

Maternal and Neonatal Outcomes According to Late-Pregnancy Serum Bile Acid Concentrations in Women with Clinically Diagnosed Intrahepatic Cholestasis of Pregnancy: A Prospective Observational Study

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Research Article

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Abstract

Background:

Intrahepatic cholestasis of pregnancy (IHCP) is a pregnancy-specific liver disorder characterized primarily by pruritus and elevated serum bile acid concentrations. Increasing maternal serum bile acid concentrations have been associated with adverse perinatal outcomes, although the strength of these associations may vary across populations. This study evaluated the association between late-pregnancy serum bile acid concentrations and maternal and neonatal outcomes among women clinically diagnosed with IHCP.

Methods:

This prospective observational study was conducted at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, from August 2022 to January 2024. Pregnant women clinically diagnosed with IHCP on the basis of pruritus without an alternative dermatological cause were enrolled after exclusion of multiple pregnancy, viral hepatitis, and chronic liver disease. Serum bile acids were measured once after 34 weeks of gestation. Participants were categorized according to serum bile acid concentration as < 20 , $20\text{--}39.9$, and $40\text{--}99.9$ $\mu\text{mol/L}$. No participant had serum bile acid concentrations ≥ 100 $\mu\text{mol/L}$. Maternal and neonatal outcomes were compared across the three groups using appropriate parametric or non-parametric tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Results:

Among 221 women, 146 (66.1%) had serum bile acid concentrations < 20 $\mu\text{mol/L}$, 64 (29.0%) had concentrations of $20\text{--}39.9$ $\mu\text{mol/L}$, and 11 (5.0%) had concentrations of $40\text{--}99.9$ $\mu\text{mol/L}$. Maternal characteristics and baseline liver biochemical parameters did not differ significantly across the groups. Mean gestational age at delivery was also similar (37.76 ± 1.52 , 37.48 ± 1.44 , and 37.45 ± 1.75 weeks, respectively; $p = 0.23$). No significant differences were observed in preterm delivery, induction or augmentation of labour, route of delivery, birth weight, meconium-stained liquor, or neonatal intensive care unit admission. Mean 1-minute Apgar scores were similar between groups ($p = 0.80$), whereas the mean 5-minute Apgar score was lower in the $40\text{--}99.9$ $\mu\text{mol/L}$ group (7.91 ± 1.76) than in the < 20 $\mu\text{mol/L}$ group (8.49 ± 1.10) and the $20\text{--}39.9$ $\mu\text{mol/L}$ group (8.23 ± 1.03 ; $p = 0.009$). However, the proportion of neonates with a 5-minute Apgar score < 7 did not differ significantly ($p = 0.82$). Two early neonatal deaths occurred, both in the < 20 $\mu\text{mol/L}$ group, corresponding to an overall rate of 0.9%; no significant between-group difference was observed. No stillbirths were observed.

Conclusion:

In this prospective cohort of women clinically diagnosed with IHCP, a single serum bile acid measurement obtained after 34 weeks was not significantly associated with most evaluated maternal or neonatal outcomes. Although mean 5-minute Apgar scores were lower among women with bile acid concentrations of 40–99.9 $\mu\text{mol/L}$, the proportion with clinically low Apgar scores did not differ significantly between groups. The small number of women with higher bile acid concentrations and absence of participants with concentrations $\geq 100 \mu\text{mol/L}$ limit conclusions regarding severe IHCP. Larger studies incorporating serial bile acid measurements and adequate representation of severe disease are warranted.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is a pregnancy-specific liver disorder characterized predominantly by pruritus, often involving the palms and soles, with biochemical evidence of cholestasis and no alternative cause of liver dysfunction. It usually develops during the second or third trimester and typically resolves after delivery. Although maternal morbidity is generally limited, IHCP is clinically important because of its potential association with adverse fetal and neonatal outcomes [1,2].

The pathogenesis of IHCP is multifactorial and involves genetic, hormonal, and environmental factors. Alterations in hepatocellular bile acid transport, including variants affecting transport proteins such as the bile salt export pump and multidrug resistance protein 3, may increase susceptibility to cholestasis during pregnancy. Pregnancy-related hormonal changes may further impair bile acid transport and contribute to the development or worsening of symptoms [2,3].

Serum bile acid concentration is an important biochemical marker in the evaluation of IHCP. However, bile acid concentrations may vary during pregnancy and can fluctuate over time, making interpretation of a single measurement challenging. Previous studies have reported associations between increasing maternal serum bile acid concentrations and adverse fetal outcomes, including preterm birth, meconium-stained liquor, fetal distress, and stillbirth [4–7]. The risk appears to be particularly relevant at very high bile acid concentrations, although the magnitude of risk and the optimal management thresholds remain subjects of ongoing clinical discussion [5–7].

Management of IHCP involves maternal symptom control, biochemical and fetal surveillance, and individualized planning of delivery according to gestational age, bile acid concentration, clinical status, and other obstetric factors. Ursodeoxycholic acid is commonly used to improve maternal pruritus and biochemical abnormalities, although evidence regarding its effect on clinically important perinatal outcomes remains inconsistent [8,9]. Decisions regarding the timing and mode of delivery require consideration of both the potential fetal risks associated with ongoing pregnancy and the neonatal risks associated with early-term or preterm delivery [5,6].

Most available evidence regarding the relationship between serum bile acid concentrations and pregnancy outcomes is derived from populations with varying diagnostic criteria, management protocols, and distributions of disease severity. Data from Indian tertiary-care settings, particularly

among women with clinically diagnosed IHCP and predominantly lower or moderate bile acid concentrations, remain comparatively limited. Furthermore, the relationship between a late-pregnancy serum bile acid measurement and maternal and neonatal outcomes in routine clinical practice has not been adequately characterized in this setting.

Therefore, this prospective observational study evaluated maternal and neonatal outcomes according to serum bile acid concentrations measured after 34 weeks of gestation among women clinically diagnosed with IHCP at a tertiary-care hospital in New Delhi. The study specifically compared outcomes across predefined serum bile acid categories of < 20, 20–39.9, and 40–99.9 $\mu\text{mol/L}$. Because no participant had serum bile acid concentrations $\geq 100 \mu\text{mol/L}$, the study was not designed to evaluate outcomes associated with severe hypercholanemia.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi, India, from August 2022 to January 2024.

Study population

Pregnant women in the third trimester attending the antenatal clinic or admitted to the obstetric wards were screened for clinically suspected intrahepatic cholestasis of pregnancy (IHCP). Women presenting with pruritus, particularly involving the palms and/or soles, without an identifiable dermatological cause were considered eligible for clinical evaluation for IHCP.

Women with multiple gestation, pruritus attributable to a dermatological disorder, viral hepatitis, or pre-existing chronic liver disease were excluded. Other clinically apparent causes of pruritus or liver dysfunction were evaluated and excluded as appropriate before enrolment.

A total of 221 women who fulfilled the study eligibility criteria and provided written informed consent were included in the final analysis.

Clinical assessment and follow-up

At enrolment, a detailed obstetric and medical history was obtained and a physical examination was performed. Maternal age, gravidity, parity, gestational age, gestational age at onset of pruritus, and relevant obstetric and clinical characteristics were recorded. The severity of pruritus was assessed using the validated 5-D Itch Scale [10].

Baseline routine antenatal investigations and liver function tests (LFTs), including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin, were performed. Participants were followed prospectively during pregnancy and up to 6 weeks postpartum. Pruritus severity and clinical status were reassessed during follow-up. LFTs were repeated every 2 weeks until 33 + 6 weeks of gestation and weekly thereafter until delivery, according to the study protocol.

Treatment with ursodeoxycholic acid (UDCA) and antihistamines was provided according to the treating team's clinical assessment and hospital protocol. Decisions regarding antenatal surveillance, induction of labour, and mode and timing of delivery were made by the treating obstetric team according to the clinical condition and obstetric indications.

Serum bile acid measurement

A venous blood sample for serum bile acid estimation was collected once after 34 weeks of gestation. Samples were collected in plain vacutainer tubes and centrifuged according to the laboratory protocol. The separated serum was stored at -20°C until analysis. Total serum bile acid concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Because serum bile acid concentration was measured only once after 34 weeks, the value obtained was considered a late-pregnancy biochemical measurement rather than a longitudinal measure of peak or cumulative bile acid exposure.

Serum bile acid categories

Participants were categorized according to the serum bile acid concentration obtained after 34 weeks:

- $< 20 \mu\text{mol/L}$
- $20\text{--}39.9 \mu\text{mol/L}$
- **$40\text{--}99.9 \mu\text{mol/L}$**

No participant had a serum bile acid concentration of $\geq 100 \mu\text{mol/L}$. Therefore, a $\geq 100 \mu\text{mol/L}$ category was not included in the comparative analysis, and the study does not provide evidence regarding outcomes associated with severe hypercholanemia.

The $< 20 \mu\text{mol/L}$ group was described as the **lower bile acid concentration group**, rather than as a separate category of “non-IHCP,” because all participants were enrolled on the basis of clinical suspicion of IHCP and bile acids were measured at a single late-gestation time point.

Study outcomes

The primary analysis evaluated differences in neonatal outcomes across the three serum bile acid categories. Neonatal outcomes included Apgar scores at 1 and 5 minutes, Apgar score < 7 at 1 and 5 minutes, birth weight, birth weight < 2.5 kg, meconium-stained liquor, neonatal intensive care unit (NICU) admission, stillbirth/intrauterine death, and early neonatal death.

Maternal outcomes included gestational age at delivery, preterm delivery (< 37 weeks), induction of labour, augmentation of labour, route of delivery (vaginal delivery or lower-segment caesarean section [LSCS]), detailed mode of delivery, type of LSCS (elective or emergency), and indications for LSCS.

Meconium-stained liquor was recorded according to the clinical grading documented at delivery. Fetal distress was recorded when it was documented as the indication for operative delivery according to the treating obstetric team's clinical assessment.

Sample size

The sample size was calculated using a previously reported proportion of adverse neonatal outcome associated with elevated bile acid concentrations and an absolute precision of 5%. The initial calculated sample size was 192 participants. Allowing for approximately 15% attrition or loss to follow-up, the target sample size was increased to 221 participants, which constituted the final study sample.

Statistical analysis

Data were entered and analysed using IBM SPSS Statistics version 21.0. Continuous variables were assessed for distribution using tests of normality and were summarized as mean $\pm$ standard deviation (SD) for approximately normally distributed variables or as median with interquartile range where appropriate. Categorical variables were presented as frequencies and percentages.

For comparisons across the three serum bile acid categories, one-way analysis of variance (ANOVA) was used for normally distributed continuous variables, while the Kruskal–Wallis test was used for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, particularly where expected cell frequencies were small.

All statistical tests were two-sided. A p-value < 0.05 was considered statistically significant. Because of the small number of participants in the 40–99.9 $\mu\text{mol/L}$ group and the absence of participants with serum bile acid concentrations $\geq 100 \mu\text{mol/L}$, findings for higher bile acid concentrations were interpreted cautiously and were not considered sufficient to establish clinical risk thresholds.

Ethical considerations

The study was approved by the Institutional Ethics Committee of VMMC and Safdarjung Hospital, New Delhi (Protocol No. IEC/VMMC/SJH/Thesis/2022/CC-154). Written informed consent was obtained from

all participants before enrolment. Participant confidentiality was maintained throughout data collection, analysis, and reporting.

RESULTS

A total of 221 pregnant women with clinically suspected/diagnosed intrahepatic cholestasis of pregnancy (IHCP) were included in the final analysis. Based on serum bile acid concentrations measured after 34 weeks of gestation, 146 women (66.1%) had bile acid concentrations $<20\text{ }\mu\text{mol/L}$, 64 (29.0%) had concentrations of $20\text{--}39.9\text{ }\mu\text{mol/L}$, and 11 (5.0%) had concentrations of $40\text{--}99.9\text{ }\mu\text{mol/L}$. No participant had a serum bile acid concentration $\geq 100\text{ }\mu\text{mol/L}$.

Baseline characteristics

The baseline characteristics of the study population are presented in **Table 1**. The mean maternal age was comparable across the three serum bile acid groups: 25.68 ± 3.75 years in the $<20\text{ }\mu\text{mol/L}$ group, 25.67 ± 3.51 years in the $20\text{--}39.9\text{ }\mu\text{mol/L}$ group, and 24.82 ± 2.79 years in the $40\text{--}99.9\text{ }\mu\text{mol/L}$ group ($p=0.78$). The distribution of maternal age categories was also similar between groups ($p=0.97$).

There was no statistically significant difference in gravidity ($p=0.53$) or parity ($p=0.45$) between the groups. The proportion of primigravida women was 42.5%, 34.4%, and 36.4%, respectively, while multigravida women accounted for 57.5%, 65.6%, and 63.6%.

The baseline biochemical parameters were also comparable. Mean total bilirubin was 0.81 ± 0.31 , 0.80 ± 0.33 , and $0.65 \pm 0.31\text{ mg/dL}$ ($p=0.27$), while mean alkaline phosphatase was 321.93 ± 80.71 , 325.42 ± 86.82 , and $318.09 \pm 82.33\text{ U/L}$ ($p=0.92$). Mean AST levels were 148.95 ± 57.47 , 154.38 ± 56.86 , and $149.00 \pm 50.75\text{ U/L}$ ($p=0.87$), and mean ALT levels were 170.43 ± 61.01 , 168.98 ± 52.65 , and $184.09 \pm 54.62\text{ U/L}$ ($p=0.61$), respectively. Overall, no significant baseline demographic, obstetric, or biochemical differences were observed across the serum bile acid categories.

Table 1. Baseline characteristics of the study population

Parameter	<20 µmol/L (n=146)	20–39.9 µmol/L (n=64)	40–99.9 µmol/L (n=11)	p value
Age, years, mean ± SD	25.68 ± 3.75	25.67 ± 3.51	24.82 ± 2.79	0.78
Age group				0.97
18–25 years	70 (47.9%)	30 (46.9%)	6 (54.5%)	
26–30 years	60 (41.1%)	27 (42.2%)	5 (45.5%)	
31–35 years	15 (10.3%)	7 (10.9%)	0 (0.0%)	
>35 years	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Gravidity				0.53
Primigravida	62 (42.5%)	22 (34.4%)	4 (36.4%)	
Multigravida	84 (57.5%)	42 (65.6%)	7 (63.6%)	
Parity				0.45
P0	82 (56.2%)	30 (46.9%)	7 (63.6%)	
P1	52 (35.6%)	24 (37.5%)	3 (27.3%)	
≥P2	12 (8.2%)	10 (15.6%)	1 (9.1%)	
Total bilirubin, mg/dL	0.81 ± 0.31	0.80 ± 0.33	0.65 ± 0.31	0.27
ALP, U/L	321.93 ± 80.71	325.42 ± 86.82	318.09 ± 82.33	0.92
AST, U/L	148.95 ± 57.47	154.38 ± 56.86	149.00 ± 50.75	0.87
ALT, U/L	170.43 ± 61.01	168.98 ± 52.65	184.09 ± 54.62	0.61

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

Maternal outcomes

Maternal outcomes according to serum bile acid concentration are presented in **Table 2**. The mean gestational age at delivery was 37.76 ± 1.52 weeks in the <20 µmol/L group, 37.48 ± 1.44 weeks in the 20–39.9 µmol/L group, and 37.45 ± 1.75 weeks in the 40–99.9 µmol/L group, with no statistically significant difference between groups (p=0.23).

Preterm delivery before 37 weeks occurred in 24 (16.4%), 11 (17.2%), and 3 (27.3%) women, respectively (p=0.65). Induction of labour was performed in 79 (54.1%), 30 (46.9%), and 4 (36.4%) women (p=0.38).

Augmentation of labour was performed in 96 (65.8%), 35 (54.7%), and 5 (45.5%) women, respectively (p=0.17).

The route of delivery did not differ significantly between groups (p=0.41). Vaginal delivery occurred in 111 (76.0%), 43 (67.2%), and 8 (72.7%) women, while LSCS was performed in 35 (24.0%), 21 (32.8%), and 3 (27.3%), respectively.

When delivery was categorized into FTNVD, emergency LSCS, PTVD, elective LSCS, instrumental delivery, and VBAC, no statistically significant difference was observed between groups (p=0.52). Among women undergoing LSCS, the distribution of elective and emergency procedures was also comparable (p=0.60). The indications for LSCS did not differ significantly between groups (p=0.83).

Table 2. Maternal outcomes according to serum bile acid concentration

Parameter	<20 µmol/L (n=146)	20–39.9 µmol/L (n=64)	40–99.9 µmol/L (n=11)	p value
Gestational age at delivery, weeks, mean ± SD	37.76 ± 1.52	37.48 ± 1.44	37.45 ± 1.75	0.23
Gestational age at delivery				0.65
<37 weeks	24 (16.4%)	11 (17.2%)	3 (27.3%)	
≥37 weeks	122 (83.6%)	53 (82.8%)	8 (72.7%)	
Induction of labour	79 (54.1%)	30 (46.9%)	4 (36.4%)	0.38
Augmentation of labour	96 (65.8%)	35 (54.7%)	5 (45.5%)	0.17
Route of delivery				0.41
Vaginal	111 (76.0%)	43 (67.2%)	8 (72.7%)	
LSCS	35 (24.0%)	21 (32.8%)	3 (27.3%)	
Mode of delivery				0.52
FTNVD	90 (61.6%)	34 (53.1%)	5 (45.5%)	
Emergency LSCS	25 (17.1%)	18 (28.1%)	3 (27.3%)	
PTVD	12 (8.2%)	5 (7.8%)	3 (27.3%)	
Elective LSCS	10 (6.8%)	3 (4.7%)	0 (0.0%)	
Instrumental delivery	6 (4.1%)	3 (4.7%)	0 (0.0%)	
VBAC	3 (2.1%)	1 (1.6%)	0 (0.0%)	
Type of LSCS				0.60
Elective	10 (28.6%)	4 (19.0%)	0 (0.0%)	
Emergency	25 (71.4%)	17 (81.0%)	3 (100.0%)	
Indication for LSCS				0.83
Failed induction of labour	3 (8.6%)	1 (4.8%)	0 (0.0%)	
Fetal distress	12 (34.3%)	10 (47.6%)	1 (33.3%)	
Other indications	20 (57.1%)	10 (47.6%)	2 (66.7%)	

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

Abbreviations: FTNVD, full-term normal vaginal delivery; LSCS, lower-segment caesarean section; PTVD, preterm vaginal delivery; SD, standard deviation; VBAC, vaginal birth after caesarean.

Neonatal outcomes

Neonatal outcomes are presented in **Table 3**. The distribution of liquor characteristics did not differ significantly across serum bile acid groups ($p=0.66$). Clear liquor was observed in 81 (55.5%), 31 (48.4%), and 5 (45.5%) deliveries, respectively. Grade 2 MSL occurred in 37 (25.3%), 20 (31.2%), and 2 (18.2%), while grade 3 MSL occurred in 27 (18.5%), 13 (20.3%), and 4 (36.4%), respectively.

Mean birth weight was 3145.23 ± 416.77 g in the <20 $\mu\text{mol/L}$ group, 3157.16 ± 397.19 g in the $20\text{--}39.9$ $\mu\text{mol/L}$ group, and 3201.45 ± 289.40 g in the $40\text{--}99.9$ $\mu\text{mol/L}$ group, with no significant difference between groups ($p=0.94$). Birth weight <2.5 kg occurred in 11 (7.5%), 3 (4.7%), and 0 (0.0%) neonates, respectively ($p=0.79$).

The mean Apgar score at 1 minute was comparable between groups (6.53 ± 1.17 , 6.50 ± 0.91 , and 6.27 ± 1.56 ; $p=0.80$). In contrast, the mean Apgar score at 5 minutes was significantly different across the groups, with values of 8.49 ± 1.10 , 8.23 ± 1.03 , and 7.91 ± 1.76 , respectively ($p=0.009$).

However, the proportion of neonates with an Apgar score <7 at 5 minutes did not differ significantly between groups: 11 (7.5%), 4 (6.2%), and 1 (9.1%), respectively ($p=0.82$). Similarly, the proportion with Apgar <7 at 1 minute was comparable between groups (59 [40.4%], 25 [39.1%], and 5 [45.5%]; $p=0.92$).

NICU admission occurred in 6 (4.1%), 4 (6.2%), and 0 (0.0%) neonates, respectively ($p=0.70$). Two early neonatal deaths occurred in the <20 $\mu\text{mol/L}$ group, while none occurred in the other groups ($p=1.000$). The overall early neonatal mortality was therefore 2/221 (0.9%). No stillbirth or intrauterine fetal death was reported.

Table 3. Neonatal outcomes according to serum bile acid concentration

Parameter	<20 µmol/L (n=146)	20–39.9 µmol/L (n=64)	40–99.9 µmol/L (n=11)	p value
Liquor				0.66
Clear	81 (55.5%)	31 (48.4%)	5 (45.5%)	
MSL grade 2	37 (25.3%)	20 (31.2%)	2 (18.2%)	
MSL grade 3	27 (18.5%)	13 (20.3%)	4 (36.4%)	
Blood-stained liquor	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Birth weight, g, mean ± SD	3145.23 ± 416.77	3157.16 ± 397.19	3201.45 ± 289.40	0.94
Birth weight				0.79
<2.5 kg	11 (7.5%)	3 (4.7%)	0 (0.0%)	
≥2.5 kg	135 (92.5%)	61 (95.3%)	11 (100.0%)	
Apgar score at 1 min, mean ± SD	6.53 ± 1.17	6.50 ± 0.91	6.27 ± 1.56	0.80
Apgar score at 5 min, mean ± SD	8.49 ± 1.10	8.23 ± 1.03	7.91 ± 1.76	0.009
Apgar <7 at 1 min	59 (40.4%)	25 (39.1%)	5 (45.5%)	0.92
Apgar <7 at 5 min	11 (7.5%)	4 (6.2%)	1 (9.1%)	0.82
NICU admission	6 (4.1%)	4 (6.2%)	0 (0.0%)	0.70
Early neonatal death	2 (1.4%)	0 (0.0%)	0 (0.0%)	1.000

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

Abbreviations: Apgar, Appearance, Pulse, Grimace, Activity and Respiration; MSL, meconium-stained liquor; NICU, neonatal intensive care unit; SD, standard deviation.

Overall findings

Overall, there was no statistically significant association between serum bile acid category and most maternal or neonatal outcomes evaluated in this cohort. Maternal outcomes, including gestational age at delivery, preterm delivery, induction or augmentation of labour, and route of delivery, were comparable across the three groups.

Among neonatal outcomes, the mean 5-minute Apgar score was significantly lower in the 40–99.9 µmol/L group compared with the lower bile acid groups (p=0.009). However, this difference was not accompanied by a significant difference in the proportion of neonates with an Apgar score <7 at 5

minutes ($p=0.82$). No significant differences were observed in birth weight, low birth weight, liquor characteristics, NICU admission, or early neonatal death.

Because only 11 women had serum bile acid concentrations of 40–99.9 $\mu\text{mol/L}$ and no participant had concentrations $\geq 100 \mu\text{mol/L}$, the findings provide limited information regarding outcomes associated with very high or severe hypercholanemia.

DISCUSSION

In this prospective observational study of 221 women with clinically suspected intrahepatic cholestasis of pregnancy (IHCP), maternal and neonatal outcomes were compared according to a single serum bile acid measurement obtained after 34 weeks of gestation. Most women had serum bile acid concentrations $<20 \mu\text{mol/L}$ (66.1%), while 29.0% had concentrations of 20–39.9 $\mu\text{mol/L}$ and 5.0% had concentrations of 40–99.9 $\mu\text{mol/L}$. No participant had a serum bile acid concentration $\geq 100 \mu\text{mol/L}$. Overall, most maternal and neonatal outcomes did not differ significantly across the three groups. A statistically significant difference was observed in the mean 5-minute Apgar score, but the proportion of neonates with an Apgar score <7 at 5 minutes did not differ significantly.

The distribution of serum bile acid concentrations is important when interpreting the findings. The majority of participants had concentrations below 20 $\mu\text{mol/L}$, and only 11 women had concentrations between 40 and 99.9 $\mu\text{mol/L}$. Therefore, the present study predominantly represents women with clinically suspected IHCP and relatively low to moderate late-pregnancy serum bile acid concentrations. The absence of participants with concentrations $\geq 100 \mu\text{mol/L}$ means that the present study cannot provide meaningful information regarding fetal risks associated with severe hypercholanemia.

Previous studies have reported associations between elevated maternal serum bile acid concentrations and adverse pregnancy outcomes. Kenyon et al. reported increased obstetric and perinatal complications in pregnancies complicated by obstetric cholestasis [10]. Brouwers et al. subsequently demonstrated that increasing bile acid concentrations were associated with adverse maternal and fetal outcomes [11]. Kant et al. also reported maternal and perinatal outcomes among women with IHCP in an Indian clinical setting [12]. These findings support the importance of serum bile acid concentration in the clinical assessment and risk stratification of IHCP.

Glantz et al. reported an association between maternal serum bile acid concentrations and fetal complication rates, with increasing concentrations associated with greater fetal risk [13,14]. Although the present study did not demonstrate statistically significant differences in most neonatal outcomes, the findings should be interpreted in the context of the relatively low distribution of bile acid concentrations in the study population and the small number of women with concentrations $\geq 40 \mu\text{mol/L}$.

In the present study, preterm delivery occurred in 16.4% of women with bile acids $<20 \mu\text{mol/L}$, 17.2% of those with concentrations of 20–39.9 $\mu\text{mol/L}$, and 27.3% of those with concentrations of 40–99.9 $\mu\text{mol/L}$ ($p=0.65$). Although the proportion was numerically higher in the highest observed category, the

difference was not statistically significant. The small number of women in this group substantially limits the statistical power to detect clinically meaningful differences. Earlier prospective work has also demonstrated that obstetric management and timing of delivery may influence the observed frequency of preterm birth in IHCP [13,15,16,17].

Similarly, no statistically significant differences were observed in induction of labour, augmentation of labour, or mode of delivery. Induction was performed in 54.1%, 46.9%, and 36.4% of women across the three groups, respectively, while LSCS rates were 24.0%, 32.8%, and 27.3%. These findings should not be interpreted as evidence that induction or caesarean delivery can safely be avoided at a particular bile acid concentration. Timing and mode of delivery should be individualized according to gestational age, maternal symptoms, serum bile acid concentrations, fetal assessment, and other obstetric indications.

The neonatal findings were generally reassuring. Birth weight, low birth weight, meconium-stained liquor, and NICU admission did not differ significantly between the serum bile acid categories. Previous studies have reported increased frequencies of meconium-stained liquor and fetal complications in women with elevated serum bile acid concentrations [10,11,14,18,19]. The absence of significant differences in the present study may partly reflect the predominance of women with lower bile acid concentrations and the limited number of participants in the higher concentration group.

A statistically significant difference was observed in the mean 5-minute Apgar score, which was 8.49 in the $<20 \mu\text{mol/L}$ group, 8.23 in the $20\text{--}39.9 \mu\text{mol/L}$ group, and 7.91 in the $40\text{--}99.9 \mu\text{mol/L}$ group ($p=0.009$). However, this finding requires cautious interpretation. The mean 5-minute Apgar score remained above 7 in all three groups, and there was no statistically significant difference in the proportion of neonates with an Apgar score <7 at 5 minutes ($p=0.82$). Therefore, the difference in mean Apgar score does not necessarily indicate a clinically important deterioration in neonatal condition.

Two early neonatal deaths occurred in the $<20 \mu\text{mol/L}$ group, corresponding to an overall early neonatal mortality of 0.9%. No early neonatal deaths occurred in the other two groups, and no stillbirths or intrauterine deaths were recorded. These findings should not be interpreted as evidence of a protective effect of lower bile acid concentrations because the number of events was very small and the study was not powered to evaluate mortality outcomes.

An important consideration is the timing and frequency of bile acid measurement. In the present study, serum bile acid concentration was measured once after 34 weeks of gestation. Serum bile acid concentrations may fluctuate during pregnancy, and a single measurement may not represent the maximum concentration experienced during pregnancy [17]. Therefore, a single late-pregnancy measurement may not adequately capture the relationship between peak bile acid concentration and adverse fetal outcomes. Serial biochemical assessment may provide a more comprehensive assessment of disease severity.

The clinical assessment of pruritus was performed using the 5-D Itch Scale, which provides a standardized approach to assessing itch severity [15]. However, symptom severity does not necessarily

correspond directly to serum bile acid concentration. Therefore, clinical symptoms and biochemical findings should be considered complementary components of IHCP assessment rather than interchangeable measures.

Treatment may also have influenced the observed outcomes. Participants received ursodeoxycholic acid and antihistamines according to clinical assessment and hospital protocol. Ursodeoxycholic acid has been widely used for symptomatic treatment of IHCP and may improve maternal pruritus and biochemical parameters [18-21]. However, evidence regarding its effect on clinically important perinatal outcomes has been inconsistent [16,22]. The present study was not designed to evaluate the efficacy of ursodeoxycholic acid or compare treatment strategies; therefore, causal conclusions regarding treatment effects cannot be drawn.

The clinical definition used for enrolment also requires consideration. Participants were enrolled on the basis of clinical suspicion of IHCP, primarily characterized by pruritus, and were subsequently categorized according to a single serum bile acid measurement. Therefore, the $<20 \mu\text{mol/L}$ group should not be interpreted simply as women without IHCP. Symptoms and biochemical abnormalities may not always occur simultaneously, and serum bile acid concentrations may vary during pregnancy [17].

Strengths and limitations

The strengths of this study include its prospective design, systematic clinical follow-up, assessment of both maternal and neonatal outcomes, and standardized measurement of serum bile acids in a tertiary-care obstetric setting. The study also contributes data from an Indian clinical population, where evidence concerning the relationship between serum bile acid concentration and pregnancy outcomes remains comparatively limited.

Several limitations should be acknowledged. First, this was a single-centre observational study, which limits generalizability. Second, only 11 participants had serum bile acid concentrations of $40\text{--}99.9 \mu\text{mol/L}$, limiting the statistical power for comparisons involving higher concentrations. Third, no participant had concentrations $\geq 100 \mu\text{mol/L}$; therefore, the study cannot evaluate outcomes associated with severe hypercholanemia. Fourth, serum bile acids were measured only once after 34 weeks, preventing assessment of temporal variation or peak exposure. Fifth, the observational design prevents causal inference, and treatment and delivery decisions were not randomized. Sixth, important adverse outcomes such as stillbirth and early neonatal death were uncommon, resulting in limited statistical power for mortality analyses. Finally, residual confounding related to gestational age at diagnosis, treatment, maternal characteristics, fetal surveillance, and obstetric management cannot be excluded.

Clinical implications

The present findings suggest that, in this cohort predominantly comprising women with serum bile acid concentrations below $40 \mu\text{mol/L}$, most measured maternal and neonatal outcomes were not significantly different across the observed bile acid categories. However, these findings should not be

interpreted as establishing a safe bile acid threshold for expectant management or delivery planning. In particular, the absence of participants with concentrations ≥ 100 $\mu\text{mol/L}$ prevents extrapolation of these findings to severe IHCP. Clinical management should continue to consider maternal symptoms, serial biochemical assessment, gestational age, fetal status, and established clinical recommendations.

Future research

Future prospective multicentre studies should include larger numbers of women across the complete spectrum of serum bile acid concentrations, particularly women with concentrations ≥ 40 and ≥ 100 $\mu\text{mol/L}$. Serial measurements from diagnosis through delivery would allow assessment of peak and changing bile acid concentrations and their relationship with fetal outcomes. Studies should also use standardized definitions of IHCP, biochemical severity, fetal distress, meconium-stained liquor, and neonatal outcomes. Such studies would help improve risk stratification and support individualized management of women with IHCP.

CONCLUSION

In this prospective cohort of women with clinically suspected IHCP, most maternal and neonatal outcomes did not differ significantly according to late-pregnancy serum bile acid concentration. A statistically significant difference was observed in mean 5-minute Apgar score, but not in the proportion of neonates with an Apgar score < 7 at 5 minutes or in other major neonatal outcomes. The predominance of women with bile acid concentrations < 40 $\mu\text{mol/L}$, the small number with concentrations of 40–99.9 $\mu\text{mol/L}$, and the absence of participants with concentrations ≥ 100 $\mu\text{mol/L}$ substantially limit conclusions regarding severe IHCP. Larger prospective studies incorporating serial bile acid measurements and adequate representation of higher bile acid concentrations are required to better define the relationship between biochemical severity and perinatal outcomes.

DECLARATIONS

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi (IEC No. VMMC/SJH/Thesis/2022/CC-154). Written informed consent was obtained from all participants before enrolment.

Consent for Publication

Not applicable. No individually identifiable participant information or images are presented in this manuscript.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

SK contributed to the study conception, data collection, analysis, and manuscript preparation. AK and VS contributed to the clinical and laboratory aspects of the study and interpretation of findings. SS contributed to study supervision, data interpretation, and manuscript review. AL contributed to study design, methodological review, data interpretation, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain participant-level clinical information and are subject to institutional ethical and confidentiality requirements. Relevant data may be made available from the corresponding author on reasonable request, subject to institutional approval and applicable ethical restrictions.

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