

# Acute Fatty Liver of Pregnancy - A Review:

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## Abstract

Acute fatty liver of pregnancy (AFLP) is a serious complication and usually occurs in second half of pregnancy. It is rare but potentially fatal complication for both mother and baby as often the diagnosis is delayed. Etiology is still unclear but known to be associated with defective fatty acid oxidation in fetus. AFLP is thought to be a rare variant of pre-eclampsia (associated in 50 to 100% of cases) and can be associated with mild to moderate disease<sup>1</sup>. It can cause multiple organ failure in case of delayed diagnosis. Early diagnosis and prompt delivery is the mainstay of treatment.

## INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a serious complication and usually occurs in second half of pregnancy. It is rare but potentially fatal complication for both mother and baby as often the diagnosis is delayed. Etiology is still unclear but known to be associated with defective fatty acid oxidation in fetus. AFLP is thought to be a rare variant of pre-eclampsia (associated in 50 to 100% of cases) and can be associated with mild to moderate disease<sup>1</sup>. It can cause multiple organ failure in case of delayed diagnosis. Early diagnosis and prompt delivery is the mainstay of treatment.

## MATERIAL AND METHOD

This review is based on a case presented as an emergency with vague symptoms at Conquest Hospital (East Sussex Hospital NHS trust), UK.

A 31 year old first pregnancy, who was known to have essential hypertension for the past 10 years controlled by Atenolol 25 mg daily (stopped after she was found to be pregnant). Her booking blood pressure was 130/78 mmHg and remained within normal range during the pregnancy. First trimester screening and anomaly scan were normal. She had 2 episodes of glucosuria at 24 and 29 weeks of gestation, therefore had a GTT (glucose tolerance test), which was normal.

She was referred by her community midwife to the hospital at 34 weeks and 5 days of gestation, feeling unwell, vomiting and shivering for 4 day's duration with reduced fetal movements and irregular tightening. On admission she

was tachycardic (PR 120/min) with blood pressure of 136/103 mmHg and urine analysis showed protein (+) and blood (+++). Blood results revealed deranged liver and renal function tests with hypofibrinogenaemia and normal hemoglobin and platelets (Hb – 15.8 gm/dl, platelets,  $171 \times 10^9$ , fibrinogen – 0.8 g/L, ALT – 713 IU/L, Alkaline Phosphate – 577 IU/L, bilirubin–101  $\mu$ mol/L, Na -137 mEq/L, K -4.6 mEq/L, Urea–6.5, Creatinine–212  $\mu$ mol/L, urates–551 mg/dl and bile acids–97 mol/L). The peripheral blood smear and serum lactate levels were normal. She was found to be hypoglycemic (2.1 mmol).

The fetal heart rate was not picked by electronic fetal monitor and an Ultrasound scan was performed which confirmed an intra uterine death. Fetal biometry was within normal limits and there was no Spalding sign or evidence of Hydrops suggesting an acute event. The differential diagnosis of Severe Pre-eclampsia, accidental hemorrhage, HELLP, Acute fatty Liver of Pregnancy (AFLP) and Cholestasis were considered. After five hours she went into spontaneous labour and delivered a stillborn male weighing 2935gms without any complication. She was transfused with 2 units of FFP (fresh frozen plasma) and 2 units of cryoprecipitate. One hour post delivery she was found to be jaundiced and very drowsy so she was transferred to intensive therapy unit (ITU). Next day in ITU she clinically deteriorated showing high temperature, disorientation, flapping tremors, low oxygen saturations, metabolic acidosis and tender right hypochondrium with palpable liver, with normal blood pressure and some improvement in biochemical parameters. She continued to be hypoglycemic and was treated with 10% dextrose. The abdominal

Ultrasound scan showed normal liver with small ascetic fluid around the liver. Her clinical and biochemical condition improved significantly after 4 days of ITU stay and was later transferred to postnatal ward.

On 8<sup>th</sup> post natal day she was clinically well with most biochemical parameters within normal limits apart from a slightly elevated bilirubin 39 gm/dl and ALT-72 IU/ml, which became normal within few weeks.

### INCIDENCE AND CHARACTERISTICS

AFLP is commoner in primigravida and there is an association with obesity, multiple pregnancies and male fetus (ratio 3:1). It is commoner in women aged 16-39 (mean age 29). The incidence is 1 in 7,000 to 1 in 15,000 pregnancies <sup>2</sup>.

The onset of AFLP complicates the second half of pregnancy (between 30<sup>th</sup> and 38 weeks of gestation) usually in the third trimester, although an early occurrence at 26 weeks has been reported <sup>3</sup>. The high maternal and fetal mortality rate may now be lower than originally believed (85%), likely due to greater awareness of the condition, earlier diagnosis, and appropriate management. Recent studies suggest figures around 9 -18 % for maternal mortality and 9-25% for fetal mortality <sup>4-6</sup> and indeed the recent UKOSS study which reported 61 cases showed no maternal mortality and 13% fetal mortality <sup>7,8</sup>.

### CLINICAL FEATURES

Diagnosis is usually delayed as the presenting symptoms are vague and share with other common conditions of pregnancy such as HELLP syndrome, obstetric cholestasis and other liver diseases. The condition almost always presents before delivery, although it is not always diagnosed until after delivery. Each woman may experience symptoms differently.

The most common symptoms are:

- Nausea and vomiting -75%
- Abdominal pain, especially in the right upper quadrant – 50%
- Malaise, headache, tiredness and confusion.
- Anorexia, jaundice (usually appears within 2 weeks of the onset of the symptoms) and possibly associated ascites.
- Signs of pre-eclampsia at presentation or at some

time during the course of illness, but hypertension and proteinuria are usually mild – 50%

- Renal impairment.
- Fulminant liver failure with hepatic encephalopathy.
- Polyuria and features of diabetes insipidus (DI).

Distinctive features of AFLP from HELLP syndrome are associated mild to moderate pre-eclampsia, profound hypoglycemia and marked hyperuricaemia.

### PATHOGENESIS

Exact pathogenesis is unknown, but the disease has been found to be linked to an abnormality in mitochondrial fatty acid oxidation in fetus. These fetuses have a genetic deficiency of mitochondrial long chain fatty acid (3-hydroxyacyl coenzyme A dehydrogenase deficiency) (LCHAD) <sup>9,10</sup>. Defective mitochondrial fatty oxidation is a recessive inborn error of metabolism and fetuses with this disorder are associated with intra-uterine growth restriction, prematurity, AFLP and HELLP syndrome if the mother is heterozygous. Newborns with defective mitochondrial fatty acid oxidation may present with hypoglycaemia, metabolic acidosis, hepatic failure and cardiomyopathy and associated with increased perinatal morbidity and mortality <sup>8</sup>.

### DIAGNOSIS

Diagnosis remains challenging since there is no specific diagnostic test for the condition and usually made by clinical and laboratory findings. Early diagnosis is important as sometimes difficult as the presenting features of AFLP are shared by other common conditions in pregnancy. Main differential diagnosis is HELLP syndrome (Hemolysis, Elevated liver enzymes and Low platelets) but other conditions such as cholestasis of pregnancy and viral hepatitis should also be considered.

The comparative features of the various differential diagnoses are shown in Table 1. Although liver biopsy would be the optimal way for confirmation of diagnosis, it is rarely used in the emergency setting because of its invasiveness, particularly in the presence of a likely clotting disorder <sup>11</sup>. Other diagnostic features therefore need to be relied upon.

These include:

1. Laboratory features may show moderate increase

in serum transaminases (Usually <1000 IU/L), conjugated hyperbilirubinaemia, increased alkaline phosphatase and severe hypoglycemia. Leucocytosis and thrombocytopenia are also common findings. Coagulopathy is a common complication of AFLP, with prolongation of Prothrombin time (PT), partial thromboplastin time (APTT) and decreased antithrombin III and fibrinogen levels.

2. Associated pre-eclampsia (hypertension, proteinuria) may be mild and there may be mild to moderate increase in serum transaminases (in HELLP, more marked features of pre-eclampsia and markedly raised in transaminases in viral hepatitis) 12.

The table below shows the differential diagnosis.

**Figure 1**

The differential diagnosis of AFLP

	HUS/TTP	Severe PET	HELLP	AFLP
Hypertension	+/-	+++	++	+/-
Proteinuria	+/-	+++	++	+/-
Thrombocytopenia	+++	++	+++	+/-
LDH	>>>	>	>>	>>
Bilirubin	>>	+/-	>	>>
AST	+/-	>	>>	>>
Fibrinogen	=	+/-	=	>
Antithrombin III	<	=	<	<
Creatinine	>	>	>	>>
Uric acid	>>>	>	>	----
Glucose	----	=	=	<

HUS- Haemolytic Uraemic syndrome

TTP- Thrombotic thrombocytopenic purpura

The diagnosis of HELLP also includes microangiopathic hemolytic anemia with characteristic schistocytes on blood smear. There can be a multi-organ failure with abnormal renal function tests. Ultrasound, computed tomography and

magnetic resonance imaging can be considered as a diagnostic test for AFLP but they are of limited value and findings may be normal. Histologically AFLP is characterized by micro vesicular hepatic steatosis which is different from HELLP syndrome which reveals periportal hemorrhage and fatty infiltration<sup>13</sup>.

**COMPLICATIONS**

The clinical condition may deteriorate rapidly and may lead to multi-organ failure if prompt delivery, early and appropriate supportive treatment is not instituted.

Common complications are <sup>14</sup>.

- Renal failure (60%),
- Hypoglycemia (53%),
- Infection (45%)
- Gastrointestinal hemorrhage (33%),
- Coagulopathy (30%),
- Severe postpartum hemorrhage
- Fulminate hepatic failure
- Stillbirth

The upper gastrointestinal hemorrhage may be caused by Mallory-Weiss syndrome, acute gastric or duodenal lesions (e.g., gastritis, duodenitis, peptic ulcers) or it can be manifestation of coagulopathy.

**MANAGEMENT**

The optimal management of the AFLP is prompt delivery and supportive care of the mother. Delay in delivery may result in adverse maternal outcome. Multidisciplinary team input is extremely important in achieving the best maternal and neonatal outcome.

Close continuous monitoring after delivery is vital as it can complicate severe postpartum hemorrhage and multi-organ failure even after delivery. Clinical condition may deteriorate rapidly. Severely ill patients require care in ITU and multi-organ failure may need assisted ventilation and dialysis.

Aggressive correction of coagulation abnormalities are the mainstay of treatment. Disseminated intra-vascular coagulation may be a severe and potential fatal complication

of AFLP. These patients may have profoundly low anti-thrombin III levels, hypofibrinogenaemia and prolonged prothrombin time and APTT levels.

Hypoglycemia should be treated aggressively before and after delivery. Large amounts of 50% intravenous glucose may be needed to correct hypoglycemia. In case of postpartum hemorrhage, besides massive transfusion ligation of internal iliac artery and even hysterectomy may be required to control the bleeding. Embolisation procedures of uterine and internal iliac arteries appear to be other possible treatment modalities<sup>15, 16</sup>.

Prompt reversal of clinical and laboratory findings usually follows delivery but resolution of coagulation process may take several days after delivery. If the woman survive the initial episode, she can get a complete recovery without long term liver damage.

### RECURRENCE

There is a limited data for recurrence but in women with history of AFLP it is advised to test the genetic abnormality of fatty acid oxidation (mutation in HADHA gene, coding alpha subunit of long chain 3-hydroxyacyl coenzyme A dehydrogenase) as recurrence is likely in those women (15-25%). But, even in women who failed to identify the genetic mutation, recurrence of AFLP can occur. Therefore, it is prudent to carefully observe the next pregnancy of woman who has a previous history of acute fatty liver of pregnancy. However recurrence was not seen in the study by United Kingdom Obstetric Surveillance System (UKOSS).

### CONCLUSION

With early recognition, appropriate referral, prompt delivery and aggressive management, morbidity and mortality of AFLP can be greatly reduced. As disease can cause rapid deterioration of both baby and mother, early and prompt delivery can improve the neonatal outcome. AFLP is an obstetric emergency and management is always based on a clinical rather than histological diagnosis.

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