



## Original Research Article

# To correlate maternal serum total bile acids and fetomaternal outcomes in obstetric cholestasis

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## Abstract

**Background:** Intrahepatic cholestasis of pregnancy (ICP) is a unique pregnancy dermatosis and cholestatic disorder characterized by pruritus in 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy. It can be diagnosed using increased level of serum bile acids and by excluding other liver and skin disorders. ICP causes significant risks to both maternal and fetal health. The main aim of this study is to analyse the differing levels of maternal serum TBA that correlate with both maternal and fetal outcomes in obstetric cholestasis.

**Materials and Methods:** A prospective observational and comparative study was carried out for over 12 months in the Department of Obstetrics & Gynaecology at Bokaro General Hospital, India. It involved 84 pregnant women with ICP. Participants were categorized into two groups based on serum TBA levels. Based on inclusion and exclusion criteria maternal and fetal outcomes were assessed through clinical history and examination, laboratory tests, and regular fetal monitoring using non-stress tests and obstetric ultrasound and Doppler studies. Statistical analysis was performed by SPSS version 24.

**Results:** 84 patients in this study were divided into two groups equally based on bile acid levels, group A (< 40 µmol/L) and group B (≥ 40 µmol/L). The mean bile acid levels in group A and group B were 16.40 ± 4.47 µmol/L and 43.86 ± 3.93 µmol/L respectively with p < 0.0001. Significant differences were observed in gestational age of 76.19% in group A delivered at 37 weeks, compared to only 9.52% in group B with p < 0.0001. 2.38% in group A and 64.29% in group B were observed in NICU admission due to respiratory distress. In group B 47.62% of babies weighed < 2.5 kg. In group B, 66.67% babies had MSAF vs 21.43% babies in group A. Other factors like APGAR score comparison also showed statistical significance.

**Conclusion:** TBA can be used as a predictive biomarker for adverse outcomes in ICP. This study states the need for early detection and intervention, especially in high-risk populations.

**Keywords:** Maternal serum total bile acids, Fetal outcomes, Maternal outcomes, Predictive biomarker, NICU admission, Low birth weight, Gestational age.

**Received:** 21-12-2024; **Accepted:** 07-03-2025; **Available Online:** 14-08-2025

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## 1. Introduction

Obstetric cholestasis (OC) alternatively called intrahepatic cholestasis of pregnancy (ICP), is a cholestasis disorder that primarily happens during second and third trimesters. This can be identified by increased levels of serum bile acids or liver aminotransferase and pruritus in cases where there are no skin rashes.<sup>1</sup> The incidence of ICP differs based on their geographical locations and ethnicity. This rate normally differs from 0.2% to 2% of pregnancies.<sup>2</sup> This condition is mostly prevalent in South America and Northern Europe. In the United States, the occurrence is normally lower in the

range of 0.2% to 0.3% of pregnancies.<sup>3</sup> Some factors like history of ICP, chronic liver disease, hepatitis C infection, multifetal pregnancies, and advanced maternal age may increase the development of ICP.<sup>4,5</sup> Also, ICP shows a high recurrence rate between 60% and 70% in subsequent pregnancies.<sup>6,7</sup>

Adverse fetal outcomes such as preterm birth, meconium-stained amniotic fluid, preterm rupture of membranes and sudden stillbirth cause challenges for patients as well as healthcare providers.<sup>8,9</sup> If there is ICP, then iatrogenic premature birth is used as a preventive

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measure for reducing the risk of sudden stillbirth.<sup>10</sup> Elevated serum total bile acid (TBA) levels are associated with immediate preterm birth, as they have a significant role in the pathophysiology of preterm labour. Additionally, high bile acid levels may induce vasoconstriction, which can cause the development of a placental villous tree that may affect fetal growth and development.<sup>11–13</sup>

Maternal serum total bile acids (TBA) can act as an essential biomarker for analysing fetomaternal outcomes in obstetric cholestasis. This can cause significant health effects on both mother as well as child. Some researchers continuously relate the elevated levels of TBA with serious obstetric risks that include the highest possibilities of preterm delivery, stillbirth and neonatal problems like low Apgar scores and the need for neonatal intensive care.<sup>14,15</sup> Some studies state that ICP severity can be classified using TBA levels. This directly influences the birth weight and meconium stained liquor incidence at the time of delivery.<sup>16</sup> Additionally, TBA levels above 40  $\mu\text{mol/L}$  can predict adverse outcomes that include the requirement of iatrogenic preterm birth.<sup>14</sup>

Early diagnosis and intervention are important for reducing the complications that are related to high bile acid levels. It is recommended for early delivery in case of high severity. Pharmacological interventions like ursodeoxycholic acid administration are commonly used for reducing the symptoms and improving the outcomes.<sup>16,17</sup>

This study aims to analyse the differing levels of maternal serum TBA that correlate with both maternal and fetal outcomes in obstetric cholestasis. There are researchers who reported that elevated levels of TBA may increase adverse outcomes like preterm birth and respiratory complications in newborns. However, in terms of the Indian population, the detailed specific outcomes of bile acid increase remain limited. By understanding the impact of different levels of TBA on maternal and fetal outcomes, this study provides clinical guidelines for managing obstetric cholestasis.

## 2. Materials and Methods

### 2.1. Study design

A hospital-based prospective observational and comparative study was carried out in Department of Obstetrics & Gynecology at Bokaro General Hospital, Bokaro Steel City, Jharkhand, India. The study was conducted over 12 months, from June 2022 to June 2023. Institutional Ethics Committee has approved the study and adhered to ethical guidelines for medical research.

### 2.2. Study population

The participants included antenatal patients attending the clinic or labour room, with gestational age between 28 and 37+6 weeks, presenting with pruritus and abnormal liver

function tests. A total serum bile acid level  $>10 \mu\text{mol/L}$  was needed for inclusion, and participants were divided into two groups based on levels of bile acid namely group A: TBA  $>10$  to  $\leq 39 \mu\text{mol/L}$  (42 patients), group B: TBA  $\geq 40 \mu\text{mol/L}$  (42 patients). Participants were followed prospectively until delivery to assess fetomaternal outcomes.

### 2.3. Inclusion and exclusion criteria

Pregnant women with singleton pregnancy and gestational age between 28 to 37+6 weeks were included in this study. Additionally, pruritus with elevated liver enzymes of ALT  $>40 \text{ U/L}$  and AST  $>40 \text{ U/L}$  and Total bile acids  $>10 \mu\text{mol/L}$  were also included.

Exclusion criteria include patients who had acute fatty liver of pregnancy (AFLP), patients with acute or chronic liver diseases and patients with dermatological diseases causing itching and rash, viral hepatitis, gestational hypertension, preeclampsia, or HELLP syndrome, multiple pregnancy, history of previous uterine surgery (e.g., cesarean section, hysterotomy, myomectomy), patients who declined consent and non ICP patients.

### 2.4. Sample size

Size of the sample was calculated by,

$$n = [(Z^2 \cdot p \cdot q) / e^2] / 1 + [(Z^2 \cdot p \cdot q) / N \cdot e^2]$$

Here,  $N=2000N$  (approximate total population),  $Z=1.96Z$  (for 95% confidence level),  $p=0.06p$  (prevalence of obstetric cholestasis),  $q=1-p=0.94q$ ,  $e=0.05$  (margin of error).

The minimum sample size was taken as 84 with 42 participants in each group.

### 2.5. Study procedure

Patients were allotted into 2 groups based on their serum bile acid levels at diagnosis: Group A (Total bile acids  $>10$  to  $\leq 39$  micromole/L) and Group B (Total bile acids  $\geq 40$  micromole/L). After informed consent was taken in the patient's own language, a detailed history and clinical examination were done. A liver function test was done once weekly, and a total bile acid assay was done for group allocation. Bile acids were repeated only if liver enzymes despite drug dose regulation to decide the time of delivery.

All patients were treated with ursodeoxycholic acid 10–12mg kg/day in 2 to 3 divided doses. Fetal surveillance was done with nonstress test weekly and ultrasound for fetal wellbeing with a Doppler study as per individual case. Delivery was planned at 37 to 38 weeks or earlier if risk of fetal compromise. Corticosteroid administration if induction is expected before 36 weeks. Any growth variance, abnormal non-stress test cardiotocography or abnormal fetal Doppler test may need immediate intervention.

Respiratory distress can be defined as any newborn child that needs intubation, continuous positive airway pressure, bag/mask ventilation, postpartum diagnosis of pneumonia, or documentation of tachypnoea by a paediatrician on examination. Babies less than 2500 grams at birth were defined as low birth weight. Apgar score that is low can be defined as a score less than 7/10 in a 1 or 5-minute recording. Maternal outcomes like PPH and blood transfusion were recorded.

Diagnosis of obstetric cholestasis (IHCP) includes skin pruritus without any rashes, typically occurring in the 2nd or 3rd trimester, total bile acids  $>10 \mu\text{mol/L}$  and liver enzymes  $>40 \text{ U/L}$ . Abdominal ultrasound to exclude other liver diseases like biliary disorders, hepatitis, AFLP, and jaundice like cholelithiasis, coagulation profile and screening for hepatitis A, B, C, and E and testing and serum total bile acid testing by using enzymatic assay method.

### 2.6. Parameters evaluated

Maternal outcomes such as mode of delivery, postpartum haemorrhage (PPH), and the need for blood transfusion are evaluated. Fetal outcomes like birth weight, Apgar scores (1 min, 5 min), intrauterine fetal demise, stillbirth, meconium-stained amniotic fluid, fetal distress, respiratory distress syndrome, and NICU admission were also calculated.

### 2.7. Blood sample collection

Blood samples were collected in plain tubes and analysed using the enzymatic bile acid assay. The method involves 3-alpha-hydroxysteroid dehydrogenase (3 $\alpha$ -HSD) catalysing the oxidation of bile acids, producing NADH from NAD<sup>+</sup>. The NADH then reacts with nitro-tetrazolium blue (NBT) to form formazan dye. The dye absorbance at 540 nm wavelength is directly proportional to bile acid levels in serum.

### 2.8. Statistical analysis

SPSS version 24 has been used in this study. Mean  $\pm$  standard deviation has been observed as continuous data, while categorical data were presented as proportions. The statistical tests used were Chi-square test for categorical data, the Gaussian single mean test for comparing continuous data, Z-proportion test for comparing categorical proportions, the paired t-test for comparing two means, and the Wilcoxon rank test for comparing Apgar scores between groups.

## 3. Results

84 patients were used in this study. They were divided into two equal groups based on their total bile acid (TBA) levels such as Group A (TBA  $>10$  to  $\leq 39 \mu\text{mol/L}$ ) and Group B (TBA  $\geq 40 \mu\text{mol/L}$ ). This has been represented in **Table 1**.

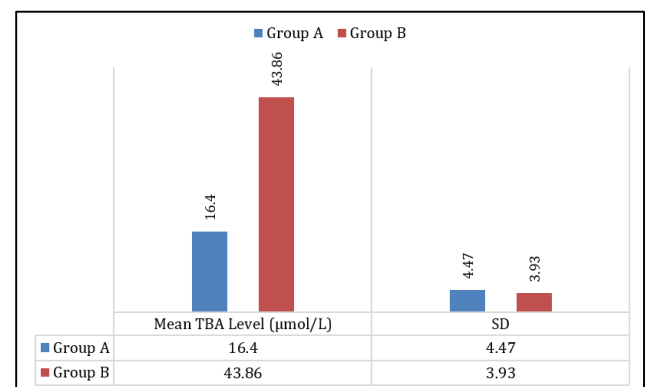
**Table 1:** Evenly distributed population of the study between the two groups

Group	No. of patients (n=84)	Percentage	Bile Acid Level
Group A	42	50%	$< 40 \mu\text{mol/L}$
Group B	42	50%	$\geq 40 \mu\text{mol/L}$

### 3.1. Clinical characteristics

### 3.2. Total bile acid at diagnosis

The mean bile acid level for Group A was  $16.40 \pm 4.47 \mu\text{mol/L}$ , while Group B had a mean level of  $43.86 \pm 3.93 \mu\text{mol/L}$ . The difference in mean total bile acid levels was statistically significant, P-value  $<0.0001$  using the paired |t| test. This has been illustrated in **Figure 1**.



**Figure 1:** Depicts the TBA levels at diagnosis in both groups

### 3.3. Maternal outcomes

The outcomes of two groups based on maternal serum levels were analysed as group A that has serum bile acid  $< 40 \mu\text{mol/L}$  and group B had serum bile acid  $\geq 40 \mu\text{mol/L}$ . The characteristics of the two groups, along with statistical comparisons are summarized in **Table 2**.

### 3.4. Gestational age

The distribution of gestational ages between the two groups was different significantly. In group A 2.38% of participants delivered between 35 weeks and 35 weeks + 6 days, compared to 45.24% in group B. The  $\chi^2$  value was calculated at 41.55 with a p-value  $< 0.0001$ , indicating a significant difference. At 36 weeks to 36 +6 days, 21.43% of group A and 45.24% of group B were noted, while at 37 weeks to 37+ 6 days the difference with 76.19% in group A compared to only 9.52% in group B. Statistical significance was obtained by Chi-square test{ $\chi^2$ -Test}.

### 3.5. Type of deliveries

In terms of delivery methods 59.52% of Group A underwent induced deliveries, while 73.81% of Group B were induced. The calculated  $\chi^2$  value was 1.906 with P-value 0.1675, indicating that there is no significant difference in two groups regarding the type of delivery.

**Table 2:** Maternal outcomes

Outcomes	Group–A (<40micromol/L)		Group–B (≥40micromol/L)		χ <sup>2</sup>   <sub>cal</sub> Results	P-value	Remarks
	No.(n=42)	%	No.(n=42)	%			
Gestational Age							
35w-35w+6days	01	2.38%	19	45.24%	41.55	<0.0001	Significant
36w-36w+6days	09	21.43%	19	45.24%			
37w-37w+6days	32	76.19%	04	9.52%			
Type of Deliveries							
Induced	25	59.52%	31	73.81%	1.906	0.1675	Not Significant
Spontaneous	17	40.48%	11	26.19%			
Induced deliveries (at different gestational age)							
<37weeks	08	32%	31	100%	29.73	<0.0001	Significant
≥37weeks	17	68%	0	0%			
Mode of Delivery							
Vaginal delivery	19	45.24%	13	30.95%	1.796	0.1802	Not significant
Caesarean section	23	54.76%	29	69.05%			
Caesarean section at gestational age							
<37weeks	04	17.39%	26	89.66%	26.92	<0.0001	Significant
≥37weeks	19	82.61%	03	10.34%			
Postpartum hemorrhage							
Present	02	4.76%	04	9.52%	0.709	0.3996	Not Significant
Absent	40	95.24%	38	90.48%			
Repeated Bile Acid needed							
Needed	05	11.90%	03	7.14%	1.107	0.4599	Not Significant
Not Needed	37	88.10%	39	92.86%			
Need for blood transfusion							
Required	02	4.76%	04	9.52%	0.709	0.3996	Not Significant
Not Required	40	95.24%	38	90.48%			

### 3.6. Induced deliveries at different gestational ages

Based on the gestational age significant differences can be observed in induced deliveries. Among those <37 weeks, 32% belonged to Group A, while 100% of Group B were induced ( $\chi^2 = 29.73$ ,  $P < 0.0001$ ). Statistical significance was obtained by Chi-square test { $\chi^2$ -Test}.

### 3.7. Mode of delivery

Regarding the mode of delivery, 45.24% vaginal deliveries were observed in group A and 30.95% in group B. There is no any significant difference observed. Cesarean sections were more prevalent with 69.05% in group B compared to 54.76% in group A.

### 3.8. Cesarean section at gestational age

Cesarean sections performed at gestational ages <37 weeks with 17.39% in group A compared to 89.66% in group B ( $\chi^2 = 26.92$ ,  $P < 0.0001$ ) have shown significant differences. This shows the relationship between serum bile levels and early surgical intervention.

### 3.9. Postpartum hemorrhage

Postpartum haemorrhage was present in two patients (4.76%) from group A and four patients (9.52%) from group B. With Chi-square analysis,  $\chi^2$  0.709 and p-value 0.3996, there was no statistical significance. This represents that the incidence of postpartum haemorrhage between the two groups have no any significant difference.

### 3.10. Repeated bile acid measurement

About the need for repeated bile acid measurements, 5 patients (11.90%) in group A needed this intervention and 3 patients (7.14%) in group B. Chi-square value ( $\chi^2$ )1.107, with a p-value 0.4599. This shows no significant difference in the requirement for repeated bile acid measurements between the groups.

### 3.11. Need for blood transfusion

The need for blood transfusions was similar between the groups, with 2 patients (4.76%) in group A requiring a transfusion compared to 4 patients (9.52%) in Group B. The  $\chi^2$  value 0.709 and the P-value 0.3996. This presents no significant difference in the need for blood transfusions based on bile acid levels.

### 3.12. Fetal outcomes

The analysis of APGAR scores at 1 minute after delivery revealed significant differences between the two groups based on maternal serum bile levels. At a score of 6, 2.38% of infants in Group A had this score when compared to

57.14% in Group B. Higher scores were more prevalent in Group A had 52.38% of infants in score 7 and 45.24% in score 8. Additionally, only 33.33% of infants in Group B received a score of 7, with 2.38% achieving a score of 8. Statistically significant difference between two groups obtained by Wilcoxon Rank test, p-value <0.0001.

**Table 3:** APGAR scores

	Group-A (< 40micromol/L)		Group-B (≥40micromol/L)		p-value	Remarks
	No.(n=42)	%	No.(n=42)	%		
APGAR score at 1minute of babies between two groups						
5	0	0%	3	7.14%	<0.0001	Significant
6	1	2.38%	24	57.14%		
7	22	52.38%	14	33.33%		
8	19	45.24%	1	2.38%		
APGAR score at 5 minutes of babies between two groups						
7	01	2.38%	25	59.52%	<0.0001	Significant
8	13	30.95%	11	26.19%		
9	28	66.67%	06	14.29%		

**Table 4:** Fetal outcomes

Outcomes	Group-A (< 40micromol/L)		Group-B (≥40micromol/L)		$\chi^2$	p-value	Remarks
	No.(n=42)	%	No. (n=42)	%			
Fetal Distress							
Yes	08	19.05%	17	40.48%	4.558	0.0328	Significant
No	34	80.95%	25	59.52%			
NICU admission/RDS (Respiratory distress of newborn)							
Yes	01	2.38%	27	64.29%	35.38	<0.0001	Significant
No	41	97.62%	15	35.71%			
Intrauterine fetal demise(IUFD)/still birth							
Yes	0	0%	0	0%	0.9999	1	Not Significant
No	42	100%	42	100%			
Meconium-Stained Amniotic Fluid (MSAF)							
Yes	09	21.43%	28	66.67%	17.23	<0.0001	Significant
No	33	78.57%	14	33.33%			
Birth Weight of Babies							
<2.5kg	05	11.90%	20	47.62%	4.33	<0.0001	Significant
2.5– 3kg	32	76.20%	22	52.38%			
>3kg	05	11.90%	00	0%			
Mean±SD	2.69±0.25kg		2.48±0.19kg				

The APGAR scores at 5 minutes were also observed. 30.95% babies in Group A had APGAR scores of 8 in 5 minutes vs 26.19% in group B while 66.67% of babies in group A had APGAR score of 9 in 5 minutes compared to 14.29% in group B. Comparison was statistically significant with p-value <0.0001. (**Table 3**)

### 3.13. Fetal distress

Fetal distress was in 19.05% of patients from group A and 40.48% of patients from group B. Chi-square value calculated was 4.558 and P-value 0.0328. This states a significant difference in two groups. The results suggest that higher bile acid levels are related with an increased risk of fetal distress.

### 3.14. NICU admission/RDS (Respiratory distress of newborn)

In terms of NICU admission for respiratory distress, only 1 baby needed admission in group A and 27 babies in group B. The calculated Chi-square value was 35.38. The P-value was <0.0001. This difference shows a strong relation between increased bile acid levels and increased NICU admissions due to respiratory distress.

### 3.15. Intrauterine fetal demise (IUFD)/stillbirth

No cases of intrauterine fetal demise or stillbirth were reported in either group. Chi-square value observed was 0.9999, with a P-value 1. No significant differences between the groups about IUFD or stillbirth.

### 3.16. Meconium-stained amniotic fluid (MSAF)

The incidence of MSAF was significantly higher in group B 66.67% compared to 21.43% in group A ( $\chi^2 = 17.23$ ,  $P < 0.0001$ ). This shows the relationship between higher bile acid levels and MSAF.

### 3.17. Birth weight of babies

Birth weights were significantly different in two groups. In group A, 11.90% of babies weighed <2.5 kg and in Group B this has increased to 47.62% with  $\chi^2 = 4.33$  and  $P < 0.0001$ . The mean birth weight for Group A was  $2.69 \pm 0.25$  kg and  $2.48 \pm 0.19$  kg in Group B. This states the impact of maternal bile acid levels on fetal growth outcomes.

## 4. Discussion

The relationship between maternal serum total bile acid (TBA) levels and fetomaternal outcomes in cases of obstetric cholestasis was correlated in this study. This study comparatively analysed the two groups based on the bile acid levels, that is group A which has TBA 10–39  $\mu\text{mol/L}$  and group B which has TBA  $\geq 40$   $\mu\text{mol/L}$ . Some significant differences have been observed between the two groups mainly in gestational age at delivery, fetal distress, NICU admissions, low birth weight, MSAF and neonatal APGAR scores. It was observed that high levels of maternal bile acids may be related to poor fetal outcomes and some adverse maternal events.

In our study, 84 patients with ICP in two groups that is group A were TBA was 10–39  $\mu\text{mol/L}$  and group B were TBA was  $\geq 40$   $\mu\text{mol/L}$ . Group A had a mean TBA of 16.4  $\mu\text{mol/L}$ , while group B had 43.9  $\mu\text{mol/L}$ , and P value < 0.0001. Similarly, Guszczynska-Losy et al.<sup>14</sup> study of 86 ICP patients found that those with TBA <40  $\mu\text{mol/L}$  had a median of 17.1  $\mu\text{mol/L}$ , while patients with TBA  $\geq 40$   $\mu\text{mol/L}$  had a significantly higher median of 66.3  $\mu\text{mol/L}$  ( $P < 0.001$ ). Both studies observed a correlation between increased bile acid levels and the severity of intrahepatic cholestasis during pregnancy.

Similarly, in the present study the participants in Group B with increased TBA levels ( $\geq 40$   $\mu\text{mol/L}$ ), had significantly higher rates of delivery before 37 weeks compared to Group A. This is like the previous research by Guszczynska-Losy et al.<sup>14</sup> that relatively higher bile acid levels lead to early delivery because of potential fetal compromise. Although the induction rates are similar between the groups, cesarean section rates were slightly higher in group B. This aligns with the findings from Gupta et al.<sup>19</sup> where higher rates of cesarean rates were at the early ICP that is  $\leq 32$  weeks. The odds ratio for cesarean delivery in early IHCP was 7.615. Additionally, Huang et al.<sup>20</sup> analysis of 19 cohort studies has also identified that ICP was significantly related to increased odds of unplanned or emergency cesarean sections with OR 1.42, 95% CI: 1.21–1.66,  $P < 0.001$ . In our study, maternal outcomes such as postpartum haemorrhage (PPH) and blood transfusion requirements showed no significant differences between the two groups. This indicates that while increased bile acid levels may affect fetal health, they have a limited impact on maternal post-delivery complications. This is similar to previous research as Kenyon et al.<sup>21</sup> also reported a 17% incidence of PPH in women with intrahepatic cholestasis of pregnancy. In the meantime DeLeon et al.<sup>22</sup> found lower rates which are 2.6% for vaginal and 6.3% for cesarean deliveries. Furrer et al.<sup>23</sup> also observed that women with IHCP have not experienced more postpartum blood loss when managed with ursodeoxycholic acid. Gupta et al.<sup>19</sup> similarly reported that 9.18% of women experienced PPH, with 61.11% of these having bile acid levels >40  $\mu\text{mol/L}$ . However, PPH was more common in women who did not receive ursodeoxycholic acid due to non-compliance or late presentation. This highlights the role of treatment adherence in maternal outcomes.

In the present study, neonates in Group B with elevated TBA levels of  $\geq 40$   $\mu\text{mol/L}$  had significantly lower APGAR scores at both 1 and 5 minutes. This says that high levels of bile acid correlate with compromised neonatal health immediately after birth. This is consistent with the hypothesis that increased bile acid exposure in utero impairs neonatal respiratory adaptation due to surfactant degradation. Moreover, fetal distress was significantly more common in group B leading to a higher rate of NICU admissions, particularly for respiratory issues of 64.29% and 2.38% in group B and group A respectively. This reinforces the association between increased bile acids and neonatal lung dysfunction. The incidence of MSAF was also higher in Group B at 66.67% and 21.43% in Group A. Birth weight has been significantly lower in group B, with increased rate of low-birth-weight neonates. This shows the possible relationship between raised bile acids ( $\geq 40$   $\text{mmol/L}$ ) and fetal growth restriction. This is supported by the hypothesis that raised levels of taurocholic acid causes placental infarction leading to uteroplacental insufficiency. Similarly, the studies by Jin et al.<sup>25</sup> and Labbe et al.<sup>26</sup> also stated the correlation between high bile acid levels (SBA  $\geq 40$   $\text{mmol/L}$ ) and increased fetal complications. The complications include

fetal distress, neonatal asphyxia, premature delivery, and cesarean sections. Jin et al.<sup>25</sup> identified that women with severe IHCP had a higher adverse neonatal outcome. This can be observed in early onset cases, similar to our findings of neonatal respiratory distress and low birth weight in Group B. In a larger cohort study, Herrera et al.<sup>27</sup> concluded that severe cholestasis, that is SBA  $\geq 100$  mmol/L, was related to significant neonatal morbidity. This suggests that even moderate increases in bile acids could lead to poor neonatal outcomes. This observation is similar to our observation that elevated TBA levels are a critical marker for neonatal respiratory distress and other complications. Additionally, Guszczynska-Losy et al.<sup>14</sup> have also been observed to be similar to our findings of higher NICU admission rates and prolonged stays in infants of mothers with severe cholestasis. In this cohort, although smaller, similar patterns of fetal distress, preterm birth, and NICU requirements in severe cholestasis cases have been observed. This states that bile acid levels directly impact neonatal outcomes. Similarly, Garcia-Flores et al.<sup>28</sup> reported increased rates of adverse outcomes, including MSAF, NICU admissions, and neonatal morbidity. From this study, we can understand that increased levels of bile acid levels in ICP patients can be considered an important risk marker for adverse neonatal outcomes, respiratory distress, and growth restrictions.

## 5. Limitations

There are few limitations in this study. One of them is that this study has a relatively small sample size and this reduced the generalizability of the results in terms of larger populations. So, there is a need for larger cohorts for confirmation of these observations. Additionally, this study design didn't follow-up on long term effects on neonate post NICU discharge. This study has also not addressed the other variables like other maternal health conditions, lifestyle factors, or treatment methods. So, there is a need to incorporate these factors in future analysis. For future studies, there is a need for larger, multicenter studies that may help in validating the results across different populations. Only single highest value of serum bile acid level at diagnosis was taken into consideration for group allocation. The possible improvement in serum bile acid levels following treatment with ursodeoxycholic acid has not been taken into consideration due to lack of resources and to avoid confusion. Need to repeat bile acids was statistically insignificant and didn't alter the study outcome.

## 6. Conclusion

This study correlates serum total bile acids with fetomaternal outcomes in obstetric cholestasis and states the implications of bile acid levels that affect pregnancy and its outcomes. The findings of this study have shown that increased bile acids are related to adverse maternal, fetal and neonatal outcomes. That includes earlier gestational age at delivery, increased rates of fetal distress, and higher NICU admissions. Along with that, newborns born to the mother with higher bile acid

levels showed lower APGAR scores. This shows the challenges immediately after the delivery. Early detection, early initiation of treatment, stringent fetal surveillance, timely intervention and delivery in our study helped in improving fetal prognosis and helped prevent still birth and fetal demise. This study supports the need for close monitoring of pregnant women for bile acid levels. Bile acid monitoring protocols and management guidelines can be integrated by policymakers or clinicians in case of high-risk pregnancies. This may help in improving the maternal and fetal health outcomes.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

## 9. Ethical Approval

Ethical No.: IEC BGH 2022/06.

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**Cite this article:** Sridhar S, Tirkey R, Sanga AJ. To correlate maternal serum total bile acids and fetomaternal outcomes in obstetric cholestasis. *Indian J Obstet Gynecol Res.* 2025;12(3):487–494.