Acute Fatty Liver

4

Aiyuan Li and Weike Tao

Background

Definition

Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal condition unique to pregnancy [1, 2]. The etiology is not fully known but likely due to mitochondrial defects in fatty acid oxidation (FAO) [3]. AFLP is a disease of late pregnancy that is frequently reversible, characterized by microvesicular fatty infiltration of hepatocytes, which can lead to multiorgan failure.

Incidence

AFLP occurs in approximately 1 in 6659 to 1 in 13,000 maternities [1, 3].

Etiology

The pathogenesis is not fully understand but has been linked to fetal mitochondrial dysfunction due to a mutation that leads to a deficiency in the enzyme, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), which is part of the mitochondrial trifunctional protein involved in FAO [4, 5].

1. There is typically fetal homozygosity for LCHAD deficiency that affects heterozygous mothers, resulting in reduced FAO in the placenta and liver. The combined decrease in FAO leads to accumulations of fatty acids, and toxic metabolites such as arachidonic acid, in the placenta and the maternal liver.
2. In addition to direct damage to hepatocytes, fatty acids cause an oxidative stress response with an abundant production of oxygen free radicals contributing to liver apoptosis and a systemic inflammatory response.
3. AFLP is characterized histologically by fatty infiltration of the liver, hepatic steatosis, which is associated with oxidative stress and mitochondrial dysfunction.
4. Deficiencies in other lipid metabolism enzymes, such as the long-chain 3 ketoacyl-CoA thiolase, palmitoyltransferase I, medium-chain acyl-CoA dehydrogenase, and short-chain acyl-CoA dehydrogenase, may also be associated with AFLP. FAO defects, other than in the mitochondria, also lead to toxic metabolites that may contribute to oxidative stress in the liver in women with AFLP. Interestingly, oxidative stress on the liver can also be caused by preeclampsia, which complicates 40% of cases of AFLP.
5. Not all mothers with AFLP have mutations involving LCHAD nor do all mothers carrying fetuses homozygous for these defects develop AFLP.

Symptoms

1. Symptoms of AFLP are non-specific.
   (a) Generalized malaise, abdominal pain, nausea, vomiting, and headache may be the initial symptoms. Nausea and vomiting may occur in 75% of cases and abdominal pain in up to 80% [6].
   (b) The above symptoms combined with mental status changes and encephalopathy occur 1–2 weeks prior to the development of jaundice that develops in 37% of patients.
2. Signs of renal and hepatic dysfunction may develop such as coagulopathy, ascites, encephalopathy, hypoglycemia, edema, lactic acidosis, and renal failure. Typically renal

A. Li, M.D.
Department of Anesthesiology and Critical Care, Hunan Provincial Women and Children's Hospital, Changsha, Hunan, China
e-mail: 502789123@qq.com

W. Tao, M.D. (✉)
Department of Anesthesiology and Pain Management, The University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: Weike.Tao@UTSouthwestern.edu

S. K. W. Mankowitz (ed.), *Consults in Obstetric Anesthesiology*, https://doi.org/10.1007/978-3-319-59680-8_4

signs manifest after hepatic ones. One study of 32 women with AFLP noted that 50% developed renal failure, 90% coagulopathy, and 55% disseminated intravascular coagulation [7].
3. In severe cases, AFLP rapidly progresses to acute liver failure.

Interaction with Pregnancy

1. This is a disease that is specific to pregnancy with a maternal mortality rate of approximately 18% [1].
2. The most common time of presentation is in the third trimester, though sometimes AFLP is not diagnosed until after delivery [5, 8].
   (a) During the third trimester, increased energy demand from fetal and placental growth causes increased fatty acid synthesis. A reduction in FAO increases susceptibility to AFLP.
   (b) Most women develop AFLP between gestational weeks 30 and 38.
3. AFLP is more common in primiparous women. Recurrence in subsequent pregnancies has been reported, with incidence estimates varying from 20 to 70%.
4. Approximately 20% of AFLP occurs in twin pregnancies. Twin pregnancies carry a 14-fold increased risk of AFLP when compared to singleton pregnancies.
5. Male fetuses are associated with 75% of AFLP cases [2, 5].
6. Approximately 50–70% of women with AFLP also develop pregnancy-induced hypertension, and symptoms may overlap with those of hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome [5].
7. Neonatal demise can occur. AFLP is associated with a 23% fetal mortality. Preterm delivery, low birth weight, neonatal apnea, and fetal distress have been reported.
8. Maternal mortality may be from hemorrhage, sepsis, renal failure, circulatory collapse, pancreatitis, and gastrointestinal bleeding.

Diagnosis

1. Symptoms involving the gastrointestinal system during the third trimester that cannot be attributed to other obvious causes should prompt a suspicion of AFLP.
2. Distinguishing AFLP from HELLP syndrome may be difficult. However, higher transaminases and bilirubin, DIC, hypoglycemia, and decreased antithrombin III may be more common in AFLP, while proteinuria and hypertension are more common in HELLP syndrome.

Table 4.1 Swansea criteria for AFLP (six or more positive categories)

Vomiting	+
Abdominal pain	+
Polydipsia/polyuria	+
Hepatic encephalopathy	+
Total bilirubin	>14 μmol/L
Blood glucose	<4 mmol/L
Uric acid	>340 μmol/L (5.7 mg/dL)
Leukocytosis	$>11 \times 10^9$/L
Ultrasound of the liver	Ascites or "bright liver"
Transaminases (ALT, AST)	>42 U/L
Blood ammonia	>47 μmol/L
Creatinine	>150 μmol/L
Coagulopathy	PT > 14s or APTT > 34s
Liver biopsy	Microvesicular steatosis

3. The Swansea criteria are commonly used to establish the diagnosis [1]. See Table 4.1. AFLP is diagnosed if six or more categories are positive.
4. Liver biopsy is no longer routinely used due to the risk of severe bleeding, and the value of imaging studies remains to be determined.

Management

1. Early diagnosis and delivery are key to a good outcome.
   (a) It is recommended that delivery should be completed within 7 days of suspected diagnosis. Maternal survival approaches 100% if delivery is completed within 7 days of diagnosis.
   (b) Maternal survival decreases to 70% if delivery is completed later than 2 weeks after diagnosis.
   (c) In severe cases, urgent cesarean delivery is usually performed. Cesarean delivery may result in improved maternal and fetal survival rates.
   (d) Either regional or general anesthesia can be administered. The extent of coagulopathy and encephalopathy will dictate anesthetic management. One study reported the use of anesthesia in 28 cesarean deliveries: 13 combined spinal-epidurals (CSE), 3 spinals, and 12 general anesthetics were performed with no anesthetic complications reported. Of note, two of the patients who had CSE had an INR > 2.1 though this practice cannot be endorsed.
2. Treatment for AFLP is generally supportive.
   (a) Treatment involves controlling hypertension, providing caloric supplementation, supporting renal function, and correcting hypoglycemia, electrolyte and acid-base disturbances, and hypoproteinemia. Admission to an intensive care unit is advised.

(b) Coagulopathy may require vitamin K, fresh frozen plasma, and cryoprecipitate transfusion.
(c) Dialysis may be indicated in severe renal dysfunction and elevated ammonia levels.
(d) Maternal lipid metabolism and mental status must be followed. If applicable, diet should be low in lipids and high in carbohydrates. FAO inhibitors, such as nonsteroidal anti-inflammatory drugs and valproic acid, should be avoided [8].
(e) Prophylactic antibiotics are often administered.
(f) Liver transplant may be required. AFLP may deteriorate postpartum but typically gradually improves. However, some patients with refractory liver failure may require transplant. Patients with encephalopathy and increased lactate and ammonia levels on admission may be more likely to require transplant.

3. With early recognition and delivery, the prognosis has significantly improved over the past few decades. There is temporary worsening of hepatic and renal function within 48 h of delivery, but improvement should follow thereafter [2, 9].
4. Fetuses born to mothers with AFLP should be maintained on a high-carbohydrate, low-fat diet and remain unfasted for more than 4 h. Aspirin, nonsteroids, tetracycline, and valproic acid should be avoided until neonatal status is established.

References

1. Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57:951–6.
2. Usta IM, Barton JR, Amon EA, Gonzalez A, Sibai BM. Acute fatty liver of pregnancy: an experience in the diagnosis and management of fourteen cases. Am J Obstet Gynecol. 1994;171:1342–7.
3. Browning MF, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. Obstet Gynecol. 2006;107(1):115–20.
4. Ibdah JA, Bennett MJ, Rinaldo P, Zhao Y, Gibson B, Sims HF, Strauss AW. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. N Engl J Med. 1999;340:1723–31.
5. Gracia PV, Lavergne JA. Acute fatty liver of pregnancy. Int J Gynaecol Obstet. 2001;72:193–5.
6. Liu G, Shang X, Yuan B, Han C, Wang Y. Acute fatty liver of pregnancy: analysis on the diagnosis and treatment of 15 cases. J Reprod Med. 2016;61:282–6.
7. Pereira SP, O'Donohue J, Wendon J, Williams R. Maternal and perinatal outcome in severe pregnancy-related liver disease. Hepatology. 1997;26:1258–62.
8. Baldwin GS. Do NSAIDs contribute to acute fatty liver of pregnancy? Med Hypotheses. 2000;54:846–9.
9. Castro MA, Fassett MJ, Reynolds TB, Shaw KJ, Goodwin TM. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol. 1999;181:389–95.