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ORIGINAL ARTICLE

Prospective Study

Acute fatty liver of pregnancy: Over six months follow-up study of twenty-five patients

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Abstract

AIM: To evaluate the prognosis of patients with acute fatty liver of pregnancy (AFLP) 6 mo or longer after discharge.

METHODS: The records of pregnant patients diagnosed with AFLP at Beijing Ditan Hospital over a 16-year period were reviewed in November 2012. Patients were monitored using abdominal ultrasound, liver and kidney functions, and routine blood examination.

RESULTS: A total of 42 patients were diagnosed with AFLP during the study period, and 25 were followed. The mean follow-up duration was 54.5 mo (range: 6.5-181 mo). All patients were in good physical condition, but one patient had gestational diabetes. The renal and liver functions normalized in all patients after recovery, including in those with pre-existing liver or kidney failure. The ultrasound findings were normal in 12 patients, an increasingly coarsened echo-pattern and increased echogenicity of the liver in 10 patients, and mild to moderate fatty liver infiltration in 3 patients. Cirrhosis or liver nodules were not observed in any patient.

CONCLUSION: Acute liver failure and acute renal failure in AFLP patients is reversible. Patients do not require any specific long-term follow-up after recovery from AFLP if their liver function tests have normalized and they remain well.

Key words: Acute fatty liver of pregnancy; Acute liver failure; Acute renal failure; Follow-up study

Core tip: Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy. Acute liver failure (ALF) and acute renal failure are the most important and threatening complication of AFLP. ALF due to viral hepatitis is known to potentially cause severe liver fibrosis and cirrhosis, but it is unknown whether the same outcome is possible for AFLP patients. The potential for continued progression or chronic sequelae is also unknown. Hence, the aim of this study was to evaluate the prognosis of patients with AFLP 6 mo or longer after discharge.

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INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy. This condition is defined as microvesicular fatty infiltration of hepatocytes during the second half of pregnancy (usually the third trimester), and it remains a common cause of liver failure during pregnancy. Since it was first described by Stander and Cadden[1] in 1934 and Sheehan[2] in 1940, numerous cases have been reported. The mortality of AFLP used to be very high, up to 85%[3], but with early recognition and prompt termination of pregnancy, the prognosis has improved, and the mortality is now estimated to be between 0% and 12.5%[4-9]. However, AFLP still causes severe maternal morbidity and in some cases mortality, especially in certain critical patients[10].

Acute liver failure (ALF) and acute renal failure (ARF) are the most important and life-threatening complications of AFLP[11,12]. ALF due to viral hepatitis is known to potentially cause severe liver fibrosis and cirrhosis, but it is unknown whether the same outcome is possible for AFLP patients. The potential for continued progression or chronic sequelae is also unknown. The aim of the present study was to evaluate the prognosis of patients with AFLP 6 months or longer after recovery. Notably, this study is the largest single-center, hospital-based follow-up investigation series worldwide.

MATERIALS AND METHODS

Patient selection criteria and exclusion criteria

AFLP was diagnosed based on clinical and laboratory criteria as follows: (1) patients with symptoms of anorexia, fatigue, nausea, vomiting, jaundice, and abnormal liver function during the third trimester of pregnancy; (2) characteristic laboratory findings; (3) ultrasound images showing a fatty liver; (4) exclusion of other causes of liver dysfunction, such as viral hepatitis, biliary tract disease, and cholestasis of pregnancy; and (5) liver biopsy sample with characteristic pathologic changes. All cases conformed to the diagnostic criteria mentioned above, except liver biopsy. Because of their severe condition, prolonged prothrombin times, reduced platelet counts, and/or the patients' refusal, only four patients underwent liver biopsy.

Study design

From January 1996 to May 2012, 42 cases of AFLP were identified at Beijing Ditan Hospital, Capital Medical University in Beijing, China. There were three maternal deaths (7.14%). In the 39 surviving patients, 25 patients consented to follow-up study. Records were reviewed in the 25 enrolled patients for presenting symptoms, laboratory findings, maternal complications, and neonatal outcomes. Demographic data included maternal age, gestational age, and comorbidities. Laboratory evaluation included measurement of liver function, complete blood cell count, coagulation profile, and renal function tests. Patients were monitored using abdominal ultrasound, liver and kidney function tests, and routine blood examination.

Ethics statement

This study was part of the research work "Correlation of mitochondrial trifunctional protein (MTP), α subunit G1528C mutation, and AFLP onset" which had been undertaken in May 2011. In accordance with the requirements of the Ethics Committee, we obtained written informed consent from the patients or the authorized clients of the patients (because some patients were in a critical state and were unable to sign the consent themselves). The authorized clients were the husband of the patients; according to Chinese law, they were the next of kin of the patients. We had informed our IRB that we obtained written informed consent from the next of kin of these participants. The Ethics Committee of Beijing Ditan Hospital, Capital Medical University approved the entire study design, methods and consent procedure used in this study. The approval number is QN 2011-06. All the data were collected anonymously.

Definitions

ALF was diagnosed based on clinical and laboratory criteria as follows: evidence of coagulopathy, usually an international normalized ratio $\geqslant$ 1.5 or a prothrombin activity $\leqslant$ 40%; serum total bilirubin $\geqslant$ 171 μmol/L or a daily rise $\geqslant$ 17.1 μmol/L; and any degree of mental alteration (encephalopathy) in a patient without preexisting liver disease and illness < 2 wk duration[13-15].

ARF was defined as the deterioration of renal function over days to weeks and a serum creatinine (Cr) $\geqslant$ 265.2 μmol/L; acute renal impairment was defined as a deterioration in renal function and a Cr > 150 μmol/L. Hypoglycemia was defined as symptoms of hypoglycemia occurring simultaneously with a blood glucose < 50 mg/dL (2.8 mmol/L).

Statistical analysis

Data were analyzed using statistical software (SPSS, Chicago, IL, United States), and $P < 0.05$ was considered statistically significant. Normally distributed data were expressed as the mean and standard deviation, and were analyzed using the *t*-test. Measured data were plotted on a receiver operating

Table 1 Laboratory findings in patients with acute fatty liver of pregnancy during hospitalization and at follow-up

Laboratory test	Peak/nadir average during hospital	Peak/nadir range during hospital	Average at follow-up	Range at follow-up
ALT (U/L)	376.4	34.0-1457.0	17.8	8.2-52.0
AST (U/L)	385.4	10.0-2144.0	18.4	10.1-42.1
TBIL (μmol/L)	258.8	16.0-225.0	12.8	4.7-23.6
Albumin (g/L)	26.0	15.0-37.3	47.2	43.9-54.2
BUN (mmol/L)	9.52	2.0-33.4	5.2	2.9-9.0
Cr (μmol/L)	207.3	66.0-522.0	55.7	45.0-67.7
UA (μmol/L)	331.1	168-542.0	262.5	176.0-390.8
Glucose (mmol/L)	3.5	1.2-6.3	5.8	4.5-16.0
WBC ($\times 10^9$/L)	22.1	4.3-56.3	5.5	3.5-5.5
HGB (g/L)	82.0	37.0-140.8	128.6	102.0-146.0
PLT ($\times 10^9$/L)	81.6	16.0-242.0	226.5	135.0-375.0

characteristic curve and referenced by sensitivity and specificity. Counted data were expressed as the frequency and rate, and χ^2 or Fisher's exact tests were used for analysis. Logistic regression was used to analyze relative factors. Data not normally distributed were expressed as the median and quartile, and analyzed using the rank sum test.

RESULTS

In the 25 enrolled patients, three patients were positive for hepatitis B, which was considered in the differential diagnosis but later excluded. All patients underwent an abdominal ultrasound examination, but a hyperechoic liver was only observed in 15 patients. The diagnosis was confirmed by liver biopsy in only one patient.

During hospitalization, the mean maternal age was 27.2 years (range: 21-34 years), and the mean gestational age at delivery was 35.3 wk (range: 26-42 wk). Delivery occurred by cesarean section in 19 patients and vaginally in six patients. The mean total duration of hospitalization was 25.5 d (range: 6-77 d). The prodromal phase lasted a mean 9 d before admission (range: 0.5-25 d). Reported symptoms included jaundice or dark urine (n = 18), nausea and vomiting (n = 16), malaise (n = 15), and abdominal pain (n = 7). Three patients did not report prodrome and had no complaints related to ALFP at the time of admission.

Laboratory results during hospitalization for the 25 patients are summarized in Table 1. All but one patient had elevated liver enzyme activities; in this particular patient, other criteria for the disease were fulfilled, and the diagnosis was confirmed by liver biopsy at the time of cesarean delivery. The total bilirubin concentration was elevated in 24 cases. Leukocytosis (leukocyte count > 11 000 cells/mm^3) was noted in 23 of 25 patients.

None of the patients underwent liver transplantation. Maternal morbidity was attributed to acute renal injury (18 cases), acute renal failure (8 cases with a urine output < 400 mL/d requiring CRRT), hepatic encephalopathy (10 cases), and postpartum hemorrhage > 500 mL (10 cases). The mean volume of blood loss was 1940 ± 1098 mL (range: 500-4000 mL). Other complications were as follows: hypoglycemia (eight cases), disseminated intravascular coagulopathy (five cases), pneumonia [four cases, all developed acute respiratory distress syndrome (ARDS) requiring mechanical ventilation], mental disturbances such as visual hallucinations, auditory hallucinations, and delusion of persecution (five cases), upper gastrointestinal hemorrhage (two cases), and acute pancreatitis (two cases). There were five cases of diabetes insipidus; all of the patients experienced acute renal injury, but only two patients experienced acute renal failure.

The mean follow-up time duration was 54.5 mo (range: 6.5-181 mo). The laboratory findings are summarized in Table 1. All patients were in good physical condition, but one patient had gestational diabetes. The renal and liver function returned to normal in all patients, including those with pre-existing liver or kidney failure. The ultrasound findings were completely normal in 12 patients; an increased coarse echo-pattern and increased echogenicity of the liver was observed in 10 patients and a mild to moderate fatty liver in 3 patients. Cirrhosis or liver nodules were not observed in any patient.

DISCUSSION

First described in 1934 by Stander and Cadden[1] as "acute yellow atrophy of the liver," AFLP is a medical and obstetric emergency and remains a common cause of liver failure during pregnancy[16]. Recent data indicate a decrease in maternal and neonatal mortalities associated with AFLP owing to increased awareness and earlier recognition of the disease based on its clinical and laboratory findings and significant changes in the facilities over the 16-year recruitment period[6,7,17].

The symptoms presently observed were similar to those found previously[4-9]. Typically, AFLP initially presents with non-specific symptoms such as acute abdominal pain, nausea, vomiting, and malaise, usually occurring during the third trimester of preg-

nancy or during the immediate puerperium. The initial symptoms of AFLP are atypical and could be overlooked, and this disease progresses rapidly and causes multiorgan dysfunction in a very short time; therefore, it is important to be especially vigilant for AFLP development.

After developing the described symptoms, complications typical of AFLP begin to appear, including renal insufficiency, encephalopathy, coma, coagulopathy, infections, ARDS, and acute pancreatitis.

ALF is a common complication of AFLP and one of the most common causes of liver failure during pregnancy. AFLP can sometimes be confused with fulminate liver failure caused by viral hepatitis. In this series, 13 of 25 patients (52%) developed ALF, and nine patients became comatose, which are findings similar to those in other studies[9,18-20]. ALF due to viral hepatitis may result in severe liver fibrosis and cirrhosis, but this does not occur in AFLP patients; we did not observe liver cirrhosis or chronic hepatitis in any of the patients during follow-up, and all have recovered well. Ober and Lecompte[21] reported that the pathologic changes in the liver are "of a reversible kind;" the clinical course and histopathologic findings clearly point to a functional failure-not a destructive form of hepatic insufficiency. Rolfes and Ishak[22] also observed that the lipid infiltration completely disappeared in as little as 5 wk of convalescence and did not progress to hepatic scarring and other chronic sequelae. We suspect that AFLP is usually self-limiting and is a reversible form of acute hepatic failure that does not generally require transplantation. Patients do not require specific long-term follow-up after recovery from AFLP if their liver function tests have normalized and they remain well.

The overall morbidity of renal impairment (Cr > 150 μmol/L) was 72.0%, and incidence of ARF requiring renal replacement treatment was 32.0%. Castro *et al*[9] reported that all AFLP patients had some degree of renal insufficiency on admission. The finding of renal insufficiency early during the course of disease suggests that the renal complications are not the result of hepatic dysfunction. In a study of autopsied patients, Rolfes *et al*[22] demonstrated the presence of sparse microvesicular fat in the kidneys of half the cases in frozen sections stained with oil red-O. The cause of ARF may be related to the inhibition of fat β-oxidation early on[23]; the hepatorenal syndrome probably contributes to the renal dysfunction as well, especially late in the course of disease. Renal function completely recovered at discharge and follow-up, suggesting that the renal damage in AFLP patients is reversible.

In conclusion, acute liver failure and acute renal failure in AFLP patients is reversible. Patients do not require any specific long-term follow-up after recovery from AFLP if their liver function tests have normalized and they remain well.

COMMENTS

Background

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy. Acute liver failure (ALF) and acute renal failure are the most important and threatening complications of AFLP. ALF due to viral hepatitis is known to potentially cause severe liver fibrosis and cirrhosis, but it is unknown whether the same outcome is possible for AFLP patients. The potential for continued progression or chronic sequelae is also unknown.

Research frontiers

In recent years, research has focused on the pathogenesis of AFLP. It is thought to be caused by a disordered metabolism of fatty acids by mitochondria in the mother, caused by deficiency in the long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) enzyme. The gene responsible for LCHAD has been isolated, and the most common mutation found in *AFLP* is the E474Q missense mutation. In another study, the authors also tested for E474Q mutation in these patients and in healthy controls; relevant data have not been published.

Innovations and breakthroughs

This study is the largest single-center, hospital-based, follow-up investigation series worldwide. The study showed that ALF and acute renal failure in AFLP patients is reversible. Patients do not require any specific long-term follow-up after recovery from AFLP if their liver function tests have normalized and they remain well.

Applications

AFLP is a rare but life-threatening complication of pregnancy. This follow-up study can provide a good reference for better understanding of the disease for both patients and doctors.

Peer-review

This is a clearly written manuscript - a small and simple study, materials and methods appear good. The article evaluated the prognosis in patients with acute fatty liver of pregnancy discharged over six months and concluded that acute liver failure and acute renal failure in AFLP patient is reversible; mothers do not need specific long-term follow-up after recovery from AFLP providing their liver function tests have normalized and they remain well.

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