

Cord blood troponin I levels: biomarker evidence of fetal cardiac injury in intrahepatic cholestasis of pregnancy



Itamar D. Futterman, MD; Hitangee Jain; Rodney A. McLaren Jr; Jonathan K. Mays, MD

BACKGROUND: Intrahepatic cholestasis of pregnancy has been linked to sudden stillbirth. The suddenness of the stillbirths in these cases have led clinicians to suspect that the pathogenesis of stillbirth in women with intrahepatic cholestasis of pregnancy is not related to asphyxia but rather to an undefined etiology. One leading hypothesis relates certain bile acid metabolites to myocardial injury.

OBJECTIVE: The purpose of this study was to determine whether cord blood troponin I levels are increased in fetuses born to mothers with a diagnosis of intrahepatic cholestasis of pregnancy.

STUDY DESIGN: A prospective, case-control study was performed at a single institution between 2017 to 2019 in which 87 pregnant patients with a diagnosis of intrahepatic cholestasis of pregnancy (total bile acids $\geq 10 \mu\text{mol/L}$) were enrolled as cases and 122 randomly selected pregnant patients (asymptomatic with intrapartum total bile acids $< 10 \mu\text{mol/L}$) were enrolled as controls. Cord blood troponin I levels were measured at delivery in both groups using a commercially available chemiluminescent immunoassay. Values $\leq 0.04 \text{ ng/mL}$ were considered negative. Values $> 0.04 \text{ ng/mL}$ were considered positive. The primary outcome was the presence of elevated troponin levels in both cases and controls as a surrogate marker for cardiac status. Our secondary outcomes included neonatal intensive care unit stay, low Apgar scores, neonatal acidosis, and hypoxia indicated by cord blood pH and base excess levels at the time of birth. Chi square and *t* tests were performed to compare social and obstetrical variables. A *P* value of $< .05$ was considered significant. A stratification by total bile acids range of $< 40 \mu\text{mol/L}$, 40 to 100 $\mu\text{mol/L}$, and $> 100 \mu\text{mol/L}$ was performed to assess the relationship between the different severities of intrahepatic cholestasis of pregnancy (by risk of fetal demise with those with total bile acids of $> 100 \mu\text{mol/L}$ considered at greatest risk) and the likelihood of a positive troponin I result. Finally, a logistic regression analysis was performed to determine if levels of $\geq 10 \mu\text{mol/L}$ were associated with elevated troponin levels.

RESULTS: The mean gestational age at delivery was 38.96 ± 1.47 and 37.71 ± 1.59 weeks of gestation in the controls and cases respectively ($P < .001$). The mean total bile acids values were $5.2 \pm 1.28 \text{ ng/mL}$ and $43.2 \pm 40.62 \text{ ng/mL}$ in the controls and cases respectively ($P < .001$). Cord blood troponin I was positive in 15 of 122 (12.30%) controls and in 20 of 87 (22.99%) cases. ($P < .001$). When further stratified by total bile acids levels of < 40 , 40 to 100, and $> 100 \mu\text{mol/L}$, we found a positive correlation between higher total bile acids levels and a positive troponin I test ($P = .002$). When controlling for gestational age at delivery, maternal age, and body mass index, higher total bile acids levels were associated with a positive troponin I level (adjusted odds ratio, 1.015; 95% confidence interval, 1.004–1.026).

CONCLUSION: Elevated troponin I was more likely to be found in patients with intrahepatic cholestasis of pregnancy than in those without intrahepatic cholestasis of pregnancy. When stratified by total bile acids levels, a positive troponin I level was more likely to be found with higher levels of total bile acids. In addition, as total bile acids levels increased, they were more likely to be associated with a positive troponin I level. Although there were no stillbirths in our cohort, our findings suggest a potential relationship between cardiac injury and high levels of total bile acids demonstrated by the presence of elevated troponin I levels in cord blood at the time of birth.

Key words: intrahepatic cholestasis of pregnancy, myocardial injury, troponin I

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Maimonides Medical Center, Brooklyn, NY (Futterman); Brooklyn College, Brooklyn, NY (Jain); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA (McLaren); Department of Obstetrics and Gynecology, New York City Health + Hospitals, Metropolitan Hospital New York, NY (Mays)

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Corresponding author: Itamar D. Futterman, MD. ldf8788@gmail.com

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AJOG Global Reports at a Glance

Why was this study conducted?

This study aimed to determine whether cord blood troponin I levels are increased in fetuses born to mothers with a diagnosis of intrahepatic cholestasis of pregnancy (ICP), serving as a surrogate marker for fetal cardiac injury and plausible explanation for intrauterine fetal demise.

Key findings

There was a positive correlation between increasing total bile acids (TBA) concentrations and elevated troponin I in cord blood of neonates born to pregnant people whose pregnancy was complicated by ICP.

What does this add to what is known?

Our findings support previous research linking fetal death by cardiac injury to ICP secondary to elevated TBA. Although a correlation between TBA and fetal cardiac injury has been explored previously, the correlation with troponin I levels is novel, suggesting that myocardial death could be mediated by bile acids.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) occurs primarily in the second and third trimester of pregnancy and is characterized by intense pruritus and the absence of a skin rash. The incidence of ICP ranges from 0.1% to 15% with significant variations between ethnic groups and geographic regions.¹ Others have described both maternal and neonatal morbidities as a consequence of ICP, including maternal hemorrhage, preeclampsia, fetal distress, meconium staining, preterm birth, neonatal respiratory distress, neonatal prematurity, and stillbirth.² Of utmost concern, however, is the incidence of stillbirth, which has been described with an estimated prevalence of 0.1% to 0.3%.^{3,4} The suddenness of the stillbirths in these cases have led clinicians to suspect that the pathogenesis of stillbirth in women with ICP is not related to asphyxia but rather to an undefined etiology. One leading hypothesis relates certain bile acid metabolites to cardiac arrhythmias and myocardial injury in animal models.⁵ Some studies have demonstrated an association between ICP and significant cardiac findings on fetal echocardiography (demonstrating fetal atrial flutter, refractory supraventricular tachycardia, and bradycardia preceding a stillbirth).^{6–10} In addition, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker used to diagnose heart failure and left ventricular

dysfunction, was found in fetal umbilical venous blood in pregnancies complicated by ICP.¹¹

Troponin I, an established biomarker associated with myocardial injury, has been shown to be absent in healthy term neonates and seems to be unrelated to maternal troponin levels at birth.¹²

Troponin I is a protein subunit found in cardiac muscle, which forms a complex with troponin C and T to regulate myocardial contraction and relaxation by facilitating the interaction between actin and myosin.¹³ Elevated concentrations of troponin I are characteristic of cardiac injury because the enzyme is exclusively released upon cardiac myocyte death.^{13,14} In addition to cardiac trauma, elevations in troponin I concentrations have been linked to both infectious and asphyxiated processes.^{15–17}

With the current evidence highlighting the difficulties in identifying fetuses at risk for cardiac and hypoxic events, we conducted this study to examine if total bile acid (TBA) levels could be associated with elevated cord-blood troponin I levels, fetal acidosis, and low Apgar scores in neonates born to mothers with ICP.

Materials and methods

A prospective, case-controlled study was performed at a single institution between 2017 and 2019 in which 87 pregnant patients with a diagnosis of ICP (TBA ≥ 10 $\mu\text{mol/L}$) were enrolled as cases and

122 randomly selected pregnant patients (asymptomatic with intrapartum TBA < 10 $\mu\text{mol/L}$) were enrolled as controls (institutional review board approval #4783). Those who received a diagnosis of ICP were followed and managed by our institutional ICP protocol previously described.¹⁸ Our institutional protocol called for measuring TBA and liver enzyme levels at the time of first clinical suspicion of ICP, usually by presenting with itching of the palms, soles, extremities, or abdomen without clear signs of a rash. Once serum TBA levels of ≥ 10 $\mu\text{mol/L}$ confirmed the diagnosis, the patient's instructions were to return for close antenatal surveillance, which included a 2 to 3 times per week fetal non-stress test and biophysical profile. Next, we offered 2 doses of betamethasone for fetal lung maturation 24 hours apart. These were offered for those diagnosed up to 36 weeks and 6 days of gestation. An amniocentesis was also offered based on the previously described benefits of both detecting fetal distress (by meconium being present at the time of amniocentesis) and by confirming lung maturation before a premature delivery. Finally, ursodeoxycholic acid titration was offered and used for symptomatic relief to treat body itching up to 600 mg 3 times per day. Unless clear contraindications for vaginal birth (nonvertex, more than 2 previous cesarean deliveries, etc.), patients were offered induction after 36 weeks and 0 days or after lung maturation was proven by amniocentesis.

Informed consent was obtained from both cases and controls. This study was approved by the internal review board at our institution. Cases included singleton, nonanomalous fetuses born to mothers diagnosed with ICP during the pregnancy. Both cases and controls were recruited close to the timing of delivery to ensure that they met all the inclusion criteria. Controls were excluded if they were found to have any of the following: TBA ≥ 10 $\mu\text{mol/L}$, liver enzymes that were 3 times higher than the normal limits, or a history of ICP in a previous pregnancy. All participants were excluded if any of the following were present: multiple gestations, labor complicated by fetal distress, preterm labor,

or hypertensive disorders of pregnancy (HDPs). Fetal distress was defined as an intrapartum diagnosis of either a persistent category II fetal heart rate tracing or a category III fetal heart rate tracing at any time during the labor process that altered the delivery management and required an emergent or urgent delivery. We deliberately waited until close to delivery to recruit patients to ensure that none of the cases or controls would have been managed by emergency delivery for nonreassuring fetal heart rate. The exclusion of patients with preeclampsia that was diagnosed in the postpartum period was to ensure that no other cause of elevated troponin was present in either cohort. This aligns with the known relationship between processes such as preeclampsia and ICP and neonatal O₂ disruption processes.¹⁹ Because we could not comment on the relationship between the timing of the preeclampsia diagnosis and how soon after an elevated troponin would ensue, all cases were excluded, including those diagnosed in the postpartum period. Those who agreed to participate and who met all inclusion criteria, after signing a consent form, underwent routine admission laboratory tests with the addition of serum TBA levels. A green top tube was used to collect cord blood serum for troponin I measurements at

the time of delivery in both groups. Troponin I measurements were performed using a commercially available chemiluminescent immunoassay manufactured by Siemens (Dimensions Vista System), PA, USA. The analytical measurement range for the assay was 0.015 to 40 ng/mL. The coefficient of variation of 10% for troponin I levels of <0.04 ng/mL was established. Values ≤0.04 ng/mL were considered negative. Values >0.04 ng/mL were considered positive. Per institutional protocol, all patients had umbilical cord blood drawn at delivery that was sent for laboratory analysis of umbilical cord gasses. All umbilical cord blood troponin I samples were run by technicians employed in the hospital laboratory. The technicians were blinded in terms of the clinical designation of the study samples. The primary outcome was the presence of elevated troponin levels in both cases and controls as a surrogate marker for cardiac status. Our secondary outcomes included, neonatal intensive care unit (NICU) stay, low Apgar scores, neonatal acidosis, and hypoxia indicated by umbilical cord blood pH and base excess levels at the time of birth. A power analysis was performed. Assuming that 8% of umbilical cord blood from patients with normal TBA levels will have elevated troponins²⁰ and that 24% of

umbilical cord blood from patients with elevated TBA will have elevated troponin I, a total of 82 patients in each group was needed to detect a difference using a 2-sided test with a beta error of 80% and an alpha error of 5%. Chi-square and *t* tests were performed to compare social and obstetrical variables. A *P* value of <.05 was considered significant. A stratification by TBA range of <40 μmol/L, 40 to 100 μmol/L, and >100 μmol/L was performed to assess the relationship between the different severities of ICP (by risk of fetal demise with those with a TBA of >100 μmol/L considered to have the greatest risk) and the likelihood of a positive troponin I result, fetal acidosis (pH <7.1), and fetal hypoxic injury (Base excess <-12). Finally, a logistic regression analysis was performed to determine if levels of ≥10 μmol/L (TBA analyzed as a categorical variable to be consistent with the definition of ICP) were associated with elevated troponin levels after adjusting for variables that were significantly different between groups in the univariate analysis. All data were analyzed using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, NC).

Results

The demographics and obstetrical outcomes are summarized in the [Table 1](#).

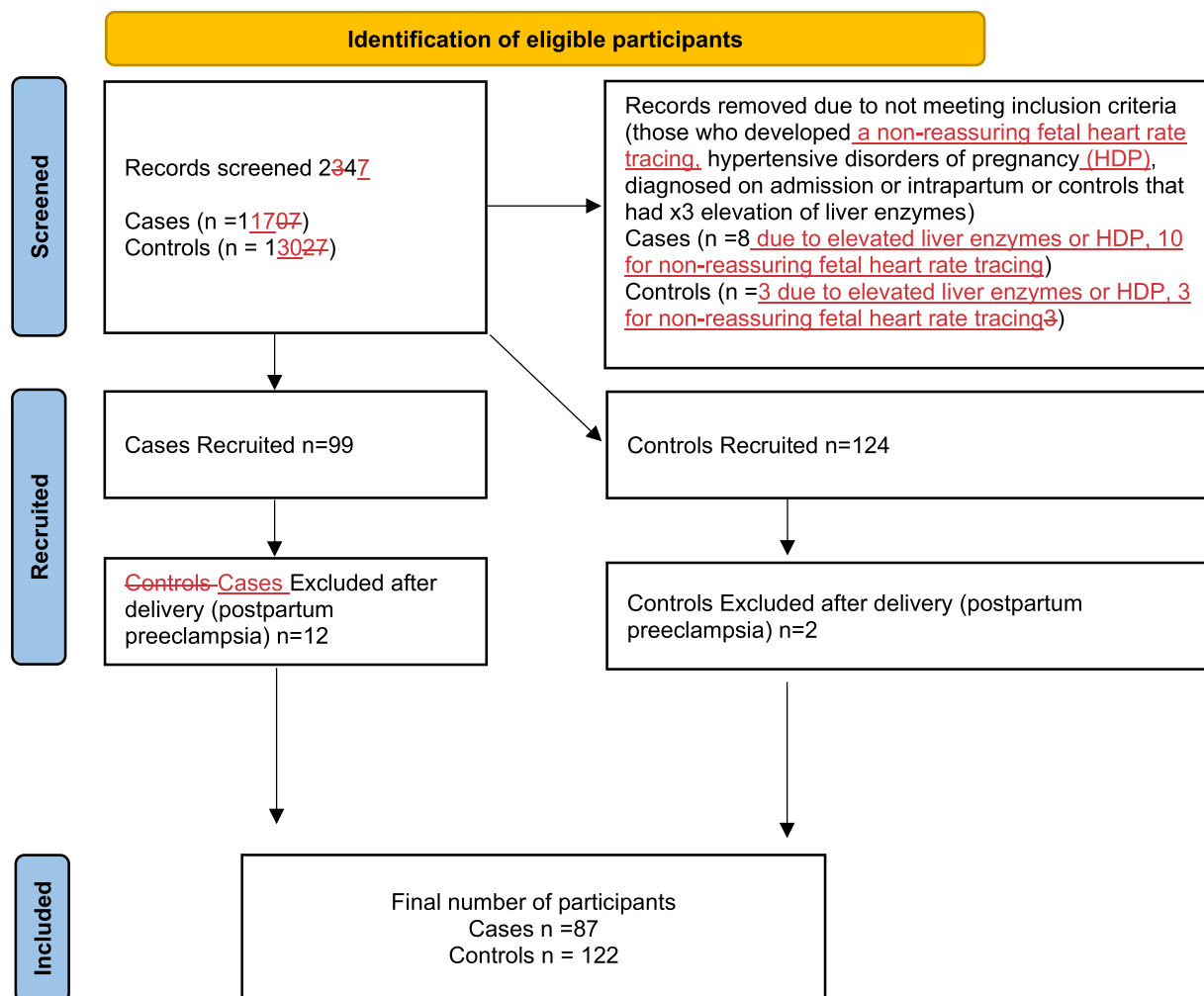
TABLE 1
Demographics and obstetrical outcomes

Variable	Controls: TBA <10 μmol/L (n=122)			Cases: TBA ≥10 μmol/L (n=87)			<i>P</i> ^a
	Mean	SD	%	Mean	SD	%	
Maternal age (y)	29.02	5.92		28.98	6.56		.96
Body mass index	32.12	5.9		31.45	7.02		.47
Gestational age (wk)	38.96	1.47		37.71	1.59		<.001
Total bile acid (μmol/L)	5.2	1.28		43.2	40.62		<.001
Aspartate transaminase	25	22.85		50.59	42.22		<.001
Alanine transaminase	19	7.26		64.3	66.05		<.001
Mode of delivery	Vaginal delivery			69/87 (79.31%)			.88
	Cesarean delivery			18/87 (20.69%)			
Induction of labor	54/122 (44%)			68/87 (78%)			<.001

SD, standard deviation; TBA, total bile acid.

^a *P* values were determined using chi-square tests for categorical variables and *t* tests for continuous variables.

Futterman. Cord blood troponin I in pregnancies with intrahepatic cholestasis of pregnancy. *Am J Obstet Gynecol Glob Rep* 2024.

FIGURE
Patient recruitment

Futterman. Cord blood troponin I in pregnancies with intrahepatic cholestasis of pregnancy. *Am J Obstet Gynecol Glob Rep* 2024.

The study flow diagram is summarized in the [Figure](#). Of 247 records screened, 117 (47%) were cases and 130 (53%) were controls. Before recruitment, 8 (7%) cases were excluded because of elevated liver enzymes or HDP and 10 (8.5%) were excluded for nonreassuring fetal heart rate tracing. Three (2%) controls were excluded because of elevated liver enzymes or HDPs, and 3 (2%) were excluded for nonreassuring fetal heart rate tracing. After recruitment, 12 (10%) cases were removed from the study because of developing postpartum preeclampsia, as well as 2 (1.5%) controls. Thus, 87 cases and 122 controls were included in the final analysis. The mean gestational age at delivery was 38.96 ± 1.47 and 37.71 ± 1.59 weeks of

gestation in the controls and cases respectively ($P < .001$). The mean TBA value was 5.2 ± 1.28 $\mu\text{mol/L}$ and 43.2 ± 40.62 $\mu\text{mol/L}$ in controls and cases, respectively ($P < .001$). The mean aspartate transaminase (AST) and alanine transaminase (ALT) values were 25 ± 22.85 U/L and 19 ± 7.26 U/L, respectively, in controls and 50.59 ± 42.22 and 64.3 ± 66.05 U/L, respectively, in cases ($P < .001$). There were no differences in maternal age, body mass index (BMI), and mode of delivery. The rates of vaginal birth were 78.69% (96/122) and 79.31% (69/87), and the rates of induction were 44% (54/122) and 78% (68/87) in the controls and cases, respectively ($P = .88$; $P < .001$). The clinical outcomes are summarized in [Table 2](#).

There were no differences between the groups in terms of arterial cord blood pH or base excess, neonatal Apgar scores, and neonatal gender. Umbilical cord blood troponin I was more likely to be positive among cases than among controls (controls: 15 of 122 [12.30%]; cases: 20 of 87 [22.99%]; $P < .001$). Of note, all newborns with elevated troponin levels were managed by observation in the NICU for 24 to 48 hours. In addition, NICU admissions for both cases and controls included all those with intraamniotic infection (IAI) per institutional protocol (NICU, controls: 24/122 [18%]; cases: 26/87 [30%]; $P = .08$ and IAI, controls: 9/122 [7%]; cases: 6/87 [7%]; $P = .91$). The average neonatal birth weight was also different between

TABLE 2
Outcomes

Variable	Controls: TBA <10 $\mu\text{mol/L}$ (n=122)			Cases: TBA ≥ 10 $\mu\text{mol/L}$ (n=87)			<i>P</i> ^a
	Mean	SD	%	Mean	SD	%	
Arteria cord pH	7.26	0.08		7.26	0.07		.93
Arteria cord pH <7.1			6/122 (4.9%)			0/87 (0%)	.43
Arterial cord base excess	-5	3.89		-5.55	3.47		.18
Arterial cord base excess <-12			1/122 (0.8%)			0/87 (0%)	1.0
Troponin I	Positive		15/122 (12.30%)			20/87 (22.99%)	<.001
	Negative		107/122 (87.71%)			67/87 (77.01%)	
Neonatal gender	Female		64/122 (52.46%)			43/87 (49.42%)	.54
	Male		58/122 (47.54%)			44/87 (50.57%)	
Birth weight (g)	3380.94	446.87		3118.76	510.92		<.001
Apgar-1 min	9	0.98		8.94	0.28		.1
Apgar-5 min	9	0.2		8.99	0.19		.63
Neonatal intensive care			24/122 (18%)			26/87 (30%)	.08
Intraamniotic infection			9/122 (7%)			6/87 (7%)	.91

SD, standard deviation; TBA, total bile acid.

^a *P* values were determined using chi-square tests for categorical variables and *t* tests for continuous variables.

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the groups (controls: 3380±446 g; cases: 3118±510 g; *P*<.001).

When further stratified by TBA levels of <40 $\mu\text{mol/L}$, 40 to 100 $\mu\text{mol/L}$, and >100 $\mu\text{mol/L}$, we found a positive association between higher TBA levels and a positive troponin I test that increased with increasing group concentration cutoffs from 12.5% to 36.8% to 45.5%, respectively (*P*=.002). When controlling for gestational age at delivery, maternal age, and BMI, higher TBA levels were found to be associated with a positive troponin I level (adjusted odds ratio, 1.015; 95% confidence interval, 1.004–1.026).

Comment

Key findings

Our findings suggest that there is a positive association between increasing TBA concentrations and elevated troponin I in the umbilical cord blood of neonates born to pregnant people whose pregnancy was complicated by ICP. These findings also suggest that TBA concentrations can be associated with an increased risk for cardiac injury in this cohort.

Results

Although an association between TBA concentrations and fetal cardiac distress has been explored previously, the association with troponin I levels is novel. These results add an important piece to the understanding of the often sudden intrauterine fetal demise (IUFD) that occurs in pregnancies with ICP by linking troponin I levels with elevated TBA levels, thereby highlighting that myocardial death is mediated by bile acids that cause end organ injury.

It has been suspected for years that the etiology of IUFD in cases of ICP was cardiac in origin. Vasavan et al¹¹ demonstrated that ICP in pregnant people with an increased concentration of TBA was positively correlated with an elevated fetal N-terminal pro-B-type natriuretic peptide (Nt-proBNP) concentration, an indicator of cardiac distress. Others have explored actual cardiac function in fetuses born to patients with ICP and found a significant impact on both systolic and diastolic function,¹¹ overall heart dysfunction, and fetal arrhythmias.^{2,5–10} Researchers have also examined the relationship between troponin I and the risk for fetal death,

hypoxia, and asphyxia unrelated to ICP. The findings suggested that umbilical cord troponin may serve as a reliable marker for adverse neonatal outcomes, because it was found to be associated with not only the presence of hypoxia, but also the degree of the hypoxic event.^{15,16,20} In addition, we did not sample maternal blood for troponin I levels, because there is evidence to suggest that it does not cross the placenta, and because we excluded those with HDPs and heart disease, we could only assume that the troponin levels measured are of fetal origin.²¹

Our results are consistent with both the standard of care and our institutional protocol, which suggested higher induction rates at an earlier gestational age for patients with ICP. These interventions are consistent with a lower average neonatal birth weight among those with TBA ≥ 10 $\mu\text{mol/L}$, because they were delivered earlier. Because there was no suspicion for other pathology (such as intrauterine growth restriction, as suggested by the results of a mean birth weight of 3118±510 g), we attributed the difference in birth weight

only to the difference in mean gestational age at the time of delivery. The lack of hypoxemia and acidosis in both the cases and controls strengthens the suspicion that a bile acids-mediated cardiac insult over time leads to the often-perceived sudden fetal demise without preceding signs of fetal distress.

Clinical implications

Our findings examined the relationship between TBA and 3 adverse neonatal outcomes, namely acidosis, low Apgar scores, and elevated umbilical cord troponin I. Although we did not find an association between elevated TBA and acidosis or low APGAR scores, the association with elevated troponin I does support previous research that linked fetal death by cardiac injury to ICP and the elevated TBA that ensued. These findings suggest that TBA concentrations maybe associated with an increased risk for cardiac injury in pregnancies complicated by ICP.

Research implications

Ursodeoxycholic acid for ICP has been used for years. Although initially thought to be beneficial for symptoms of itching related to ICP, its clinical benefit was recently presented in a large systematic review, which suggested that its use reduces the rate of IUFD.²² Our study may serve a clue as to why ursodeoxycholic acid decreases the risk for IUFD. Our results that suggest that there is an association between higher levels of TBA and elevated troponin levels may explain why with lowered levels of TBA (by means of ursodeoxycholic acid), the risk for cardiogenic mediated-IUFD may be lowered. Further research in the form of animal studies and laboratory research is needed to better understand the relationship between ursodeoxycholic acid use and its ability to reduce the rate of IUFD and to better understand the association we have uncovered here between TBA and elevated troponin levels (as a marker for cardiac injury).

Strengths and limitations

This study had several limitations. Although powered with the adequate

sample size to avoid a type II error, we used the estimated incidence of elevated troponin in umbilical cord blood rather than the incidence of cardiac injury, because the latter would be difficult to estimate. Furthermore, our study was not powered to address the risk for fetal acidosis or low Apgar scores and perhaps it presents a type II error for those adverse outcomes. All controls delivered at term. This detail should be considered when interpreting our results because we do not know how gestational age affects troponin levels. With that said, the fact that there were no differences in fetal acidosis and hypoxemia between the 2 groups reassures us that despite the lower average gestational age at birth among the cases, gestational age itself may not have had a strong impact on our study's results. Given the small sample size and geographic location, our study inevitably carries the risk for sampling bias and lack of generalizability. Still, it can also be justified considering the largely homogenous patient population in our institution, largely serving a Hispanic population (comprising 85/87 cases) whose incidence of ICP has been described previously.²³ Another limitation of our study is our inability to further discuss neonatal follow-up in the NICU, including the use of neonatal echocardiogram and potentially relevant findings or troponin levels trend. This is mainly because of the fact that those records were recorded separately, and the study team did not have access to them. Lastly, we did not track who did and did not receive ursodeoxycholic acid among cases and therefore we cannot comment on its effect on troponin levels.

The strengths of this study include its approach to studying the relationship between umbilical cord blood troponin I levels and TBA concentrations for pregnant people diagnosed with ICP. The stratification of TBA concentrations into 3 categories to identify a trend between the severity of ICP and umbilical cord blood troponin I levels is a unique approach to examining this relationship. The stratification also matches that of guidelines of preterm delivery for pregnant people with ICP, which can range

from 36 to 39 weeks' gestation based on severity indicated by TBA levels. In addition, this study was conducted at a single institution with an institutional ICP protocol,¹⁸ providing consistent and standardized care practices.

Conclusion

This study demonstrated further insight into the potential mechanism of cardiac insult and IUFD in cases with ICP. Our results suggest a positive association between increasing levels of TBA and cardiac injury, demonstrated by elevated troponin I levels in the umbilical cord blood at birth. Our findings are consistent with previous research that has examined changes in cardiac function after exposure to bile acids in cases of ICP, demonstrating that they serve as a direct insult to the fetal and neonatal myocardium. Indirectly, our study further supports previous research and current recommendations for the use of ursodeoxycholic acid,²⁴ because it may serve as a potential mediator to reduce the risk of cardiac insult by reducing TBA concentrations. Further research is needed to fully understand the relationships between TBA, cardiac injury, the potency of ursodeoxycholic acid, and its role in reducing the risk for cardiac injury. ■

CRediT authorship contribution statement

Itamar D. Futterman: Writing – review & editing. **Hitangee Jain:** Writing – review & editing. **Rodney A. McLaren:** Validation, Methodology, Formal analysis. **Jonathan K. Mays:** Validation, Supervision, Data curation, Conceptualization.

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