acute liver failure is severe liver injury (significant elevation in transaminases, jaundice, and coagulopathy) with encephalopathy developing within 28 days of the initial symptom (usually jaundice) in the absence of preexisting liver disease.⁹³ A number of guidelines have been published for the management of patients with acute liver failure.^{63,64,93,94} Centers with experience in the management of acute liver failure typically practice using specific protocols designed to anticipate and address the complications seen in these patients. When acute liver failure is suspected, transfer to a tertiary care center with an experienced liver transplant service should be initiated. The patient should be monitored in an intensive care unit with frequent assessment of neurologic status and degree of encephalopathy. Testing that may help to confirm a diagnosis and expedite potential liver transplantation listing should be done as soon as possible.

The neurologic sequelae of acute liver failure can be devastating, and interventions that slow the progression of cerebral edema are a mainstay of care.^{63,93} Hepatic encephalopathy is frequently seen in acute fatty liver of pregnancy and can range from mild to severe with increased intracranial pressure. Cerebral edema and intracranial hypertension contribute significantly to the morbidity and mortality associated with acute liver failure.^{63,93} Although lactulose and rifaximin are used to manage hepatic encephalopathy in chronic liver disease, they have no role in the management of encephalopathy in acute liver failure.^{63,64,93} *N*-Acetylcysteine administration has demonstrated clinical benefit in cases of paracetamol overdose because of its ability to replenish glutathione stores and improve the balance of oxygen delivery and consumption within the injured liver. There are data to suggest some benefit of *N*-acetylcysteine therapy in non–drug-induced forms of acute liver failure with minimal adverse effects; thus, it may be considered in patients with moderate to severe acute fatty liver of pregnancy.^{63,66,95} Nonconvulsive seizures can occur in the presence of severe acute liver failure; however, there is no evidence to support the prophylactic administration of antiepileptics.^{63,96}

Cerebral edema and intracranial hypertension may develop rapidly in patients with acute liver failure. Patients with worsening mental status (greater than West Haven Grade II encephalopathy: somnolence, gross disorientation) should be intubated for airway protection and management of ICP.⁹³

Approximately 50% of acute liver failure patients with high-grade encephalopathy (West Haven III or IV: somnolent but arousable or worse) have significant intracranial hypertension.⁹⁷ ICP monitoring is the gold standard for the diagnosis and management of intracranial hypertension and has been recommended for the care of these patients.^{93,98} Invasive ICP monitoring remains controversial, however, because of the risk of intracranial hemorrhage in the setting of coagulopathy. Furthermore, although it has been shown to increase the use of interventions aimed at reducing ICP, ICP monitoring has not been shown to improve outcomes in patients with acute liver failure.^{97,99} In practice, the use of ICP monitoring in patients with acute liver failure is institution-dependent. In an international survey of 22 large-volume liver transplant centers, a little more than 50% reported monitoring ICP in patients with acute liver failure.⁷⁵ Recommended target parameters are an ICP of less than 20 mmHg and a cerebral perfusion pressure of more than 50 mmHg.⁹³ Noninvasive modalities for ICP assessment have not been shown to be accurate in acute liver failure patients.¹⁰⁰

Recommended measures to treat cerebral edema and reduce ICP include elevation of the head of the bed to 30°, the use of propofol sedation in intubated patients, the avoidance of hypercapnia, and the administration of hypertonic saline (200 ml of 2.7% NaCl or 20 ml of 30% NaCl) and mannitol with the endpoint of therapy targeted to blood osmolality M 320 milliosmoles/liter.^{93,101–103} The benefits of extracorporeal liver support systems (*i.e.*, molecular adsorbent recirculating system and high-volume plasmapheresis) are uncertain, and they are not routinely used.

Infections are common and can occur at any site including the lungs, urinary tract, blood, and surgical sites. As such, antibiotic administration should be strongly considered when infection is suspected, or the possibility for progression of illness is high.⁶⁶ Acute liver failure in young, robust patients often occurs with a hyperdynamic systemic inflammatory response that is associated with a low effective intravascular volume and preserved or increased cardiac output that may be challenging to distinguish from early sepsis.¹⁰⁴ Although routine use of prophylactic antibiotics in acute liver failure is not recommended, broad spectrum antibiotics should be empirically administered in patients who display worsening hypotension or unexplained progression of encephalopathy.⁹³ Although prophylactic antibiotics and antifungals do not improve survival in acute liver failure, given the high risk of infection and potential morbidity in patients with acute liver failure, regular periodic surveillance cultures should be performed, and there should be an extremely low threshold to initiate therapy in these patients if suspected based on clinical exam.⁹³

Empiric correction of coagulopathy with vitamin K is recommended in acute liver failure, and administration of blood products and antifibrinolytic agents is recommended based on the degree of hemorrhage, presence of abnormal lab values, and clinical judgment. There is no

definitive threshold for transfusion.⁶⁴ Prognostic evaluation is dependent on coagulation variables; therefore, aggressive transfusion in the absence of active hemorrhage is not recommended. Nutritional support *via* enteral or parental route is important to treat hypoglycemia and support the catabolic state of acute liver failure.⁶³

Circulatory dysfunction is common in acute liver failure. Fluid resuscitation and vasopressors are used to maintain adequate cerebral perfusion pressure and systemic pressures.⁶³ Pulse pressure variation determined by pulse contour analysis may predict fluid responsiveness in intubated and mechanically ventilated patients with acute liver failure.¹⁰⁴ Relative adrenal insufficiency may warrant a trial of stress dose steroids when patients have persistent hypotension not responsive to fluids or norepinephrine, although the data for this practice are not well supported in acute liver failure.^{63,64} Intubation and mechanical ventilation may be required and facilitate general care and control of respiratory parameters. Renal replacement therapy may be necessary, and metabolic derangements and electrolyte abnormalities can be challenging to manage.

Liver Transplantation

The role of liver transplantation in acute fatty liver of pregnancy with fulminant hepatic failure remains controversial. The current guidelines to identify appropriate candidates for liver transplantation are challenging to apply to this particular population because the most commonly used set of criteria for patients with acute liver failure, the King's College Criteria, has not been validated in the setting of pregnancy-induced liver disease.¹¹ The majority of patients with pregnancy-related acute liver failure have progression over less than 7 days characterized by significant coagulopathy with bleeding complications requiring aggressive management with blood product transfusion. This makes it difficult to assess the status of hepatic coagulation factor production.¹¹ The bilirubin lactate and etiology score may be a better prognostic indicator in pregnancy-related liver failure because it has better accuracy in predicting the outcome of transplant-free survival *versus* death in patients with non-paracetamol-induced liver failure, but this score has not been validated for use in pregnant patients.¹⁰⁵ The bilirubin lactate and etiology score uses bilirubin, lactate, and etiology of liver failure to determine appropriate candidates for transplantation. The score does not include the international normalized ratio, which is helpful in the case of acute fatty liver of pregnancy because peripartum blood product transfusions may significantly correct international normalized ratio, which may then inaccurately reflect the severity of liver dysfunction.¹⁰⁵

There have been successful cases of liver transplantation after delivery of the fetus in acute fatty liver of pregnancy.^{3,51,106,107} There are also patients who were listed for transplantation and during the waiting period actually improved and were removed from the transplant list with

subsequent discharge and full recovery.¹⁰⁸ Given that delivery of the fetus results in nearly universal improvement in liver dysfunction, postpartum auxiliary liver transplantation may serve as a reasonable option for mothers who need temporary hepatic support. Leaving the native liver *in situ* maintains the ability to eventually remove the transplanted liver and avoid long-term immunosuppression. Successful cases have been reported with the transplanted liver functioning long enough to allow recovery of the native organ leading, to eventual removal and retransplantation of the auxiliary graft.¹⁰⁹ The associated challenges include longer operative time, increased risk of bleeding complications and anastomotic leaks, and difficulty assessing native liver recovery and function.¹¹⁰ In refractory cases of acute fatty liver of pregnancy, orthotopic liver transplantation has been reported with positive long-term outcomes.^{11,51,111} All forms of transplantation remain a matter of multidisciplinary management and are reserved for advanced cases with lack of improvement in the setting of intensive critical care.

Duration and Recovery

The time to recovery after delivery is dependent on overall disease severity and presence of complications. Most women experience clinical recovery within 3 to 4 days after delivery, but normalization of lab studies often lags (fig. 3).⁴ Patients frequently have an initial worsening of clinical and laboratory values in the immediate postpartum period.¹² Most affected

women have prolonged hospitalizations compared to uncomplicated deliveries, with the sickest patients potentially remaining hospitalized for more than a month. Intensive care unit stays are common and can also be protracted.

Laboratory evidence of ongoing hepatocellular damage typically peaks at the time of delivery and begins to improve within 2 days. Worsening hepatic transaminitis after delivery may indicate severe ischemic liver damage or evolving sepsis. Jaundice often worsens after delivery partially because of ongoing hemolysis,⁴ and bilirubin tends to peak 1 to 5 days after admission.¹⁶ Albumin levels fall postpartum but return to normal by 3 weeks after delivery.⁹ Cholesterol production and bilirubin conjugation and clearance are slow to improve.⁴ The majority of patients have normal liver function tests by 4 to 8 weeks postdelivery.^{9,16}

Laboratory values including international normalized ratio, procoagulant levels, antithrombin III, and clotting factors may remain abnormal for up to a week postpartum.^{4,16} Disseminated intravascular coagulation scores may remain elevated for up to 5 days after delivery, suggesting persistent hemostatic dysfunction.⁴ Prolonged activated partial thromboplastin time persists for several days and may not respond to vitamin K.¹⁶ Fibrinogen levels begin to recover 3 days after delivery.⁴ Leukocytosis typically resolves within 2 weeks.⁹ Platelet counts generally reach a nadir 1 to 2 days after delivery and recover within a week postpartum.^{4,9} Acute kidney injury and diabetes insipidus usually show improvement after delivery by 10 days.^{4,15}

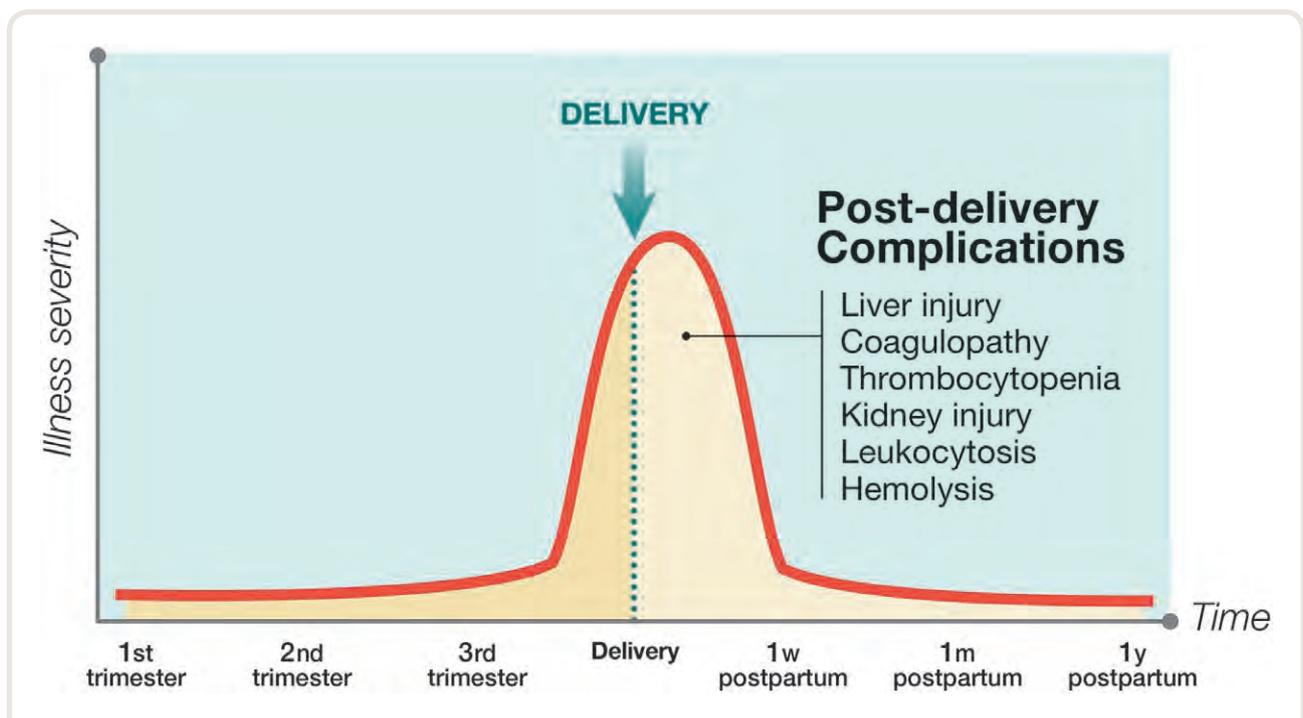


Fig. 3. Trajectory of illness.

In one study of patients followed postdelivery, all demonstrated a complete recovery of liver function with no evidence of cirrhosis or chronic hepatitis, and this highlights the need for urgent management when acute fatty liver of pregnancy is diagnosed and aggressive supportive care because the acute liver failure nearly always resolves with delivery of the fetus.⁵³ Subsequent biopsies taken in patients 2.5 months after resolution of acute fatty liver of pregnancy showed no scarring, suggesting that permanent fibrosis or long-term liver damage is uncommon.⁵

Conclusions

With advancements in the understanding of the pathophysiology of acute fatty liver of pregnancy, detection of patients at risk will likely improve and assist in early recognition and aggressive intervention, resulting in improvement in maternal and fetal outcomes. Early diagnosis and referral to an experienced tertiary care center contribute to improved management with decreased morbidity and mortality. The obstetric and anesthesia management strategies require consideration of the individual patient, coexisting conditions, lab values, clinical course, and anticipated trajectory of illness. Acute fatty liver of pregnancy patients have the potential to develop severe complications and may require intensive care management during the peripartum period. A multidisciplinary approach is required to safely and effectively manage these complex patients. Early detection coupled with advancements in critical care management have changed acute fatty liver of pregnancy from being a highly fatal complication of pregnancy to a treatable entity.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Naoum: 55 Fruit Street, GRB 444, Boston, Massachusetts 02114. eminaoum@gmail.com. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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