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MATERNAL-FETAL MEDICINE

Acute fatty liver of pregnancy in a Chinese Tertiary Care Center: a retrospective study

Gezi Chen[1] · Kai Huang[2] · Bingrui Ji[1] · Chen Chen[1] · Cai Liu[1] · Xiaojuan Wang[1] · Xianlan Zhao[1]

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Abstract

Purpose To describe some prenatal clinical features and laboratory findings of AFLP and provide the clinicians with potential predictors in postpartum recovery time.

Methods Forty-four cases of AFLP previously treated in the First Affiliated Hospital of Zhengzhou University were retrospectively reviewed.

Results The maternal and fetal mortalities after treatment were both 18.2%. The main symptoms of AFLP were nausea and vomiting (63.6%), jaundice (61.4%). Moreover, the most common maternal complication was acute renal dysfunction (79.5%), followed by DIC (47.7%) and MODS (38.6%). The level of platelets, total protein and total bilirubin were found to be correlated with postpartum recovery time (Pearson correlation coefficient 0.434, $P=0.008$; 0.466, $P=0.005$; 0.484, $P=0.003$).

Conclusions AFLP is a rare, but lethal complication in the third trimester. Termination of pregnancy should be applied once AFLP was highly suspected. Prenatal platelets, total protein and total bilirubin may be potential predictors of postpartum recovery.

Keywords Acute fatty liver of pregnancy (AFLP) · Clinical features · Recovery time · Potential predictors

Introduction

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication occurring mostly in the third trimester. It is often fatal to both mother and fetus [1]. The incidence of AFLP was reported to be 1:7000–15,000 in recent epidemiological studies [2]. Over the past decades, maternal and perinatal deaths from AFLP have declined with advances in supportive obstetric care. The maternal mortality is now estimated to be about 18%, while neonatal mortality has ranged from 7 to 58% [3–6].

AFLP is characterized by maternal liver failure and may be accompanied by several complications including kidney injury, disseminated intravascular coagulation (DIC), hypoglycemia, and encephalopathy [1, 7, 8]. The complicated clinical manifestations as well as an insufficient understanding of the disease make the precise diagnosis and effective treatment of AFLP challenging. Most investigators assume that earlier recognition and prompt delivery may have the best maternal and fetal outcomes [9–12]. Thus, a full understanding of the risk factors, clinical features, and test findings of AFLP is pivotal. The purpose of this investigation was to describe some prenatal clinical features and laboratory findings of AFLP and provide the clinicians with potential predictors in postpartum recovery time.

Materials and methods

The study included patients with AFLP who were admitted to the First Affiliated Hospital of Zhengzhou University, the largest hospital in China, from January 2011 to February 2018. Approval for the study was obtained from the institutional review board at our hospital. The need for informed consent was waived by the Ethics Committee because the study was an observational, retrospective study using a database from which the patients' identification information had

✉ Gezi Chen
dr.echochen@gmail.com

✉ Xianlan Zhao
dr.xlzhao@hotmail.com

[1] Department of Obstetrics, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

[2] Center for Reproductive Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

been removed. Data extracted from these medical records included demographic characteristics, symptoms and signs, laboratory findings, clinical course, and maternal and perinatal outcomes.

Swansea criteria and AFLP triad were applied to confirm the diagnosis of AFLP. Women with hepatic disorders caused by viral hepatitis, biliary tract disease, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, cholestasis of pregnancy and other liver diseases were excluded.

Descriptive statistical analysis was performed with SPSS (Statistical Package for Social Science, SPSS Inc, Chicago, IL, USA) version 17.0. Pearson correlation analysis was used to evaluate the associations between variables of interest and clinical outcomes. Data were expressed as mean ± SD. A value of $P < 0.01$ was considered statistically significant.

Results

The general characteristics of AFLP patients and fetus are shown in Table 1. The mean age of these 44 patients was 27.4 ± 4.7 years and mean gestational age was 35.5 ± 2.9 weeks. Amongst them, 24 patients (54.5%) was primigravida and 20 patients (45.5%) was multigravida. There were 7 twins and 2 triplet pregnancies. 8 of the 44 patients (18.2%) ended up with death. Delivery occurred by cesarean delivery in 38 patients (86.4%) and vaginally in 6 patients (13.6%). For all infants including 39 males (70.9%) and 16 females (29.1%). There were 10 fetal deaths which involved 6 intrauterine fetal deaths (10.9%) and 4 neonatal deaths (7.3%). Three of the vaginal deliveries were intrauterine fetal deaths. Eight patients were transported from local hospital after delivery. The other 36 patients were terminated in our care center.

As seen in Table 2, the initial symptoms varied considerably, but nausea and vomiting (63.6%) were the most common. Jaundice was observed in 27 of these 44 patients (61.4%). Abdominal ultrasound was performed in all patients, which demonstrated ascites in 17 patients (38.6%). All patients had at least one of the symptoms. The most common maternal complication was acute renal dysfunction (79.5%), followed by DIC (47.7%) and MODS (38.6%). Among all women with AFLP, pancreatitis and hypertension were found in 6 and 12 patients, respectively.

Table 3 displayed the main laboratory findings of AFLP patients shortly before delivery. Pearson correlation coefficients between recovery time and each prenatal factors were calculated. The level of platelets, total protein and total bilirubin were found to be correlated with postpartum recovery time (Pearson correlation coefficient 0.434, $P = 0.008$; 0.466, $P = 0.005$; 0.484, $P = 0.003$). Furthermore, scatter diagrams were used to clearly describe the level of prenatal factors between recovery and death group, and the relationship between the recovery time and prenatal factors (Fig. 1). The scatter plot exhibited a negative correlation in platelets count, total protein and recovery time. Meanwhile, there was a positive correlation in total bilirubin and recovery time.

Table 1 General maternal and fetal characteristics of AFLP patients

Variables	Measures
Age (years)	27.4 ± 4.7
Gestational age (weeks)	35.5 ± 2.9
Gravida (*n*, %)	
Primigravida	24 (54.5%)
Multigravida	20 (45.5%)
Maternal death (*n*, %)	8 (18.2%)
Time from diagnosis to delivery (h)	9.7 ± 8.4
Recovery time (day)	16.0 ± 10.1
Delivery (*n*, %)	44
Cesarean section	38 (86.4%)
Vaginal	6 (13.6%)
Twin pregnancy	8 (18.2%)
Triplet	2 (4.5%)
Gender (*n*)	55
Male (*n*, %)	39 (70.9%)
Female (*n*, %)	16 (29.1%)
Fetal death	10 (18.2%)
Intrauterine death	6 (10.9%)
Neonatal death	4 (7.3%)

Table 2 Clinical manifestations and complications of patients with AFLP

Symptoms	*n*	%
Nausea, vomit	28	63.6
Headache/dizziness	6	13.6
Jaundice	27	61.4
Pruritus	7	15.9
Hypertension	12	27.3
Ascites	17	38.6
Pneumonia	12	27.3
Acute renal dysfunction	35	79.5
Pancreatitis	6	13.6
DIC	21	47.7
MODS	17	38.6

Table 3 Prenatal laboratory findings and relationships with maternal recovery time

Laboratory findings	Normal range	Maternal outcomes		Pearson correlation	
		Recovery	Death	Correlation coefficient	*P* value
Leukocyte (10^9/L)	3.5–9.5	16.81 ± 7.57	17.06 ± 6.08		0.079
Hemoglobin (g/L)	115–150	100.83 ± 21.96	93.75 ± 18.28		0.17
Platelets (10^9/L)	125–350	122.03 ± 70.51	84.13 ± 79.81	0.434	0.008
PT (s)	8.8–13.6	19.47 ± 10.91	25.69 ± 4.75		0.148
APTT (s)	26–40	53.40 ± 14.79	74.83 ± 23.14		0.115
Fibrinogen (g/L)	2–4	1.10 ± 0.91	0.76 ± 0.43		0.511
Glucose (mmol/L)	3.6–6.1	3.65 ± 1.26	2.66 ± 1.22		0.945
AST (U/L)	15–46	342.52 ± 517.96	226.88 ± 117.44		0.147
ALT (U/L)	9–69	402.02 ± 622.37	125.88 ± 99.97		0.13
Total protein (g/L)	63–82	54.65 ± 7.97	42.78 ± 9.37	0.466	0.005
Albumin (g/L)	35–50	27.07 ± 4.46	23.15 ± 3.40		0.03
Total bilirubin (μmol/L)	3–22	129.00 ± 89.78	237.09 ± 143.55	0.484	0.003
Direct bilirubin (μmol/L)	0–5	98.99 ± 66.52	189.83 ± 89.07		0.018
Uric acid (μmol/L)	149–506	488.5 ± 116.00	585.63 ± 101.40		0.643
Creatinine (μmol/L)	58–110	152.20 ± 59.20	181.75 ± 86.72		0.012
Blood urea nitrogen (mmol/L)	2.5–7.1	7.33 ± 5.08	9.24 ± 4.33		0.012

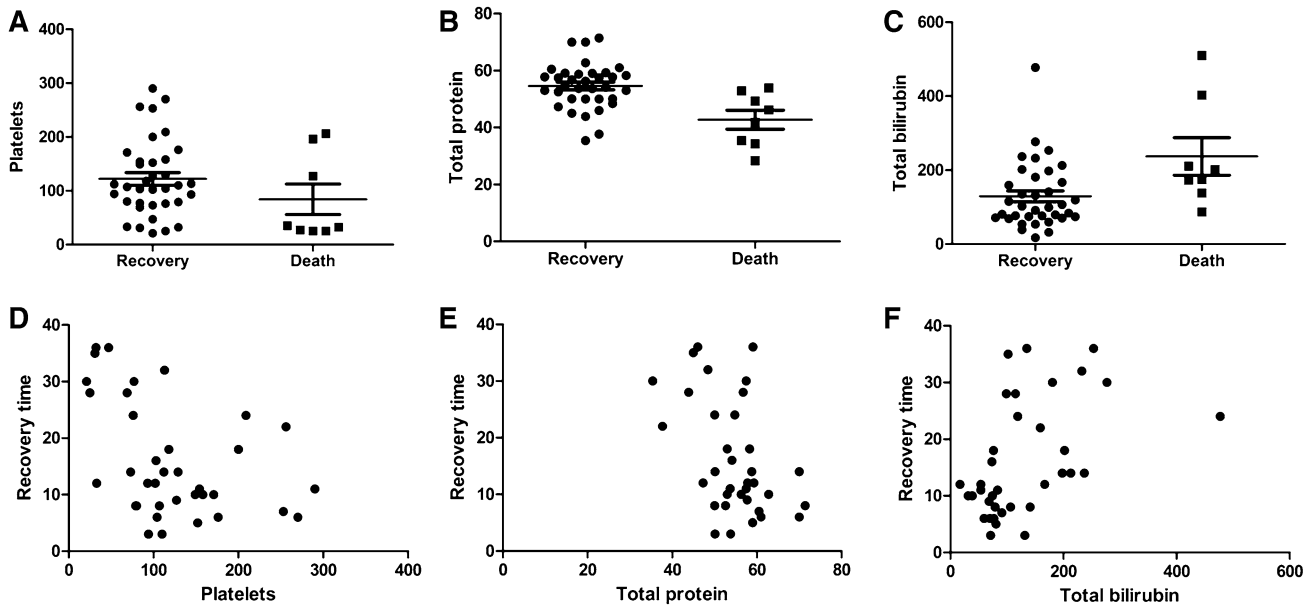

Fig. 1 Scatter diagrams of prenatal factors between recovery and death group, and relationship with postpartum recovery time including platelets (**a**, **d**), total protein (**b**, **e**), and total bilirubin (**c**, **f**)

Discussion

First described by Sheehan in 1940, AFLP is considered to be a rare, but potentially lethal disease during late pregnancy or early puerperium [13]. Recent data revealed a decline in maternal mortality associated with AFLP due to early recognition of the disease, prompt delivery and intensive supportive care. A recent survey found that maternal mortality worldwide had decreased from almost 100% to less than 10% in past decades [14]. As a tertiary referral center for critical patients, maternal mortality of AFLP in our hospital was 18.2%, which is consistent with previous reports [15–17]. Several risk factors have been identified for AFLP, of which male sex of fetus, primigravida and multiple pregnancy are the most commonly

reported [1, 11, 18, 19]. In the current study, the proportion of male fetuses and multiple pregnancy was 70.9% and 20.4%, respectively, which were more frequent than previously reported [20].

The Swansea criteria have been proposed as a diagnostic tool for AFLP by Ch'ng in 2002 [21]. During clinical practice, the Swansea criteria was confirmed to have a good sensitivity and became one of the most frequently used diagnostic criteria for AFLP [19]. There were no typical symptoms in the early stage of AFLP. In general, clinically common manifestations of AFLP reported included nausea, vomiting, abdominal pain, jaundice, ascites, and hypertension [22]. In our study, the main prodromic symptoms were nausea and vomiting (63.6%) while the most common sign was jaundice (61.4%). Abnormal laboratory findings included elevated hepatic aminotransferase, PT, APTT, bilirubin, leukocytes level and decreased platelets and glycemia. A patient positive for at least 6 of the Swansea criteria in the absence of another explanation of liver dysfunction, mainly HELLP syndrome, should be considered for a diagnosis of AFLP. Laboratory evidence of acute hepatic failure accompanied by moderate renal impairment, hypoglycemia or DIC may help to distinguish AFLP from other liver diseases [18]. However, in some cases AFLP and preeclampsia may appear simultaneously.

Although liver biopsy is the gold standard in the diagnosis of AFLP, it is barely performed due to the invasive nature and the presence of coagulopathy. Ultrasound and CT were commonly undertook to support the diagnosis of AFLP, but imaging evidences of fatty infiltration in the liver may be non-specific. Nevertheless, latest research has demonstrated that a peripartum excess of fat detected on MRI may be helpful to distinguish AFLP from HELLP syndrome [23]. MRI may be a diagnostic imaging tool for AFLP.

In the present study, major complication of AFLP was acute renal dysfunction, which occurred in 35 of 44 patients (79.5%). However, renal failure in AFLP patients were usually moderate and rarely associated with unfavorable prognosis. Furthermore, DIC and MODS were severe complications of AFLP which were always related to poor outcomes especially death. In the study, DIC and MODS appeared in 47.7% and 38.6% patients, respectively, which were higher than previous study. Partly may be because referrals to our hospital were mostly in progressive stage. Pancreatitis was considered to be indicative of poor prognosis. Six of our patients were diagnosed as pancreatitis, two of them ended up with death. Fetal loss rate in patients with pancreatitis was also higher (50%), two of them were intrauterine death.

Immediate termination of pregnancy followed by postpartum intensive care is the most effective treatment to achieve desirable maternal and fetal outcomes. However, conflicts exist over whether delivery should be by induction of labor or cesarean section [24]. Several studies have reported lower perinatal mortality following cesarean section in AFLP. Whereas, some other researchers recommend labor induction with close monitoring to decrease the morbidity of maternal complications. Wang et al. have performed a systematic review and meta-analysis to determine the maternal and perinatal outcomes in AFLP between two mode of pregnancy termination and suggest that cesarean section is associated with better pregnancy outcomes for both mother and fetus [25]. In our study, termination of pregnancy was immediately performed when patients were diagnosed as AFLP. The median time from diagnosis to delivery was 9.7 h.

The underlying mechanism in the development of AFLP is still unclear. Fetal fatty acid oxidation defects (FAOD) may be involved in the initiation of AFLP. Several studies have demonstrated that deficiency of long-chain 3-hydroxyacyl-coenzyme CoA dehydrogenase (LCHAD), a portion of the mitochondrial trifunctional protein (MTP), was associated with the occurrence of AFLP [26]. The most common mutation is located in exon 15 of the alpha-subunit. Meanwhile, other mutations that cause mitochondrial trifunctional protein (MTP) deficiency may also be associated with AFLP, including short-chain acyl-CoA dehydrogenase (SCAD) and medium-chain acyl-CoA dehydrogenase (MCAD). However, FAOD have also been found to develop preeclampsia and HELLP syndrome [2, 27]. Further studies should be proposed to explore the precise mechanisms of AFLP.

In conclusion, AFLP is an obstetric emergency which may lead to poor prognosis. Nausea and vomiting with no other explanations accompanied by acute liver failure in the third trimesters should be highly suspected as AFLP. Once AFLP was diagnosed clinically, termination of pregnancy should be applied. Bilirubin and PT levels may be helpful in the prognosis assessment of the disease. Our knowledge about this rare disease was still limited. Therefore, further studies focus on the pathogenesis of AFLP should be suggested.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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