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Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy

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Abstract

Objective—We sought to determine predictors of adverse neonatal outcomes in women with intrahepatic cholestasis of pregnancy (ICP).

Study Design—This study was a multicenter retrospective cohort study of all women diagnosed with ICP across 5 hospital facilities from January 2009 through December 2014. Obstetric and neonatal complications were evaluated according to total bile acid (TBA) level. Multivariable logistic regression models were developed to evaluate predictors of composite neonatal outcome (neonatal intensive care unit admission, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, transient tachypnea of the newborn, mechanical ventilation use, oxygen by nasal cannula, pneumonia, and stillbirth). Predictors including TBA level, hepatic transaminase level, gestational age at diagnosis, underlying liver disease, and use of ursodeoxycholic acid were evaluated.

Results—Of 233 women with ICP, 152 women had TBA levels 10–39.9 $\mu\text{mol/L}$, 55 had TBA 40–99.9 $\mu\text{mol/L}$, and 26 had TBA $\geq 100 \mu\text{mol/L}$. There was no difference in maternal age, ethnicity, or prepregnancy body mass index according to TBA level. Increasing TBA level was associated with higher hepatic transaminase and total bilirubin level ($P < .05$). TBA levels $\geq 100 \mu\text{mol/L}$ were associated with increased risk of stillbirth ($P < .01$). Increasing TBA level was also associated with earlier gestational age at diagnosis ($P < .01$) and ursodeoxycholic acid use ($P = .02$). After adjusting for confounders, no predictors were associated with composite neonatal morbidity. TBA 40–99.9 $\mu\text{mol/L}$ and TBA $\geq 100 \mu\text{mol/L}$ were associated with increased risk of meconium-stained amniotic fluid (adjusted odds ratio, 3.55; 95% confidence interval, 1.45–8.68 and adjusted odds ratio, 4.55; 95% confidence interval, 1.47–14.08, respectively).

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Conclusion—In women with ICP, TBA level $100 \mu\text{mol/L}$ was associated with increased risk of stillbirth. TBA $40 \mu\text{mol/L}$ was associated with increased risk of meconium-stained amniotic fluid.

Keywords

bile acid; intrahepatic cholestasis of pregnancy; neonatal outcome; ursodeoxycholic acid

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy characterized by pruritus, elevated total serum bile acids, and elevated liver enzymes. ICP is associated with increased risk of preterm birth (19-60%), meconium passage <37 weeks (17.9%), intrapartum nonreassuring fetal heart tracing (22-41%), respiratory distress syndrome (RDS) (29%), and stillbirth (0.75-7%).¹⁻⁴ Based on high rates of stillbirth and neonatal morbidity, early delivery is often advocated to reduce the risk of term stillbirth. In the absence of evidence-based guidelines for optimal timing of delivery, induction of labor at 36-37 weeks of gestation or after documenting fetal lung maturity is frequently recommended for pregnancies complicated by ICP.^{2,5,6}

Many studies have attempted to find the predictors of adverse neonatal outcome in women with ICP.⁷⁻¹⁰ Serum total bile acid (TBA) level $>40 \mu\text{mol/L}$ has been associated with increased risk of meconium staining, low Apgar scores, preterm delivery, and stillbirth.^{1,8} Other predictors such as level of transaminases, history of cholelithiasis, and hepatitis virus infection have been studied but the results are inconclusive.^{9,10} A more comprehensive investigation involving multiple neonatal outcomes and a wide variety of outcome predictors is needed to establish guidelines for optimal timing of delivery in pregnancies complicated by ICP. The aim of our study was to evaluate a wide variety of predictors of adverse neonatal outcomes in a large cohort of women with ICP in the United States.

Materials and Methods

We performed a multicenter retrospective cohort study of all women diagnosed with ICP across 5 regional hospitals including MedStar Washington Hospital Center (Washington, DC), MedStar Georgetown University Hospital (Washington, DC), Medstar Franklin Square Medical Center (Baltimore, MD), Medstar Harbor Hospital (Baltimore, MD), and Virginia Hospital Center (Arlington, VA) from January 2009 through December 2014. All participating institutions obtained institutional review board approval. Women with the diagnosis of ICP were identified through the electronic perinatal database in each hospital. Subsequent chart abstraction was undertaken to collect relevant outcome data. ICP was diagnosed by presence of pruritus without a rash and documented maximum serum TBA level of $10 \mu\text{mol/L}$. Women with TBA level $<10 \mu\text{mol/L}$ and pregnancies complicated by multiple gestations or infants with congenital and chromosomal abnormalities were excluded. Ursodeoxycholic acid was considered first-line therapy for the treatment of ICP in the study cohort at the discretion of the managing physician. Fetal monitoring was performed at each institution for patients with cholestasis of pregnancy. While there is some variation depending on gestational age of diagnosis, each patient received weekly or twice weekly biophysical profile following diagnosis with delivery planned for 36 1/7 to 37 6/7

weeks of gestation. Women with ICP were categorized based on their TBA level into 3 groups (10-39.9, 40-99.9, and 100 $\mu\text{mol/L}$). Information on maternal demographics, medical comorbidities, and serum biochemical parameters were collected for evaluation.

Pregnancy outcomes including delivery gestational age, spontaneous preterm delivery, iatrogenic preterm delivery, birthweight, mode of delivery, oligohydramnios, intrauterine growth restriction, placental abruption, preterm premature rupture of membrane (PPROM), concerning fetal heart tracing, chorioamnionitis, endometritis, postpartum hemorrhage, transfusion, stillbirth, neonatal intensive care unit (NICU) admission, hyperbilirubinemia, meconium-stained amniotic fluid, RDS or transient tachypnea of the newborn (TTN), and composite neonatal outcome were ascertained. A composite adverse neonatal outcome was created and defined as any of the following: NICU admission, hypoglycemia, hyperbilirubinemia, RDS, TTN, mechanical ventilation use, oxygen by nasal cannula, pneumonia, and stillbirth. PPRM was defined by rupture of membrane <37 weeks' gestation. Concerning fetal heart tracing was defined as recurrent variable or late decelerations with moderate variability, prolonged decelerations, or category 3 tracing. Providers who were caring for the women reviewed and independently characterized fetal heart tracings. Since fetal heart tracings were not accessible to authors, authors accepted the providers' interpretation. For analysis of concerning fetal heart tracing, women with nonlabor cesarean delivery were excluded. Hyperbilirubinemia was defined by neonatal hyperbilirubinemia that required phototherapy. Hypoglycemia was defined by neonatal hypoglycemia that required intravenous infusion. Diagnosis of RDS and TTN were made by the managing neonatologist and based on standard clinical guidelines.

Predictors for composite neonatal outcome including TBA level, gestational age at diagnosis of ICP, ursodeoxycholic acid use, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and preexisting liver disease were evaluated by multivariable logistic regression model.

Categories of TBA level were evaluated as a predictor for composite neonatal outcome, NICU admission, meconium-stained amniotic fluid, hyperbilirubinemia, RDS or TTN, and mechanical ventilation. Also, subgroup analysis was conducted after excluding women with iatrogenic preterm delivery.

A univariate receiver operating characteristic curve was also used to predict composite neonatal complications in association to TBA level. Sensitivity and specificity were calculated.

A previous study using a similar composite adverse neonatal outcome (fetal distress, major congenital anomalies, hyperbilirubinemia, meconium staining of amniotic fluid at delivery, meconium aspiration, pneumonia, respiratory distress and sepsis) reported that infants from women with TBA level 100 $\mu\text{mol/L}$ had a 60% chance of adverse neonatal outcome, whereas infants from women with TBA level 40-99.9 $\mu\text{mol/L}$ and 10-39.9 $\mu\text{mol/L}$ had a 19% and 29% chance of adverse neonatal outcome, respectively.¹⁰ We hypothesized that infants from women with TBA level 10-39.9 $\mu\text{mol/L}$ had a 20% chance, infants from women with TBA level 40-99.9 $\mu\text{mol/L}$ had a 40% chance, and infants from women with TBA level

100 $\mu\text{mol/L}$ had a 60% of chance of composite neonatal outcome. A sample size of 206 (123 women with TBA level 10-39.9, 62 women with TBA level 40-99.9, and 21 women with TBA level $\geq 100 \mu\text{mol/L}$) could achieve 80% power to detect a 20% difference in composite adverse neonatal outcome between TBA level 10-39.9 and 40-99.9 $\mu\text{mol/L}$ and 95% power to detect a difference of 40% between TBA level 10-39.9 and $\geq 100 \mu\text{mol/L}$ ($\alpha < .05$). We assumed 10% of data may be incomplete and sample size of 227 was calculated.

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc, Cary, NC). The maximum documented TBA level for a patient was categorized into 3 groups: 10-39.9, 40-99.9, and $\geq 100 \mu\text{mol/L}$. Student *t* test or Mann-Whitney *U* was used to assess continuous variables according to their distribution. The χ^2 analysis and Fisher exact test were used for the analysis of categorical variables. Multivariable logistic regression analysis was used to assess effects on composite neonatal outcomes, controlling for maternal age, race, site, any hypertensive disease, any diabetes, body mass index (BMI), and gestational age at delivery. For all tests, a *P* value $< .05$ was considered statistically significant.

Results

There were 72,970 women from all 5 centers who delivered from January 2009 through December 2014. ICP was a presumed diagnosis in 421 women (0.58%). Of these 421 women, 131 women were excluded due to lack of bile acid data in the inpatient record and 57 women were excluded because their documented TBA level was $< 10 \mu\text{mol/L}$. Of the remaining 233 women, 152 women had a TBA level 10-39.9 $\mu\text{mol/L}$, 55 had a TBA level 40-99.9 $\mu\text{mol/L}$, and 26 had a TBA level $\geq 100 \mu\text{mol/L}$. The overall incidence of confirmed ICP in women with a singleton gestation was 0.3% in our cohort.

Demographic and clinical data are shown in Table 1. There were no significant differences in maternal age, race, parity, prepregnancy BMI, any hypertensive disease, any diabetes, induction of labor, history of liver or biliary disease, maternal hepatitis B and C infection, and improvement of pruritus among the 3 groups of TBA level. The rate of induction of labor was high (89-91%) regardless of the level of bile acid. Increased TBA level was associated with higher AST, ALT, and total bilirubin level ($P < .05$). Women with TBA level 40-99.9 and $\geq 100 \mu\text{mol/L}$ were more likely to be on ursodeoxycholic acid and have early gestational age at diagnosis than women with TBA level $< 40 \mu\text{mol/L}$ ($P = .02$ and $< .01$, respectively).

Pregnancy outcomes are shown in Table 2. Women with TBA level 40-99.9 and $\geq 100 \mu\text{mol/L}$ were more likely to have preterm delivery < 37 weeks' gestation ($P = .01$). There was no difference in spontaneous preterm delivery among the 3 groups. Women with TBA level 40-99.9 and $\geq 100 \mu\text{mol/L}$ were more likely to have iatrogenic preterm delivery ($P < .01$), meconium-stained amniotic fluid ($P < .01$), and composite neonatal outcome ($P < .01$). All 4 stillbirths were found in the TBA $\geq 100 \mu\text{mol/L}$ group ($P < .01$). There was no significant difference in oligohydramnios, intrauterine growth restriction, mode of delivery, PPRM, placental abruption, chorioamnionitis, endometritis, postpartum hemorrhage, transfusion, NICU admission, hyperbilirubinemia, RDS or TTN, and mechanical ventilation use among

the 3 groups of TBA level. Concerning fetal heart tracing was higher in women with bile acid level 40-99.9 and $100 \mu\text{mol/L}$, but the difference was not statistically significant ($P = .08$).

As shown in Table 3, after adjusting for confounders, there were no predictors associated with increased risk of composite neonatal outcome. Also, we conducted a subgroup analysis by excluding any women who had iatrogenic preterm delivery (data not shown). There were no predictors associated with increased risk of composite neonatal outcome.

Table 4 shows the multivariable logistic regression analysis in which bile acid levels were used as a categorical predictor for composite neonatal outcome and individual neonatal outcomes. TBA level 40-99.9 and $100 \mu\text{mol/L}$ were associated with increased risk of meconium-stained amniotic fluid after adjusting for maternal age, prepregnancy BMI, any hypertensive disorder, any diabetes, and gestational age at delivery. After excluding any women who had iatrogenic preterm delivery, TBA level 40-99.9 $\mu\text{mol/L}$ was associated with increased risk of meconium-stained amniotic fluid.

Characteristics of stillbirth cases are shown in Table 5. In our study, stillbirth occurred at 24-37 weeks of gestation in women with TBA level 114-509 $\mu\text{mol/L}$. Most of these patients (3 of 4) were followed by weekly or twice weekly biophysical profiles and had reassuring findings within 1 week of stillbirth. One case that did not have biophysical profiles was diagnosed at 23 weeks of gestation and had stillbirth at 24 weeks of gestation. One case was characterized by worsening bile acid level despite ursodeoxycholic acid treatment. In another case, stillbirth occurred even with improving bile acid level (114-36 $\mu\text{mol/L}$). The patient was on ursodeoxycholic acid and last bile acid level was performed within 1 week of stillbirth.

A univariate receiver operating characteristic curve analysis indicated that the optimal cutoff for TBA level was 69 $\mu\text{mol/L}$; yielding a 33.0% sensitivity and 89.5% specificity for composite adverse neonatal outcome (area under curve 0.59). The cutoff for TBA level 40 $\mu\text{mol/L}$ would yield a 47.8% sensitivity and 72.7% specificity, while the cutoff for TBA level 100 $\mu\text{mol/L}$ would yield a 20% sensitivity and 93.0% specificity.

Comment

We found that women with increased TBA level (40-99.9 and $100 \mu\text{mol/L}$) were more likely to be on ursodeoxycholic acid and to have higher liver transaminase levels, total bilirubin level, iatrogenic preterm delivery, and meconium-stained amniotic fluid. After adjusting for confounders, increased TBA level (40-99.9 and $100 \mu\text{mol/L}$) was not associated with increased rate of composite neonatal outcome, NICU admission, hyperbilirubinemia, RDS or TTN, and mechanical ventilation use. However, increased TBA level (40-99.9 and $100 \mu\text{mol/L}$) was associated with increased risk of meconium-stained amniotic fluid even after adjusting for confounders. There were 4 cases of stillbirth, all of which had TBA level $100 \mu\text{mol/L}$.

Induction of labor for women with ICP was very common in our practice. Many authors have advocated the implementation of elective early delivery for ICP⁷. This is based on

studies showing that most stillbirths occurred >37 weeks of gestation.³ However, at present, the American Congress of Obstetricians and Gynecologists does not have a recommendation on optimal timing of delivery for women with ICP. To date, there are no randomized studies investigating the optimal timing of delivery. One decision analysis study and large retrospective study showed that delivering at 36 weeks of gestation was optimal strategy considering risk of stillbirth and risk of prematurity.^{6,11} However, these studies did not consider the level of bile acid, which could influence the risk of stillbirth. In our study, iatrogenic preterm delivery was higher as TBA level increased, especially in women with TBA level $\geq 100 \mu\text{mol/L}$. This may reflect concerns with risk of stillbirth that prompted providers to deliver <37 weeks of gestation.

The rate of stillbirth in women with ICP is reported to be 1.5-2.4%, but it has been documented to be as high as 7%.^{3,5,8,12} Importantly, all the cases of stillbirth in our cohort occurred in women with TBA level $\geq 100 \mu\text{mol/L}$ and the rate of stillbirth in this group was 15% in our cohort. This was consistent with previous research showing 10% risk of stillbirth in women with TBA level $\geq 100 \mu\text{mol/L}$.¹³

Ursodeoxycholic acid, a tertiary bile acid present in normal human serum, is common treatment of ICP.⁷ In 1 randomized control study of 125 women with ICP, there was significant reduction in pruritus in women with ursodeoxycholic acid treatment compared with placebo group.¹⁴ One metaanalysis of randomized controlled trials reported ursodeoxycholic acid improved pruritus and liver function test results including bile acid level.¹⁵ A recent Cochrane review showed decreased rates of preterm delivery in women with ursodeoxycholic acid treatment, but did not show improvement in spontaneous preterm delivery, stillbirth, NICU admission, and meconium-stained amniotic fluid.¹⁶ However, no single randomized study has demonstrated improved neonatal outcome.¹⁶ In our study, after adjusting for confounders, ursodeoxycholic acid use was not associated with a reduction in the risk of composite neonatal outcome.

TBA level $\geq 40 \mu\text{mol/L}$ is a wellknown predictor of adverse neonatal outcome in ICP.^{1,8} In this study, although there was a trend toward an increased risk of neonatal morbidity, there was no statistically significant difference in composite neonatal outcome across bile acid groups after adjusting confounders. We speculate that this is primarily due to a small sample size and lack of a control group consisting of normal singleton pregnancies. We did find that TBA $\geq 40 \mu\text{mol/L}$ was associated with an increased risk of meconium-stained amniotic fluid even after adjusting for confounders. The optimal cutoff for TBA level was $69 \mu\text{mol/L}$ with low sensitivity but with relatively high specificity in predicting composite adverse neonatal outcome.

Early onset of disease has been reported to be a risk factor of adverse neonatal outcomes. However, previous research did not adjust for bile acid and liver transaminase levels.^{14,20} It is important to adjust for bile acid and transaminase levels, since early onset of disease is also reported to be associated with higher level of bile acid and liver enzymes.¹² In our study, after adjusting for confounders, early onset of disease was not associated with increased risk of composite neonatal outcome.

As previously discussed, meconium-stained amniotic fluid occurs more likely at later compared to earlier gestation,¹⁸ and it is associated with fetal acidemia.^{19,20} Interestingly, in our study, higher rate of meconium-stained amniotic fluid was seen in women with TBA 40-99.9 and 100 $\mu\text{mol/L}$ even after controlling for gestational age. The basis for this clinical finding is not completely understood, but may be related to high TBA levels, which results in fetal distress and meconium passage at an earlier gestational age.

The major limitation of our study is its retrospective nature. We could not access prenatal data that were not included in the inpatient record. There were 131 women who were excluded due to lack of TBA results and 57 others who were not included because the TBA documented in their inpatient record was $<10 \mu\text{mol/L}$. There were 33 women missing AST level, 34 women missing ALT level, and 78 women missing total bilirubin level. Due to the large number of missing total bilirubin levels, we could not evaluate adjusted odds ratio of total bilirubin level. Due to our retrospective design, some women had serial bile acid level measurements and some women had only 1 value reported. As a result, we could only evaluate outcomes based on maximum documented bile acid level and not trending bile acid levels over time. Our study was not large enough to evaluate rare outcomes such as neonatal asphyxia, sepsis, and intracranial hemorrhage. Also, authors did not have access to fetal heart tracings; we relied on the interpretation of the providers. Lastly, our composite neonatal outcomes were based on previous literature review and included significant factors that alter neonatal prognosis or prolong neonatal hospital stay.^{1,8,9,12,14-17}

The strength of our study is the consideration of a wide variety of predictors and inclusion of various neonatal outcomes. We used adjusted odds ratio not only for known risk factors such as maternal complications and gestational age at delivery, but also possible predictors such as bile acid level, gestational age at diagnosis, ursodeoxycholic acid use, AST, ALT, and preexisting liver disease when we evaluated composite neonatal outcome. Our results are generalizable as we included multiple centers with diverse ethnicities. To our knowledge, our study is so far the largest multicenter study in the United States to report outcomes in 233 patients with ICP.

Bile acid level 100 $\mu\text{mol/L}$ was associated with an increased risk of stillbirth. This information may help providers when they are considering timing of delivery for gestations complicated by ICP. The optimal cutoff for TBA level was 69 $\mu\text{mol/L}$ for an adverse composite neonatal outcome. In our study, ursodeoxycholic acid was not associated with a reduction in the risk of composite neonatal outcome. Further large prospective trials are required to determine the efficacy of ursodeoxycholic acid and optimal timing of delivery to balance the risks of neonatal prematurity and stillbirth in pregnancies complicated by ICP.

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Table 1
Demographic data and pregnancy comorbidities of patients with intrahepatic cholestasis of pregnancy by bile acid level

Variable	TBA 10–39.9 $\mu\text{mol/L}$ n = 152	TBA 40–99.9 $\mu\text{mol/L}$ n = 55	TBA 100 $\mu\text{mol/L}$ n = 26	P value
Mean maternal age, y, $\pm$ SD	29.7 $\pm$ 6.0	30.4 $\pm$ 5.6	30.2 $\pm$ 7.4	.73
Nulliparous	66 (43.4)	28 (50.9)	12 (46.2)	.63
Race/ethnicity				.22
White	52 (34.2)	23 (41.8)	11 (42.3)	
African American	37 (24.3)	5 (9.1)	7 (26.9)	
Hispanic	39 (25.7)	14 (25.5)	3 (11.5)	
Asian	16 (10.5)	7 (12.7)	2 (7.7)	
Other	8 (5.3)	6 (10.9)	3 (11.5)	
Induction of labor	116 (88.6)	40 (88.9)	21 (91.3)	1
Prepregnancy BMI, ^a kg/m ²				.41
Underweight/normal weight	83 (54.6)	37 (67.3)	14 (53.9)	
Overweight	36 (23.7)	12 (21.8)	7 (26.9)	
Obese	33 (21.7)	6 (10.9)	5 (19.2)	
Any diabetes	13 (8.6)	10 (18.2)	1 (3.9)	.09
Preexisting	2 (1.3)	1 (1.8)	0 (0)	1
Gestational	11 (7.2)	9 (16.4)	1 (3.9)	.11
Any hypertensive disease	16 (10.5)	5 (9.1)	0 (0)	.23
Chronic hypertension	5 (3.3)	0 (0)	0 (0)	.48
Preeclampsia	11 (7.2)	4 (7.3)	0 (0)	.47
Gestational hypertension	4 (2.6)	2 (3.6)	0 (0)	.83
ICP in prior pregnancy	22 (25.9)	10 (37.0)	4 (26.7)	.54
History of liver or biliary disease ^b	16 (10.5)	4 (7.3)	5 (19.2)	.24
Maternal hepatitis B infection	1 (0.7)	0 (0)	0 (0)	1
Maternal hepatitis C infection	7 (4.6)	2 (3.6)	2 (7.7)	.79
Smoking	9 (6.0)	0 (0)	0 (0)	.14
Ursodiol use	67 (44.1)	35 (63.6)	16 (61.54)	.02
Improvement of pruritus	49 (43.0)	14 (32.6)	8 (34.78)	.44
Gestational age at diagnosis, mean $\pm$ SD	34.2 $\pm$ 3.9	33.6 $\pm$ 4.3	30.6 $\pm$ 5.8	< .01
Highest AST, IU/L, mean $\pm$ SD	97.7 $\pm$ 114.3	172.04 $\pm$ 161.33	215.77 $\pm$ 271.88	< .01
Highest ALT, IU/L, mean $\pm$ SD	64.3 $\pm$ 68.7	120.71 $\pm$ 112.95	120.77 $\pm$ 120.77	< .01
Highest ALP, IU/L, mean $\pm$ SD	228.9 $\pm$ 101.4	267.73 $\pm$ 99.2	270.56 $\pm$ 107.31	.06
Total bilirubin, mg/dL, mean $\pm$ SD	0.496 $\pm$ 0.320	0.626 $\pm$ 0.490	0.856 $\pm$ 1.005	.02

Numbers shown as n (%) unless otherwise specified.

ALP, alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *ICP*, intrahepatic cholestasis of pregnancy; *TBA*, maximum documented total bile acid.

^aUnderweight <18.5, normal weight 18.5–24.9, overweight 25.0–29.9, obese 30.0–34.9, and morbidly obese ≥35.0;

^bIncludes cholecystitis, cholelithiasis, and liver sarcoidosis.

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Table 2
Pregnancy outcomes of patients with intrahepatic cholestasis of pregnancy by bile acid level

Variable	TBA 10–39.9 $\mu\text{mol/L}$ n = 152	TBA 40–99.9 $\mu\text{mol/L}$ n = 55	TBA 100 $\mu\text{mol/L}$ n = 26	P value
Gestational age at delivery, wk				.01
22–<34	2 (1.3)	1 (1.8)	2 (7.7)	
34–<37	27 (17.8)	16 (29.1)	11 (42.3)	
37	123 (80.9)	38 (69.1)	13 (50.0)	
Spontaneous preterm delivery	7 (4.6)	4 (7.3)	1 (3.85)	.71
Iatrogenic preterm delivery	22 (14.5)	13 (23.6)	12 (46.2)	< .01
Birthweight group, g				.18
<2500	12 (7.9)	9 (16.4)	5 (19.2)	
2500–4000	137 (90.1)	46 (83.6)	21 (80.8)	
>4000	3 (2.0)	0 (0)	0 (0)	
Mode of delivery				.64
Vaginal	89 (58.6)	33 (60.0)	15 (57.7)	
Operative vaginal	5 (3.3)	0 (0)	2 (7.7)	
Cesarean	58 (38.2)	22 (40.0)	9 (34.6)	
Oligohydramnios	4 (2.6)	1 (1.8)	2 (7.7)	.28
IUGR ^a	7 (4.6)	5 (9.1)	1 (4.0)	.46
PPROM ^b	6 (4.0)	3 (5.5)	1 (3.9)	.88
Concerning fetal heart tracing ^c	50 (39.1)	26 (57.8)	9 (50.0)	.08
Placental abruption	3 (2.0)	0 (0)	0 (0)	.70
Chorioamnionitis	4 (2.6)	4 (7.3)	0 (0)	.22
Endometritis	2 (1.3)	2 (3.7)	0 (0)	.56
Postpartum hemorrhage	15 (9.9)	7 (12.7)	0 (0)	.17
Transfusion	2 (1.3)	2 (3.6)	1 (3.9)	.26
Stillbirth	0 (0)	0 (0)	4 (15.4)	< .01
NICU admission	31 (20.4)	15 (27.3)	4 (18.2)	.52
Hyperbilirubinemia ^d	17 (11.3)	13 (23.6)	5 (22.7)	.06
Meconium-stained amniotic fluid	15 (10)	14 (25.9)	9 (36.0)	< .01
RDS or TTN	16 (10.6)	8 (14.6)	3 (13.6)	.71
Mechanical ventilation use	9 (6.0)	6 (11.0)	3 (13.6)	.21
Composite neonatal outcome ^e	48 (32.0)	26 (49.1)	16 (61.5)	< .01

Numbers shown as n (%) unless otherwise specified.

IUGR, intrauterine growth restriction; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membrane; *RDS*, respiratory distress syndrome; *TBA*, maximum documented total bile acid; *TTN*, transient tachypnea of newborn.

^aBirthweight <5%;

^bBefore 37 wk gestation;

^cRecurrent variable or late deceleration with moderate variability, prolonged deceleration, or category 3 tracing;

^dRequiring phototherapy;

^eIncludes any of: NICU admission, hypoglycemia requiring intravenous fluid, hyperbilirubinemia requiring phototherapy, meconium-stained amniotic fluid, RDS/TTN, mechanical ventilation use oxygen by nasal cannula, pneumonia, and stillbirth.

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Table 3
Adjusted ORs for predictors of composite neonatal outcome in intrahepatic cholestasis of pregnancy

Variable	CNO, adjusted OR ^a (95% CI) ^b
TBA, $\mu\text{mol/L}$ ^c	
40–99.9	1.22 (0.41–3.63)
100	2.90 (0.67–12.61)
GA at diagnosis, wk ^d	
0–<34	0.23 (0.05–1.12)
34–<37	0.26 (0.06–1.12)
Ursodeoxycholic acid use	2.44 (0.77–7.73)
AST, IU/L ^e	
40–79.9	2.09 (0.37–11.96)
80	0.80 (0.10–6.166)
ALT, IU/L ^f	
40–79.9	0.37 (0.06–2.41)
80	0.67 (0.10–4.80)
Preexisting liver disease ^g	0.264 (0.05–1.56)

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CI*, confidence interval; *CNO*, composite neonatal outcome; *GA*, gestational age; *OR*, odds ratio; *TBA*, maximum documented total bile acid.

^a Adjusted for maternal age, race, site, any hypertensive disorder, any diabetes, body mass index, GA at delivery, TBA level, GA at diagnosis of intrahepatic cholestasis of pregnancy, ursodeoxycholic acid use, AST and ALT, and preexisting liver disease;

^b Includes any of: neonatal intensive care unit admission, hypoglycemia requiring intravenous fluid, hyperbilirubinemia requiring phototherapy, meconium-stained amniotic fluid, respiratory distress syndrome/transient tachypnea of newborn, mechanical ventilation use oxygen by nasal cannula, pneumonia, and stillbirth;

^c Reference category is 0–39.9 $\mu\text{mol/L}$;

^d Reference category is < 37 wk of gestation;

^e Reference category is 0–< 40 IU/L;

^f Reference category is 0–<40 IU/L;

^g Includes hepatitis B and C virus infection, cholecystitis, cholelithiasis, and liver sarcoidosis.

Adjusted odds ratio for total bile acid level in intrahepatic cholestasis of pregnancy

Table 4

Variable	CNO, adjusted OR (95% CI) ^{a,b}	NICU, adjusted OR (95% CI) ^a	Meconium-stained amniotic fluid, adjusted OR (95% CI) ^a	Hyperbilirubinemia, adjusted OR (95% CI) ^{a,c}	RDS or TTN, adjusted OR (95% CI) ^a	Mechanical ventilation, adjusted OR (95% CI) ^{a,d}
TBA, ^e 40–99.9 μ mol/L	1.221 (0.411–3.626)	1.13 (0.46–2.75)	3.55 (1.45–8.68)	2.31 (0.804–6.65)	1.49 (0.51–4.31)	2.37 (0.65–8.67)
TBA, ^e 100 μ mol/L	2.904 (0.669–12.608)	0.42 (0.09–1.92)	4.55 (1.47–14.08)	2.13 (0.50–9.16)	0.82 (0.15–4.44)	1.55 (0.25–9.49)
After excluding iatrogenic preterm deliveries ^f						
TBA, ^e 40–99.9 μ mol/L	1.30 (0.32–5.28)	0.83 (0.31–2.27)	3.55 (1.41–9.60)	2.92 (0.73–11.63)	0.83 (0.22–3.14)	2.37 (0.65–8.67)
TBA, ^e 100 μ mol/L	4.28 (0.71–25.83)	N/A	3.56 (0.90–14.20)	1.71 (0.83–36.67)	N/A	N/A

CI, confidence interval; CNO, composite neonatal outcome; OR, odds ratio; N/A, not applicable (there was no patient with outcomes); NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; TBA, maximum documented total bile acid; TTN, transient tachypnea of newborn.

^a Adjusted for maternal age, prepregnancy body mass index, any hypertensive disorder, any diabetes, and gestational age at delivery;

^b Includes any of: NICU admission, hypoglycemia requiring intravenous fluid, hyperbilirubinemia requiring phototherapy, meconium-stained amniotic fluid, RDS/TTN, mechanical ventilation use oxygen by nasal cannula, pneumonia, and stillbirth;

^c Requiring phototherapy;

^d Continuous positive airway pressure;

^e Reference category is 0–39.9;

^f Induction of labor at <37 wk of gestation.

Table 5
Characteristics of stillbirth cases

Characteristic	Case A	Case B	Case C	Case D
Maternal age, y	20	32	25	39
Gestational age at stillbirth, wk	37 1/7	35 3/7	24 1/7	35 5/7
Onset of pruritus, wk	35	31	23	32
Gestational age at diagnosis, wk	37	33	20	32
Initial bile acid level, $\mu\text{mol/L}$	261	106.1	128	57
Highest bile acid level, $\mu\text{mol/L}$	261	509.1	128	114
Last bile acid level, $\mu\text{mol/L}$	261	509.1	128	36
Highest AST, IU/L	54	112	37	356
Highest ALT, IU/L	91	124	26	424
Ursodeoxycholic acid use	No	Yes (1200 mg/d)	Yes (1000 mg/d)	Yes (1000 mg/d)
Fetal monitoring	BPP	BPP	None	BPP
Birthweight, g	2981	2051	438	2927
Sex of fetus	Male	Female	Female	Male
Karyotype testing	46 XY	N/A	46XX	N/A
Congenital abnormalities	No	No	No	No
Maternal complications	None	Liver sarcoidosis	Elevated transaminases prior to pregnancy	None

In case A, bile acid was sent at 36 wk of gestation, but there were no results until 37 1/7 wk of gestation. In meantime, she was monitored by BPP. Case A, B had BPP 10/10 day before stillbirth.

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *BPP*, biophysical profile; *N/A*, not applicable.