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Acute Fatty Liver of Pregnancy

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening condition that develops in the third trimester of pregnancy. AFLP shares similar clinical features with other more common pregnancy-associated conditions. However, early correct diagnosis is important for maternal and fetal survival. Once the diagnosis has been established, immediate delivery and maternal intensive support should be undertaken. Both parents and the infant should be tested for deficiencies of the mitochondrial fatty acid oxidation, especially for long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, as many cases of AFLP are related to disruption of this physiological enzymatic pathway.

Keywords: acute fatty liver of pregnancy, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Swansea criteria, newborn metabolic screening

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) usually presents after 30 weeks of gestation, it has an incidence of about 1 in 15,000 pregnancies[1] and is a potentially lethal condition, for both mother and baby. It is characterized by a lack of necrosis and inflammation, although there is a large fatty penetration of hepatocytes at a microvesicular level. Risk factors include first pregnancy, co-existing diagnosis of other liver diseases – including preeclampsia (PE) –, male fetus, and multiple gestations.[1]

DIAGNOSIS

Clinical features consist of nausea and vomiting, abdominal pain, fatigue, polydipsia, and polyuria, as well as jaundice with rapid progression to acute liver failure. The associated complications include encephalopathy, coagulopathy, hypoglycemia, and renal failure. Laboratory findings include elevated liver enzymes, hyperbilirubinemia, hyperuricemia, hyperammonemia, and hypoglycemia.[1]

The differential diagnosis of AFLP includes several maternal diagnoses such as PE, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and intrahepatic cholestasis of pregnancy (IHCP). In all four conditions,

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there is an elevation in liver enzymes and hyperbilirubinemia. In PE there is hypertension and proteinuria, and in severe cases, abdominal pain, headache with visual disturbance, and thrombocytopenia. HELLP syndrome is a life-threatening condition that manifests with proteinuria with or without hypertension, thrombocytopenia with hemolysis, abdominal pain, and headache. The predominant features of IHCP are pruritus, jaundice, and high serum bile acids. Even if the differential diagnoses can be present by themselves, in about 30% of women with AFLP there is accompanying PE or HELLP syndrome.[1]

The gold standard method for the positive diagnosis of AFLP is liver biopsy and the demonstration of microvesicular fatty infiltration.[2] However, liver biopsy is seldom performed and potentially dangerous, especially in the presence of coagulation disorders. Consequently, the diagnosis is usually made by application of the Swansea criteria,[3] which combine clinical and laboratory markers. A positive screening result for AFLP is given if at least six of the following are present: abdominal pain, vomiting, polyuria/polydipsia, encephalopathy, hyperbilirubinemia, low glucose levels, hyperuricemia, hyperammonemia, raised white cell blood count, ascites or intense liver image on ultrasound scan assessment, high transaminases values, renal injury, coagulopathy, and hepatic microvesicular steatosis (Table 1).

ETIOLOGY

Advances in molecular technologies suggest that AFLP may be caused by dysfunctional mitochondrial processes in both the mother and the fetus.[4] In the mitochondria, there is a pathway specialized in achieving energy from free fatty acids – the fatty acid oxidation (FAO) pathway, which becomes active when glycogen stores are depleted, during fasting and ketogenesis. The by-products of FAO can be used by the brain, heart, liver, and skeletal muscles in lack of glucose. The process of FAO requires several steps in order to be accomplished. The fatty acids are first transported by special carriers to the mitochondrial inner membrane, where they are split in a cascade of four enzymatic processes.

Shortage of the third enzyme, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), leads to abnormal and potentially toxic levels of medium- and long-chain fatty acids. This condition is the consequence of an autosomal recessive (AR) disorder and, in its heterozygous state, has been diagnosed in some pregnant patients with AFLP, while in its homozygous state can be diagnosed in some of their babies.[5,6] The enzyme deficiency is most commonly caused by a mutation in the alpha-unit of the tri-functional protein gene where guanine is replaced by cytosine in position 1528, which alters amino acid 474 from glutamic acid to glutamine (E474Q). This mutation is identified in 65% to 90% of LCHAD-deficient patients.[7] As the mutation is AR, it should not, in normal conditions, cause anomalous fatty acid oxidation in the mother. Nevertheless, when both the father and the mother are heterozygous for the mutation, the fetus could acquire the abnormal genes from both, and would, therefore, be incapable of metabolization of long-chain fatty acids.

The fetal unmetabolized free fatty acids flow back through the placenta to the mother's blood, straining the maternal liver function and overwhelming the already reduced hepatic enzyme activity, ensuing the appearance of clinically visible AFLP.[8] Postnatally, the metabolic hepatic strain in the mother lowers and explains why the maternal FAO ultimately comes back to normal in the postpartum period.[9] Keeping this hypothesis in mind, babies delivered from mothers with AFLP should always be checked for abnormalities of FAO. Otherwise, LCHAD deficiency would probably be diagnosed later in infancy, when its consequences could be irreversible. In LCHAD-deficient infants, toxic by-products of FAO can build up in the mitochondria and can lead to degeneration and fatty infiltration of the skeletal and cardiac muscle fibers. There can also be hepatomegaly and liver dysfunction because of lipid deposition, jaundice, and progressive impairment of the bilirubin metabolism. LCHAD deficiency can also lead to sud-

TABLE 1. Swansea criteria for the probability of acute fatty liver of pregnancy[1,3]

Six or more of the criteria below should be considered diagnostic of AFLP in a woman with no other liver conditions of pregnancy (PE or HELLP)
• Vomiting
• Encephalopathy
• Polydipsia/polyuria
• Abdominal pain
• Bilirubin more than 0.8 mg/dL
• Elevated urea above 950 mg/dL
• Hypoglycemia less than 72 mg/dL
• Leukocytosis more than 11,000/mL
• Ascites
• ALT values above 42 U/L
• Ammonia values above 66/µmol
• Coagulation function or prothrombin time more than 14 seconds
• Acute kidney injury or creatinine more than 1.7 mg/dL
• "Intense liver" on ultrasound image
• Microvesicular steatosis on liver biopsy

den infant death, especially when the infants experience severe fasting or vomiting, making them metabolically dependent on gluconeogenesis from the lipid metabolism.[10]

The recurrence of AFLP is documented with subsequent pregnancies, and the theoretical risk is 25%, but in clinical practice, just several cases have been reported. Genetic testing for a fetus in future pregnancies can be offered if mutations in the parents are known.[8]

PROGNOSIS AND MANAGEMENT

AFLP may lead to extremely severe consequences for both the mother and the fetus. Early recognition of the condition with delivery and full supportive maternal care are extremely important for the outcomes of both mother and child. The postpartum course of the mother largely depends on the early recognition of AFLP – the time from the development of the first symptoms to delivery.

Recent data report a decrease over time in maternal and fetal mortality associated with AFLP, as we have come to understand more about the condition. Early diagnosis is of utmost importance as it carries an increased risk of maternal and fetal mortality and morbidity, with 2% maternal and 11% fetal reported death rates.[2]

The principles of treatment for AFLP involve three key steps: timely diagnosis, rapid delivery, and thorough maternal care, which are the pillars of survival in AFLP. Laboratory results in AFLP do not always match the gravity of the condition; therefore, suspicion of AFLP and a low threshold of admission for patient monitoring should be undertaken. Before delivery, the mother should be stabilized by a comprehensive and experienced team that can offer airway support, hypertension treatment, and correction of hypoglycemia, coagulation, and electrolyte function. The care of these patients should be provided by specialists in intensive care, gastroenterology, and perinatology. Continuous infusion of intravenous fluids and blood, assessment of vital signs, and evaluation of mental health are also utterly important. Fetal assessment is also crucial prior to delivery. Delivery should be achieved upon stabilization of the mother. Vaginal birth is not contraindicated in AFLP and should be tried if the maternal situation allows it. In clinical practice, however, delivery by caesarean section is often chosen as the maternal function is deteriorating fast. Postnatally, women that have suffered from AFLP should be closely monitored for bleeding as they can suffer from severe coagulopathy. Disseminated intravascular coagulopathy is often the presenting symptom of AFLP (90%), and it might be severe. Intraabdominal hemorrhage is a serious negative feature in pregnancy-related liver disease and is common regardless of the way of delivery.[11,12] Seldom is it possible that this patient might present non-obstetric hemorrhage such as Mallory-Weiss rupture, a conditions that requires interventional therapies. Transfusion of blood products and fluids is often needed.[13,14] Hypoglycemia is another important consequence that can develop in AFLP, and glucose infusion may be needed. Pancreatitis has been reported in some affected patients, with devastating consequences – infections and retroperitoneal bleeding, especially in the setting of coagulopathy. Maternal serum amylase and lipase, and imaging examinations, such as computed tomography and magnetic resonance, may be valuable in examining pancreatic involvement.[15] Encephalopathy can be the very first symptom and in the setting of AFLP can quickly progress to cerebral edema, convulsions, and coma.[16] Cases of diabetes insipidus have also been reported. Hypothetically, this is due to raised values of vasopressinase that metabolizes arginine vasopressin.[17]

Anesthesia in AFLP is a challenge as there are multiple pathologies involved in these patients, and currently there are no protocols and only scant guidelines. It has to be customized to the patients' need, and it might require blood transfusion, vasopressors, and electrolyte replacement. Multidisciplinary management is mandatory to manage this critical patient.[18]

In severe cases, liver transplantation has been performed for AFLP. This topic remains controversial as in some cases women on the waiting list were removed following improvement of their hepatic function and complete recovery. Auxiliary liver transplantation with keeping the native liver in situ and removal of the transplanted liver after full recovery has been reported.[16,18] However, in a retrospective study Kushner *et al.*[19] have shown that women undergoing liver transplant for AFLP had a lower outcome compared with women of the same age who had a transplant for acute liver failure. Survival graft at 5 years was lower among pregnant women, which might be explained through a higher rejection rate during pregnancy.

CONCLUSION

As seldom as it is, acute fatty liver of pregnancy remains a life-threatening condition that develops toward the last part of the pregnancy. Early diagnosis, though difficult because of the features shared with other more common pregnancy-associated conditions, is the cornerstone for maternal and fetal survival. Immediate delivery and maternal intensive support should be undertaken. Both parents and the infant should be checked for deficiencies in the fatty acid oxidation, especially for LCHAD deficiency.

CONFLICT OF INTEREST

Nothing to declare.

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