

Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy

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Abstract

Purpose Intrahepatic cholestasis of pregnancy (ICP) is a disease associated with high-perinatal morbidity and mortality rates. It is important to have parameters that aid in predicting fetal outcomes. Certain parameters affecting asphyxia in newborns to mothers with ICP are evaluated in this study.

Methods One hundred eighty-seven cholestatic pregnancies were analyzed, retrospectively. Fetal asphyxia was defined as an APGAR score of less than 7 at 5 min postpartum. Predictors of asphyxia in ICP were analyzed by binary multivariate logistic regression analysis.

Results Thirty-six of the cholestatic pregnancies ended up having an asphyctic newborn at the time of delivery (19.2%). There was a statistically significance difference in the levels of total bile acids (TBA) (42.4 ± 15.2 vs. 33.8 ± 12.9 $\mu\text{mol/L}$, $P < 0.01$), HDL cholesterol (54.2 ± 15.9 vs. 61.3 ± 12.2 , $P = 0.01$), total cholesterol (279.0 ± 51.4 vs. 257.7 ± 51.6 , $P = 0.02$), and triacylglycerol (299.4 ± 94.6 vs. 260.4 ± 118.7) between the asphyctic and nonasphyctic group. Binary multivariate logistic regression analysis demonstrated that TBA levels (OR 1.04, 95% CI 1.01–1.08, $P = 0.03$) and exposure time (OR 1.11, 95% CI 1.05–1.17, $P < 0.01$) were the most important independent variables predicting fetal asphyxia in ICP.

Conclusions In this study, it has been demonstrated that for the evaluation of fetal status, increased TBA levels in the mother and increased exposure time for the fetus to these increased values of TBA within the maternal circulation system help to predict increased risk of asphyxia in newborns to ICP mothers.

Keywords Fetal asphyxia · Cholestasis · Pregnancy · Bile acid

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease unique to pregnancy that has an, as of yet, undefined etiology and pathogenesis. ICP is characterized by pruritus, elevated serum aminotransferases, and increased total bile acid (TBA) levels with a typical onset in the second half of pregnancy; there is spontaneous regressions of signs and symptoms after delivery [1, 2]. This syndrome has been associated with increased fetal distress, premature delivery, perinatal asphyxia, and intrauterine fetal loss [3, 4]. Serum transaminases are

increased from two- to tenfold depending on the case. Increases exceeding that level rarely occur and would suggest other causes. Serum bile acids are also typically elevated from 10- to 100-fold. However, the correlation between the rise in serum transaminases and bile acids is poor. Recent studies suggest that elevated serum bile acids may even be used as a diagnostic criteria for ICP [3, 5]. In addition to serum bile acids and transaminases, alkaline phosphatase levels also can be found to be elevated. Bilirubin, although it does show some elevations in this condition, rarely increases above 6 mg/dL and jaundice is not common.

Even though any association between maternal mortality and ICP has not been demonstrated, perinatal morbidity and mortality has been a major problem with this disease. The incidence of prenatal problems, such as risk of preterm delivery (19–60%), fetal distress (22–41%), and even fetal death (0.4–1.6%), are increased, complicating the pregnancy [2]. The cause of the prenatal complications is not known but increased levels of serum bile acids may be a contributing factor. In a recent study, Glantz et al. [4] came to a conclusion that the risk of fetal complications do not occur until bile acid levels exceed 40 $\mu\text{mol/L}$. Unfortunately, antepartum fetal monitoring has questionable efficacy in predicting and reducing fetal morbidity [6, 7].

Previous studies have reported an association between ICP and respiratory distress syndrome (RDS) [8, 9]. They suggested using scoring systems that included TBA level and exposure time to predict RDS in neonates.

Various strategies have been proposed to predict and improve obstetric outcomes in ICP patients. However, in several studies, investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance and that only delivery after establishment of fetal lung maturity may reduce fetal mortality rate [7, 10]. It is the general consensus that decisions concerning obstetric management in this disease must weigh the risk of premature delivery against the risk of sudden death in utero. Also, the fact that induction of labor due to fetal distress is associated with a higher frequency of complications such as surgical delivery compared with spontaneous labor [1] must be taken into consideration. In order to achieve uncomplicated term delivery (≥ 37 weeks) in patients with ICP, it is imperative to ascertain early prognostic markers for poor fetal outcome.

The aim of this study is to re-evaluate biochemical parameters as potential predictors of fetal asphyxia in patients with ICP.

Materials and methods

The study was performed, retrospectively, among 187 pregnancies complicated by ICP who applied, from January

2004 to July 2008, to the perinatology department of our hospital, a tertiary care maternity center. The study was approved by a local ethics committee.

Intrahepatic cholestasis of pregnancy was defined as persistent pruritus in combination with increased TBA ($\geq 11 \mu\text{M}$). Ultrasonography of the abdomen and serological scan of viral hepatitis were performed to exclude other causes of liver diseases in all patients before enrollment. Patients with chronic liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, and ongoing viral infections affecting the liver (hepatitis A, B and C virus, cytomegalovirus, herpes simplex virus, and Epstein–Barr virus) were excluded.

Intrahepatic cholestasis of pregnancy patients with concurrent disease (e.g., gestational diabetes, preeclampsia, or hyper/hypothyroidism) were not enrolled in our study group.

All patients studied had undergone treatment with ursodeoxycholic acid (UDCA) (500 mg BID) at the time they were diagnosed. Blood samples at the time of diagnosis were also recorded and taken into consideration in the study because UDCA treatment may have changed biochemical measurements during the pregnancy period.

Plasma was stored at -20°C before analysis. Blood samples for serum liver tests and fasting serum bile acids were taken and evaluated at the time of the first presentation of the patient. Serum liver tests were determined using routine laboratory techniques. Bile acids were analyzed by gas-liquid chromatography, plasma total cholesterol and triacylglycerol were assayed by enzymatic colorimetric tests, and high-density lipoprotein (HDL) cholesterol was evaluated by an immunoinhibition method on an automated Cobas Integra 800 analyser (Roche, UK). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula that states that total cholesterol quantity minus triacylglycerol/5 minus HDL cholesterol equals LDL cholesterol levels.

In the 48-h period preceding the expected time of delivery, patients enrolled in the study received Doppler velocimetric evaluation of fetal blood flow and non-stress tests to assess fetal well being. Pulsed-wave Doppler ultrasound of fetuses was performed with the Logic5 Pro device (General Electric, WI, USA) using 3.5- or 5-MHz probes. All recordings were obtained in the absence of fetal breathing and body movements. The following parameters were obtained and evaluated such as umbilical artery pulsatility index (UA PI), middle cerebral artery pulsatility index (MCA PI), and their numeric ratio (UA PI/MCA PI). Doppler velocimetry results were considered abnormal when, adjusted for gestational age, UA PI was higher than the 95th percentile, MCA PI was less than the 5th percentile, and UA/MCA ratio was greater than the 95th percentile [11].

Throughout the pregnancy period, fetal status was monitored in the same hospital every week. Pregnancy outcome and newborn status (e.g., term and mode of delivery, APGAR score at 1 and 5 min, asphyxial events, and newborn weight) were assessed by obstetricians and neonatologists. Fetal asphyxia was defined as an APGAR score of less than 7 at 5 min postpartum.

Statistical analysis

The results are expressed as mean \pm SD. Comparison of parametric data was analyzed using Student's *t* test, and non-parametric data were analyzed by χ^2 test between two groups. Correlation analysis was assessed by Kendall's tau_b correlation. Binary logistic regression was performed using the enter method to identify the independent variables predicting asphyxia. The fit of the model was assessed by the Hosmer–Lemeshow goodness-of-fit test. Statistical analysis was conducted with SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). All reported *P* values were two-sided, and *P* < 0.05 was considered statistically significant.

Results

One hundred eighty-seven patients were included in the study. The mean age of patients was 27.1 ± 4.5 (range 17–39), mean gestational age at delivery was 37.5 ± 1.1 weeks (range 35–39), mean exposure time to altered biochemical values was 35.6 ± 11.0 days (range 17–63). The sample included both primiparous (43; 23%) and multiparous women (144; 77%). Fifteen (8%) of the multiparous patients had a history of pruritus during previous pregnancy; of these, women 9 had a history of preterm delivery and 2 had a history of intrauterine fetal death. All patients were treated with UDCA. Gallstones were encountered in 17 (9.1%) cases. No stillbirths were observed. The mean APGAR score at the first minute was 7.3 ± 1.2 , and at 5 min was 8.3 ± 1.6 . Thirty-six newborns were declared as asphytic (19.2%). Pregnancy ended prematurely in 22 (11.7%) cases. Postnatal development was normal in all babies except one, which died on the fourth day postpartum due to complications of fetal asphyxia. Table 1 compares the clinical and biochemical parametric variations of the patients who delivered babies with APGAR < 7 and with APGAR \geq 7. There was a statistical significance in levels of TBA (42.4 ± 15.2 vs. 33.8 ± 12.9 $\mu\text{mol/L}$, *P* < 0.01), HDL (54.2 ± 15.9 vs. 61.3 ± 12.2 , *P* = 0.01), total cholesterol (279.0 ± 51.4 vs. 257.7 ± 51.6 , *P* = 0.02), and triacylglycerol (299.4 ± 94.6 vs. 260.4 ± 118.7) between the asphytic and non-asphytic group. There was no statistical significant difference in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and LDL cholesterol levels between the groups.

Table 1 Characteristics of asphytic and nonasphytic groups at time of diagnosis

	Group 1 (APGAR < 7) (n = 36)	Group 2 (APGAR \geq 7) (n = 151)	<i>P</i>
Age	22.8 \pm 3.8	26.7 \pm 4.4	0.22
Weight (kg)	72.4 \pm 4.7	72.1 \pm 5.8	0.71
AST (U/L)	216.1 \pm 80.6	198.5 \pm 81.5	0.24
ALT (U/L)	225.5 \pm 66.6	201.6 \pm 81.2	0.12
AP (U/L)	553.4 \pm 136.3	601.1 \pm 143.5	0.07
TBA ($\mu\text{mol/L}$)	42.4 \pm 15.2	33.8 \pm 12.9	<0.01
Total cholesterol (mg/dl)	279.0 \pm 51.4	257.7 \pm 51.6	0.02
LDL cholesterol (mg/dl)	155.5 \pm 47.1	152.2 \pm 43.0	0.67
HDL cholesterol (mg/dl)	54.2 \pm 15.9	61.3 \pm 12.2	0.01
Triacylglycerol (mg/dl)	299.4 \pm 94.6	257.7 \pm 51.6	0.03

ALT alanine aminotransferase, AST aspartate aminotransferase, AP alkaline phosphatase, TBA total bile acids, HDL high-density lipoprotein, LDL low-density lipoprotein

Table 2 Characteristics of asphytic and non-asphytic groups at time of delivery

	Group 1 (APGAR < 7) (n = 36)	Group 2 (APGAR \geq 7) (n = 151)	<i>P</i>
Exposure time (days)	38.1 \pm 7.9	30.2 \pm 8.2	<0.01
Cesarean section	11/36 (30.6%)	66/151 (43.7%)	0.18
Labor induction	17/36 (47.2%)	55/151 (36.4%)	0.23
Abnormal Non-stress test	7/36 (19.4%)	14/151 (9.3%)	0.13
Abnormal fetal Doppler values	8/36 (22.2%)	16/151 (10.6%)	0.09

Exposure time of the disease in asphytic group was significantly long than the non-asphytic group. There was no difference in the ratio of caesarean section, labor induction, abnormal non-stress test results, and abnormal fetal Doppler values between the two groups (Table 2).

The correlation coefficient between asphyxia and TBA, HDL, total cholesterol, triacylglycerol levels, and exposure time were respectively 0.19, -0.17, 0.14, 0.13, 0.29 (*P* < 0.05).

To expose potential factors that may help to predict fetal asphyxia in ICP, we used a binary multivariate logistic regression model. The factors that were found to be significant were selected for this model. Hosmer–Lemeshow statistic for the model was $\chi^2 = 8.715$, *df* = 8, *P* = 0.367. TBA levels (OR 1.04, 95% CI 1.01–1.08, *P* = 0.03) and exposure time (OR 1.11, 95% CI 1.05–1.17, *P* < 0.01) were the independent variables that significantly predicted fetal asphyxia in ICP (Table 3).

Table 3 Logistic regression analyzing factors affecting the occurrence of fetal asphyxia

	Odds ratio	95% CI	P
TBA ($\mu\text{mol/L}$)	1.048	1.016-1.081	0.03
Exposure time (days)	1.114	1.057-1.174	<0.01

TBA total bile acids

Discussion

Even though ICP decreases a pregnant patient's quality of life, it does not increase her mortality rate. However, fetal well being is in great jeopardy in this disease. The potential fetal complications include prematurity, meconial amniotic fluid aspiration, asphyxia, RDS, and intrauterine fetal death (IUFD). Even more dangerous than the aforementioned complication are complications such as intrauterine fetal death that may occur without any early warning signs of fetal distress on antenatal monitoring. The exact mechanism of these fetal complications is not clear. To date, there is no method that has been declared trustworthy for antenatal fetal monitoring in ICP [12]. Screening with non-stress tests or biophysical assessment was not proven to be a reliable predictor of fetal distress. Sudden fetal death, although rare before 37 weeks of pregnancy, does occur in 1–2% of cases [13]. As a result, in ICP patients, it has been recommended that delivery not be delayed after 37–38 weeks of gestation. In severe cases, when necessary, delivery has been suggested to be initiated even at the 36th week if fetal lung maturity has been established [3, 10, 14].

Total serum bile acid levels appear to be a better predictor of fetal outcome and can be used in antenatal monitoring of fetal well being. This may be explained by the fact that high bile acid concentrations decrease the surfactant formation and impair fetal lung maturation [8, 9]. Direct correlations between the intensity of elevation of bile acids and increased fetal risk have been observed and likewise fetal complications in ICP are rarely encountered in cases with TBA levels less than 40 $\mu\text{mol/L}$ [4]. The placenta plays a major role in protecting the fetus from the adverse effects of potentially toxic endogenous substances such as TBA [15]. Increased levels of TBA in maternal circulation, however, enhance placental transport and facilitate the generation of certain placental hormones which leads to significant constriction among chorionic vessels [16].

In animal models, hypercholanemia in the breeding animal impairs the ability of the trophoblasts to control the transport of bile acids [17], resulting in an inversely directed gradient on the two sides of the placenta and intensified vectorial transfer of bile acids to the fetus in a manner opposite that of the normal physiological system [18]. Interestingly, total serum bile acid elevation in pregnancy

does not always indicate ICP. A study from Argentina has shown that asymptomatic hypercholanemia of pregnancy, defined as TBA >11 $\mu\text{mol/L}$ in healthy pregnant women, did not result in the clinical problems of ICP [19]. However, in a case of diagnosed ICP with low TBA levels, sudden intrauterine fetal death at 39 weeks and 3 days of pregnancy has been reported [6]. Judging from the studies performed among ICP patients, there is certainly an inconsistency about the sufficiency of the utility of TBA levels in predicting fetal outcome. Therefore, it is important to assess other clinical factors that are possibly associated with fetal asphyxia as well, and to use this combined information to evaluate all of the data and make informed decisions concerning the management of an ICP patient.

Some authors suggested the possibility of a cumulative toxic effect of TBA on the fetus [6]. Supporting this hypothesis, our study concludes that elevated TBA levels and long exposure time increases the risk of asphyxia in fetuses born to ICP mothers, which points to a cumulative toxic effect of the altered biochemistry.

In our study, non-stress tests and fetal Doppler examinations failed to show fetal asphyxia before delivery. Previous studies also confirmed that traditional antenatal screening tests used routinely for prediction of fetal distress were not beneficial in cases of fetal asphyxia appearing in ICP [12].

Ursodeoxycholic acid is the most commonly applied treatment of choice for ICP today. Recent studies show a significant restoration in serum bilirubin, ALT, bile acid levels, as well as a trend towards a decrease in the intensity of the clinical complaints, mainly pruritus, in combined or mono therapies with UDCA. However, no statistically significant difference in fetal complication rates could be reported after the treatment [20–22]. All patients of our research group underwent UDCA therapy, so the efficacy of the drug was not questioned in our study.

The obstetrical management of ICP is, as of yet, not unequivocal although most obstetricians prefer intensive maternal–fetal surveillance and induction of labor at 37–38 weeks of gestation. In conclusion, our study suggests that levels of TBA and exposure time are the two most important predictive factors for fetal asphyxia in ICP. These factors may be used in planning time of delivery for better fetal outcomes and can help physicians have a more reasoned approach to the management of the patient with ICP.

Conflict of interest statement None.

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