ARTICLE REVIEW

Acute Fatty Liver in Pregnancy: A Rare but Catastrophic Complication of Late Pregnancy

Nigar Sadaf[1], Rubina Hussain[2]

ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a sudden catastrophic illness occurring almost exclusively in the third trimester, where microvesicular fatty infiltration results in encephalopathy and hepatic failure.[1] Although the exact pathogenesis is unknown but the disease has been linked to an abnormality in fetal fatty acid metabolism. This abnormality is a deficiency in the LCHAD (long-chain 3-hydroxyacyl-coenzyme A dehydrogenase) enzyme. Clinical manifestation usually manifests in the third trimester (35 to 36 weeks of gestation) but some cases occur with a range of 28 to 40 weeks. The diagnosis of acute fatty liver of pregnancy is challenging task for clinician because of the nonspecific clinical presentation which may mimic conditions such as acute viral hepatitis, pre-eclampsia, HELLP syndrome. Ultrasound, CT, MRI may be used to diagnose this disease. Liver biopsy is the gold standard for the diagnosis of AFLP. The condition was previously thought to be universally fatal[2] but aggressive treatment by stabilizing the mother with intravenous fluids and blood products in anticipation of early delivery has improved prognosis. Liver transplantation may be the option for severe liver failure patients. The mortality from AFLP is approximately 18% and deaths are usually secondary to sepsis, renal failure, circulatory collapse, pancreatitis or gastrointestinal bleeding.

KEY WORDS: *Fatty, Liver, Pregnancy*.

[1] Nigar Sadaf

Senior Registrar, Department of Obstetrics & Gynaecology, Ziauddin University Hospital

[2] Rubina Hussain

Professor, HOD and Chairperson, Department of Obstetrics & Gynaecology, Ziauddin University Hospital.

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a rare, potentially life threatening, pregnancy related disease that affects 1 in 7,000 to 16,000 pregnancies[3] For the first time, it was described by Sheehan in 1940 as an “acute yellow atrophy of the liver".[4] It is characterized by micro-vesicular staetosis in the liver. The fore most cause of AFLP is thought to be due to mitochondrial dysfunction in the oxidation of fatty acids, cause by the deficiency in the LCHAD (Long chain hydroxyacyl-coenzyme A dehydrogenase) enzyme in mother[5], leading to an accumulation of fat in hepatocytes. The infiltration of fatty acids causes acute liver insufficiency, which leads to most of the symptoms present in this condition. In the past, maternal and perinatal mortality rate were reported to be as high as 75% and 90%, respectively but Sibai (2007) cites an average mortality rate of 7% with 70% preterm delivery rate and perinatal mortality rate of approximately 15%.[6]Despite the accumulation of data about this condition, the exact pathogenesis has yet to be determined. At present supportive care and expeditious delivery remains the best treatment. The present article provides a review of AFLP, including etiology, pathophysiology, clinical presentations, diagnosis and management.

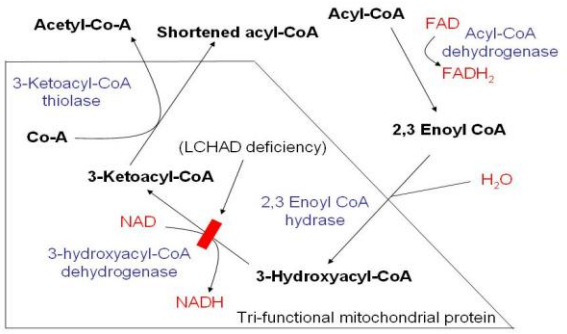
DISCUSSION

Etilogy

T Recent molecular advances suggest that AFLP may be a result of mitrochondrial dysfunction.[7]The process of mitrochondrial fatty acid beta oxidation consists of series of transport steps and four enzymatic reactions. This path way generates energy from free fatty acids, for the brain, heart, liver and skeletal muscles during fasting, when the glycogen stores are depleted. Deficiency of third enzyme, long-chain 3-hydroxyacyl-co A dehydrogenase (LCHAD) results in the 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 ([8]).

In 1995, the gene responsible for LCHAD has been isolated, and the most common genetic mutation found in acute fatty liver of pregnancy, is the E474Q missense mutation. This mutation is associated with approximately 65% to 90% of the LCHAD-deficient patients.[9] 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.[10] Delivery of the infant eliminates the metabolic hepatic stress for the mother and perhaps explains why the fatty acid oxidation eventually normalizes postpartum.[5]

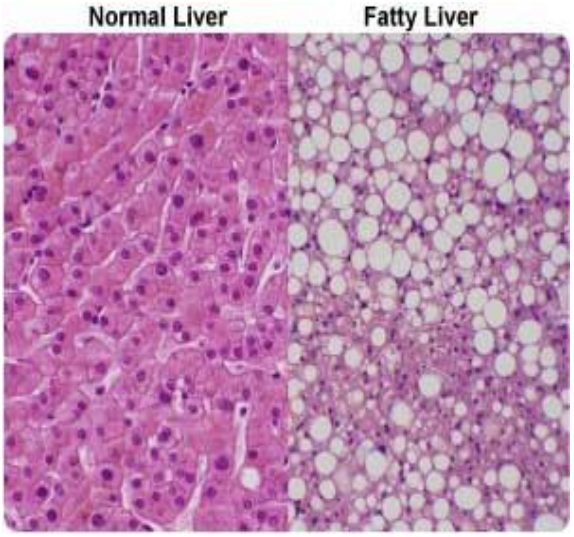
Figure 1: Schematic Demonstrating Mitochondrial Fatty Acid Beta-oxidation and Effects of LCHAD deficiency



Pathology

The diagnosis of AFLP can be made by a frozen section that is stained with Oil red O stain, that shows microvesicular staetosis (small collection of fats within the liver cells).The microvesicular staetosis usually spare the zone one of the liver, which is the area closest to the hepatic artery. On the regular trichrome stain, the liver cell cytoplasm shows a foamy appearance due to prominence of fat . Necrosis is rarely seen. The diagnosis can be enhanced by electron microscopy which can be used to confirm the presence of microvesicular staetosis and specifically the presence of megamitochondria and paracrystalline inclusions.[11,33]

Figure 2: Normal and Fatty Liver



Pathophysiology

The exact pathophysiology of AFLP is unknown. AFLP is unique to pregnancy. There does not appear to be a predilection for any geographical area or race. It appears to occur more commonly in primiparous women than multiparous women 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%.[12] This fat accumulation, along with ammonia production by the hepatocytes, leads to eventual coaguloapthy and hypoglycemia secondary to evolving hepatic failure.[13]

The liver is usually noted to be small, soft and yellow, most probably as a result of hepatocytolysis and atrophy of the liver cells.[12] Furthermore, the kidney, pancreas, brain and bone marrow may also demonstrate microvesicular fat infiltration.[13]

Epidemiology

Acute fatty liver of pregnancy is rare with an approximate incidence of 1 in 7000 to 1 in 16,000 deliveries.[14] The condition occurs more commonly in primigravida, twin pregnancy, and pregnancies carrying a male fetus. Maternal mortality is now estimated to be 12.5%–18%, with a neonatal mortality rate of 7%–66%.[4] It is more common with multiple gestations and possibly in women who are underweight. One of the largest population-based studies included 1,132,964 pregnancies at 229 hospitals in the United Kingdom between 2005 and 2006.[15] There were a total of 57 women diagnosed with acute fatty liver of pregnancy (5 cases per 100,000 pregnancies, 95% CI 3.8-6.5). Of these, 18 percent of women had twin pregnancies and 20 percent were underweight (body mass index <20).

Clinical Manifestation

Acute fatty liver of pregnancy (or hepatic lipidosis of pregnancy) usually manifests in the third trimester of pregnancy, but may occur any time in the second half of pregnancy, or in the puerperium, the period immediately after delivery.[16] Isolated case reports of AFLP have shown that it can occur as early as 26 weeks and as late as the immediate postpartum period.[13] Monga and Katz reported a case diagnosed at 22 weeks gestation.[17,34] 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.[9] 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.[18] Tenderness in the right upper quadrant or midepigastric area may be present.[17] The liver is usually small and nonpalpable.

In patients with more severe disease, pre-eclampsia may occur, which involves elevation of blood pressure and accumulation of fluid (termed edema).This may progress to involvement of additional systems, including acute renal failure[19], hepatic encephalopathy[20], and pancreatitis.[21] There have also been reports of diabetes insipidus complicating this condition.[22] Other systemic effects include respiratory failure, sometimes requiring assisted ventilation, ascites,[23] and gastrointestinal bleeding from gastric ulceration and Mallory-Weiss syndrome.[24] Hepatorenal syndrome eventually develops and leads to oliguria and acute tubular necrosis.[25] The prevalence of common signs and symptoms of AFLP is listed in Table 1.

Table 1: Common Signs and Symptoms of Acute Fatty Liver of Pregnancy

Common Signs and Symptoms	Prevalence
Jaundice	>70
Abdominal Pain (usually right upper quadrant, midepigastric or radiating to back)	50-60
Central Nervous System (altered sensorium, confusion, disorientation, psychosis, restlessness, seizures or even coma)	60-80
Disseminated Intravascular Coagulation	55
Nausea and Vomiting	50-60
Gastrointestinal Bleeding	20-60
Acute Renal Failure	50

Laboratory Findings

Table 2 summarizes some of the common laboratory findings of AFLP. Many laboratory abnormalities are seen in acute fatty liver of pregnancy. Liver enzymes are elevated, with the AST and ALT enzymes ranging from minimal elevation to 1000 IU/L, but usually staying in the 300-500 range.[16] In addition, laboratory findings may be consistent with disseminated intravascular coagulation (DIC), specifically prolongation of prothrombin time, low fibrinogen and low antithrombin levels.[35] In AFLP the values are abnormal not due to consumption of clotting factors but rather due to decreased production by damaged liver.[26] Hepatic injury results in decreased gluconeogenesis and, therefore, decreased blood glucose levels. Some patients may develop pancreatitis, which can result in elevated amylase, lipase and increased blood sugar. Maternal kidneys become affected, blood creatinine and uric acid can become elevated leading to metabolic acidosis.

Table 2: Summary of Laboratory Findings in Acute Fatty Liver of Pregnancy

Hematology	
Hemaglobin	Normal
Hematocrit	Normal
White Blood Cells	↑
Platelets	Normal to ↓
Liver Studies	
Aspartate Aminotransferase	↑↓
Alanine Amoniotransferase	↑↓
Gamma-glutamytransferase	↑
Alkaline Phosphatase	↑↓
Actate Dehydrogenase	Normally initially, then ↓

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. According to the Swansea criteria, six or more of the following features are used to diagnose AFLP in the absence of other explanations: vomiting; abdominal pain; polydipsia/polyuria; encephalopathy; elevated bilirubin >14 µmol/L (0.8 mg%); hypoglycemia <4 mmol/L (72 mg%); elevated urate >340 µmol/L (5.7 mg%); leukocytosis >11 × 109/L; ascites or bright liver on ultrasound; elevated transaminases; elevated ammonia >47 µmol/L (27.5 mg%); renal impairment creatinine >150 µmol/L (1.7mg%); coagulopathy (PT >14 sec or APTT >34 sec), or microvesicular steatosis on liver biopsy.[27]

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. Initial treatment involves supportive management with intravenous fluids, intravenous glucose and blood products, including fresh frozen plasma and cryoprecipitate to correct DIC. This should occur in an intensive care setting and in consultation with physicians well-versed in the care of critically ill patients. The fetus should be monitored with cardiotocography. After the mother is stabilized, arrangements are usually made for delivery. This may occur vaginally, but, in cases of severe bleeding or compromise of the mother's status, a caesarian section may be needed.[16] Spontaneous resolution usually follows delivery.

Lastly, one should not overlook other potential complications of AFLP (i.e. pancreatitis), which usually develop after the onset of hepatic and renal dysfunction.[21] Thus, it may be worthwhile to do serial screening of serum lipase and amylase for several days after the onset of

hepatic dysfunction. Liver transplantation is rarely required for treatment of the condition, but may be needed for mothers with severe DIC, those with rupture of the liver, or those with severe encephalopathy, pancreatitis and gastrointestinal bleeding.[28] Severe cases of AFLP in the postpartum period may be treated by using postpartum plasma exchange as reported by Martin et al. Patients with severe encephalopathy, on ventilator support, or with severe liver or renal insufficiency who failed to respond to conventional management, underwent plasma exchange.

All patients showed improved signs and laboratory values.[29] Jin et al reported success with plasma exchange in 39 patients.[30] Chu et al achieved success in combining plasma exchange with continuous hemodiafiltration for patients with multiple organ dysfunction.[31] No specific surgical treatment exists for AFLP. Because of coagulation problems, careful evaluation of the genital tract for lacerations after vaginal delivery or maintaining good haemostasis during caesarean delivery should be practiced.[32] Maternal deaths are caused by sepsis, hemorrhage, aspiration, renal failure, circulatory collapse.[36]

The prognosis for women who develop AFLP is excellent, assuming they survive the acute event. However case of chronic pancreatitis has been descried, occurring about 3 months after recovery and discharge from the hospital.[37] In the past, the neonatal mortality rate had been estimated to be very high; however ,with prompt recognition and treatment, the mortality rate has dramatically reduced to 23%.[38]

REFERENCES

[1] 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: 115-120

[2] Mjahed K, Charra B, Hamoudi D, Noun M, Barrou L (2006). "Acute fatty liver of pregnancy". Arch. Gynecol. Obstet. 274 (6): 349–353.doi:10.1007/s00404-006-0203-6. PMID 16868757.

[3] MadhusudanDey and Kumar Reema. Acute fatty liver of pregnancy; Article information N Am J Med Sci.2012 November; 4(11):611-612

[4] Rajasri AG, Srestha R, Mitchell J. Acute fatty liver of pregnancy (AFLP)-an overview. J Obstet Gynaecol. Apr 2007; 27(3):237-40.{Medline}.

[5] Bellig LL. "Maternal acute fatty liver of pregnancy and the associated risk for long-chain 3-hydroxyacyl-coenzyme a dehydrogenase (LCHAD) deficiency in infants". Adv Neonatal Care Feb 2004; 4(1): 26–32.{Medline}

[6] Sibai BM. Imitators of severe preeclampsia. Obstet Gynecol. 2007; 199:956–66. [PubMed].

[7] Rahman TM, Wendon J. Severe hepatic dysfunction in pregnancy. QJM. 2002;95:343–57.[PubMed]

[8] Wanders RJ, Vreken P, den Boer ME, Wijburg FA, van Gennip AH, IJlst L. Disorders of mitochondrial fatty acyl-CoA beta-oxidation. J Inherit Metab Dis. 1999; 22: 442–87. [PubMed]

[9] Hin Hin Ko, Eric Yoshida. Acute fatty liver of pregnancy. Can J Gastroenterol 2006; 20(1):25-30

[10] Tein I. Metabolic disease in the fetus predisposes to maternal hepatic complications of pregnancy. Pediatr Res. 2000; 47: 6–8. [PubMed]

[11] Bacq Y (1998). "Acute fatty liver of pregnancy". Semin. Perinatol. 22 (2): 134–140.doi: 10.1016/S0146-0005(98)80045-1. PMID 9638907.

[12] Sheehan HL. The pathology of acute yellow atrophy and delayed chloroform poisoning. J Obstet Gynaecol Br Emp. 1940; 47: 49–62.

[13] McNulty J. Acute fatty liver of pregnancy. In: Foley MR, Strong TH, Garite TJ, editors. Obstetric Intensive Care Manual. 2. New York: The McGraw-Hill Companies Inc; 2004. pp. 207–15.

[14] C. L. Ch'ng, M. Morgan, I. Hainsworth, and J. G. C. Kingham, “Prospective study of liver dysfunction in pregnancy in Southwest Wales,” Gut, vol. 51, no. 6, pp. 876–880, 2002. View at Publisher • View at Google Scholar • View at Scopus

[15] M. Knight, C. Nelson-Piercy, J. J. Kurinczuk, P. Spark, and P. Brocklehurst, “A prospective national study of acute fatty liver of pregnancy in the UK,” Gut, vol. 57, no. 7, 2008. pp. 951–956.

[16] Ko H, Yoshida EM (2006). "Acute fatty liver of pregnancy". Can. J. Gastroenterol. 20 (1): 25–30. PMC 2538964.PMID 16432556.

[17] Jwayyed SM, Blanda M, Kubina M. Acute fatty liver of pregnancy. J Emerg Med. 1999;17:673–7.[PubMed]

[18] Simpson KR, Luppi CJ, O’Brien-Abel N. Acute fatty liver of pregnancy. J Perinat Neonatal Nurs.1998; 11:35–46. [PubMed]

[19] Koroshi A, Babameto A (2002). "Acute renal failure during acute fatty liver of pregnancy". Nephrol. Dial. Transplant. 17 (6): 1110–1112.doi:10.1093/ndt/17.6.1110. PMID 12032205.

[20] Aggarwal R (2003). "Hepatic encephalopathy in pregnancy". Indian J Gastroenterol. 22 Suppl 2: S78–80. PMID 15025263.

[21] Moldenhauer JS, O'brien JM, Barton JR, Sibai B (2004). "Acute fatty liver of pregnancy associated with pancreatitis: a life-threatening complication". Am. J. Obstet. Gynecol. 190 (2): 502–505.[PubMed]

[22] Kennedy S, Hall PM, Seymour AE, Hague WM (1994). "Transient diabetes insipidus and acute fatty liver of pregnancy". Br J Obstet Gynaecol 101 (5): 387–91. doi:10.1111/j.1471-0528.1994.tb11909.x.PMID 8018608.

[23] Bacq Y. Liver diseases unique to pregnancy: A 2010 update. Clin Res Hepatol Gastroenterol. 2011;35:182–93. [PubMed]

[24] Ibdah JA. Acute fatty liver of pregnancy: An update on pathogenesis and clinical implications. World J Gastroenterol. 2006;12:7397–404. [PubMed]

[25] Castro MA, Fassett MJ, Reynolds TB, et al. 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.

[26] Sibai BM. Imitators of severe pre eclampsia. Semin Perinatol. Jun2009;33(3):196 205.[Medline]

[27] Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. Lancet. 2010; 375:594–605. [PubMed]

[28] Pereira SP, O'Donohue J, Wendon J, Williams R (1997). "Maternal and perinatal outcome in severe pregnancy-related liver disease". Hepatology26 (5): 1258–1262. doi:10.1002/hep.510260525. PMID 9362370.

[29] Martin JN Jr, Briery CM, Rose CH, Owens MT, Bofill JA, Files JC. Postpartum plasma exchange as adjunctive therapy for severe acute liver of pregnancy. J Clin Apher 2008;23(4):138-43[Medline]

[30] Jin F, Cao M, Bai Y, Zhang Y, Yang Y, Zhang B. Therapeutic effects of plasma exchange for the treatment of 39 patients with acute fatty liver of pregnancy. Discov Med. May 2012;13(72):369-73.[Medline]

[31] Chu YF, Meng M, Zeng J, Zhou HY, Jiang JJ, Ren HS, et al. Effectiveness of combining plasma exchange with continuous hemo diafiltration on acute fatty liver of pregnancy complicated by multiple organ dysfunction. Artif Organs. Jun 2012; 36(6):530-4. [Medline]

[32] Castro MA, Goodwin TM, Shaw KJ, Ouzounian JG, McGehee WG. Disseminated intravascular coagulation and antithrombin 111depression in acute fatty liver of pregnancy. Am J Obstet Gynaecol. Jan 1996; 174 (1Pt 1):211-6 [Medline].

[33] Reyes H, Sandoval L, Wainstein A, et al. Acute fatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. Gut 1994; 35:101.

[34] Monga M, Katz AR. Acute fatty liver in the second trimester. Obstet Gynecol. 1999;93:811–3.[PubMed]

[35] Usta IM, Barton JR, Amon EA, et al. Acute fatty liver of pregnancy: an experience in the diagnosis and management of fourteen cases. Am J Obstet Gynecol 1994; 171:1342-7.

[36] RanjanV, Smith NC,.Acute fatty liver of pregnancy. J Obstet Gynaaecol.1997; 17: 285-6. [Pub Med]

[37] Apiratpracha W, Yoshida EM, Scudamore CH, Weiss AA, Byrne MF.Chronic pancreatitis, a sequel of acute fatty liver of pregnancy. Hepatobiliary Pancreat Dis Int. Feb2008;7(1):101-4

[38] Fesenmeier MF, Coppage KH, Lambers DS, Barton JR, Sibai BM. Acute fatty liver of pregnancy in 3 tertiary care centers. Am J Obstet Gynecol. 2005; 192: 1416–9. [PubMed]