# Acute Fatty Liver of Pregnancy in a Taiwanese Tertiary Care Center: A Retrospective Review

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## SUMMARY

**Objective:** To evaluate the demographics, clinical presentations, laboratory findings, and maternal and fetal outcomes in patients with acute fatty liver of pregnancy.

**Materials and Methods:** A retrospective review was conducted of the records of pregnant patients with a diagnosis of acute fatty liver in a tertiary medical center over a 22-year period.

**Results:** Eighteen patients with acute fatty liver of pregnancy were recruited, all of whom developed the disease in the third trimester. Eleven women (61%) were primigravid and four (22%) had twin pregnancies; six (33%) were diagnosed antepartum, and the other 12 (67%) were diagnosed postpartum. There were two maternal deaths (11%) and four fetal deaths (18%). The most common complications apart from severe liver dysfunction were acute renal failure (83%), hypoglycemia (61%), and disseminated intravascular coagulation (61%).

**Conclusion:** Women who become acutely ill during the third trimester of pregnancy should undergo tests for acute fatty liver of pregnancy, including laboratory tests for assessing liver function and coagulation profile. [*Taiwan J Obstet Gynecol* 2010;49(2):156–159]

**Key Words:** acute fatty liver of pregnancy, disseminated intravascular coagulation, fetal death, hypoglycemia, renal failure

## Introduction

Liver dysfunction is seen in less than 3% of women at delivery. It is usually directly related to pregnancy and resolves spontaneously during puerperium [1]. However, more serious conditions can develop, one of the most dangerous of which is acute fatty liver of pregnancy (AFLP), a rare but often lethal disease of the third trimester. The reported incidence ranges from 1 in 6,659 to 1 in 13,000 births [2,3]. AFLP is characterized by profound liver failure and may be accompanied by renal failure, disseminated intravascular coagulation, hypoglycemia, and encephalopathy [4]. The maternal mortality, once reported to be above 70%, is now estimated to be about 18%; reported neonatal mortalities have ranged from 7% to 58% [2,5–7]. Early recognition and prompt delivery result in favorable maternal and fetal outcomes.

The manifestations of AFLP may be confused with those of severe preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count syndrome), thrombotic microangiopathies, systemic lupus erythematosus, viral hepatitis, biliary tract disease, and cholestasis of pregnancy. Given the wide differential diagnosis and the need for prompt delivery to avert death, it is important to diagnose AFLP quickly and accurately. As a result of its relative rarity, however, few large case series have been reported in the literature. It is hoped that as more information on this disease becomes available, pooling of data will allow more robust recommendations to be made. In this study, we therefore reviewed our 22-year experience of AFLP.

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## Materials and Methods

The study included patients with AFLP who were managed at Mackay Memorial Hospital, a tertiary care center with 5,000 deliveries per year in Taiwan, from January 1984 to December 2006. AFLP was diagnosed in the presence of acute hepatic failure in the third trimester of pregnancy and comprised clinical findings, including abdominal pain, nausea or vomiting, and laboratory evidence of hepatic failure, including elevated aminotransferase and bilirubin levels, hypoglycemia, hyperammonemia, and signs of coagulopathy [2,8,9]. Hypertension and proteinuria were usually absent. Other causes of liver disorder in pregnancy, such as viral hepatitis, biliary tract disease, HELLP syndrome and cholestasis of pregnancy, were excluded. AFLP was more likely than HELLP syndrome to manifest with marked hypoglycemia, hyperammonemia, and an increased clotting time. Although HELLP syndrome or preeclampsia may coexist with AFLP, the findings of reduced hepatic metabolic activity clearly distinguish these different processes [2,8,9].

Data extracted from the medical records included demographic characteristics (maternal age, gestational age, and associated medical conditions), symptoms and signs, laboratory findings, clinical course, and maternal and fetal outcomes. Approval for this study was obtained from the institutional review board at Mackay Memorial Hospital.

## Results

There were 136,214 deliveries over the study period of 22 years. Among these, 18 patients were identified with AFLP. The incidence of AFLP was thus 1 in 7,568 births. Eleven of the 18 women were primigravid, and four had twin pregnancies. AFLP was diagnosed in six women antepartum, in 10 on the day after delivery, and in two on the third day after delivery. The acute illness occurred in the third trimester (mean, 35.6 gestational weeks; range, 30–39 gestational weeks) in all cases. Cesarean deliveries were performed in 13 cases: seven for fetal distress, three for malpresentation, one for prolonged labor, one for placental abruption, and one for unfavorable cervix. Progressive jaundice was the most common symptom (94%), followed by malaise (78%), dark urine (67%), nausea and vomiting (50%), fever (50%), and abdominal pain (50%). Abdominal ultrasound was performed in 17 cases, which demonstrated diffusely increased hepatic echogenicity and fat infiltration in 14 cases and ascites in all 17. There were four stillbirths, and the mean Apgar scores of the live newborns were low (Table 1). Delivery was preterm for eight women, three of whom had twin pregnancies. Seven babies had meconium staining. All the live-born infants survived and were doing well at follow-up.

**Table 1.** Clinical features of patients ($n = 18$) and babies ($n = 22$)*

| | |
|---|---|
| Maternal age, mean ± SD (yr) | 30 ± 5 |
| BMI before delivery, mean ± SD (kg/m$^2$) | 24.3 ± 1.2 |
| Gestational age at diagnosis, mean ± SD (wk) | 35.6 ± 2.8 |
| Maternal death, *n* (%) | 2 (11) |
| Delivery, *n* (%) | |
| Cesarean section | 13 (72) |
| Vaginal | 5 (28) |
| Fetal weight, mean ± SD (g) | 2,385 ± 739 |
| Fetal death, *n* (%) | 4 (18) |
| Sex of baby, *n* (%) | |
| Male | 13 (59) |
| Female | 9 (41) |
| Mean Apgar score | |
| 1 min | 4.9 |
| 5 min | 6.2 |

**Four patients had twin pregnancies. SD = standard deviation; BMI = body mass index.*

**Table 2.** Maternal complications associated with acute fatty liver of pregnancy of 18 patients

| Complication | *n* (%) |
|---|---|
| Acute renal failure | 15 (83) |
| Hypoglycemia | 11 (61) |
| Disseminated intravascular coagulation | 11 (61) |
| Postpartum hemorrhage | 6 (33) |
| Wound hematoma/dehiscence | 5 (28) |
| Pulmonary edema | 3 (17) |
| Gastrointestinal tract bleeding | 2 (11) |
| Encephalopathy | 2 (11) |
| Acute pancreatitis | 2 (11) |

The most common maternal morbidities were acute renal failure, hypoglycemia, and disseminated intravascular coagulation (Table 2). Three women required intubation, two of whom died. One of these had renal failure, liver dysfunction and disseminated intravascular coagulation causing massive postpartum hemorrhage following a cesarean section. She remained in the intensive care unit for 45 days and eventually died of sepsis and multiple organ failure. The other fatality had been transferred from another hospital with acute pancreatitis leading to multiple organ failure, and died on the second day. Among the patients who had a complication of acute renal failure, only one was subjected to transient hemodialysis during her hospital stay.

**Table 3.** Laboratory findings in mothers with acute fatty liver of pregnancy ($n = 18$)

| Laboratory test | On admission, mean (range) | Peak/nadir, mean (range) |
|---|---|---|
| Glucose (mg/dL) | 65 (5–95) | 57 (5–95) |
| Aspartate aminotransferase (IU/L) | 208 (19–2, 208) | 513 (87–3, 088) |
| Alanine aminotransferase (IU/L) | 156 (22–893) | 235 (73–893) |
| Bilirubin (mg/dL) | 8.5 (1.7–20.7) | 12.7 (1.7–33.6) |
| Cholesterol (mg/dL) | 103 (51–242) | 83 (47–108) |
| Blood urea nitrogen (mg/dL) | 29 (11–55) | 38 (15–95) |
| Creatinine (mg/dL) | 2.4 (0.6–4.4) | 3.1 (0.6–5.2) |
| Ammonia (μmol/L) | 75 (20–183) | 88 (20–207) |
| Prothrombin time (s) | 24.3 (13.8–60) | 25.4 (13.8–60) |
| Partial thromboplastin time (s) | 68.9 (50.4–96) | 83.2 (50.4–120) |
| Fibrinogen (mg/dL) | 158 (60–295) | 145 (52–295) |
| Platelets ($\times 10^3/mm^3$) | 121 (13–219) | 68 (13–195) |

Table 3 summarizes the important laboratory findings obtained at admission, and the nadir or peak values measured during hospitalization. Other abnormal findings included prolonged prothrombin time (mean, 25.4 seconds; range, 13.8–60.0 seconds) and partial thromboplastin time (mean, 83.2 seconds; range, 50.4–120.0 seconds), and reduced fibrinogen (mean, 145 mg/dL; range, 52–295 mg/dL). The mean cholesterol level was strikingly low. Patients also had persistent leukocytosis and hyperuricemia. Renal dysfunction occurred in 15 women, presenting after the appearance of liver failure and resolving before the recovery of liver function in all cases. Abnormal laboratory findings gradually improved after delivery in all 16 surviving mothers. The average hospital stay was 19.4 days (range, 2–45 days), including 7.6 days (range, 2–20 days) in the intensive care unit. Five of the women who survived were known to have a subsequent pregnancy, but none had a recurrence of AFLP.

## Discussion

Recent data indicate a decrease in maternal and neonatal mortalities associated with AFLP due to increased awareness and earlier recognition of the disease [7], based on its clinical and laboratory findings. Although there may have been significant changes in the care facilities over the 22-year recruitment period, the maternal and neonatal outcomes in the current series were similar to those in previous reports [4,7,10–14]. Laboratory evidence of acute hepatic failure combined with some degree of renal impairment may help to distinguish AFLP from other causes of peripartum jaundice. Disseminated intravascular coagulation in this syndrome appears to result from both diminished hepatic synthesis of coagulation factors and increased procoagulant consumption [10,11]. The low cholesterol levels in our patients were particularly notable, a finding that helps to differentiate AFLP from HELLP syndrome [4]. Hypocholesterolemia, hypofibrinogenemia, and coagulopathy are reflections of severe liver dysfunction [15], as are marked hypoglycemia, elevated serum bilirubin, and abnormal liver enzymes. The incidence of acute renal failure in AFLP is over 50% [15], but it is frequently of only moderate severity and does not usually require dialysis.

Diagnostic imaging modalities such as computerized tomography or sonography are not considered to be very helpful in the diagnosis of AFLP [2]. Liver biopsy is the standard method for confirming the diagnosis [10,12, 16], but it is rarely indicated and may indeed be contraindicated because of coagulopathy. A careful history taking and physical examination, together with confirmatory laboratory results, are often sufficient to make the diagnosis [2,9].

We observed two patients with AFLP whose conditions were complicated by acute pancreatitis. Acute pancreatitis has previously been reported as a complication of AFLP, but it proved to be lethal in one of our patients. Moldenhauer et al [17] considered it to be indicative of a poor prognosis. Establishing a diagnosis of acute pancreatitis may be difficult, but it has been associated with a high maternal death rate and fetal loss rate [18]. Previous authors have thus recommended screening patients with AFLP for pancreatitis.

AFLP has never reportedly resolved before delivery. Expeditious delivery is, therefore, fundamental to its treatment, although controversy exists over whether delivery should be by cesarean section or induction of labor [7]. Induction and vaginal delivery within 24 hours have produced favorable results [10]. We suggest cesarean section based on other obstetric indications, as proposed by Sibai [10], and not on the presence of AFLP alone. Perioperative care of patients with severe hepatic

dysfunction requires meticulous attention to hemostasis because of the presence of coagulopathy. Cryoprecipitate or fresh frozen plasma should be used to correct the prothrombin time [19]. Resolution of the disease is usually spontaneous following prompt delivery, although the need for liver transplantation has been reported in a few cases. However, that remains a potentially dangerous procedure and one that is not widely available [14]. As with any relatively rare disease, it is not feasible to define clinical guidelines based on controlled studies. Therefore, it seems prudent to urge early diagnosis and prompt delivery in cases of AFLP [12,20].

Although our data are very limited, at least five women in this series went on to have subsequent uncomplicated pregnancies. Too little is known about the risk of recurrence to make firm recommendations, but the results of this study suggest that recurrences are unlikely. Further data on the recurrence risk would be of great help when counseling women who have survived AFLP.

Patients should also be followed up in the light of the association between various defects in fatty acid oxidation in the offspring and liver disease in the mother [8,21]. Yang et al [21] identified a particular enzyme defect in five of 27 families in which the women had a history of AFLP. They recommended screening newborns whose mothers have had AFLP for this mutation, to assist with genetic counseling and nutritional therapy for the baby [21]. Although likely to be rare, such inborn errors of metabolism should be considered, given the rarity of AFLP itself.

This retrospective study adds to the information currently available for AFLP. The key to its early diagnosis is a high index of suspicion. Liver and coagulation functions should be carefully evaluated in women in the third trimester of pregnancy who become acutely ill, particularly with otherwise unexplained nausea and vomiting [22]. Prompt delivery of the pregnancy is indicated if the findings are consistent with AFLP.

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