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Intrahepatic cholestasis of pregnancy and perinatal outcomes in a tertiary care hospital

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Abstract

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a reversible hepatobiliary disorder specific to pregnancy, predominantly manifesting in the third trimester. It is characterized by pruritus and elevated serum bile acid levels and is associated with adverse fetal outcomes. This study aimed to evaluate the maternal and perinatal outcomes in pregnancies complicated by IHCP and to analyze the association between bile acid concentrations and neonatal complications.

Materials and Methods: A prospective observational study was conducted on 142 pregnant women diagnosed with IHCP at a tertiary care center from January 2023 to January 2025. Participants were categorized based on serum bile acid levels into mild (10–40 µmol/L), moderate (41–100 µmol/L), and severe (>100 µmol/L) groups. Maternal liver function parameters and perinatal outcomes were assessed and statistically analyzed.

Results: Pruritus was observed in all patients. A significant rise in serum aminotransferases (ALT, AST) and bilirubin correlated with increasing bile acid levels ($p<0.001$). Adverse perinatal outcomes—including low APGAR scores, NICU admissions, and intrauterine fetal demise—were more frequent in patients with moderate-to-severe IHCP. Two cases of intrauterine demise occurred in the moderate group.

Conclusion: IHCP is associated with significant maternal biochemical derangements and fetal morbidity. Serum bile acid levels are a useful marker for predicting adverse neonatal outcomes. Early diagnosis, close monitoring, and timely delivery are essential to improving perinatal prognosis.

Keywords: intrahepatic cholestasis; pregnancy, serum bile acids; liver function; perinatal outcomes; fetal distress; pruritus; pregnancy; preterm delivery; intrauterine demise

Introduction

Intrahepatic cholestasis of pregnancy (IHCP), also known as obstetric cholestasis, is a pregnancy-specific liver disorder that typically manifests in the late second or third trimester. It is a diagnosis of exclusion, characterized by pruritus—often severe and primarily affecting the palms and soles—without a primary dermatologic cause, and is biochemically marked by elevated serum bile acid concentrations and abnormal liver function tests, particularly increased transaminases (AST/ALT). IHCP usually resolves spontaneously within a few days postpartum, confirming its reversible and pregnancy-related nature.

The global incidence of IHCP varies widely, ranging from 0.2% to 2% in the general population, with higher prevalence reported in certain ethnic groups and geographical regions such as South America and South Asia. It affects 1.2 -1.5 % Indian Asian women. The pathogenesis of IHCP is complex and remains

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incompletely understood. However, a multifactorial etiology is widely accepted, involving the interplay of genetic predisposition (e.g. mutation of ABC - B4 gene, ABC B11, ATP 8B1, ABC C2, NR 1 H4), hormonal influences (notably elevated estrogen and progesterone metabolites in late pregnancy), and environmental triggers (such as selenium deficiency and seasonal variation).

Although maternal prognosis is generally favorable, IHCP is associated with a spectrum of adverse perinatal outcomes. These include spontaneous preterm labor, meconium-stained amniotic fluid, neonatal respiratory distress, low birth weight, and more alarmingly, increased risk of unexplained stillbirth, particularly when maternal serum bile acid levels exceed 40 μmol/L. Emerging evidence indicates that the severity of elevated serum bile acid levels correlates with fetal risk, making bile acid concentration a potential prognostic marker and therapeutic guide in IHCP management.

Despite advances in prenatal care, IHCP continues to pose diagnostic and management challenges, especially in low-resource settings. There remains a pressing need to improve understanding of the clinical spectrum and biochemical correlations in IHCP to inform timely interventions and optimize perinatal outcomes.

This study aims to elucidate the obstetric outcomes of IHCP, with a special focus on the correlation between serum bile acid levels and perinatal complications.

Materials and methods

A prospective observational study was conducted in the Department of Obstetrics and Gynaecology at MLN Medical College & SRN Hospital, Prayagraj, from January 2023 to January 2025. Ethical approval was obtained from the Institutional Ethics Committee, and informed written consent was taken from all participants. A total of 142 pregnant women diagnosed with IHCP were recruited from among 3744 deliveries conducted at the institution during the study period.

Women presenting with pruritus, particularly over the palms and soles or as generalized itching without any visible dermatological lesions or elevated liver enzyme like Serum transaminases (ALT and AST) raised to more than twice the upper limit of normal were evaluated clinically. In all such cases serum bile acid levels were assessed. Patients with bile acid concentrations >10 μmol/L were diagnosed as having IHCP, in accordance with established diagnostic parameters. Only women with singleton pregnancies who delivered at our institution and were willing to participate were included in the study. Treatment was started irrespective of gestational age at diagnosis.

Women were excluded if they had known dermatological conditions causing pruritus, viral hepatitis, HELLP syndrome, acute fatty liver of pregnancy, obstructive jaundice, or pre-existing chronic liver diseases. Those with other systemic comorbidities or who did not provide informed consent were also excluded.

Based on serum bile acid levels, participants were classified as: Mild IHCP: 10–40 μmol/L; Moderate IHCP: 41–100 μmol/L; Severe IHCP: >100 μmol/L.

All enrolled women underwent routine antenatal surveillance, including non-stress testing, modified biophysical profiles, and obstetric ultrasonography. Perinatal outcomes such as gestational age at delivery, birth weight, APGAR scores at 1 and 5 minutes, meconium-stained liquor, NICU admission, and intrauterine fetal demise were documented. All patients were followed up to 4 weeks postpartum to assess neonatal outcomes.

Statistical Analysis

All collected data were compiled and analyzed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). Descriptive statistics were applied to summarize baseline characteristics. Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean ± standard deviation (SD). For comparison of continuous variables across bile acid categories, One-Way Analysis of Variance (ANOVA) was employed. The association between categorical variables and serum bile acid levels was analyzed using the Chi-square (χ^2) test or Fisher's exact test. A p value of <0.05 was considered statistically significant in all tests.

Results

This prospective observational study enrolled 142 pregnant women diagnosed with intrahepatic cholestasis of pregnancy (IHCP). The most common age group was 26–30 years (40.8%), followed by 18–25 years (33.1%). Women aged ≥35 years constituted only 4.2% of the study cohort. A majority were primigravida (53.5%), while 33.8% were multigravida (G2–G4), and 12.7% were grand multigravida (G5 or more). Regarding the gestational age at termination, most women delivered between 37–39+6 weeks (81.0%), while 16.9% delivered preterm (<37 weeks), and 2.1% had delivery at or beyond 40 weeks (Table 1).

Table 1: distribution of participants according to age, gravidity and period of gestation at termination (n = 142).

Parameter	*Categories*	*n (%)*
Age (years)	18-25	47 (33.1%)
	26–30	58 (40.8%)
	31–34	31 (21.8%)
	≥35	6 (4.2%)
Gravidity	G1	76 (53.5%)
	G2-G4	48 (33.8%)
	≥ G5	18 (12.7%)
Period of Gestation (POG) in weeks at termination	< 37	24 (16.9%)
	37–39+6	115 (81.0%)
	≥ 40	3 (2.1%)

Pruritus was reported universally across all categories of serum bile acid levels, confirming it as the hallmark clinical symptom of IHCP. A decline in perceived fetal movements was noted in 13.3% of women with bile acids 10–40 µmol/L, rising to 20.0% in the 41–100 µmol/L group and 50.0% in those with levels >100 µmol/L, indicating a direct relationship between bile acid severity and fetal compromise (Table 2).

Table 2: Clinical Features in Relation to Serum Bile Acid Levels (µmol/L).

Feature	*10–40 µmol/L (n=113)*	*41–100 µmol/L (n=25)*	*>100 µmol/L (n=4)*
Pruritus	113 (100%)	25 (100%)	4 (100%)
↓ Fetal movements	15 (13.3%)	5 (20.0%)	2 (50.0%)

Biochemical analysis revealed a progressive rise in liver transaminases and serum bilirubin with increasing bile acid concentrations. The mean ALT levels were 79.5 ± 21.8 U/L, 165.0 ± 38.2 U/L, and 224.0 ± 40.7 U/L across the mild, moderate, and severe groups, respectively ($p<0.001$). Similarly, AST levels increased significantly (76.5 ± 19.7 U/L to 180.0 ± 34.1 U/L; $p<0.001$). Alkaline phosphatase (ALP) also showed a statistically significant elevation ($p=0.04$). Total serum bilirubin was highest in the moderate group (1.15 ± 0.27 mg/dL; $p<0.001$) (Table 3).

Table 3: Correlation of different parameters of liver function test with serum bile acid levels (µmol/L).

Parameters	*10–40 µmol/L (n = 113)*	*41-100µmol/L (n = 25)*	*>100 µmol/L (n = 4)*	*p-value*
ALT (U/L)	79.5 ± 21.8	165.0 ± 38.2	224.0 ± 40.7	<0.001
AST (U/L)	76.5 ± 19.7	134.5 ± 34.8	180.0 ± 34.1	<0.001
ALP (U/L)	310.0 ± 94.5	336.0 ± 90.7	324.0 ± 87.9	0.04
Serum Bilirubin (mg/dL)	0.68 ± 0.21	1.15 ± 0.27	1.00 ± 0.16	<0.001

With regard to neonatal outcomes, the incidence of meconium-stained liquor (MSL) was comparable across mild, moderate and severe categories and was not statistically significant —23.00% in the mild group, 20.0% in the moderate group, and 25.0% in the severe group ($p=0.942$). APGAR scores <7 at 1 and 5 minutes were significantly more frequent in neonates born to mothers with higher bile acids ($p=0.041$ and $p=0.038$, respectively). Two intrauterine demises (8.0%) were observed in the moderate category, while none occurred in the mild or severe categories ($p=0.005$). NICU admission rates rose proportionally from 8.8% to 25.0% across the three groups ($p=0.021$) (Table 4).

Table 4: Correlation of neonatal outcomes with serum bile acid levels (µmol/L).

Neonatal Parameters	*10–40 µmol/L (n=113)*	*41-100µmol/L (n=25)*	*>100 µmol/L (n=4)*	*p-value*
Meconium stained liquor (MSL)	26 (23.00%)	5 (20.0%)	1 (25.0%)	0.942
APGAR <7 at 1 min	4 (3.5%)	2 (8.0%)	1 (25.0%)	0.041
APGAR <7 at 5 min	1 (0.9%)	1 (4.0%)	1 (25.0%)	0.038
IUD	0 (0.0%)	2 (8.0%)	0 (0.0%)	0.005
NICU Admission	10 (8.8%)	5 (20.0%)	1 (25.0%)	0.021

Discussion

Intrahepatic cholestasis of pregnancy (IHCP) continues to be a significant obstetric challenge due to its association with adverse perinatal outcomes. The present study reaffirms the established association between rising maternal serum bile acid levels and deteriorating perinatal parameters, emphasizing the need for timely surveillance and intervention.

In our study, the majority of IHCP cases were seen in the 26–30-year age group, with over half being primigravidae, consistent with the demographic profile reported by Chappell et al. [1], who observed a similar trend in IHCP presentation among young primigravida women. Although our study found a predominance of primigravida, a somewhat differing pattern is noted by Wang et al. [2], who reported that multiparity (≥1) was independently associated with a higher risk of IHCP (aRR 1.54). Likewise, Bansal et al. [3] and Sharma et al. [4] reported greater IHCP prevalence among multigravida in their respective cohorts. The discrepancy may reflect regional differences in fertility trends, parity-related hormonal changes, or early identification and referral patterns in our population.

In our study, 16.9% of IHCP patients delivered preterm (<37 weeks). This is comparable to the findings by Geenes et al. [5], who reported a preterm delivery rate of 19% in cholestatic pregnancies. Similarly, Ovadia et al. [6] demonstrated that preterm delivery, especially iatrogenic, is significantly associated with bile acid levels >40 μmol/L, likely due to clinician-initiated early delivery to prevent stillbirth. The elevated bile acids are believed to increase uterine contractility and sensitivity to oxytocin, precipitating early labor, as well as, higher rate of iatrogenic preterm delivery due to rising bile acid levels and our concern for fetal well-being and and to prevent still birth. 2.1 % of IHCP patients appeared at or beyond 40 weeks of period of gestation at our institute with mild IHCP and delivered under close fetal surveillance.

In our study pruritus, the hallmark symptom, was universally present across all bile acid levels, aligning with the findings of Reyes et al. [7], who identified pruritus as a diagnostic cornerstone in IHCP. The pathophysiology of pruritus in IHCP is multifactorial. Hormonal mediation plays a central role. Elevated progesterone metabolites, particularly epiallopregnanolone sulfate, activate TGR5 receptors on cutaneous sensory neurons, leading to cholestatic itching (Abu-Hayyeh et al. [8]. Neurogenic stimulation via the autotaxin–lysophosphatidic acid (LPA) axis is another key mechanism. Increased autotaxin activity leads to accumulation of LPA, which activates TRPV1/TRPA1 channels on nerve endings, directly triggering pruritus (Kremer et al., 2010 [9]; Kremer et al., 2012 [10]). Additionally, bile acids may exert a direct pruritogenic effect and may also influence central opioid pathways, although their correlation with itch intensity is inconsistent in clinical studies [11].

Decreased fetal movement was reported in 13.3% of patients with mild IHCP, 20% in moderate, and 50% in severe categories. These results resonate with the observations of Brouwers et al. [12], who emphasized that bile acid-induced vasoconstriction and placental dysfunction contribute to intermittent fetal hypoxia, which clinically manifests as reduced fetal movements.

There was a statistically significant rise in liver enzymes and bilirubin levels with increasing bile acid concentration. The mean ALT increased from 79.5 U/L in mild to 224.0 U/L in severe cases ($p < 0.001$). These findings correlate with the work of Glantz et al. [13], who noted that elevated aminotransferases often accompany high bile acids in IHCP, serving as markers of hepatocellular injury. Jhirwal et al. [14] similarly reported that LFTs, particularly ALT and AST, correlate positively with the severity of cholestasis. In our study, mean ALP levels rose progressively with increasing serum bile acid concentrations—310 ± 94.5 U/L in the mild group, 336 ± 90.7 U/L in the moderate group, and 324 ± 87.9 U/L in the severe group—with statistical significance ($p = 0.04$), suggesting mild hepatic cholestasis. Medscape et al. [15] noted that ALP can be elevated up to four-fold in IHCP, but interpret this rise cautiously, as placental production contributes markedly to serum ALP during pregnancy.

Despite statistical correlation, ALP's elevation in IHCP is not pathognomonic. Its placental origin and steady increase throughout pregnancy diminish its utility as a direct cholestatic marker. The modest ALP rise observed in our study likely reflects a combination of pregnancy physiology and mild hepatic cholestasis, rather than isolated hepatobiliary obstruction. In our study, mean serum bilirubin levels rose significantly with increasing bile acid concentrations—0.68 ± 0.21 mg/dL in the mild group (10–40 μmol/L), 1.15 ± 0.27 mg/dL in the moderate group (41–100 μmol/L), and 1.00 ± 0.16 mg/dL in the severe group (>100 μmol/L), with a statistically significant p-value of <0.001. This finding reflects the hepatic impact of rising bile acid burden, albeit within largely physiological limits. Similar trends were reported by Kumar et al. [16], where bilirubin levels in IHCP patients showed significant elevation in moderate-to-severe disease, correlating with bile acid concentration and fetal risk. Likewise, Geenes et al. [5] observed that even mild elevations in bilirubin—when seen alongside bile acid rise—could indicate cholestatic dysfunction, especially when pruritus is present.

Sharma et al. [4] documented a mean total bilirubin of 1.12 ± 0.28 mg/dL in moderate IHCP cases, closely aligning with our findings. Notably, bilirubin elevation was seen to parallel transaminase and bile acid trends, reinforcing its supporting role in IHCP biochemistry. Although serum bilirubin is not the most sensitive indicator of IHCP severity, its elevation indicates hepatocyte transport dysfunction and reduced clearance of conjugated bilirubin into bile canaliculi. The cholestatic block at the hepatocellular or canalicular level, aggravated by hormonal and genetic factors, may impair bilirubin excretion as bile acids accumulate (Marschall et al., 2021 [11]). This explains the significant elevation seen in moderate cases in our study.

In our study meconium-stained amniotic fluid (MSL) was observed in 23% of mild, 20% of moderate, and 25% of severe IHCP cases in our study (p = 0.942, not significant). A similar trend was documented by Lee et al. [17], who found that while MSL is common in IHCP, its incidence does not correlate linearly with bile acid levels. The pathophysiology likely involves bile acids stimulating colonic motility in the fetus, but this does not always escalate proportionately with serum levels.

In terms of perinatal outcomes, our study shows the frequency of APGAR scores <7 at 1 minute increased significantly with disease severity: 3.5% (mild), 8.0% (moderate), and 25% (severe) (p = 0.041). This trend was even more pronounced at 5 minutes (p = 0.038). These results are supported by the findings of Puljic et al. [18], who noted that neonatal depression is more frequent in cases with high maternal bile acid levels, likely due to bile acid-induced pulmonary vasoconstriction and surfactant inactivation in the neonate.

In our study NICU admission was required in 8.8% of mild, 20% of moderate, and 25% of severe IHCP cases (p = 0.021). This is consistent with the data presented by Cheng et al. [19], who showed a rising NICU admission rate with increasing maternal bile acids. The necessity of intensive care is often due to neonatal respiratory distress, low APGAR score at 1 minute and 5 minute, or metabolic imbalance secondary to in-utero exposure to bile salts.

The most concerning observation in our study was the occurrence of intrauterine demise (IUD) in the moderate group (41–100 µmol/L), which supports the hypothesis that adverse outcomes can occur even before bile acid levels cross the >100 µmol/L threshold. Ovadia et al. [6] highlighted this unpredictability and recommended increased antenatal surveillance and timely delivery for bile acid levels >40 µmol/L, a recommendation our findings reinforce.

Thus, the findings of this study align with global evidence and underscore the role of maternal serum bile acid as a critical marker in the risk stratification and management of IHCP. Early diagnosis, vigilant biochemical monitoring, and timely intervention remain pivotal to improving neonatal outcomes in pregnancies complicated by IHCP.

Conclusion

IHCP poses significant risks to fetal well-being, with elevated bile acid levels associated with abnormal liver function tests and increased incidence of adverse neonatal outcomes. Regular monitoring of bile acids and liver enzymes is crucial in these pregnancies. Early identification and appropriate timing of delivery, especially in moderate to severe cases, can mitigate complications. Further multicentric studies are warranted to establish standardized management protocols tailored to bile acid severity.

Conflicts of interest

Authors declare no conflicts of interest.

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