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Research Paper

Acute fatty liver of pregnancy: A Rarity

Medical Science

KEYWORDS : Poaceae ,Grasses, Sabarmati river.

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is an uncommon but potentially fatal complication that occurs in the third trimester or early postpartum period. It was first described in 1940 by Sheehan (1) as an "acute yellow atrophy of the liver". AFLP is characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis. It has an incidence of approximately one in 10,000 to 15,000 pregnancies (2). In the past, maternal and perinatal mortality were reported to be as high as 75% and 85%, respectively (3). More current data showed that with prompt diagnosis and treatment, the maternal and perinatal mortality have greatly decreased, to approximately 18% and 23%, respectively (1,4,5). Despite the accumulation of data about this condition, the exact pathogenesis has yet to be determined. At present, supportive care and expeditious delivery remain the best treatment. The present article provides a review of AFLP, including etiology, pathophysiology, clinical presentations, diagnosis and management.We are reporting a case of 20 year old G2A1 who presented to us with history of fever and was later diagnosed to be having acute fatty liver which is a rare entity.

CASE REPORT:

A 20 yr old lady by name Manjula hailing from Kempanahalli,channagiri who is G2A1 was referred to the emergency department with a working diagnosis "G2A1 WITH 30WKS OF GESTATION WITH VERTEX PRESENTATIONWITH FEVER WITH THROMBOCYTOPENIA FOR EVALUATION ".Patient conceived after 6 months of last abortion and was diagnosed to be pregnant 1 ½ months back. Patients LMP-18.12.13 EDD-25.10.14 .On examination patients vitals were stable and per abdomen uterus was 28 wks and relaxed.Patient was being worked up for fever.Patient developed icterus on the third day of admission and ultrasound showed fatfy liver and her Liver function tests were deranged.Patient was taken up for emergency LSCS and 1.3 kgs female baby was extracted.Post op period patient became breathless and her neurological status deteriorated and patient developed irrelevant speech and so patient was shifted to ICU and was intubated and ventilated ,patients renal parameters got deranged and patient went int acute renal failure with thrombocytopenia with ARDS.Patient expired the next day.All these events could be explained as consequences of Acute fatty liver in pregnancy.

CLINICAL PRESENTATION

The majority of women who are diagnosed with AFLP are in the third trimester of pregnancy and the mean gestational age is 35 to 36 weeks, with a range of 28 to 40 weeks (5,6). Isolated case reports (1,3,7,8) of AFLP have shown that it can occur as early as 26 weeks and as late as the immediate postpartum period. Monga and Katz (9) reported a case diagnosed at 22 weeks gestation. Clinical findings in AFLP vary because it may occur with varying degrees of clinical severity and in conjunction with other third trimester symptoms, making early diagnosis of AFLP difficult. Patients often present with nonspecific symptoms such as anorexia, nausea, vomiting, malaise, fatigue, headache and abdominal pain. On physical examination, the patient is usually febrile and jaundiced, which is very common and eventually occurs in more than 70% of patients with AFLP as the condition progresses (10). Tenderness in the right upper quadrant or midepigastric area may be present (8). The liver is usually small and nonpalpable. In severe cases, the patient can present with multisystem involvement including acute renal failure, encephalopathy, gastrointestinal bleeding, pancreatitis and coagulopathy. Some women may also have pre-eclampsia as well, with edema and hypertension. It is believed that the hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, pre-eclampsia, thrombotic thrombocytopenia purpura and AFLP may all be a spectrum of the same illness. Transient diabetes insipidus may also occur, but is very rare (1,2).

AFLP also has a detrimental effect on the fetus. One of the complications of AFLP is maternal metabolic acidosis secondary to impaired clearance of serum lactate by damaged hepatocytes (1,3). Maternal metabolic acidosis directly affects fetal acid-base status (1,4). Therefore, prompt correction of maternal metabolic acidosis is essential to the fetal well-being. Expeditious birth may be necessary.

LABORATORY FINDINGS

Patients will often have an elevated white blood cell count (greater than 15×10^9/L), but a normal hematocrit unless hemorrhage has occurred (1,4). Hemolysis and thrombocytopenia may also be present (1,5). The prothrombin and partial thromboplastic times are both prolonged, and fibrinogen levels are below normal (1,4,5). Disseminated intravascular coagulopathy occurs when fibrin split products are found (75% of patients) (4,6). Abnormalities in liver biochemistry include elevated serum aminotransferases (ie, serum aspartate amino-transferase and alanine aminotransferase) levels of 300 U/L to 500 U/L, but the range has been reported to be from normal to 1000 U/L (1,3). Elevated serum aminotransferases may also be associated with raised serum ammonia, amino acid levels and lactic acidosis, uric acid, hyperbilirubinemia and hypoglycemia secondary to impaired hepatic glycogenolysis (1,7). Alkaline phosphatase may be elevated up to 10 times normal; however, alkaline phosphatase can also be increased during the third trimester normally (1). Lastly, the blood urea nitrogen and creatinine may also be elevated, and acute renal failure may complicate severe cases (1,4).

DIAGNOSIS

The diagnosis of AFLP can be challenging because the initial clinical presentation may be nonspecific. The patient's history, clinical features and biochemical abnormalities may mimic conditions such as acute viral hepatitis, pre-eclampsia, HELLP syndrome, intrahepatic cholestasis or others. Because AFLP is uncommon, the best approach to any pregnant women with liver dysfunction is to quickly rule out other, more likely, causes. One of the most common multiorgan diseases of late pregnancy is pre-eclampsia (3). Although women with AFLP can also have pre-eclampsia, patients with pre-eclampsia alone are not usually jaundiced and do not usually have hypoglycemia, as seen in AFLP (7). Furthermore, AFLP often presents more acutely than pre-eclampsia, which can develop over several days or weeks. In addition, pre-eclampsia rarely presents with severe coagulopathy such as disseminated intravascular coagulation. Besides pre-eclampsia, acute viral hepatitis should also be ruled out in pregnant women with symptoms of liver dysfunction. In viral hepatitis, patients usually have much higher levels of serum

transaminases, with values often well above 1000 U/L, and serology tests will be positive. Moreover, uric acid levels are rarely elevated in fulminant hepatitis and signs of pre-eclampsia are absent in viral hepatitis. Finally, intrahepatic cholestasis of pregnancy can cause jaundice as well; however, it is characterized by intense pruritus and elevated alkaline phosphatase, and is not associated with abdominal pain, nausea, vomiting, liver failure or disseminated intravascular coagulation (4,8).

Both ultrasound examination and computed tomography may demonstrate fatty infiltration of the liver; however, the sensitivity and specificity of these imaging studies are insufficient to make a definitive diagnosis of AFLP. False negative results are common (5,9). Historically, the necessity of liver biopsy in making the diagnosis of AFLP originated with Ober and Lecompte in 1955 (2) because this condition was clinically indistinguishable from fulminant infectious hepatitis. However, liver biopsy can cause complications in the presence of coagulopathy. Nowadays, serological markers for viral hepatitis and clinical and biochemical findings for AFLP are available, thus, liver biopsy is not mandatory for diagnosis in most cases and clinically is rarely performed (2,1). Although AFLP shares features with other, more common, illnesses, a careful history and physical examination, in conjunction with compatible laboratory and imaging results, are often sufficient to make the diagnosis. Liver biopsy should not be performed to confirm a diagnosis of AFLP or to distinguish AFLP from severe pre-eclampsia, because management of both conditions are the same. Vigil-De Gracia and Lavergne (2,2) suggested that liver biopsy may be justified in cases when liver function does not return to normal postpartum, and in those cases where the definitive diagnosis in the early stages of AFLP is necessary as the primary indication for delivery. Histologically, one will see microvesicular steatosis with sparing of zone 1. There will be pericentral pallour with lobular disarray and vacuolization of the centrizonal hepatocytes. Special stains, such as oil red O, must be applied to fresh-frozen specimens to demonstrate fat (2,3). There may be patchy hepatocellular necrosis; however, widespread necrosis or inflammation is absent (1,6).

MANAGEMENT

Early diagnosis, prompt delivery and intensive supportive care are the cornerstones in the management of AFLP. Because the laboratory findings in AFLP frequently do not reflect the gravity of the problem, a high level of suspicion, with low threshold of admission to monitor, should be taken. If the patients are at high risk for multisystem organ failure and death, admission to the intensive care unit is generally recommended. Before delivery, maternal stabilization should be achieved before delivery, which includes airway management, treatment of hypertension, and correction of hypoglycemia, electrolyte and coagulation abnormalities. Careful maintenance of intravenous fluids and blood products, as well as frequent maternal vital signs assessment, and evaluation of changes in mental status are all crucial. Furthermore, frequent fetal assessment is also needed. Therefore, collaboration among different specialties such as intensive care, gastroenterology and perinatology are essential.

Once the mother is stabilized, delivery of the fetus is the next step. Vaginal birth is probably the best approach if tolerated; however, caesarean birth is often performed because of rapidly deteriorating maternal-fetal status. During the postpartum recovery period, hemodynamic monitoring is necessary because patients with AFLP are at high risk of bleeding as a result of coagulopathy. Transfusion of fluids and blood products may be needed. Besides risk of bleeding, patients are also at risk of hypoglycemia and glucose infusion may be needed. Lastly, one should not overlook other potential complications of AFLP (ie, pancreatitis), which usually develop after the onset of hepatic and renal dysfunction (2,4). The development of pseudocysts with secondary infections or hemorrhagic pancreatitis with resultant retroperitoneal bleeding can be difficult to control, especially when patient has coagulopathy. Thus, it may be worthwhile to do serial screening of serum lipase and amylase for several days after the onset of hepatic dysfunction. Imaging studies such as computed tomography or magnetic resonance imaging may be useful in assessing the development of pseudocysts or hemorrhagic pancreatitis.

Liver transplantation has rarely been performed for AFLP. A recent review of the American United Network for Organ Sharing (UNOS) database for the HELLP syndrome revealed that during the 16-year period between 1987 and 2003, there were only eight liver transplants performed for this pregnancy-associated condition (2,5). In their case report, Ockner et al (2,6) described a 35-year-old woman whose multisystem failure was rapidly reversed after liver transplantation. Therefore, they suggested that orthotopic liver transplantation should be considered for those women with fulminant hepatic failure due to AFLP, who manifest signs of irreversible liver failure despite delivery and aggressive supportive care. Similarly, Pereira et al (2,7) recommended that liver transplantation should be reserved for those patients with hepatic encephalopathy, severe metabolic acidosis or worsening coagulopathy, or those with liver rupture complicated by hepatic necrosis as indicated by computed tomography.

ETIOLOGY

Recent molecular advances suggest that AFLP may be a result of mitochondrial dysfunction (1,7). The process of mitochondrial fatty acid beta-oxidation consists of a series of transport steps and four enzymatic reactions. Normally, special carrier transporters transport fatty acids to the mitochondrial inner membrane, where they are then broken down by four enzymes. This pathway generates energy from free fatty acids for the brain, heart, liver and skeletal muscle during fasting, when the glycogen stores are depleted. Deficiency of the third enzyme, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) results in accumulation of medium- and long-chain fatty acids. It is an autosomal recessive disorder and the heterozygous LCHAD deficiency has been identified in some women with AFLP (2,8).

In 1991, Schoeman et al (2,9) reported the association between recurrent AFLP cases and LCHAD defect, suggesting that affected women might have an inherited enzyme deficiency in beta-oxidation, predisposing them to AFLP. In 1993 and 1994, respectively, Wilcken et al (3) and Treem et al (3,1) reported six families of children with LCHAD deficiency; all had been born to mothers who suffered from AFLP or HELLP syndrome during pregnancy. Further retrospectives studies by Ibdah et al (3,2) also showed an association between LCHAD deficiency and AFLP.

In 1995, the gene for LCHAD was isolated, and genetic mutations associated with this deficiency were identified. The most common mutation occurs in the alpha-unit of the tri-functional protein gene (1528G→C), which alters amino acid 474 from glutamic acid to glutamine (E474Q), replacing the acidic and negatively charged side chain with a neutral, amide-containing residue. This mutation is associated with approximately 65% to 90% of the LCHAD-deficient patients (3,3). The precise mechanism by which LCHAD deficiency in a fetus causes severe liver disease in mother is unclear. It is hypothesized because the mutation is recessive, under normal physiological conditions the mother does not have abnormal fatty acid oxidation. However, when both parents are heterozygous for this abnormality and the fetus acquires both of these mutations, the fetus will be unable to oxidize long-chain fatty acids. The unmetabolized free fatty acids return via the placenta to the mother's circulation, which strains maternal hepatic activity and overwhelms any diminished maternal hepatic enzyme activity, resulting in the symptoms of AFLP (3,4). Delivery of the infant eliminates the metabolic he-

patic stress for the mother and perhaps explains why the fatty acid oxidation eventually normalizes postpartum (3.5).

This hypothesis, however, is not unequivocally accepted, as some investigators have not been able to confirm the association between AFLP and LCHAD deficiency (3,6). One possible explanation is that although there are a number of mutations leading to LCHAD deficiency, only specific genetic defects will lead to an increased risk of AFLP. Ibdah et al (3.2) evaluated 24 children with LCHAD deficiency; 19 of them were either homozygotes for a mutation in which glutamic acid was replaced with glutamine (E474Q) or compound heterozygotes (glumtamine mutation plus a different mutation on the other allele). Fifteen mothers of these children (79%) had AFLP or HELLP, or both. On the other hand, pregnancy-related liver disease was not seen during pregnancies in children who had other mutations or had at least one wild-type allele (3,1). In a relatively recent cohort study by Yang et al (3,7), the number of children with LCHAD deficiency born to mothers with AFLP was estimated to be between 15% and 20% of all AFLP-complicated pregancies. On the other hand, only less than 2% of HELLP-complicated pregnancies are associated with fetal LCHAD deficiency with the G1528C on one or both alleles (7,8).

What is the impact of LCHAD deficiency in infants? The toxic products of LCHAD deficiency accumulate in the mitochondria and can cause degeneration and fatty infiltration of muscle fibres (3,4). This affects both skeletal and cardiac muscle development. The liver becomes enlarged with lipid depositions within the hepatocytes. There may be progressive jaundice associated with impaired bilirubin metabolism. Inherited LCHAD deficiency usually presents clinically in the neonatal period or in early childhood, frequently after a period of fasting or viral illness. At the time of diagnosis, infants frequently have severe liver failure, severe cardiomyopathy and hypoketotic hypoglycemic encephalopathy (3,1). These symptoms may be difficult to reverse. Typically, a diet low in long-chain fatty acids and supplemented with medium-chain triglycerides is recommended (3,5). Dietary therapy may improve long-term prognosis, although it has not been successful in preventing irreversible ophthalmological changes such as pigmentation of the fundus of the eye.

LCHAD deficiency can be suddenly lethal as well, especially when the infants experience an illness with associated fasting or vomiting, which make them metabolically reliant upon gluconeogenesis by lipid metabolism. Because of the severe complications from LCHAD deficiency, molecular testing for this deficiency should be performed in infants as well as in affected mothers and fathers (1,2). Although there are a number of mutations for LCHAD deficiency, testing only for E474Q might be sufficient because fetuses of affected mothers almost always have the E474Q mutation on at least one allele.

PATHOPHYSIOLOGY

In AFLP, there is a progressive lipid accumulation within the hepatocytes. The normal fat content of the liver is approximately 5%. In women with AFLP, this percentage can range from 13% to 19% (1). This fat accumulation, along with ammonia production by the hepatocytes, leads to eventual coaguloapthy and hypoglycemia secondary to evolving hepatic failure (3,7). The liver is usually noted to be small, soft and yellow, most probably as a result of hepatocytolysis and atrophy of the liver cells (1). Furthermore, the kidney, pancreas, brain and bone marrow may also demonstrate microvesicular fat infiltration (7).

As discussed above, deficiency of the enzyme LCHAD seems to predispose women to AFLP. Besides LCHAD deficiency, other clinical characteristics of pregnancy have also been identified as potential risk factors: primigravidas (first pregnancy), pre-eclampsia, male fetus and multiple gestation (1,4). However, there is no causal relationship identified between these potential risk factors and AFLP as yet (10). There is one hypothesis that multiple gestations may place women at increased risk for AFLP because there is an increased production of fatty acid metabolites by more than one fetus (3). Ethnicity does not seem to be associated with AFLP. Drugs have also been proposed to be associated with AFLP and there is one case report (4) reporting the association between the use of acetylsalicylic acid and AFLP. The hypothesis is that nonsteroidal anti-inflammatory drugs, including salicylates, have been shown to inhibit trifunctional protein and, thus, long-chain fatty acid oxidation in mitochondria, which may precipitate the development of AFLP in a heterozygous (for LCHAD mutation) mother carrying a homozygous fetus (4).

OUTCOMES

Maternal outcomes

As mentioned previously, the mortality from AFLP is approximately 18% and deaths are usually secondary to sepsis, renal failure, circulatory collapse, pancreatitis or gastrointestinal bleeding (5). Among those who survived, the liver function tests may have shown continued deterioration for up to one week postpartum but then slowly recover. Similarly, on computed tomography, the liver volume will also decrease and recover some time postpartum (9). The resolution of the disease is indicated by the initial improvement of hepatic dysfunction. Liver enzymes, ammonia and coagulation studies will begin to normalize and will be followed by a decrease in serum creatinine, as long as there is no permanent renal damage (10). Full clinical recovery usually occurs in several weeks with no long-term sequelae, although histological changes in the liver may persist for months (1).

Recurrence of AFLP in subsequent pregnancies can occur. Although the theoretical recurrence risk in subsequent pregnancies is 25% with a mother carrying a homozygous mutant or compound heterozygous fetuses, it is uncommon and only a few cases have been documented . However, this may be an underrepresentation, because many women may refrain from having further pregnancies after the first occurrence. Therefore, affected women should still be informed, counselled and tested, along with their infants who may be affected, for LCHAD deficiency. If the patient decides to be pregnant again, she should be closely monitored for any early signs of acute fatty liver.

Fetal outcomes

In the past, the neonatal mortality rate had been estimated to be as high as 85%; however, with prompt recognition and treatment, the mortality rate has dramatically decreased to approximately 23%. Although the perinatal survival rate has improved, evidence of fetal compromise is not uncommon and can be present even while the mother is clinically stable. The reasons for increased fetal distress and neonatal death in the absence of maternal clinical decompensation is not very clear. However, this could be related to the need for expedited, premature delivery. Therefore, close fetal surveillance and neonatal care are essential.

CONCLUSION

AFLP is an uncommon, life-threatening disorder developing in the third trimester of pregnancy or early postpartum period. Early diagnosis sometimes can be difficult because AFLP shares features with other common disorders such as pre-eclampsia, viral hepatitis or cholestasis of pregnancy. However, careful history and physical examination, in conjunction with compatible laboratory and imaging results, are often sufficient to make the diagnosis, and liver biopsy is rarely indicated. Prompt delivery of the infant and intensive supportive care remain as the mainstay treatment for AFLP.

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