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Original Article

Acute fatty liver of pregnancy: a retrospective analysis of 13 cases

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Abstract: Objective: Acute fatty liver of pregnancy (AFLP) is a rare life-threatening complication of pregnancy that occurs in the third trimester or the immediate period after delivery. This retrospective study aims to explore the early diagnosis methods and the principle of treatments of AFLP. Methods: The clinical presentation, complications, clinical diagnosis and management were determined in patients with acute fatty liver of pregnancy (AFLP). The maternal-perinatal mortality was analyzed with SPSS software (Version No. 16.0). Fisher exact texts were utilized to evaluated the difference of maternal-perinatal mortality. Study design: The clinical features, laboratory results, maternal and neonatal outcomes and treatments of thirteen AFLP patients were described retrospectively at Renji Hospital, School of Medicine, Shanghai Jiaotong University from Jul. 2007 to Aug. 2015. Results: All cases presented with a prodrome of digestive symptoms: rapidly progressing jaundice, nausea, vomiting, upper abdominal pain. (9/13, 69%). Laboratory results included quickly progressed cholenzyme separation (9/13, 69%), coagulation disorder (11/13, 85%), hypoproteinemia (9/13, 69%), hypoglycemia (5/13, 38%), renal impairment (11/13, 85%), elevated ammonia (8/13, 62%), negative hepatitis virus (100%). The mortality of maternal was 2/13 (15%), no neonatal death. The time between delivery and onset of 7 AFLP patients was over one week, all of these 7 patients had MOSF and 2 of them died, the maternal mortality was 28.57%, compared with the patients who's time between delivery and onset was within one week, the maternal mortality had statistical difference ($P<0.05$). The main treatments included prompt delivery and intensive supportive care. Giving intravenous albumin or in addition to dopamine and terlipressin were effective in the treatment of hepatorenal syndrome and also helpful to the recovery of liver function. Conclusions: Early diagnosis, prompt delivery and intensive supportive care are the cornerstones in the successful treatment of AFLP.

Keywords: Acute fatty liver of pregnancy (AFLP), early diagnosis, prompt delivery, intensive supportive care, hepatorenal syndrome

Introduction

Acute fatty liver of pregnancy (AFLP) is a rare life-threatening complication of pregnancy that occurs in the third trimester or the immediate period after delivery occurs in approximately one in 7,000 to one in 15,000 pregnancies [1, 2]. It was first described in 1940 by Sheehan as an "acute yellow atrophy of the liver" [3]. AFLP is characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis [4]. The maternal and perinatal mortality were reported to be as high as 18% and 23% [5, 6]. Serious complications included disseminated intravascular coagulation (DIC), hepatorenal syndrome, hepatic encephalopathy, respiratory failure, multiple organ system failure (MOSF) and infections. In this study, we retrospectively reviewed the clinic data of 13 patients diagnosed AFLP. Clinical features, laboratory results, maternal and neonatal outcomes of each patients we documented, the treatments were discussed.

Patients and methods

We performed a retrospective study of 13 patients with AFLP between July 2007 and August 2015 in Renji Hospital affiliated to Shanghai Jiaotong University School of Medicine. Data including demographic characteristics (maternal age, gestational age, parity his-

Table 1. Clinical features of patients with AFLP (n=13)

Symptoms	n	%
Digestive symptoms	9	69
Rapidly progressing jaundice	9	69
Nausea and vomiting	7	53
Upper abdominal pain	3	23
Diarrhea	2	15
Hypertension	3	23
Skin pruritus	2	15
Thirst with decreased fetal movement	1	7

tory, number of fetus), clinical manifestations, laboratory findings, mode of delivery, complications and outcomes were determined for all participants. The treatments were discussed. The study was approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiaotong University and written informed consents were obtained from all patients. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Statistical analysis

Data collected was carried out with SPSS software (Version No.16.0). Fisher exact texts were utilized to evaluated the difference of maternal-perinatal mortality.

Results

Clinical presentations

In our study, 12 patients were primiparas (92%), 1 patient was multipara (8%), 10 patients were single pregnancy (80%), 3 patients were twin pregnancies (20%). The mean maternal age was 27.8±3.74 years (23-35 years). All patients manifested in the third trimester of pregnancy. The mean gestational age was 36.2 weeks (33^{+5}-42^{+5} weeks). 7 of 16 fetuses (44%) were male. None of the patients had hepatitis history.

The usual symptoms included digestive symptoms (69%, 9/13) such as rapidly progressing jaundice, nausea, vomiting, upper abdominal pain. Other symptoms included hypertension (23%, 3/13), skin pruritus (15%, 2/13), thirst with decreased fetal movement (7%, 1/13) (**Table 1**).

Laboratory examinations: The characteristic laboratory examination was the quickly progressed cholenzyme separation (69%, 9/13). Alanine aminotransferase mainly mild elevated (mild 8/13, 62%; severe 5/13, 38%), asparate aminotransferase all severe elevated ,but soon they all quickly decreased., while bilirubin quickly elevated day by day (mild 3/13, 23%; moderate 3/13, 23%; severe 7/13, 54%). 11 cases had coagulation dysfunction (85%), 11 cases had renal impairment (85%), 9 cases had hypoalbumin (69%), 5 cases had hypoglycemia (38%), 8 cases had hyperammonia (62%), 11 cases had leukocytosis (85%), all had negative hepatitis virus (100%). All were carried out abdominal ultrasound showed bright liver (snow flake sign), 7 cases were carried out CT examination showed fatty liver (**Table 2**).

Management

Prompt delivery within 24 hours while the diagnosis established was the cornstone management of all these 13 cases of AFLP. Before delivery the coagulation abnormalities were initial corrected, blood products transfusion including fresh frozen plasma, platelet, fibrinogen, prothrombin complex. 12 patients were performed caesarean birth (92%), 1 patient was vaginal birth (8%). 11 patients underwent general anesthesia (92%), 1 patient underwent epidural anesthesia (8%). 5 patients were sent to the Intensive Care Unit (ICU) (38%). During the postpartum recovery period, prevention and management of complications were most important. Hemodynamic monitoring and continuing to supply blood products to correct DIC. Careful maintenance of intravenous fluids was also important. Using the third/fourth-generation cephalosporins was helpful to prevent or treat infections. Intravenous albumin infusions were used to treat hypoalbumin. Vasoactive drug such as dopamine, trey vasopressin and terlipressin combined with albumin infusion were very effective in the treatment of hepatorenal syndrome. Duphalac liquid oral combined with enema and intravenous ornithine aspartate were effective in the treatment of hepatic encephalopathy. Respiratory machine were used in the treatment of respiratory failure. Other treatments included hepatoprotectant drugs such as intravenous glucose, coenzyme complex, polyenephosphatidylcholine,

Table 2. Laboratory findings in cases with AFLP (n=13)

Laboratory findings	n	%	Normal value
Quickly progressed cholenzyme separation	9	69	
Alanine aminotransferase elevated			0-75 (U/L)
Mild elevated (≤225 U/L)	8	62	
Severe elevated (>225 U/L)	5	38	
Asparate aminotransferase elevated			10-28 (U/L)
Severe elevated (>84 U/L)	13	100	
Total bilirubin elevated			3.4-18 (μmol/L)
Mild elevated (≤36 μmol/L)	3	23	
Moderate elevated (37-90 μmol/L)	3	23	
Severe elevated (>90 μmol/L)	7	54	
Ammonia elevated	8	62	9-50 (μmol/L)
Bile acid elevated	11	85	0.01-10 (μmol/L)
Albumin decreased	9	69	34-54 (g/L)
Creatinine elevated	11	85	45-104 (μmol/L)
Blood urea nitrogen elevated	11	85	2.9-8.2 (μmol/L)
Hypoglycemia	5	38	<3.9 mmol/L
Leukocytes elevated	11	85	4-10 (10^9/L)
Platelets decreased	8	62	101-320 (10^9/L)
Fibrinogen decreased	11	85	2-4 (g/L)
D-dimer elevated	11	85	0-0.5 (mg/L)
PT prolonged	11	85	9.4-12.5 (s)

Table 3. Management in cases with AFLP (n=13)

Variable	n	%
Vaginal delivery	1	8
Cesarean section	12	92
General anesthesia	11	92 (11/12)
Epidural anesthesia	1	8 (1/12)
Intensive Care Unit	5	38
Mean hospitalization days	16.1	16.1±10.80
Mean gestational age	36.2	36.2±2.27

reduced glutathione, ademetionine 1,4-butanedisulfonate, ursodeoxycholic acid (**Table 3**).

Complications and outcomes

11 patients had DIC (85%), 1 patient had postpartum hemorrhage (8%). 11 patients had hepatorenal syndrome (85%), 11 patients had infections (85%), 9 patients had hypoproteinemia (69%), 5 patients had hypoglycemia (38%), 4 patients had hepatic encephalopathy (31%), 4 patients had respiratory failure (31%), 7 patients had MOSF (54%). Of the 7 MOSF patients, there were two patients died because of infections and MOSF. The mean hospitalization was 16.1 days (7-38 days). There were 10 preterm neonates (77%), 2 term neonates (15%), 1 post term neonates (8%). The number of male and female neonates were 7 and 9 respectively. Four neonates had mild birth asphyxia (25%), two of them had severe birth asphyxia (13%), ten were normal (62%). The mean neonatal weight was 2481 g (±568.6 g) (**Table 4**).

Discussion

The exact pathogenesis of AFLP has yet to be determined. The hypothesis was the deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in fetus cause characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis of maternal liver [7-9]. AFLP usually presents in the third trimester of pregnancy, the mean gestational age was 36th weeks. In our report the mean gestational age was 36.2 weeks.

AFLP is a rare and life-threatening disease though the maternal mortality of this disease has now been reduced significantly to 12.5% compared with the early years of 1980s (85%) [10], but it still should be aroused considerable attention because its complications are still severe that will cause high maternal mortality. Early diagnosis and effective treatment are the cornerstones to decrease the maternal mortality of AFLP. Reyes et al reported [2] that patients were survived while the pregnancy were terminated within one week after the clinical onset of AFLP, if the delivery time delayed to more than two weeks after onset, 30% patients would die at the first day of delivery because the disease had progressed severely. For all the cases reported in China, the time between delivery and onset of all death reports were 14 days, while that of the survivals were 8.5 days [11]. In our study, the time between delivery and onset of 7 AFLP patients was over one week, all of these 7 patients had MOSF and 2 of them died, the maternal mortality was 28.57%, compared with the patients who's

Table 4. Complications and outcomes

Complications and outcomes	n	%
Maternal (N=13)		
DIC	11	85
Postpartum hemorrhage	1	8
Infections	11	85
Hepatorenal syndrome	11	85
Hepatic encephalopathy	4	31
Respiratory failure	4	31
MOSF	7	54
Hypoproteinemia	9	69
Hypoglycemia	5	38
Maternal death	2	15
Neonatal (N=16)		
Preterm	10	77
Term	2	15
Postterm	1	8
Normal	10	62
Mild birth asphyxia	4	25
Severe birth asphyxia	2	13
Male	7	44
Female	9	56
Mean Birth weights	2481 g	2481±568.6 g

time between delivery and onset was with one week, the maternal mortality had statistical difference (P<0.05). The usual symptoms in its early stage were non-specific and it made the early diagnosis difficult. The most frequently used diagnostic criteria for AFLP is the Swansea criteria, which was proposed by Ch'ng et al [12], and the AFLP-triad of Vigil-de Gracia and Montufar-Rueda [13]. In our study the most typical features of AFLP include: (1) It presented in the third trimester of pregnancy and progressed rapidly. (2) The main clinical symptoms were digestive symptoms, especially the quickly progressed jaundice. (3) Quickly progressed cholenzyme separation with negative hepatitis virus (4) Severe complications including DIC, hepatorenal syndrome, hepatic encephalopathy and MOSF (5) Leukocytosis (6) Hypoglycemia (7) Abdominal ultrasound or CT showed bright liver. So we suggested that patient who had quickly improved cholenzyme separation and coagulation dysfunction in the third trimester with negative hepatitis virus should be highly suspected AFLP.

No report for curing of AFLP before delivery. Prompt delivery is crucial for controlling the development of AFLP. The maternal and perinatal mortality had been reported to be significantly lower following cesarean section (16.2% and 10.6%) compared with vaginal delivery (48.5% and 26.5%) [14]. Vaginal birth may occur under such conditions: the pluripara group especially in the active phases of labor, the estimated fetal weight was low. Which kind of anesthesia in CS is appropriate, general, regional or epidural anesthesia, should be according to the condition of patient's coagulation [15]. In our study, 11 cases performed general anesthesia (92%) because of coagulation dysfunction. Some authors suggested general anesthesia wasn't appropriated for AFLP because it may worsen or confuse the clinical appearance of encephalopathy [16].

The main death reason was MSOF, including DIC, hepatorenal syndrome, hepatic encephalopathy, respiratory failure and infections. Intensive supportive care should be admitted.

Before delivery we should give blood products transfusion to correct DIC though it couldn't be correct to the normal level. After birth still correct DIC. Lyophilizing thrombin powder and noradrenaline could be used in treating digestive tract hemorrhage. Low-molecular-weight heparin should be administered in the hypercoagulable patient at 24 hours after delivery because it can improve liver microcirculation and facilitate live regeneration.

Hepatorenal syndrome (HRS) is a sort of renal dysfunction which is generally reversible and occurs because of advanced liver disease. Although it is not completely raveled, the most characteristic reason underlying renal dysfunction in HRS is renal vasoconstriction [17]. HRS was first classified into two groups, Type 1 and Type 2, by the International Ascites Club in 1994. According to this classification, Type 1 HRS is associated with doubling of initial serum creatinine to a level of more than 2.5 mg/dL or reduction in creatinine clearance because of a decreased glomerular filtration rate to a level less than 20 mL/min in a time period shorter than 2 weeks. Type 1 HRS usually occurs following a precipitating factor such as infectious conditions, particularly spontaneous bacterial peritonitis (SBP) which is considered the most important factor for HRS [18-21]. The HRS of AFLP is type 1. The pathophysiology is "periph-

Table 5. Relation of serum albumin level & the recovery of renal and liver function (8 cases)

Case number	Date of CS	Date of Cr decreased to normal	Date of Bilirubin & bile acid began to decrease	Minimal Albumin (g/L)	Albumin while Cr Decreased to normal (g/L)	Time interval Between CS & Cr decreased to normal (d)	Time interval Between Cr decreased to normal and bilirubin & bile acid began to decrease (d)
N5	2012.1.9	2012.1.11	2012.1.11	22.9	23.5	2	0
N6	2012.1.13	2012.1.17	2012.1.18	19.9	26.7	4	1
N7	2012.5.5	2012.5.13	2012.5.14	21.6	29.3	8	1
N8	2013.4.9	2013.4.16	2103.4.16	27.5	34.3	7	0
N9	2013.12.4	2013.12.11	2013.12.12	21.8	32.8	7	1
N11	2014.9.1	2014.9.5	2104.9.6	28.2	35.2	4	1
N12	2015.2.19	2015.2.22	2015.2.23	33.3	34	3	1
N13	2015.8.24	2015.8.27	2015.8.28	24.8	26.9	3	1
Mean				25.00	30.33	4.75	0.75

eral arterial vasodilation hypothesis" proposed by Schrier RW et al [22]. In AFLP patients, arterial vasodilators could not been inactivated because of the dysfunction of liver, then the peripheral arterial vasodilation lead to hypovolemia, and decreased peripheral arterial pressure. The intense intrarenal vasoconstriction decreased the perfusion of renal vessel lead to the glomerular filtration rate decreased. So the important treatment of hepatorenal syndrome is to increase renal blood perfusion, such as intravenous abulmin (1.5 g/kg upon diagnosis, and then 1 g/kg after 48 h) or plasma, the dopamine can be used to expand plasma volume. Excessive diuresis should be avoided. Vasopressin analogues such as terlipressin or norepinephrine can lead to other intra-peritoneal organs arterial vasoconstriction but renal arterial vasodilation, and then increase renal blood perfusion. Infusion albumin is also helpful to facilitate liver regeneration, lighten tissue edema and promote wound healing. Elevated serum albumin can also predict the recovery of renal and liver function. In our study, in 8 cases serum creatinine value decreased to normal as soon as their mean serum albumin level were elevated to 30.3 g/L or more (23.5~35.2 g/L). At the same time or one day later, serum levels of bilirubin and bile acid were also decreased (**Table 5**). In our study, 8 cases had effective treatment of hepatorenal syndrome, 6 of them were only given intravenous albumin, while the other 2 patients were given intravenous abulmin in addition to dopamine and terlipressin.

Hepatic encephalopathy is another fatal complication of AFLP patients. Our research showed the AFLP patients should taken lower-protein diet, meanwhile they should have liquid duphalac from oral combined with enema that could decrease the absorption of bacteria-derived intestinal toxins. Acid suppressing drugs and protection of gastric mucosa drugs should be administered to prevent stress-induced ulcer, because gastrointestinal bleeding would develop hepatic encephalopathy. The patients who had grade III or IV hepatic encephalopathy should be performed endotracheal intubation and used respiratory machine [23].

Third/fourth-generation cephalosporins or Tienam was essential to prevent or treat infections. The patients with hepatorenal syndrome should reduce the doses of antibiotics. It is also important to prevent fungal infections. Intravenous gamma globulin could be used to boost immunity.

Chinese herbs, hepatoprotectants and hepatocyte growth factor are useful to improve liver function. Our research suggested the disease would progressed quickly during 5 to 7 days and the liver function would begin to recover at 2-3 weeks after delivery, but the jaundice treatment would undergo a long term process (usually undergo 1.5 month).

Blood purification therapy should be recommended when patients have intractable fluid overload, hyperkalemia, acidosis or pulmonary edema. It is also used before liver transplantation in the renal failure patients. Molecular absorbent recirculating system (MARS) and artificial liver plasma replacement could remove water-insoluble abulmin-bound toxins

in plasm (such as bilirubin and bile acid). These two treatments are also effective in AFLP, but the cost will be very expensive. The applications include: early and middle stage hepatic failure, INR1.5~2.6, BPC>50*10^9/L. Relative contraindications are severe bleeding, allergy to blood products, myocardial or cerebral infarction and circulatory failure. Liver transplantation is the last treatment in severe AFLP.

Conclusion

AFLP is an uncommon, life-threatening disease developing in the third trimester of pregnancy. Early diagnosis, prompt delivery and intensive supportive care are the cornerstones in the successful treatment of AFLP. The patient who has quickly improved cholenzyme separation and coagulation dysfunction in the third trimester with negative hepatitis virus should be highly suspected AFLP. The treatment of MOSF including DIC, hepatorenal syndrome, hepatic encephalopathy, respiratory failure and infections were important to decrease the mortality of AFLP patients. Giving intravenous abulmin or dopamine and terlipressin to AFLP patients were effective in the treatment of hepatorenal syndrome and also helpful to the recovery of their liver function.

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Disclosure of conflict of interest

None.

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