Pregnancy Outcomes of Patients with Acute Fatty Liver of Pregnancy

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Abstract

Background: Limited data exists regarding the pregnancy and infant outcomes of Acute Fatty Liver of Pregnancy (AFLP).

Methods: Retrospectively collect the mothers with AFLP and without AFLP in our center from 1/2008 to 6/2018. The primary assessment was to analyze and compare the frequency of negative maternal and fetal outcomes. The secondary assessment was to identify the predictors of negative maternal and fetal outcomes.

Results: Compared to 220 matched mothers, 55 AFLP mothers were younger (P<0.001), fewer pregnancies (P=0.033), with more pregnancy induced hypertension (P<0.001), twins (P=0.002), fetal growth restriction (P=0.044) and fetus male (P<0.001). 3 (5.5%) of AFLP patients were diagnosed in the postpartum period. The mean gestational ages were 35.25±5.80 weeks at diagnosis of AFLP before delivery and Jaundice (89.1%), nausea or vomiting (58.2%), anorexia (49.1%), fatigue (45.5%) and like cold drinks (30.9%) were the main prodromal symptoms. The median duration from diagnosis to delivery was 1.55±4.62 days and 75% (39/52) patients terminate the pregnancy at the day of diagnosis. 78.8% (41/52) patients received cesarean section for terminating the pregnancy. 53.6% (22/41) patients received preventive plasma transfusion before the surgery and no one received artificial liver support during the treatment. In comparison, higher frequency of 16 maternal complications, severe negative outcomes (27.3% vs. 0.9%) and newborn asphyxia (24.6% vs. 0.9%) were observed in AFLP population. 3 mothers (mortality rates: 5.5%) died of multiple organ system failure and 6 fetal/infant (death rates: 9.8%) died of distress. When compared to those without negative outcomes, younger mothers (P=0.042), more singleton rates (P=0.041), increased mean value of ALT (P=0.011) and T-Bilirubin (P=0.014), decreased prothrombin activity (P=0.011) were predictors of the negative fetal outcomes. Although no statistical significance for the small sample size, the occurrence of refractory postpartum hemorrhage (0% vs. 31.3%), hysterectomy (0% vs. 12.5%), negative maternal outcomes (16.7% vs. 56.3%) were significantly decreased in patients with postpartum hemorrhage exceeded 500ml.

Conclusions: Several symptoms were found to be the main prodromal symptoms of AFLP. Higher frequency of adverse maternal and fetal outcomes was observed in mothers with AFLP than common people. We found five potential risk factors of negative fetal outcome. Intrauterine balloon pressure might prevent further postpartum bleeding, but need further verification.

Introduction

Acute fatty liver of pregnancy (AFLP) is a rare disease with an incidence of 1 per 7000 to 16,000 pregnancies. It mostly occurs in the third trimester of pregnancy or during early postpartum period. Prompt recognition of the disease and early termination of pregnancy is essential to improve the overall outcome of both mothers and infants. Primipara, male fetus, and multiparous women are considered as risk factors of AFLP. Genetic mutation in
long-chain 3-hydroxyl coenzyme A dehydrogenase probably leads to abnormal β-oxidation of fatty acids in fetal mitochondria and contributes to microvesicular fatty infilfiltration of the liver of mothers. However, the pathogenesis of AFLP is not yet completely elucidated. Due to better understanding of the disease and the implementation of artificial liver support therapy (ALST) in clinic and the popularization of intensive care unit, the mortality of AFLP for both suffering mothers and infants has dramatically decreased in recent years.

However, AFLP remains a serious disease with high mortality from to 16.5%-26.7% in recent study and Little data exist regarding the measures to improve disease outcome in AFLP. We conducted a comparative study about the negative maternal outcomes (maternal complications and mortality) and fetal/infant outcomes. Also, we evaluate the role of intrauterine balloon and plasma transfusion by comparing AFLP mothers with and those without negative outcomes.

**Materials And Methods**

**Patient Selection and study design**

Retrospective analysis of case records was carried out between January 2010 and June 2019 in the departments of the Beijing YouAn Hospital in China, a tertiary care hospital for liver diseases, including pregnant women diagnosed to have AFLP during pregnancy. The relevant institutional ethics review committee approved the trial (approval number: Jing-you-ke-lun-zi [2013]02-hao) and the need for informed consent was waived.

Patients at our clinic and in-patient services were screened for the following eligibility criteria: age between 20 and 45 years; clinical diagnosed as AFLP (The diagnosis of AFLP was based on both clinical features and laboratory findings, including: (a) symptoms of anorexia, nausea, vomiting, jaundice, fatigue, and abnormal liver function during the third trimester of pregnancy or early postpartum period; (b) characteristic laboratory findings (e.g. elevated alanine transaminase, bilirubin and serum creatinine levels, prolonged prothrombin time, and hypoglycaemia); (c) ultrasonography images examination showing fatty liver or liver biopsy sample, with characteristic pathological changes, where available. (d) All patients exhibited six or more of the Swansea criteria, which objectively confirmed the diagnosis of AFLP.) during the pregnancy. A group of pregnant mothers without AFLP were randomly selected (based on the birth date in the same month and age match) in a 1:4 ratio to serve as the control group. Key exclusion criteria—evidence of liver failure caused by other reasons including cirrhotic, Wilson disease, activated hepatitis B or C, hemophagocytic lymphohistiocytosis, hepatocellular carcinoma, or cytotoxic drugs.

**Study Procedures and Data Collections**
Using an electronic medical record system and paper charts, the following data from the clinic and inpatient services at YouAn Hospital were collected for analysis: baseline information before delivery including age, gravidity, parity, pregnancy complication and obstetric complications before AFLP including hypothyroidism during pregnancy, pregnancy induced hypertension (PIH), gestational diabetes (GDM), placenta previa, Lab of AFLP onset and the same gestational weeks in non-AFLP patients including platelet, hemoglobin, alanine transaminase (ALT), albumin, total bilirubin, prothrombin activity and creatinine, pertinent physical findings. For women with AFLP, additional data collection was performed that included documentation of gestational weeks at the time of the diagnosis and clinical signs. Data regarding medications, pregnancy complications, and obstetric complications were also collected during the delivery or after the delivery.

**Outcome Measurements**

Our primary outcomes were the frequency of negative maternal outcomes (maternal complications and mortality) and fetal/infant outcomes. Negative maternal outcomes including obstetrical complications, liver failure, renal failure, coagulation disorders, shock and Infection. The aforementioned outcomes will be compared between groups. Our secondary outcomes was to identify the predictors of negative outcomes of both mothers and fetal/infant. Also we evaluate the role of intrauterine balloon in reducing postpartum hemorrhage, hysterectomy and plasma transfusion. The severe negative outcomes of mothers include death, hysterectomy, shock, multiple organ system failure (MOF), hepatorenal syndrome, hepatic encephalopathy stage III-IV, failure to complete recovery, placental abruption grade III-IV, refractory postpartum hemorrhage (3000ml or more), PTA<20%, refractory infections (fungi, severe pneumonia, acute pancreatitis). Negative outcomes of fetal/infant were defined as Asphyxia of newborn (Apgar score 0-7) and fetal/infant death. (including liver failure, renal failure and coagulation disorders).

**Statistical Analysis**

Baseline characteristics and laboratory results were summarized for two groups by means of descriptive statistics, including percentage, means ± standard deviation (SD), and 95% CI. For the quantitative variable, the t-test was used to compare group differences. For categorical variables, the chi-square test was used for group comparisons. Significance level was set at P < 0.05; all data were analyzed by SPSS 23.0 (SPSS, IBM., NewYork).

**Results**

**Study Population and Baseline values**

During the enrollment period, the consecutive medical records of 511 pregnant women at our center were reviewed. Among them, 236 patients were excluded due to other reasons of liver failure (Fig. 1) and 55 were diagnosed with AFLP and enrolled into group A. 220
patients without AFLP and other liver diseases were selected as control and assigned to group B. All patients in group A were further assigned into group A1 if the intrauterine balloon was used to prevent the postpartum hemorrhage or group A2 if not. The patients who were screened and enrolled into the different study groups are shown in Fig. 1.

The clinical characteristics of patients at delivery in each group are shown in Table 1. When compared to patients without AFLP (group B), patients with AFLP were significantly younger (28.53±4.71 vs. 31.31±4.20, P<0.001) and had fewer numbers of pregnancies (1.741±0.915 vs. 2.109±1.173, P=0.033). The rates of Pregnancy induced hypertension (21.8% vs. 2.7%, P<0.001), twins (10.9% vs. 1.4%, P=0.002), fetal growth restriction (FGR) (7.3% vs. 1.4%, P=0.044) and fetus male (96.4% vs 55%, P<0.001) before the diagnosis of AFLP were higher in group A than group B. The incidence of GDM seems less in group A than in group B (5.5% vs. 13.2%), but there was no significant difference between two group (P=0.11). Besides, the rates of other pathological pregnancy including hypothyroidism during pregnancy and placenta previa were not different between groups. The mean values of ALT (219.18±240.11 vs. 14.35±27.65, P<0.001), total bilirubin (160.83±112.54 vs. 9.33±5.44, P<0.001), TBA (89.45±56.89 vs. 3.26±4.11, P<0.001) and CRE (162.91±89.84 vs. 46.83±11.62, P<0.001) were significantly higher in group A than in group B and the mean values of PLT (130.53±70.16 vs. 205.35±56.03, P<0.001), HGB (104.27±23.44 vs. 120.13±12.40, P<0.001), albumin (25.54±4.67 vs. 33.26±3.99, P<0.001) and prothrombin activity (40.44±23.37 vs. 119.05±13.23, P<0.001) were significantly lower in group A than in group B. Also, the incidence of hypoglycemia (61.8% vs. 20.9%, P<0.001) was significantly higher in group A than in group B (Table 1).

**Characteristics and outcomes of the AFLP patients in our center**

The clinical characteristics of the AFLP patients from the chosen studies were summarized in Table 2. Among all the patients of group A, 3 (5.5%) were diagnosed in the postpartum period. The mean gestational ages were 35.25±5.80 weeks in patients diagnosed before delivery and the mean days were 2.33±0.57 days in patients diagnosed after delivery. Jaundice, Nausea or vomiting, anorexia, fatigue, like cold drinks, abdominal distension, diarrhea, bleeding (gingiva etc), right epigastric pain, disgusting oil, fever, pruritus and insomnia were found in 49 (89.1%), 32 (58.2%), 27 (49.1%), 25 (45.5%), 17 (30.9%), 9 (16.4%), 6 (10.9%), 6 (10.9%), 5 (9.1%), 4 (7.3%), 4 (7.3%), 1 (1.8%) and 1 (1.8%) patients at the time of diagnosis, respectively. The median duration from diagnosis to delivery was 1.55±4.62 days and 75% (39/52) patients terminate the pregnancy at the day of diagnosis. (suppl Table 1). 78.8% (41/52) patients received cesarean section for terminating the pregnancy. 53.6% (22/41) patients received preventive plasma transfusion before the surgery and no one received artificial liver support during the treatment. During the surgery 25.45% (14/55) patients received intrauterine balloon after the terminating of pregnancy to prevent postpartum hemorrhage. No patient underwent liver
transplantation. The mean gestational weeks at delivery were 36.26±2.58 weeks in group A, which were significant earlier than group B.

As show in **table 2**, a significantly higher frequency of obstetrical complications including placental abruption (12.7% vs. 0.5%, P<0.05), meconium stained II-III (40% vs. 8.6%, P<0.05), and postpartum hemorrhage (52.7% vs. 12.3%, P<0.05) in group A than group B. No difference was found in the occurrence of oligohydramnios (7.3% vs. 6.4%, p = 0.807) between two groups. More patients need cesarean section (74.5% vs. 49.5%, P<0.05), intrauterine balloon (21.8% vs. 3.2%, P<0.05), preventive plasma transfusion (40% vs. 0%, P<0.05), hysterectomy (or uterine artery embolism) (5.5% vs. 0%, P<0.05), Blood Transfusion during the admission (61.8% vs. 1.8%, P<0.05) and intensive care unit admission (61.8% vs. 0.9%, P<0.05) in group A than group B. After the terminating the pregnancy, more patients in group A had poor wound healing of perineotomy or abdominal section than group B (14.5% vs. 0.5%, P<0.05). In terms of non obstetrical complication, 83.6% coagulation disorders, 47.3% acute hepatic failure, 85.5% Renal insufficiency, 98.2% rising of total bile acids, 47.3% ascites, 18.2% encephalopathy, 3.6% hepatorenal syndrome, 7.3% MOF, 1.8% Shock and 12.7% infections (2 fungi infection, 1 severe pneumonia, 1 acute pancreatitis, 1 bacterial peritonitis, 1 biliary tract infection and 1 pressure sore) were found in group A. However, only one patients with slight coagulation disorders and 2.3% patients with rising of total bile acids in group B. Finally, three mothers in group A were died of multiple organ system failure and 1 mothers did not complete recovery for too weak. In terms of fetal/infant complications, a significantly higher frequency of Preterm delivery (47.5% vs. 5.4%, P<0.05), fetal distress (45.9% vs. 3.1%, P<0.05), Asphyxia of newborn (24.6% vs. 0.9%, P<0.05), NICU admission (19.7% vs. 1.3%, P<0.05) and fetal/infant death (9.8% vs. 0, P<0.05) in group A than in group B.

When compared to those without negative outcomes, predictors of negative Fetus and Infants outcomes were younger mothers (27.00±2.57 vs. 29.21±5.28, P=0.042) more singleton rates (100% vs. 72.73%, p=0.041), higher mean values of ALT (328.80±277.48 vs. 164.60±194.25, P=0.011) and T-Bilirubin (208.46±108.89 vs. 130.63±107.46, P=0.014), lower mean value of Prothrombin activity (29.51±23.10 vs. 46.50±22.31, P=0.011). Besides, more patients in this group received preventive plasma transfusion (70.6% vs. 27.3%, P=0.002) and intrauterine balloon pressure (47.1% vs. 15.9%, P=0.011). (**Table 3**). There was no predictors of negative maternal outcomes were found in baseline values. (**suppl 2**).

**The role of intrauterine balloon pressure in preventing further postpartum bleeding**

To further evaluate the role of intrauterine balloon pressure, we stratified the 28 patients with postpartum hemorrhage more than 500ml into group A1 (received intrauterine balloon pressure) and group A2 (other methods instead intrauterine balloon pressure). Compared to patients in group A2, less patients but without statistical
Discussion/conclusions

AFLP remains a serious disease with high mortality from to 16.5%-26.7% for severe complications such as DIC, renal function impairment, hepatic encephalopathy, hypoglycemia, MOF, etc. Because the scarcity of AFLP, more comparative studies are needed about its clinical characteristics, treatment and outcomes.

Due to its characters of quick onset, rapid progression and fetal relation, prompt recognition and early termination of pregnancy is essential to improve the overall outcome of both mothers and infants. Primipara, male fetus, and multiparous women are considered as risk factors of AFLP. Except for these factors, we also found PIH and FGR were the risk factors of AFLP in Chinese population. AFLP patients seem to have less GDM (5.5% vs. 13.2%) but without statistical significance. There is disagreement in the published literature regarding the symptoms and clinically common manifestations of AFLP and we found that jaundice, nausea or vomiting, anorexia, fatigue and like cold drinks were the main prodromal symptoms. Fatigue and like cold drinks were easily ignored symptoms. Previous studies found that classical features of ascites or bright liver were only seen in a quarter of patients who underwent abdominal ultrasonography. In our patients underwent cesarean section, the rates of ascites were 46.3%. When compared to common patients, the abnormal values of laboratory test such as ALT, CRE, TBA, total bilirubin and PTA might be more sensitive in patients with AFLP. Although liver biopsy is the gold standard for diagnosis of AFLP, it was not done in our study and most previous studies for the invasive nature of the procedure, severe coagulation disorders and typical clinical findings at the time of diagnosis.

Except for early diagnosis, immediate delivery and comprehensive supportive treatment remains the mainstay in the management of AFLP. Similar to earlier studies, the common non obstetric complications observed among our patients were coagulation disorders (83.6%), acute hepatic failure (47.3%), renal insufficiency (85.5%), rising of total bile acids (98.2%), ascites (47.3%), encephalopathy (18.2%), 12.7% infections (including 2 fungi infection, 1 severe pneumonia, 1 acute pancreatitis, 1 bacterial peritonitis, 1 biliary tract infection and 1 pressure sore), 7.3% MOF and 1.8% Shock. In previous study, acute liver failure and ARF are the most significant and life-threatening complications of AFLP. Renal replacement therapy could prevent and reverse the further worsening of acute kidney injury. ALST has been widely used in the management of acute or chronic liver failure caused by various etiologies, which, to some extent, alleviates liver...
injury and provides a homeostatic environment for hepatocyte regeneration\textsuperscript{15-16}. In our center, no patients received ALST, however, 40\% percent patients received plasma Transfusion at the time of their admission. Timely terminating the pregnancy and plasma trans fusion could improve the clinical outcomes of most patients. AFLP is an quick onset and rapid progression disease. Acute liver failure in several hours to several days affect the synthetic function, such as coagulation factors and fibrinogens. In previous study, potential factors influencing adverse maternal outcome were male fetus, postpartum diagnosis of AFLP, intrauterine fetal death, disseminated intravascular coagulation, prothrombin time and activated partial thromboplastin time. The factors could be improve were coagulation disorders, including disseminated intravascular coagulation, prothrombin time and activated partial thromboplastin time. Timely 800-1200ml plasma transfusion could supply these supplement, which make it possible for a safe surgery to immediate delivery. After the removing of the etiology of AFLP, the disabled liver cells recovered quickly. The mortality rates were 5.6\%-26.7\%\% in previous studies in patients received ALST\textsuperscript{4-5}. The 5.5\% mortality rates in our study were not only lower previous study with ALST, but also significantly lower than the 85\% in the 1980 before the advent of ALST\textsuperscript{16}, suggesting that timely preventive plasma transfusion and immediate surgery is an effective method in improving the survival of AFLP patients. All 3 dead in our center were caused by the MOF were occured in 2008-2010 when the comprehensive support was not well. All the alive patients were occured from 2010 to 2019, which indirectly suggesting the importance of comprehensive support in the management of AFLP.

Another study revealed 2 complications, postpartum hemorrhage and multiple organ dysfunctions (MOF), were associated with the outcome of AFLP patients undergoing postpartum. Our study evaluate the role of intrauterine balloon pressure, we stratified the 28 patients with postpartum hemorrhage more than 500ml. Compared to patients who received our methods to control postpartum hemorrhage, intrauterine sac pressure could reduce the occurrence of refractory postpartum hemorrhage \( \geq 2000\) ml in delivery\textsuperscript{(0\% vs.31.3\% ), Hysterectomy(0\% vs.12.5\% ),Negative maternal outcomes(16.7\% vs.56.3\%)\). However, for the restriction of sample size, there were no statistical significance in the above complications.

Given the retrospective nature of our study, we were unable to determine the long time outcomes of AFLP. Besides, the details between the risk factors and negative fetal/infant outcomes could not be explained. Also, for the low incidence of AFLP, multicenter comparative studies were need to verify the value of preventive plasma transfusion and postpartum intrauterine balloon pressure in improving the outcomes of mothers.

In conclusion, the main prodromal symptoms of AFLP were jaundice, nausea or vomiting, anorexia, fatigue and like cold drinks among our patients. Higher frequency of adverse maternal and fetal/infant outcomes was observed in mothers with AFLP when
compared to the mothers without AFLP. We found that younger mother, singleton pregnancy, higher mean values of ALT and T-Bilirubin, lower mean value of Prothrombin activity were the potential risk factors for negative fetal/infant outcome. Preventive plasma transfusion and intrauterine balloon pressure might help improve the maternal outcomes, but need further verify.

Declarations

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Abbreviations

AFLP, acute fatty liver of pregnancy; ALT, alanine aminotransferase; ALST, artificial liver support therapy; PIH, pregnancy induced hypertension; GDM, gestational diabetes; MOF, multiple organ system failure.

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Contributions

Dr. Ming Wang proposed the concept and designed the study. Drs. Wang, Chang, Zhu, Liu, Meng and Yu contributed to the acquisition of data. Dr. Wang and performed the statistics and interpreted the data and wrote the manuscript with assistance from Dr. Wu. All authors provided inputs for the manuscript. All authors read and approved the final manuscript.
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**Ethics declarations:**

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional ethics review committee approved the trial (approval number: Jing-you-ke-lun-zi [2013]02-hao), and the need for informed consent was waived.

**Consent for publication:** Not applicable.

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

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**Tables**

Due to technical limitations, tables are available only in the supplemental section as a download.

**Figures**

![Figure 1: Disposition of Mothers and Infants](image)

- **Figure 1. Disposition of Mothers and Infants**

  - 511 patients were assessed for the eligibility
  - 220 pregnant patients without AFLP were selected as control group
  - 55 patients with AFLP were enrolled into AFLP group
  - 220 mothers gave birth to 222 Infants (2 pairs of twins)
  - 55 mothers gave birth to 61 Infants (6 pairs of twins)
  - Other etiology of liver failure were excluded:
    - Drug toxic: 2
    - Chronic hepatitis E: 1
    - Chronic hepatitis C: 3
    - Chronic hepatitis B: 139
    - HLH: 7
    - Liver cirrhosis: 84
  - Patients without postpartum hemorrhage were excluded: 27

- **AFLP**: Acute fatty liver of pregnancy; **HLH**: hemophagocytic lymphohistiocytosis

**Figure 1**

Disposition of Mothers and Infants
Supplementary Files

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