

A Case Series of Fatal Fulminant Hepatic Failure in Postpartum Females Secondary to Acute Fatty Liver of Pregnancy

Anant Parasher¹, Vandana Mohan²

ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a dreaded complication seen mostly in the third trimester of pregnancy. It carries significant perinatal and maternal mortality and requires early diagnosis and intervention to prevent maternal and fetal death. If untreated, AFLP can lead to complications, such as, disseminated intravascular coagulation (DIC), renal failure, clotting disorders and coagulopathy, hypoglycemia, fulminant hepatic failure, and eventually multiorgan dysfunction. Even though induction of labor with delivery remains the only real cure for this disease, some other therapies for complicated cases include plasmapheresis with renal replacement, and the use of molecular absorbent recirculating system (MARS). Orthotopic liver transplantation has proved to be effective in cases that progress to multiorgan failure despite aggressive therapy. Here, we present two cases who presented to the hospital with near term pregnancies and features of AFLP. Both the patients rapidly worsened postpartum due to persistent bouts of hypoglycemia and rapidly developing fulminant hepatic failure. Despite all our efforts, both the patients expired a few days after admission.

Keywords: Acute fatty liver of pregnancy, Hypoglycemia, Liver transplant, Molecular absorbent recirculating system.

Journal of Postgraduate Medicine, Education and Research (2020); 10.5005/jp-journals-10028-1434

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a dreaded complication seen mostly in the third trimester of pregnancy.¹ It carries significant perinatal and maternal mortality and requires early diagnosis and intervention to prevent maternal and fetal death. Sheehan first described this disease as an "Acute yellow atrophy of the liver" in 1940, and it has been mentioned in detail in many case reports thereafter.²

Acute fatty liver of pregnancy is usually seen to occur around the 36th week of gestation or immediately postpartum. Risk factors include primiparity, pregnancy with a male fetus, multiple gestations, advanced maternal age, and low body mass index (BMI) of the mother. Recurrence of the disease in a subsequent pregnancy is very uncommon.³

CASE DESCRIPTIONS

Case 1

A 23-year-old primiparous woman with a gestation period of 35 weeks and 6 days presented to the hospital in preterm labor. There was a history of being generally unwell for 4 days before presentation with nausea, vomiting, and yellowish discoloration of the eyes for the same duration with no pruritus. There was no history of fever or diarrhea with an unremarkable antenatal history. She had no chronic illnesses and gave no history of ingestion of paracetamol, sodium valproate, or any herbal medication. Clinical examination revealed a moderately jaundiced patient who was fully conscious at the time of initial examination. The blood pressure, pulse, and temperature were 108/72 mm Hg, 106/minute, and 37.4°C, respectively. Respiratory and cardiovascular examinations were normal. The abdomen was soft and there was no hepatomegaly or splenomegaly. The height of the fundus was at 35 weeks, with a normal and healthy fetal heart rate.

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How to cite this article: Parasher A, Mohan V. A Case Series of Fatal Fulminant Hepatic Failure in Postpartum Females Secondary to Acute Fatty Liver of Pregnancy. *J Postgrad Med Edu Res* 2020;XX(X):1–5.

Source of support: Nil

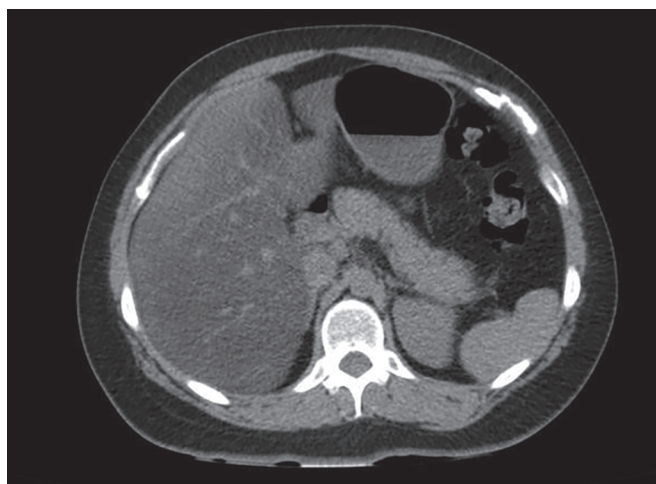
Conflict of interest: None

She soon progressed to a spontaneous vaginal delivery of a healthy newborn girl with little to no postpartum hemorrhage. The vital signs remained normal with blood pressure in the range of 102–106/66–72 mm Hg and a saturation of 96% on room air. The blood and renal tests were initially normal, and so were the total protein and serum albumin. Total bilirubin was raised with a higher direct bilirubin fraction and mildly elevated alkaline phosphatase levels. An abdominal ultrasound (USG W/A) was done which was suggestive of increased hepatic echogenicity. The viral markers (anti-HAV, anti-HEV, HBsAg, and anti-HCV) and the rapid diagnostic test (RDT) for malaria were both negative.

After a couple of days, the clinical picture started to deteriorate with a rising white blood cell count, anemia, dyselectrolytemia, and rising blood urea and serum potassium levels. The platelet count was mildly decreased with elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). There were several and recurrent episodes of hypoglycemia which were corrected with a loading bolus of 50% dextrose followed by 10% dextrose infusions 8 hourly. She was also transfused 3 units of fresh

Table 1: (Case 1) Investigations over the course of hospital stay

	Day 1 (on admission)	Day 2	Day 3
Hb (g/dL)	11.2	8.4	5.1
TLC (per mm ³)	10,600	14,900	20,800
Platelet (per mm ³)	118,000	98,000	62,000
Blood urea (mg/dL)	36	54	78
Serum creatinine (mg/dL)	1.1	2.7	4.6
Na ⁺ /K ⁺ (mEq/L)	138/4.2	132/4.3	126/5.4
Total/direct bilirubin (mg/dL)	7.1/3.8	10.9/6.6	14.6/10.4
SGOT/SGPT (U/L)	67/82	122/117	436/312
ALP (IU/L)	146	189	217
PT/INR	12/1.2	14.3/1.5	17.5/2.2
RBS (mg/dL)	74	59	42
USG W/A	Fatty liver with increased hepatic echogenicity		

**Fig. 1:** Ultrasound whole abdomen showing fatty liver changes

frozen plasma and 2 units of red cell concentrate in view of anemia and the suspicion of coagulopathy. A provisional diagnosis of AFLP was made, and treatment was upgraded to broad-spectrum antibiotics and additional supportive care.

On the fourth day post-delivery, the patient became confused with a deepening yellowish discoloration of the skin and sclera. She started having vomiting with multiple episodes of hematemesis. Thereafter, she had recurrent episodes of seizures with continuously decreasing SpO₂ levels and required intensive care unit (ICU) admission and endotracheal intubation for the same. Despite all efforts, the patient collapsed and expired later that same night.

The various investigations done throughout the course of hospital stay have been shown below in Table 1. The ultrasound whole abdomen has been shown in Figure 1.

Case 2

A 25-year-old pregnant woman presented in a drowsy state to the emergency department with a history of vomiting, right upper abdominal pain and distension for 5 days, and yellowish discoloration of skin and urine for 2 days before presentation. There was no history of fever or altered sensorium, bleeding manifestations, hypertension, diabetes, or drug/alcohol abuse.

The patient was Gravida 2 Parity 1 Live 1 with a period of gestation (POG) of 37 weeks and 2 days.

On examination, the patient was conscious but semi-oriented and drowsy. The patient had a low BMI of 16.4 kg/m², with a blood pressure of 102/74 mm Hg and a pulse rate of 98 beats/minute. There was moderate pallor with pedal edema but no cyanosis, clubbing, or lymphadenopathy. Icterus was present in the sclera. Abdominal examination revealed tenderness in the right hypochondrium and a palpable liver just below the right subcostal margin. Fundal height corresponded to POG with the fetus in cephalic presentation and reassuring fetal heart rate. On central nervous system (CNS) examination, the patient had a Glasgow Coma score of 11/15. Pupils were mid-dilated and reacting normally. Reflexes were normal and the bilateral plantar response was indeterminate. There was slight rigidity noted in both the upper and lower limbs. Power was adequate in both the upper and lower limbs, and sensory examination was grossly normal. There were no significant findings in the respiratory and cardiac examinations.

Emergency ultrasound of the whole abdomen (USG W/A) revealed a mildly enlarged liver with fatty infiltration, along with moderate ascites. The hepatobiliary tree was normal with no signs of obstruction or dilatation of the common bile duct. Tests for HIV, HBV, and HCV done by enzyme linked immunosorbent assay (ELISA) were negative and IgM antibodies to HAV and HEV were not found. A urine toxicology screen obtained was negative. Three hours later, she had a normal vaginal delivery of a healthy male newborn, with excessive blood loss. Another two units of platelets and one unit of red cell concentrate were transfused.

Over the next couple of days, the patient's condition started to deteriorate with deepening of jaundice, persistent nausea and vomiting, and persistent bouts of hypoglycemia despite dextrose supplementation. Although the blood pressure was maintained in the range of 96–100/70–74 mm Hg on intravenous fluids, the deteriorating hepatic function tests and increasing serum ammonia and creatinine levels signified worsening of hepatorenal function. Even on the continued antibiotic cover and supportive treatment, the patient maintained the same status with no signs of improvement. She gradually became altered with worsening sensorium and irrelevant talk, for which an emergency noncontrast computed tomography (NCCT) brain was done which was suggestive of non-specific changes of encephalopathy. Soon, vasopressor support

was required to maintain optimum blood pressure, and continuous dextrose infusions were maintained to counteract the persistent hypoglycemia. The patient's condition was worsened by decreasing urine output secondary to acute kidney injury, which was suspected due to the non-resolving septicemia.

A diagnosis of fulminant hepatic failure with hepatic encephalopathy due to AFLP was strongly suspected in view of blood work and ultrasound findings, and the antibiotic cover was upgraded to a combination of intravenous piperacillin–tazobactam (4.5 g stat f/b 2.25 g 8 hourly), teicoplanin (400 mg stat f/b 200 mg every alternate day) and metronidazole (500 mg 8 hourly). Subsequently, in view of the continuously falling SpO₂ levels even on high flow oxygen, the patient was intubated and shifted to the ICU. A NCCT whole abdomen was done, which was suggestive of an enlarged liver with fatty infiltration.

On the fifth day of admission, the patients were planned for hemodialysis in view of the decreasing urine output and rising serum potassium levels. Multiple petechial hemorrhages were seen over the abdomen, arms, and thighs which led to the suspicion of disseminated intravascular coagulation (DIC) and was treated by transfusion of platelets and fresh frozen plasma. The patient had her first episode of hematemesis a few hours after her dialysis, which was followed the next day by generalized tonic–clonic seizures. Despite supportive care and anti-epileptic medication, SpO₂ levels collapsed to 78%, with a blood glucose level of 46 mg/dL. The patient went into cardiorespiratory arrest soon after, and acute respiratory distress syndrome (ARDS) was suspected. Cardiopulmonary resuscitation (CPCR) was continued but despite intense critical care support and mechanical ventilation, the patient expired later in the day.

The various investigations done throughout the course of hospital stay have been shown below in Table 2. The imaging

studies (ultrasound whole abdomen, NCCT abdomen, and NCCT head) have been shown in Figures 2 to 4, respectively.

DISCUSSION

Acute fatty liver of pregnancy is a dreaded complication that mostly manifests in the third trimester of pregnancy or sometimes in the early postpartum period. It is a condition unique to a pregnancy and is characterized by microvesicular steatosis in the liver due to fatty acid infiltration. This infiltration of fatty acids causes acute liver insufficiency, which leads to most of the symptoms that present in this condition. Acute fatty liver of pregnancy can result in high fetomaternal morbidity and mortality if not diagnosed and treated

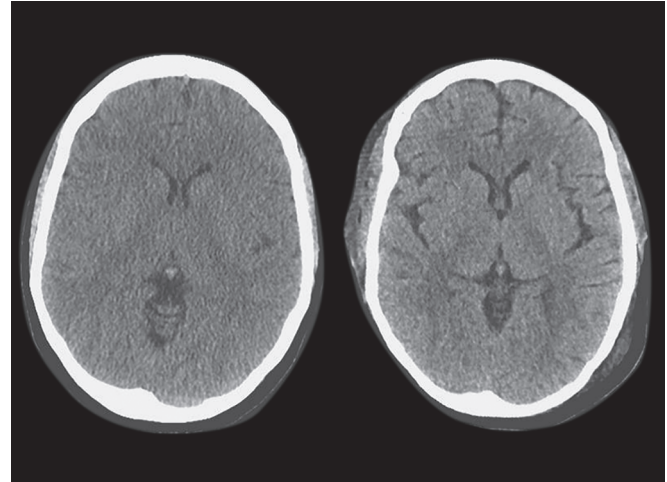


Fig. 2: (USG fatty liver)—USG W/A showing increased hepatic echogenicity

Table 2: (Case 2) Investigations and blood parameters throughout the course of treatment

	Day 1 (on admission)	Day 2	Day 3	Day 4	Day 5
Hb (g/dL)	8.6	9.4	9.1	7.6	5.5
TLC (per mm ³)	12,600	16,700	19,600	23,000	21,700
Platelet (per mm ³)	98,000	86,000	65,000	54,000	44,000
Blood urea (mg/dL)	56	68	92	112	154
Serum creatinine (mg/dL)	1.4	2.3	5.6	8.6	11.2
Na ⁺ /K ⁺ (mEq/L)	132/4.4	130/4.5	131/4.8	128/5.2	131/5.8
Total/direct bilirubin (mg/dL)	5.1/2.8	8.9/5.6	14.6/11.2	18.3/12.6	21.3/15.6
SGOT/SGPT (U/L)	674/408	868/502	1,236/667	1,902/1,190	2,320/1,670
ALP (IU/L)	185	167	188	210	198
PT/INR	16/2.1	17/2.1	18.2/2.3	19.1/2.5	19.2/2.8
RBS (mg/dL)	68	56, 68	54	62	46
Ascitic fluid protein/sugar	1.8/42				
Ascitic fluid cytology (TLC/DLC)	550/110				
S. uric acid (mg/dL)		8.6			
S. ammonia (µg/dL)		52		84	
USG W/A	Fatty liver with moderate ascites			Fatty liver with massive ascites, no e/o insulinoma	
NCCT W/A				Hepatomegaly with fatty infiltration, massive ascites	
NCCT head				Non-specific changes of encephalopathy	

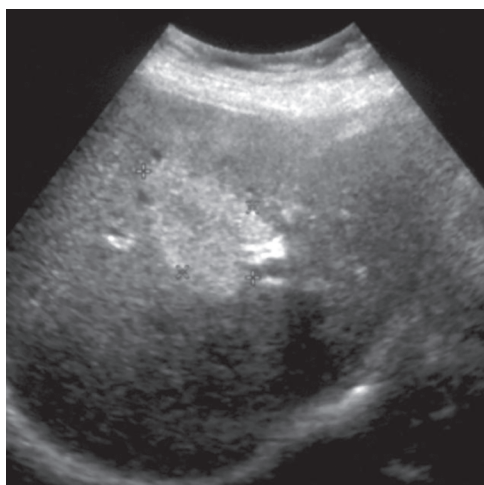


Fig. 3: (AFLP NCCT)—NCCT W/A with findings of hepatomegaly and fatty infiltration

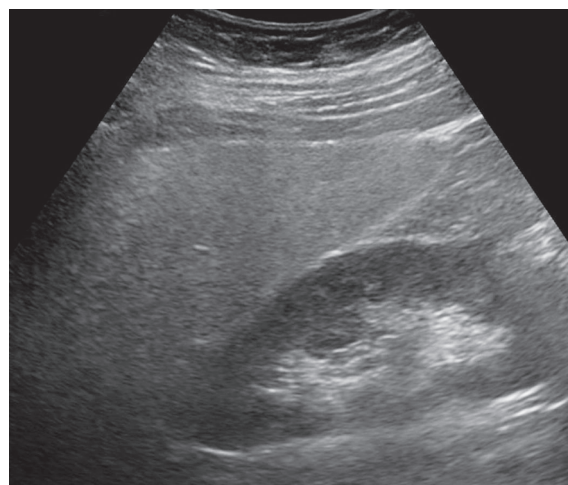


Fig. 4: (NCCT head hepatic encephalopathy)—NCCT head showing changes of encephalopathy

early. While the majority of cases resolve after delivery, rarely some patients may progress to fulminant hepatic failure with the need for liver transplantation.⁴

Pathophysiology

The pathogenesis is proposed to be an abnormality in the metabolism of long-chain fatty acids in the fetus due to a deficiency in the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). This defect leads to an excess of fetal long-chain fatty acids entering the maternal circulation, overwhelming the capacity of the maternal liver to adequately metabolize these fatty acids. This subsequently leads to their deposition in the maternal liver, which substantially decreases the hepatic metabolic activity, leading to an increase in the serum bilirubin levels.⁵

CLINICAL FEATURES

The typical patient presents with a couple of weeks of anorexia, nausea and vomiting, and right upper quadrant pain. Some pathognomonic features include severe jaundice, coagulopathy, encephalopathy, hypoglycemia, and ascites. Intrauterine complications including death are not uncommon in severe cases. About 50% of patients with AFLP have a background of preeclampsia, and some patients may also show features of HELLP syndrome.^{1-3,6-8} If untreated, AFLP can lead to complications, such as, DIC, renal failure, clotting disorders and coagulopathy, hypoglycemia, fulminant hepatic failure, and eventually multiorgan dysfunction.⁴

Diagnosis

Although the gold standard for diagnosis of AFLP is liver biopsy, it is rarely necessary and frequently evaded as it can cause complications in the presence of coagulopathy. The Swansea diagnostic criteria are an alternative to liver biopsy, according to which six or more of the following findings are required for the diagnosis of AFLP in the absence of another cause.⁷

- Vomiting.
- Abdominal pain.
- Polydipsia/polyuria.
- Encephalopathy.

- Elevated bilirubin $>14 \mu\text{mol/L}$.
- Hypoglycemia $<4 \text{ mmol/L}$.
- Elevated urea $>340 \mu\text{mol/L}$.
- Leukocytosis $>11 \times 10^9/\text{L}$.
- Ascites or bright liver on ultrasound scan.
- Elevated transaminases (AAT or ALT) $>42 \text{ IU/L}$.
- Elevated ammonia $>47 \mu\text{mol/L}$.
- Renal impairment: creatinine $>150 \mu\text{mol/L}$.
- Coagulopathy: prothrombin time >14 seconds or APPT >34 seconds.
- Microvesicular steatosis on liver biopsy.

Typical laboratory findings are elevated aminotransferases— aspartate transferase (AST) elevation greater than alanine transferase (ALT), both <6 times above upper limit of normal, hyperbilirubinemia, hyperuricemia, high white blood cell (WBC) count (above $15,000 \text{ cells}/\mu\text{L}$), hypoglycemia, high ammonia levels, and coagulopathy with or without DIC. The important differential diagnoses to be considered are fulminant viral hepatitis and severe HELLP syndrome. HELLP is usually encountered in the setting of severe preeclampsia, with prominent periportal hemorrhages and fibrin deposition seen on liver histology. Acute fatty liver of pregnancy, on the other hand, is seen to be frequently associated with encephalopathy, coagulopathy, hypoglycemia, and renal failure, along with characteristic histological findings of microvesicular fatty infiltration.^{5,9,10}

Management

Prompt induction of labor and immediate termination of pregnancy via delivery/cesarean section is the only true definitive therapy for AFLP. The suspected patient should be transferred to a tertiary care hospital as soon as possible to ensure early stabilization of the mother and efficient fetal monitoring.⁴ Supportive management should be initiated before delivery, which includes maintenance of an adequate airway, prevention/treatment of hypoglycemia, and correction of electrolyte and coagulation abnormalities.

Management of severe and persistent hypoglycemia with continuous dextrose infusions supplemented with thiamine is necessary to avoid coma and death. Blood glucose should be monitored closely until hepatic function recovers and the patient can tolerate a regular diet. Careful maintenance of intravascular

volume with necessary intravenous fluids and blood products, frequent assessment of maternal vital signs, and evaluation of changes in mental status are crucial. Supportive care and management of complications should be instituted along with the management of acute hepatic failure.⁸

Recently, few cases have been reported with successful treatment *via* the use of molecular absorbent recirculating system (MARS) in patients with severe AFLP. Plasma exchange/plasmapheresis with continuous renal replacement therapy has also been tried in some complicated cases with severe encephalopathy, patients on ventilator support, severe liver, or renal insufficiency who failed to respond to conventional management, and patients with multiorgan dysfunction.^{11–13}

The majority of females with AFLP show a gradual improvement in symptoms, and in hepatic function soon after delivery.⁶ Genetic screening for β -fatty acid oxidation defects should be advised for these patients, as most homozygous fetuses are seen to be carried by heterozygous mothers with AFLP.¹⁴ Although most females recover postpartum, some cases might decompensate with hepatic encephalopathy, fulminant hepatic failure, and death. Early diagnosis and management with prompt termination of pregnancy have been seen to improve the prognosis, with better maternal and fetal outcomes.^{4,6}

CONCLUSION

Acute fatty liver of pregnancy is an uncommon but potentially fatal complication seen mostly in the third trimester of gestation. The patient usually presents with anorexia, nausea, vomiting, and abdominal pain, along with jaundice developing over 1–2 weeks. Primiparous females and females with low BMI are seen to be more commonly predisposed to this condition. Early diagnosis becomes quite essential to improve prognosis and to anticipate hepatic failure in these cases. As in both our cases, the patients were malnourished females with a term pregnancy who had presented with symptoms of AFLP. Although an early diagnosis was made and the delivery was induced on the first day of admission, the condition of both females worsened rapidly post-delivery. This was quite an uncommon occurrence as most cases of AFLP usually start improving and resolve in a few weeks postpartum. This event could be attributed to the poor BMI and nutritional status of both patients, associated with possible herbal medication intake which was not reported/denied in the history. Unfortunately, both the patients could not be saved despite our best efforts, signifying the fact that AFLP is a lethal condition, even with early diagnosis and the best possible management.

Even though induction of labor with delivery remains the only real cure for this disease, some other therapies for complicated

cases include plasmapheresis with renal replacement, and the use of MARS. Orthotopic liver transplantation (OLT) has proved to be effective in cases that progress to multiorgan failure despite aggressive therapy, but is neither widely feasible nor available in most centers today.

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