

# Acute Fatty Liver of Pregnancy Presenting as Fulminant Hepatic Failure: An Uncommon Disease

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## Abstract

Acute Fatty Liver of Pregnancy (AFLP), though rare, is an obstetric emergency which carries a high incidence of maternal and perinatal mortality, despite optimal care. It is a catastrophic disease affecting women in the third trimester of pregnancy or in the post-partum period. It is usually a diagnosis of exclusion and requires a strong index of suspicion for a timely diagnosis and prompt intervention. We report a case of 24-year-old prime at 34-week gestation, presented with malaise, nausea, vomiting, jaundice, disorientation and absent fetal movements. Intrauterine death of fetus occurred. Supportive management in an intensive care unit resulted in successful outcome. By this case report we once again wish to emphasize the value of a timely diagnosis with a high level of clinical suspicion and supportive laboratory investigations including imaging; the need for early termination of pregnancy; and adequate supportive care as the key management options for AFLP. Further, we wish to explore the current treatment options available for AFLP and discuss a few novel therapeutic strategies such as plasma exchange in treating such cases and the pros and cons associated with these treatment modalities.

**Keywords:** Acute Fatty Liver of Pregnancy, Plasma exchange, Obstetric emergency, Intrauterine death

## Introduction

In pregnancy, pathological conditions causing abnormality of liver function tests need to be differentiated from normal physiologic changes. AFLP is a disease of the third trimester that is unique to human pregnancy and was described by Sheehan in 1940 [1]. The condition was associated with high mortality rates but this has improved because of early diagnosis and prompt delivery of the fetus [2]. The approximate incidence of AFLP is 1: 7,000 to 1: 20,000 [2]. Conditions unique to pregnancy that because liver dysfunction include intrahepatic cholestasis of pregnancy, pre-eclampsia, Haemolysis Elevated Liver Enzymes Low Platelet count (HELLP) syndrome and AFLP. While intrahepatic cholestasis of pregnancy (ICP) and pre-eclampsia are frequently seen, AFLP is rare and potentially life-threatening. The pathogenesis of AFLP remains unclear but there is emerging evidence of the genetic basis of AFLP where defective mitochondrial fatty acid beta-oxidation in the fetus is implicated in some cases of AFLP [3]. The process of Beta-oxidation of fatty acids in hepatic mitochondria is a complex sequence of events requiring several essential enzymes: mitochondrial trifunctional protein and its alpha-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), are the two en-

zymes of this metabolic process, whose autosomal inherited genetic mutations are most closely associated with AFLP, especially the G1548C mutation of LCHAD [4]. We present a case where the diagnosis was delayed with subsequent poor outcome of the fetus.

## Case Report

A 24-year-old prime at 34-week's gestation was admitted to our hospital with a history of absence of fetal movements for the two days and increased somnolence for past one day. She also complained of malaise, nausea, vomiting, and yellow colored urine with no pruritus, abdominal pain and fever since last ten days. There was no history of joint pain, diarrhea or flu like symptoms. She was booked and the Antenatal Clinic (ANC) visits were unremarkable. She had no history of travel to a malaria endemic area. She had no chronic illnesses and gave no history of paracetamol, aspirin, sodium valproate or herbal medicine ingestion. Supportive treatment for acute viral hepatitis was given at a private clinic. She was detected to be hypertensive in the third trimester and was on tablet Alpha-methyl dopa 500 mg three times a day.

Physical examination revealed a well-nourished, somnolent, but

easily arousable woman. Her temperature was 37.2°C, pulse rate was 110/min, respiratory rate 18/ min, and blood pressure 100/80 mmHg. She was oriented to person, place, and time, and her focal neurological findings were noncontributory. She was icteric, with mild pallor and edema of the legs. Flapping tremor was present. Abdomen was nontender, soft and there was no hepatomegaly or splenomegaly. Some ascites was noted. Ultrasonography revealed demise of the 34-week fetus and a fatty liver.

Complete blood counts revealed a hemoglobin: 7.8g/ dl (normal 12-16 g/dl), MCV-29.5 pg (normal 27-32pg), MCH-33.5 Fl (normal 32-36fL), white blood cell count: 12,600/cumm, and platelet count: 106,000/cumm. ESR was 36 mm in 1st hour. CRP was 203 mg/dl (normal less than 5 mg/dl) Peripheral smear was negative for hemolysis and serum lactate dehydrogenase (S.LDH) levels were 238 mg/dl (normal 180- 430 mg/dl). Reticulocyte count was normal, 1.3% (normal 0.2-3%) Liver function tests showed aspartate aminotransferase: 188 U/l (normal less than 40U/L), alanine aminotransferase: 155 U/l (normal less than 31 U/L), total bilirubin: 6.3 mg/dl (normal less than 2 mg/dl), direct bilirubin: 5.7 mg/dl, alkaline phosphatase: 298 U/l (normal 30-120 U/l) and albumin: 2.6 g/dl (normal 33-52 g/dl). Biochemical tests revealed blood urea: 64 mg/dl (normal 15-48 mg/dl), serum creatinine: 1.92 mg/dl (normal 0.5-1.3 mg/dl), serum glucose: 3.7 mmol/L (normal 3.9-5.6 mmol/L), and serum ammonia: 139 µmol/L (normal 11-51 µmol/L). Serum electrolyte showed sodium 129 mmol/ (normal 135-145 mmol/L), potassium 5.4 mmol/L (normal 3.5-5.0 mmol/L). Serum uric acid was raised 7.9 mg/dl (normal 3.7-5.2 mg/dl). Coagulogram revealed a prothrombin time of 32 seconds with international normalized ratio (INR) of 3.2. Urine analysis showed mild proteinuria. Serology tests like HBsAg, Anti HCV, IgM Anti HAV, IgM Anti HEV and HIV were all negative. ANA was negative. A presumptive diagnosis of AFLP was made.

Considering the patient's increasing somnolence and absence of cervical dilatation, it was decided to perform an emergency lower segment caesarean section (LSCS) without a trial of labor. LSCS was performed three hours after admission under general anesthesia before which she received 10mg vitamin K, four units of platelet-rich plasma to correct her coagulopathy.

Intraoperatively, she received 1000ml crystalloids, another 4 units of fresh frozen plasma (FFP), and two units of packed red cells. Her estimated blood loss was 800 ml. As her urinary output (u/o) was 40 ml, she was given 40 mg furosemide, after which her u/o increased to 100 ml. At the end of the operation, she was extubated after reversal when she followed commands. She was shifted to the ICU in view of the altered liver function, renal failure, and disseminated intravascular coagulation (DIC), and was put on broad-spectrum antibiotics to combat the concomitant overwhelming sepsis as evidenced by a rising CRP. She had several episodes of hypoglycaemia (1.9–2.7 mmol/l) which were corrected with 25% dextrose. Ursodeoxycholic acid was also initiated during the course to treat the worsening cholestasis. N-acetylcysteine (NAC) and L-ornithine L-aspartate were started as a hepatoprotective measure. Her blood culture was positive for *Acinetobacter* for which she received antibiotics as per culture and sensitivity report. Her bilirubin and liver enzymes started to decrease and platelets increased from day 5. She made a gradual recovery. Her liver and kidney function returned to normal and she was discharged on

day 11. During discharge complete blood counts revealed a hemoglobin: 12.0g/ dl (normal 12-16 g/dl), MCV-29.0 pg (normal 27-32pg), MCH-33.7 fL(normal 32-36fL), white blood cell count: 7780/cumm, and platelet count: 234,000/cumm. ESR was 36 mm in 1st hour. CRP was 18.1 mg/dl (normal less than 5 mg/dl). Liver function tests showed aspartate aminotransferase: 42U/l(normal less than 40U/L), alanine aminotransferase: 53 U/l(normal less than 31 U/L), total bilirubin: 1.8 mg/dl(normal less than 2 mg/dl), alkaline phosphatase: 298 U/l(normal 30-120 U/l) and albumin: 3.9 g/dl(normal 3.3-5.2 g/dl). Biochemical tests revealed blood urea: 28 mg/dl(normal 15-48 mg/dl), serum creatinine: 0.6 mg/dl(normal 0.5-1.3 mg/dl), serum glucose: 7.1 mmol/L(normal 3.9-5.6 mmol/L), and serum ammonia: 31 µmol/L(normal 11-51 µmol/L). Serum electrolyte showed sodium 143 mmol/ (normal 135-145 mmol/L), potassium 3.7 mmol/L(normal 3.5-5.0 mmol/L). Serum uric acid was 3.6 mg/dl(normal 3.7-5.2 mg/dl).Coagulogram revealed a prothrombin time of 14 seconds with international normalized ratio (INR) of 1.1.

## Discussion

This case highlights the importance of a high index of suspicion of the condition in women presenting with jaundice in pregnancy. Jaundice during pregnancy has many causes like cholestasis, cholelithiasis, viral hepatitis, pre-eclampsia with or without HELLP syndrome, and AFLP. Intrahepatic cholestasis of pregnancy may present during the third trimester but itching is the characteristic symptom and serum bilirubin concentration is rarely higher than 6mg/ dl. Ingestion of drugs and herbal remedies that could lead to hypoglycaemia was ruled out from the history. Cholelithiasis may occur at any time during pregnancy and is accompanied by pain in the right upper quadrant, and fever, and USG is usually diagnostic. Acute viral hepatitis in pregnancy presents as a systemic illness with fever, nausea, vomiting, fatigue, and jaundice, however, aminotransferase concentrations are markedly elevated (>500U/liter). Sepsis was unlikely as the patient had no tachycardia or hypotension and remained normothermic. All these causes were ruled out in our case on the basis of presentation, symptoms, and investigations.

Pre-eclampsia with liver involvement, HELLP syndrome, and AFLP manifest specific patterns, particularly in relationship with the timing of gestational age, however, they share many similarities in clinical features and laboratory abnormalities, and differentiation between them may be difficult. HELLP syndrome (1 in 5000) is seen more frequently than AFLP (1 in 13000) [5, 8]. In our case, the patient was at risk for both conditions as she was young and nulliparous. The blood pressure was however normal and urinalysis was negative for proteinuria. The manifestations of pre-eclampsia are usually observed in the second half of pregnancy, whereas the symptoms of HELLP syndrome and AFLP frequently appear in the third trimester [5-7]. The incidence of HELLP syndrome is much higher (1: 5,000) than that of AFLP (1: 13,000) [8]. Severe coagulopathy, jaundice, hepatic encephalopathy, ascitis, hypoglycemia, and a mild to moderate elevation of transaminase levels are the key features of AFLP [5-7, 9-11].

Histology findings differ in these two conditions, with prominent periportal hemorrhages and fibrin deposition being characteristic of HELLP syndrome, while micro vesicular fatty infiltration fa-

vours AFLP [3]. In our case, the clinical features of severe liver dysfunction appeared at the gestational age of 34 weeks. The symptoms initially mimicked those of acute viral hepatitis but clinical and laboratory evidence of severe coagulopathy, modest elevation of serum transaminase and bilirubin levels, hypoglycemia, an elevated ammonia value, and a low albumin level favored the diagnosis of AFLP over HELLP syndrome.

“Acute yellow atrophy of the liver,” a rare and fatal complication of pregnancy, was first described by Stander and Cadden in 1934 [11]. The liver biopsy is diagnostic but is not always feasible especially in patients with severe coagulopathy and it seldom influences acute management [5]. Ultrasound and computed tomography have been used but the sensitivity and specificity of these imaging studies are insufficient to make a definitive diagnosis, and false negative results are common [13]. In our case, presence of coagulopathy did not allow us to perform liver biopsy.

The pathogenesis, still poorly understood, is postulated to be an abnormality in the metabolism of long chain fatty acids in the fetus, where a deficiency in the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), will lead to an excess of fetal long chain fatty acids entering the maternal circulation, overwhelming the capacity of the maternal liver to handle long chain fatty acids, resulting in their deposition in the maternal liver and ultimately culminating in hepatic failure [14].

AFLP, though rare, continues to be a life-threatening condition to date, and is usually seen to occur around the 36th week of gestation. Proposed risk factors in developing AFLP, include primiparity, pregnancy with a male fetus, multiple gestations, advanced maternal age, and low body mass index of the mother [15, 16]. The condition is neither infectious nor inherited [17]. Also, the recurrence of the disease in a subsequent pregnancy is said to be very rare [5].

The clinical presentation of AFLP is usually with non specific symptoms, but the possibility of AFLP should be considered in all pregnant women presenting with symptoms such as anorexia, nausea, vomiting, headache, fatigue and abdominal pain, towards the latter part of the 2nd trimester or in the 3rd trimester, as cases have been reported in as early as 22 weeks of gestation [18].

The usual laboratory investigation abnormalities seen in AFLP, include an elevated international normalized ratio (INR), a modest elevation in serum transaminases, an elevated bilirubin level, and thrombocytopenia with or without disseminated intravascular coagulation (DIC). Hyperuricemia, along with acute kidney injury (AKI) has also been reported in severe cases [19]. Although the diagnosis can be confirmed by a liver biopsy, this is generally not encouraged in all cases, as the clinical evidence remains adequate in many instances, and also due to the accompanying coagulopathy with risk of intra-abdominal bleeding [3]. Ultra sound scanning remains the imaging modality of choice being both safe and convenient.

The disease, if not intervened early, may be complicated with upper gastro-intestinal bleeding due to altered coagulation profile, AKI, infection, pancreatitis or hypoglycemia [3]. As a result of early diagnosis and intervention, the worldwide maternal mortality

recorded as 100% in the past, have now reached rates <10%. But on the contrary, the fetal mortality remains high around 20% [20]. A recent multicenter retrospective study conducted in China, has reported an association of a male fetus, post-partum diagnosis of AFLP (as in the case of our patient), intrauterine fetal death, DIC, altered Prothrombin time (PT) and activated partial thromboplastin time (APTT) as potential factors influencing maternal outcomes [21].

The diagnosis of AFLP remains largely clinical, and the clinical diagnosis of AFLP is according to the “Swansea criteria”, which is a collection of symptoms, signs, biochemical and imaging findings, where the presence of six or more of its components, in the absence of another cause, helps in establishing a clinical diagnosis of AFLP (Table 1) [22].

**Table 1: Swansea criteria for AFLP.**

Clinical	Vomiting Abdominal pain Polydipsia/polyuria Encephalopathy
Biochemical- Hepatic	Bilirubin >14 µmol/l AST/ALT >42 IU/l Ammonia >47 µmol/l
Renal	Urate >340 µmol/l Creatinine >150 µmol/l
Endocrine	Glucose < 4 mmol/l
Hematological	Leucocytosis >11 x10 <sup>9</sup> /l Coagulopathy-PT >14secs or APTT >34 secs (often with Plt count >100 x10 <sup>12</sup> /l)
Radiological	Abdominal USS bright Liver echo texture /ascites
Histological-Liver Biopsy	Micro vesicular steatosis

Our patient described in the case report fulfilled almost all the criteria to be diagnosed with AFLP.

The accepted and currently recommended mode of treatment of this catastrophic disease entity remains the prompt delivery of the fetus, following the diagnosis of AFLP as early diagnosis and intervention has been shown to result in better maternal as well as fetal outcomes [16, 23-25]. Termination of the pregnancy may be in the form of induced labor, but generally caesarian section is the better option, as the mortality rate of mothers who undergo Lower segment caesarian section (LSCS), is shown to be lower than for those who deliver vaginally [24]. There is usually improvement of symptoms 1 to 2 days after delivery Intensive supportive treatment and continuous close monitoring in the immediate post-partum period remains equally important for a successful outcome, and patients who remain critically ill should ideally be managed at tertiary care hospitals with a multidisciplinary team involving intensivists, obstetrician, hepatologist, neonatologist, and if indicated the organ transplant unit [26]. Mortality is attributed to complications of the disease in the form of Acute respiratory distress syndrome

(ARDS), hepatic failure, renal insufficiency, sepsis, DIC, encephalopathy, haemorrhagic shock either due to intra-abdominal bleeding or upper gastrointestinal haemorrhage, finally culminating in multi organ dysfunction. In the setting of fulminant hepatic failure, liver transplantation remains to be the last resort.

N-acetylcysteine(NAC), a precursor of Glutathione, has also shown some success in patients with Non-Acetaminophen-induced Acute liver failure(NAI-ALF), attributed to its anti-inflammatory, anti-oxidant, inotropic and vasodilatory effects which improve the microcirculation and oxygenation of vital organs, providing a survival benefit, as reported by Mumtaz K. et al following a prospective study of 47 patients with NAI-ALF [27].

Novel treatment modalities such as plasmapheresis and the use of activated protein C have been practiced in specialized centers, with variable outcomes. According to a report by R.S.M Mohommad et al, on 3 cases of AFLP complicated with multiorgan failure, treated with repeated sessions of plasmapheresis, the results look promising, but this modality of treatment still needs to be explored in detail [22-24]. Plasmapheresis appears to be a promising treatment option in managing patients with AFLP, as it replaces the function of the liver in part, by removal of ammonia, endotoxins, bilirubin, and inflammatory cytokines from the maternal circulation. Also, the timing of initiation of plasma exchange seems to play an important role in altering the course of the disease as shown by a study of 39 patients with acute fatty liver of pregnancy, as reported by Jin F, et al [28].

Before 1980, both the maternal and fetal mortality rates were about 85% and major causes were cerebral edema, gastrointestinal hemorrhage, renal failure, coagulopathy, and sepsis [29]. Mortality has been reduced to less than 10% at present because of better recognition and appropriate management. Our patient presented rather late to us after the development of hepatic encephalopathy, acute renal failure, DIC, and fetal demise.

## Conclusion

AFLP is a rare, life-threatening complication of third trimester with variable presentation which requires a high index of suspicion for early diagnosis. Delay in the diagnosis is associated with morbid complications with high mortality and this case highlights the importance of a high index of suspicion of the condition in women presenting with jaundice in pregnancy. While the natural history of the disease is improvement within 24–48 hours of delivery, it is recommended that patients who are critically ill at the time of presentation, who develop complications, or who continue to deteriorate despite emergency delivery, should be managed in the intensive care unit.

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