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RESEARCH ARTICLE

POTENTIAL RISK FACTORS FOR ONSET AND FETAL MORTALITY IN ACUTE FATTY LIVER OF PREGNANCY

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ABSTRACT

Background: Acute Fatty Liver of Pregnancy (AFLP) is a rare but potently fatal complication that occurs in the third trimester or the immediate postpartum period. It is a sudden catastrophic illness hence an obstetric emergency that is associated with a higher maternal and fetal mortality if diagnosis is hampered.

Objectives: The aim of this study is to explore potential risk factors influencing fetal outcome and survival.

Patients and Methods: A retrospective study of 33 patients with a diagnosis of Acute fatty liver of pregnancy between 2009 and 2014 in our institution (Qilu Hospital of Shandong University) was performed. Fetal outcome were analyzed under different variables using Windows Microsoft Excel 2010.

Results: Average maternal age of these 33 women was 27.03 ± 4.85 years and average age of with mothers Intrauterine fetal death (IUFD) was 26.66±3.05 years. Mean gestational age was 35.5±2.8 weeks. AFLP was frequently seen in Gestational age less than 36 weeks, multigravids, primiparas, women carrying male fetuses and singleton pregnancies. Fetal death was frequent in nulliparous mothers and male fetuses.

Conclusion: Gestational age less than 36 weeks, primigravidity, male fetus, singleton pregnancy might all be risk factors for fetal mortality, while multigravida, is a potential risk factor for AFLP onset. Nulliparity and male fetus might be potential risk factors for both AFLP onset and fetal mortality associated with AFLP.

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INTRODUCTION

Acute fatty liver of pregnancy (AFLP) initially termed "Acute yellow atrophy of the liver" is an out of the ordinary but potently fatal complication that occurs in the third trimester or the immediate postpartum period (Ko, 2006). It is considered an emergency for both mother and fetus (Liu, 2017).This condition is characterized by accumulation of micro-vesicular fat that literally "crowds out" normal hepatocytic function. Maternal mortality of AFLP used to be exceedingly high, up to 85% (Kaplan, 1985), but with early recognition and prompt termination of pregnancy, the prognosis has ameliorated[23]. Previous reports state that inheritance patterns such as long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency in the fetus, can lead to fetal fatty oxidation defects, which predisposes the mother to AFLP (Bellig, 2004; Browning *et al*., 2006; Strauss *et al*., 1999). The mother is affected by this fetal fatty oxidation defect due to physiologic metabolic changes during gestation that bring about increased demand for fatty acids (Liu *et al*., 2017). In that the fetus and placenta share a consistent genotype, a failure in fetal fatty acid oxidation affects the placenta in a similar fashion hence making the placenta unfit to carry out normal metabolic pathways. AFLP has a clinical spectrum of severity. In the worst cases, symptoms usually develop over several days. Persistent nausea and vomiting are major complaints, and there are varying degrees of malaise, anorexia, epigastric pain and progressive jaundice. Investigations postulated that an early recognition of AFLP influences the best maternal and fetal outcomes.New criteria were developed that might facilitate an earlier diagnosis or that could be used to confirm it (Nelson *et al*., 2013). One of such was the Swansea criteria brought forward by Ch'ng *et al*. (2002) and subsequently verified by

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the United Kingdom Obstetrical Surveillance System (Knight *et al*., 2008). Acute Fatty liver of pregnancy recurring in subsequent pregnancy is uncommon but few cases have been described (Usta *et al*., 1994). The aim of our study is to explore potential risk factors for the onset of Acute fatty liver of Pregnancy and analyze factors affecting fetal outcome and survival.

METHODS

This is a Retrospective study of Acute fatty liver of pregnancy among pregnant women in the east of china.

Sample Collection

The data reported in this study were obtained by review of medical records of 33 patients admitted to QILU Hospital of Shandong University with a diagnosis of Acute fatty liver of pregnancy between 2009 and 2013.

Diagnostic Protocols

AFLP was diagnosed on the basis of clinical and laboratory criteria as follows: (1) patients with clinical features such as nausea and vomiting, dizziness, malaise, jaundice, abdominal pain and or abdominal distension, heartburn, fever and hemorrhagic tendency during pregnancy or early puerperium; (2) characteristics laboratory findings including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin and creatinine levels, leukocytosis, prolonged prothrombin time (PT), reduced fibrinogen and hypoglycemia (3) evidence of ascites or fatty changes of liver (bright liver) demonstrated by B-ultrasound and computed tomography (CT). Liver biopsy was not performed on any of the patients.

Exclusion Criteria

Women with viral hepatitis (with the exception of hepatitis B), other forms of hepatitis (drug-induced, alcohol induced etc) were excluded from this study. We also excluded other liver conditions which occur during late pregnancy or the early puerperium.

Demography

Data on Demographic characteristics such as: maternal age, childbearing history and comorbidities, fetal sex, gestational age at onset of AFLP, clinical manifestations, laboratory findings, mode of current delivery and pregnancy outcome were determined for all subjects.

Statistical analysis

Fetal outcome were analysed under different variables using Windows Microsoft Excel 2010.

RESULTS

Average maternal age of these 33 women was 27.03 ± 4.85 years. The average hospital stay duration was 12.0 ± 7.1 days. Mean gestational weeks was 35.5±2.8 weeks.The mean birthweight for 23 infants 78.7% recorded was 2697.60 ± 739.28ranging 1200g-3700g.There was a single3% maternal death and 3(9.1%) fetal death.

Obesity was determined using the body mass index (BMI), and 10 (21.25%) of these women were obese with a BMI>30 As illustrated in Table 1, approximately 90.9% of the fetuses survived while 9.1% died. More foetuses were less than or equal to 36 weeks of gestation in the death group compared to those in the survival group (66.7% versus 56.7%), but on the other hand there were more above 36 weeks of gestation in the survival group with none in the death group(36.7% and 0%). Primi-gravida (G=1) fetuses were more frequent in the death group compared to those in the survival group (100% versus 33.3%), however in multigravida (G≥2), foetuses were frequent in the survival group compared to those in the death group (63.3% versus 0%). In the death group, most of the fetuses were from nulliparous women (P=0) compared to the survival group (66.7% versus 46.7%), but in primipara (P=1), there were more fetuses in the survival group compared to those in the death group (43.3% versus 33.3%). In multi-para (P≥2) fetuses were only frequent in the survival group compared to the death group (6.7% and 0%).

Table 1. Stratification Analysis of fetal influencing factors

	Outcome of baby	
Factors	*Survival n (%)*	*Death n (%)*
Total	30 (90.9)	3 (9.1)
Gestation(weeks):		
≤36	17 (56.7)	2 (66.7)
>36	11 (36.7)	0 (0)
Unknown	2(6.7)	1 (33.3)
Gravidity:		
1	10(33.3)	3 (100)
≥2	19 (63.3)	0 (0)
Unknown	1 (3.3)	0 (0)
Parity		
=0	14(46.7)	2 (66.7)
=1	13 (43.3)	1(33.3)
=2	2 (6.7)	0 (0)
Unknown	1(3.3)	0 (0)
Number of fetus:		
1	26(86.7)	3 (100)
2	4 (13.3)	0 (0)
Fetal sex:		
Male	17 (56.7)	1 (33.3)
Female	11 (36.7)	0(0)
Unknown	2 (6.7)	2 (66.6)
Delivery mode:		
CS	26 (86.7)	1(33.3)
V	1 (3.3)	1 (33.3)
Unknown	3(10)	1 (33.3)

CS: Caesarean Section; V: Vaginal delivery

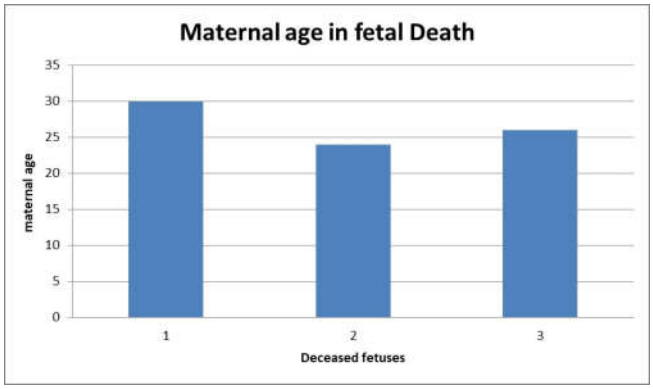

Figure 1. Maternal age in F etal death

In singleton pregnancy there were more fetuses in the death group compared to the survival group (100% versus 86.7%), while in twin pregnancy more fetuses were in the survival group and none in the death group (13.3% and 0%) respectively. Male fetuses were frequent in the survival group than those in the death group (56.7% versus 33.3%). Female fetuses were also more frequent in the survival group (36.7%) compared to those in the death group (0%). There were many unknown fetal sex in the death category (66.6%) compared to those in the survival category (6.7%) respectively. Caesarean Section (CS) was more common in surviving fetuses compared to deceased foetuses (86.7% versus 33.3%). As shown in figure 1,the mean maternal age in all fetal mortality is 26.66±3.05 years which means fetuses belonging to mothers whose age is within this limit are susceptible to mortality. The time period from onset which is admission into our institution to delivery was 6.11±5.33 hours. Most of the laboratory findings at onset of the disease were demonstrative of hepatic dysfunction with a mean serum Total bilirubin (TBIL) of 108.97±104.4 (umol/l), Aspartate Transaminase (AST) 272.3±314.4(u/l), Alanine Aminotransferase (ALT) 211.4±172.65(u/l), and serum Albumin 26.97±4.77(g/l). Mean creatinine levels were 125.95±67.516 (umol/l).

DISCUSSION

In our study the mean gestational weeks was 35.63±2.57 weeks.This is similar to other studies reporting that AFLP usually occur in women that are in their third trimester of pregnancy (Ilham Aldika Akbar *et al*., 2017; Mjahed, 2016; Riely, 1987). Commonly observed symptoms at onset of AFLP are; jaundice, abdominal pain, nausea, vomiting and malaise which are similar to those from other studies (Knight *et al*., 2008; Mellouli *et al*., 2012; Riely, 1987). Initially these symptoms are atypical and might probably be ignored, and the condition worsens causing multi-organ dysfunction within a very short time period; hence it is noteworthy to be on the alert for AFLP onset. All fetal death were Intra-uterine fetal death (IUFD) in this study. Mostly fetal death occurred in fetuses whose gestational age is less than or equal to 36 weeks and none in gestational age greater than 36 weeks of gestation which implies that in this study gestational age less than 36 weeks is a potential risk factor for fetal mortality. We discovered the mean maternal age in all dead fetuses to be 26.66±3.05 years, hence mothers within this age limit must be monitored. However maternal age and association with fetal mortality must be thoroughly investigated in subsequent studies (Bellig, 2004). Frequently mentioned risk factors in other studies include multiple pregnancy (Rajasri *et al*., 2007; igil-de Gracia, 2011), primigravida (Holzman *et al*., 2001) and male fetuses (Cheng *et al*., 2014; Treem *et al*., 1996). In our study there were more male foetuses (56.2%) compared to female foetuses (34.3%), and death occurred mostly in the male fetuses which implies that not only is carrying a male fetus a potential risk factor for AFLP onset, but it might probably imply that it is also a risk factor for fetal mortality while carrying a female fetus might be a protecting factor against fetal mortality. However the fetal sex was unknown in 66% of the deceased fetuses which might contradict this postulation. Singleton pregnancy was more frequent than multiple pregnancy hence the former might be a potential risk factor for the onset of AFLP. Also fetal mortality was frequent in singleton pregnancy (100%) which probably means it poses a risk for fetal mortality while multiple pregnancy might protect the fetus against fetal mortality.These findings differs from that of other investigators stating that multiple gestations might put women at increased risk of developing AFLP due to the fact that there is an increased production of fatty acid metabolites by more than one fetus (Davidson *et al*., 1998; Ko *et al*., 2006). If vaginal delivery cannot be achieved immediately, CS is the preferred delivery method. 84.3% of the deliveries in this study was by CS and survival rate was higher than death in these fetuses. Considering the severity of these women, CS was the appropriate pregnancy termination method,which is consistent to Wei's report (Wei, 2010). 59.3% of the women in this study were multigravid at onset of AFLP compared to a 40.6% of primigravid. This frequency of multigravids in our study differs from other studies (Holzman *et al*., 2001) that identified primgravida as a potential risk factor for AFLP onset. On the other hand, all fetal death (100%) reported in this study were from primigravid mothers, hence pointing out primigravidity to be a potential risk factor for fetal death in AFLP.

An investigator identified Primiparity to be a potential risk factor for AFLP onset (Zhou, 2013). These findings are contrary to our study in which nulliparas (50%) were more frequent compared to primiparas (43.7%) and multiparas (6.3%). Also fetal death was more frequent in nulliparous mothers. These suggest that nulliparity is both a risk factor for AFLP onset and fetal mortality in AFLP. The highly suspected or diagnosed cases of AFLP must be handled as an obstetrics emergency, with immediate termination of pregnancy. Early diagnosis and intervention brings about more preferable maternal and fetal outcomes. The management of AFLP requires maternal stabilization following delivery and supportive care (Rajasri, 2007). In this current study, all pregnancies were terminated within 24 hours of highly suspected or diagnosed AFLP and the outcomes were remarkable.

Conclusion

Gestational age less than 36 weeks, primigravidity, male fetus, singleton pregnancy might be risk factors for fetal mortality, while multigravida, male fetusare potential risk factors for AFLP onset. Nulliparity might be a potential risk factor for both AFLP onset and fetal mortality associated with AFLP.

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