Original Article

# Acute Fatty Liver of Pregnancy: A Retrospective Analysis of 56 Cases

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## Abstract

**Background:** Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication occurring in the third trimester. It is often fatal to both mother and fetus. The complicated clinical manifestations as well as an insufficient understanding of the disease make the precise diagnosis and effective treatment of AFLP challenging. A full understanding of the risk factors, clinical features, and test findings of AFLP is critical for its timely diagnosis and treatment.

**Methods:** We performed a retrospective study of 56 patients with AFLP between June 2008 and July 2013. We analyzed the clinical features, laboratory results, perioperative management, and patient outcomes.

**Results:** The initial symptoms varied considerably, with nausea and vomiting (13/56, 23%) being the most common. Liver-function indexes were remarkable, including elevated levels of serum alanine aminotransferase (262.16 ± 281.71 U/L), aspartate aminotransferase (260.98 ± 237.91 U/L), lactic dehydrogenase (1011.76 ± 530.34 U/L), and direct bilirubin (85.59 ± 90.02 μmol/L). Coagulation disorders were indicated by abnormal levels of fibrinogen (245.95 ± 186.11 mg/dL), D-dimer (2.46 ± 4.01 mg/L), and fibrin degradation products (43.62 ± 48.71 mg/L). The main maternal complications were hypoproteinemia (75%), coagulopathy (54%), and acute renal failure (39%). Multivariate logistic regression analysis identified prothrombin time (PT; odds ratio [*OR*] = 1.558, 95% confidence interval [*CI*] =1.248–1.946, *P* = 0.016) and international normalized ratio (INR; *OR* = 40.034, 95% *CI* = 2.517–636.693, *P* = 0.009) as risk factors. The perinatal infant death rate was related to gestational age at delivery (*OR* = 1.298, 95% *CI* = 1.040–1.618, *P* = 0.021), direct bilirubin (*OR* = 1.05, 95% *CI* = 1.008–1.094, *P* = 0.020), and fibrin degradation products (*OR* = 0.973, 95% *CI* = 0.950–0.996, *P* = 0.021).

**Conclusions:** Nausea and vomiting may be the most common symptoms of AFLP. Indexes of liver dysfunction and coagulation disorders should also be considered. PT and INR are risk factors for fatal complications in patients with AFLP, and perinatal mortality is linked to the level of fibrin degradation products. Timely delivery is crucial to controlling the development of AFLP.

**Key words:** Acute Fatty Liver of Pregnancy; Clinical Features; Pathogenesis

## Introduction

Acute fatty liver of pregnancy (AFLP), first described in the early 1950s as "acute yellow atrophy of the liver,"[1] is an idiopathic disorder with extremely high mortality (10–85%) in the third trimester.[2,3] The characteristics of AFLP include rapidly progressing hepatic dysfunction and a high risk of coagulation disorders,[4-6] triggered by microvesicular fatty infiltration of the hepatocytes,[7] with unknown cause. AFLP is a rare condition with an incidence of 1/7000–1/16000, which can occur at any age, has no unique clinical characteristics, and develops rapidly, posing a threat to both maternal and fetal health.[8]

There are no specific symptoms and no reliable examinations for AFLP, making an early diagnosis difficult. Gastrointestinal symptoms, including anorexia, vomiting, and abdominal pain, are the most common presenting symptoms. However, the sensitivity of ultrasound, computed tomography (CT), and magnetic resonance imaging is disappointing.[9] Liver biopsy is more reliable but can cause complications in the event of coagulopathy.[10]

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When AFLP is diagnosed or highly suspected, prompt pregnancy termination and supportive treatment are crucial, and even a slight delay may lead to death in light of the rapid progression of the disease.[2,7,11] There have been no reported case of continued pregnancy without increasing deterioration of liver-function.

In this retrospective study, we collected information from 56 patients with AFLP, including clinical features, laboratory results, perioperative management, and outcomes, to provide references for future clinical practice.

## Methods

### Subjects and methods

We performed a retrospective study of 56 patients with AFLP between June 2008 and July 2013.

The diagnosis of AFLP was based on the Swansea criteria, proposed by Ch'ng *et al*.[12] and the AFLP-triad of Vigil-de Gracia and Montufar-Rueda,[11] including (1) clinical symptoms such as anorexia, nausea, vomiting, abdominal pain, pruritus, jaundice, and hemorrhagic tendency in the third trimester; (2) characteristic laboratory findings including elevated alanine aminotransferase (ALT), bilirubin, and creatinine levels, leukocytosis, prolonged prothrombin time (PT), reduced fibrinogen, and hypoglycemia; and (3) liver biopsy, ultrasound imaging, or CT examination showing fatty liver. Women with viral hepatitis or hepatotoxicity, pharmaceutical hepatitis, or other hepatic diseases were excluded from this study.

Data including demographic characteristics (maternal age, marriage, childbearing history, and associated medical conditions), clinical manifestations, laboratory findings, mode of delivery, and pregnancy outcome were determined for all participants.

### Statistical analysis

Descriptive statistical analysis was performed using Statistical Package for the Social Sciences software, version 17.0 (IBM, Chicago, IL, USA). Group comparisons for quantitative data, presented as the mean ± standard deviation (SD), were performed using unpaired Student's *t*-tests. Qualitative data, given as number (*n*) and percentage (%), were compared using Chi-square and Fisher's exact tests. Multivariate logistic regression models were used to adjust for covariate effects on the odds ratio (*OR*). A value of $P < 0.05$ was considered statistically significant.

## Results

### Clinical presentations

Data for 56 women diagnosed with AFLP were analyzed in this study. The mean maternal age was 29.59 ± 6.16 years (17–49 years). Thirty-nine patients (70%) were primiparous and 20 (36%) were primigravidae. There were five twin pregnancies (9%), and 41 of 61 fetuses (67%) were male.

The clinical features are shown in Table 1. The mean gestational age at AFLP onset was 33.68 ± 4.15 weeks (17.43–39.29 weeks). A total of 54% of patients showed premonitory symptoms at 32–36 weeks, but 12 (21%) showed symptoms after 37 weeks. The initial symptoms varied considerably, but nausea and vomiting (13/56, 23%) were the most common. Nausea and vomiting, upper abdominal pain, skin pruritus, fatigue, hypoglycemia, or hypertension were observed in >50% of patients, with 91% having at least one of these symptoms.

**Table 1: Clinical features of patients with AFLP (*n* = 56)**

| Clinical features/symptoms | *n* | % |
|---|---|---|
| Nausea and vomiting | 36 | 64 |
| Upper abdominal pain | 34 | 61 |
| Fatigue | 34 | 61 |
| Hypoglycemia | 32 | 57 |
| Hypertension | 31 | 55 |
| Skin pruritus | 30 | 54 |
| Jaundice | 25 | 45 |
| Hemorrhagic tendency | 14 | 25 |
| Diarrhea | 9 | 16 |
| Edema | 4 | 7 |

AFLP: Acute fatty liver of pregnancy.

### Auxiliary examinations

Blood tests revealed different degrees of liver dysfunction in 49 patients (88%). AFLP was confirmed in the other seven (13%) by ultrasound or CT, with no hematological evidence. The ultrasound results were positive in 43% (23/53) of the women who underwent ultrasound examination. Varying degrees of renal dysfunction occurred in 29 cases (52%).

The laboratory results are shown in Table 2. The liver-function indexes included elevated serum ALT (262.16 ± 281.71 U/L), aspartate aminotransferase (260.98 ± 237.91 U/L), lactic dehydrogenase (1011.76 ± 530.34 U/L), and direct bilirubin (85.59 ± 90.02 μmol/L). Coagulation disorders were indicated by abnormal levels of fibrinogen (245.95 ± 186.11 mg/dL), D-dimer (2.46 ± 4.01 mg/L), and fibrin degradation products (43.62 ± 48.71 mg/L). PT was prolonged in 54% of patients (normal <14.5 s). Fasting blood glucose was reduced in 32 patients (57%) (<3.5 mmol/L) though the average glucose level in all 56 patients (4.03 ± 1.23 mmol/L) was at the lower level of normal.

### Management

Once AFLP was diagnosed or highly suspected, timely delivery was the primary consideration. Among all 56 cases, 41 (73%) underwent surgery within 48 h after diagnosis (mean 1.65 ± 2.60 days, range 0–14 days). Comprehensive, positive support was also provided, including energy supplements, treatment of hypertension and organ dysfunction, and the correction of electrolyte disturbances, hypoproteinemia, and coagulation abnormalities.

The management procedures are listed in Table 3. Anti-infective prophylactic therapy was ordered in 95% of patients, and 63% of patients received blood or blood

**Table 2: Blood laboratory findings in cases with AFLP ($n$ = 56)**

| Blood laboratory test | Range | Mean ± SD | Normal value | Change |
|---|---|---|---|---|
| Alanine aminotransferase (U/L) | 8–1000 | 262.16 ± 281.71 | 9–52 | ↑↑ |
| Aspartate aminotransferase (U/L) | 20–850 | 260.98 ± 237.91 | 14–36 | ↑↑ |
| Lactic dehydrogenase (U/L) | 131–2256 | 1011.76 ± 530.34 | 313–618 | ↑↑ |
| Alkaline phosphatase (U/L) | 53–802 | 249.53 ± 164.76 | 40–110 | ↑↑ |
| Total bilirubin (μmol/L) | 8.5–349.9 | 103.80 ± 96.32 | 3–24 | ↑↑ |
| Direct bilirubin (μmol/L) | 2.10–302.80 | 85.59 ± 90.02 | 0–5 | ↑↑ |
| Albumin (g/L) | 15.4–63.6 | 29.17 ± 7.61 | 35–50 | ↓ |
| Glucose (mmol/L) | 1.10–6.25 | 4.03 ± 1.23 | 3.9–6.1 | |
| Blood ammonia (μmol/L) | 1.6–201.9 | 52.76 ± 42.53 | 9–33 | ↑ |
| PT (s) | 9.0–32.9 | 15.57 ± 5.94 | <14.5 | ↑ |
| INR | 0.77–2.86 | 1.33 ± 0.46 | 1.0 ± 0.1 | ↑ |
| Fibrinogen (mg/dL) | 21.00–587.00 | 245.95 ± 186.11 | 300–600* | ↓ |
| D-dimer (mg/L) | 0.07–25.69 | 2.46 ± 4.01 | 63–246 | ↓↓ |
| Fibrin degradation product (mg/L) | 2.1–214.1 | 43.62 ± 48.71 | 2.5–7.2 | ↑↑ |
| Creatinine (μmol/L) | 32.00–311.00 | 119.84 ± 77.72 | 62–102 | ↑ |
| Platelets ($10^9$/L) | 38–4655 | 145.05 ± 75.43 | 100–450 | |
| Leukocytes ($10^9$/L) | 2.63–29.40 | 11.64 ± 4.85 | 4–10 | ↑ |
| Cholesterol (mmol/L) | 1.28–9.39 | 4.20 ± 1.91 | 2.82–5.72 | |

*300–600 mg/dL is the normal distribution of fibrinogen in the third trimester. PT: Prothrombin time; INR: International normalized ratio; AFLP: Acute fatty liver of pregnancy.

**Table 3: Hospital management in cases with AFLP ($n$ = 56)**

| Variable | Range/$n$ | Mean ± SD/% |
|---|---|---|
| Pregnancy outcomes | | |
| Gestational age at delivery (weeks)* | 19.00–40.29 | 35.86 ± 3.67 |
| Vaginal delivery | 11 | 20 |
| Cesarean section | 45 | 80 |
| Maternal treatment | | |
| Anti-infective prophylactic therapy | 53 | 95 |
| Blood and components transfusion | 35 | 63 |
| Platelet-transfusions | 16 | 29 |
| Liver protection | 36 | 64 |
| Medical/surgical Intensive Care Unit | 32 | 57 |
| Plasma exchange + CRRT | 4 | 7 |
| Enteroclysis and catharsis | 4 | 7 |
| Extended time* (days) | 0–14 | 1.65 ± 2.60 |
| Hospitalization days (days) | 1–32 | 8.11 ± 5.46 |

*Extended time means the time from diagnose to termination. SD: Standard deviation; AFLP: Acute fatty liver of pregnancy; CRRT: Continuous renal replacement therapy.

component transfusions. Thirty-two (57%) patients were sent to the Intensive Care Unit (ICU) because of a high risk of multisystem organ failure or death.

## Complications and outcomes

The complications and outcomes are shown in Table 4. The main maternal complications were hypoproteinemia (75%), coagulopathy (54%), and acute renal failure (39%), and there were high risks of ascites (36%) and disseminated intravascular coagulation (DIC, 32%). Eleven patients (20%) were diagnosed with preeclampsia, among 31 women with hypertension. Four (7%) of the 32 patients transferred to the ICU died. Two patients refused further therapy and were voluntarily discharged. DIC and multiple organ dysfunction syndromes (MODS) were the main causes of death.

The gestational age at delivery was 35.86 ± 3.67 weeks (19.00–40.29 weeks). Ten infants died perinatally (16%), including seven fetal deaths (13%). Intrauterine fetal distress (26%) was the most common neonatal complication, and only six neonates had an Apgar score of 10 at 1 min.

## Risk factors for fatal complications of acute fatty liver of pregnancy

Among the 56 AFLP patients, 21 had serious complications (38%), including DIC and/or MODS. Univariate analysis identified total bilirubin, direct bilirubin, PT, international normalized ratio (INR), fibrinogen, and fibrin degradation products as significantly associated with these complications ($P < 0.05$) [Table 5], and multivariate logistic regression analysis further indicated that PT ($OR = 1.558$, 95% confidence interval [$CI$] =1.248–1.946, $P = 0.016$) and INR ($OR = 40.034$, 95% $CI = 2.517$–$636.693$, $P = 0.009$) were risk factors [Table 6].

## Risk factors for perinatal death in cases of acute fatty liver of pregnancy

There were 10 (10/61, 16%) perinatal infant deaths as the result of various complications. Single-factor analysis showed significant associations between gestational weeks at onset, gestational age at delivery, total bilirubin, direct bilirubin, glucose, and fibrin degradation productsand perinatal infant death ($P < 0.05$) [Table 7]. Multivariate logistic regression analysis further suggested that perinatal infant death was related to gestational age at delivery ($OR = 1.298$, 95% $CI = 1.040$–$1.618$, $P = 0.021$), direct bilirubin ($OR = 1.050$, 95% $CI = 1.008$–$1.094$, $P = 0.020$), and fibrin degradation products ($OR = 0.973$, 95% $CI = 0.950$–$0.996$, $P = 0.021$) [Table 8].

## Discussion

AFLP has aroused considerable attention because of its extremely high maternal and fetal mortalities.[2,3] However, the etiology and pathogenesis of AFLP are unclear, and its lack of specific symptoms makes the early diagnosis and effective treatment difficult. Further research is therefore needed to identify the risk factors for AFLP. Multiple pregnancy,[11,13] male fetus,[14,15] primigravida,[16,17] and preeclampsia[13,18] are the most commonly reported risk factors. However, the rates of primigravidae (36%) and preeclampsia (20%) in the current study were lower than previously reported (50–75%),[13,16-18] suggesting that further studies are needed to confirm the importance of these factors in the development of AFLP. Furthermore, twin pregnancies (9%) and male fetuses (64%) were more frequent in our study compared with previous reports,[19,20] suggesting that multiple pregnancy and carrying a male fetus might also be risk factors for AFLP, and more attention should, therefore, be paid to pregnant women with these risk factors.

There are currently no uniform diagnostic criteria for AFLP though the most frequently used are the Swansea criteria, proposed by Ch'ng *et al*.,[12] and the AFLP-triad of Vigil-de Gracia and Montufar-Rueda.[11] However, our results suggest that laboratory findings of markedly elevated levels of serum transaminase (>200 U/L) and direct bilirubin (>60 μmol/L) should be considered in the diagnosis of AFLP. Multivariate logistic regression analysis also showed that perinatal death was linked to the levels of direct bilirubin, suggesting that high levels of direct bilirubin may be a useful factor to aid the diagnosis of AFLP. Hypertension (55%), hypoglycemia (57%), and fetal distress (26%) with no obvious reason should also be considered as possible signs of AFLP, when other diseases have been excluded. The positivity rates of ultrasound for AFLP varied greatly from 33%[21] to 82%[22] in previous reports. Our rate of 43% was consistent with

**Table 4: Pregnancy outcomes of 56 AFLP women and 61 neonates**

| Complication | Range/*n* | Mean ± SD/% |
|---|---|---|
| Maternal | | |
| Hypoproteinemia | 42 | 75 |
| Coagulopathy | 30 | 54 |
| Hemorrhage* | 24 | 43 |
| Acute renal failure | 22 | 39 |
| Ascites | 20 | 36 |
| Disseminated intravascular coagulation | 18 | 32 |
| MODS | 14 | 25 |
| Preeclampsia | 11 | 20 |
| Hepatic encephalopathy | 11 | 20 |
| Pulmonary infection | 12 | 21 |
| Pulmonary edema | 7 | 13 |
| Gestational diabetes mellitus | 5 | 9 |
| Maternal death | 4 | 7 |
| Neonatal | | |
| Preterm | 37 | 61 |
| <34 weeks | 12 | 20 |
| 34–37 weeks | 25 | 41 |
| Intrauterine fetal distress | 16 | 26 |
| Neonatal Intensive Care Unit | 18 | 30 |
| Fetal death | 10 | 16 |
| Birth weight (g) | 488–3790 | 2871.41 ± 820.30 |
| Birth weight <2000 g | 13 | 21 |

*Hemorrhage included perinatal gastrointestinal and vaginal bleeding. AFLP: Acute fatty liver of pregnancy; SD: Standard deviation; MODS: Multiple organ dysfunction syndrome.

**Table 5: Univariate analysis of the risk factors of serious complications in AFLP**

| Items | With serious complications | Without serious complications | *P* |
|---|---|---|---|
| Case number, *n* | 21 | 35 | |
| Male fetus, *n* | 15 | 26 | 0.815 |
| Multiple pregnancy, *n* | 2 | 3 | 0.904 |
| Primigravidae, *n* | 5 | 15 | 0.15 |
| Gestational weeks at onset (weeks) | 33.93 ± 2.48 | 33.53 ± 4.90 | 0.739 |
| Gestational age at delivery (weeks) | 35.53 ± 2.46 | 36.05 ± 4.25 | 0.615 |
| The days of delayed pregnancy (days) | 1.00 ± 1.37 | 2.06 ± 3.09 | 0.146 |
| Alanine aminotransferase (U/L) | 211.80 ± 176.65 | 253.69 ± 300.76 | 0.566 |
| Aspartate aminotransferase (U/L) | 241.71 ± 187.74 | 259.17 ± 270.28 | 0.796 |
| Total bilirubin (μmol/L) | 178.65 ± 92.65 | 57.56 ± 64.90 | <0.001 |
| Direct bilirubin (μmol/L) | 21.89 ± 17.06 | 13.42 ± 8.98 | 0.019 |
| Glucose (mmol/L) | 4.06 ± 1.28 | 4.55 ± 1.18 | 0.16 |
| PT (s) | 20.33 ± 5.22 | 12.36 ± 3.03 | <0.001 |
| INR | 1.74 ± 0.44 | 1.10 ± 0.26 | <0.001 |
| Fibrinogen (mg/dL) | 92.18 ± 51.64 | 329.43 ± 179.43 | <0.001 |
| D-dimer (mg/L) | 3.30 ± 5.69 | 3.80 ± 11.53 | 0.852 |
| Fibrin degradation product (mg/L) | 72.81 ± 59.75 | 22.39 ± 30.90 | <0.001 |
| Preeclampsia, *n* | 6 | 5 | 0.193 |
| Fetal death, *n* | 6 | 4 | 0.105 |

Value are *n* or mean ± standard deviation. AFLP: Acute fatty liver of pregnancy; PT: Prothrombin time; INR: International normalized ratio.

**Table 6: Logistic regression analysis of serious complications in AFLP**

| Items | *B* | SE | Wald | df | *OR* | 95% *CI* | | *P* |
|---|---|---|---|---|---|---|---|---|
| Total bilirubin | 0.002 | 0.008 | 0.059 | 1 | 1.002 | 0.986 | 1.018 | 0.808 |
| Direct bilirubin | −0.007 | 0.036 | 0.044 | 1 | 0.993 | 0.925 | 1.065 | 0.834 |
| PT | 0.443 | 0.113 | 15.292 | 1 | 1.558 | 1.248 | 1.946 | 0.016 |
| INR | 3.690 | 1.412 | 6.833 | 1 | 40.034 | 2.517 | 636.693 | 0.009 |
| Fibrinogen | −0.010 | 0.006 | 2.992 | 1 | 0.990 | 0.980 | 1.001 | 0.084 |
| Fibrin degradation product | 0.018 | 0.014 | 1.680 | 1 | 1.018 | 0.991 | 1.047 | 0.195 |

PT: Prothrombin time; INR: International normalized ratio; *OR*: Odds ratio; *CI*: Confidence interval; AFLP: Acute fatty liver of pregnancy; SE: Standard error.

**Table 7: Univariate analysis of the influence factors of perinatal mortality**

| Items | Death | Survival | *P* |
|---|---|---|---|
| Case number, *n* | 10 | 51 | |
| Male fetus, *n* | 7 | 34 | 0.837 |
| Multiple pregnancy, *n* | 0 | 5 | 0.275 |
| Primigravidae, *n* | 5 | 15 | 0.298 |
| Gestational weeks at onset (weeks) | 30.75 ± 5.82 | 34.34 ± 3.42 | 0.012 |
| Gestational age at delivery (weeks) | 32.51 ± 5.82 | 36.59 ± 2.57 | 0.010 |
| The days of delayed pregnancy (days) | 2.80 ± 4.34 | 1.36 ± 2.00 | 0.122 |
| Alanine aminotransferase (U/L) | 218.00 ± 243.85 | 258.55 ± 284.85 | 0.882 |
| Aspartate aminotransferase (U/L) | 242.20 ± 233.15 | 254.89 ± 245.04 | 0.678 |
| Total bilirubin (μmol/L) | 139.80 ± 133.32 | 262.09 ± 170.77 | 0.044 |
| Direct bilirubin (μmol/L) | 18.22 ± 15.53 | 95.80 ± 85.98 | 0.007 |
| Glucose (mmol/L) | 5.29 ± 2.33 | 4.18 ± 0.79 | 0.012 |
| PT (s) | 16.78 ± 5.79 | 14.96 ± 5.49 | 0.370 |
| INR | 1.43 ± 0.51 | 1.31 ± 0.45 | 0.496 |
| Fibrinogen (mg/dL) | 206.11 ± 186.88 | 253.92 ± 187.04 | 0.487 |
| D-dimer (mg/L) | 1.23 ± 0.83 | 4.11 ± 10.38 | 0.414 |
| Fibrin degradation product (mg/L) | 71.81 ± 51.54 | 37.30 ± 49.80 | 0.007 |
| Preeclampsia, *n* | 3 | 17 | 0.959 |
| Maternal death, *n* | 2 | 2 | 0.082 |

Values are *n* or mean ± standard deviation. PT: Prothrombin time; INR: International normalized ratio.

**Table 8: Logistic regression analysis of influence factors of perinatal mortality**

| Items | *B* | SE | Wald | df | *OR* | 95% *CI* | | *P* |
|---|---|---|---|---|---|---|---|---|
| Gestational weeks at onset | 0.036 | 0.205 | 0.030 | 1 | 1.036 | 0.693 | 1.549 | 0.861 |
| Gestational age at delivery | 0.260 | 0.113 | 5.346 | 1 | 1.298 | 1.040 | 1.618 | 0.021 |
| Total bilirubin | 0.005 | 0.004 | 1.359 | 1 | 1.005 | 0.997 | 1.012 | 0.244 |
| Direct bilirubin | 0.049 | 0.021 | 5.422 | 1 | 1.050 | 1.008 | 1.094 | 0.020 |
| Glucose | −0.494 | 0.368 | 1.805 | 1 | 0.610 | 0.297 | 1.254 | 0.179 |
| Fibrin degradation product | −0.028 | 0.012 | 5.295 | 1 | 0.973 | 0.950 | 0.996 | 0.021 |

*OR*: Odds ratio; *CI*: Confidence interval; SE: Standard error.

this, confirming that ultrasound is not a reliable method for the diagnosis of AFLP.

It is notable that there was a high tendency for bleeding or DIC. Multivariate logistic regression analysis in the current study showed that PT and INR were risk factors for fatal complications in AFLP patients, and perinatal mortality was linked to the level of fibrin degradation products, highlighting the importance of monitoring coagulation function, as well as indicating the connection between coagulation function and prognosis in AFLP cases.

Timely delivery is crucial for controlling the development of AFLP.[17] Perinatal mortality has been reported to be significantly lower following cesarean section compared with vaginal delivery.[18] Among four patients who died in the current study, two died within 7 days of developing premonitory symptoms, supporting the rapid onset and progression of AFLP. Multivariate logistic regression analysis also showed that perinatal mortality was inversely linked to gestational age at delivery; however, it is inappropriate to allow the pregnancy to continue if AFLP is highly suspected, considering the increasing risk of intrauterine fetal distress or fetal death and the rapid progression of AFLP.

Difficulties associated with making a correct diagnosis and administering effective treatment for AFLP are not only

attributable to its diverse manifestations and unpredictable complications but also to a lack of understanding of its causes and mechanisms. Protein malnutrition has previously been suggested to be responsible for the liver changes in AFLP.[23] Alternatively, AFLP may occur in individuals with disorders of fatty acid oxidation (FAO),[24] primarily deficiency of long-chain 3-hydroxyacyl-coenzyme A (LCHAD), a constituent of the mitochondrial trifunctional protein (MTP) complex of the inner mitochondrial membrane, which has been suggested as amitochondriopathy. Several studies have indicated that LCHAD gene mutation may contribute to the onset of AFLP,[25-27] and AFLP with LCHAD and MTP deficiencies is genetically transmitted as an autosomal recessive disorder.[24] Infants born to mothers with AFLP also have deficiencies in LCHAD and abnormalities in the FAO cascade caused by mutations in Glu47G1n of the α-subunit of the MTP complex.[28] In contrast, fetuses homozygous for an FAO deficiency can induce fatty acid accumulation in the liver of a heterozygous mother, leading to maternal liver dysfunction. It may, therefore, be advisable to screen newborns of mothers with AFLP for this mutation, to assist with genetic counseling and nutritional therapy.[29]

Prompt pregnancy termination is currently the only way to control the development of AFLP, emphasizing the possible role of the placenta in the pathogenesis of AFLP.[30] The placenta is known to use fatty acids to function, and the placenta expresses all enzymes of the FAO cascade, mainly during the second trimester. It is possible that placentas of LCHAD-deficient fetuses may be a source of fatty acids, the metabolites of which may exert a toxic effect on the maternal liver, leading to the presentation of AFLP in the third trimester.[31,32] AFLP is thus not only a hereditary disease but also a metabolic disease. Despite their rarity, such inborn errors of metabolism should be considered, given the severity of AFLP.

This retrospective study provided detailed information on the characteristics of patients with AFLP and identified nausea and vomiting as the most common presenting symptoms. Nausea and vomiting in the third trimester, with no obvious cause, should thus alert doctors to the possibility of AFLP and trigger close monitoring. Liver-dysfunction indexes and coagulation disorders should also be considered, and laboratory findings including markedly elevated levels of serum transaminase (>200 U/L) and direct bilirubin (>60 μmol/L) should be noted. PT and INR are risk factors for fatal complications in AFLP patients, and perinatal mortality is also linked to the level of fibrin degradation products. However, further studies are needed to explore the pathogenesis of AFLP. A better understanding of the features of AFLP will aid in its timely diagnosis and treatment, including prompt termination of pregnancy, thus helping increase the cure rate, reduce mortality, and improve pregnancy outcomes.


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## Conflicts of interest

There are no conflicts of interest.

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