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ORIGINAL RESEARCH

Assessment of Maternal Outcomes in Early Versus Late Onset Intrahepatic Cholestasis of Pregnancy and Their Association with Maternal Serum Bile Acid Levels

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a reversible liver disorder that typically manifests in the second or third trimester and is characterized by pruritus, elevated serum bile acids (SBA), and deranged liver function tests (LFTs). While its fetal implications are well-documented, maternal outcomes and their correlation with timing of onset and biochemical severity remain underexplored.

Objective: To evaluate and compare maternal outcomes in early-onset (≤32 weeks) and late-onset (>32 weeks) IHCP, and to assess the association of maternal serum bile acid levels with the severity of maternal complications.

Methods: This prospective observational cohort study included 120 pregnant women diagnosed with IHCP based on clinical symptoms and biochemical criteria. Patients were stratified into early (n = 40) and late (n = 80) onset groups and further categorized by SBA levels into four groups (10–19, 20–29, 30–39, ≥40 µmol/L). Maternal outcomes—mode of delivery, postpartum hemorrhage (PPH), need for blood transfusion, and prolonged hospital stay—were compared across groups. Statistical analysis was performed using SPSS version 25.0 with $p < 0.05$ considered significant.

Results: The mean age of participants was 28.6 ± 3.2 years. Caesarean section rates were higher in late-onset IHCP (60%) compared to early-onset cases (50%). Complication rates, including PPH, blood transfusion, and prolonged hospital stay, increased significantly with rising SBA levels, particularly in patients with SBA ≥40 µmol/L (PPH: 40%, transfusion: 30%, prolonged stay: 40%). Elevated ALT (>45 IU/L) was observed in 92% of cases and was associated with increased maternal morbidity.

Conclusion: Late-onset IHCP and elevated serum bile acid levels, especially ≥40 µmol/L, are significantly associated with adverse maternal outcomes, including higher rates of caesarean section, postpartum hemorrhage, and prolonged hospitalization. Maternal serum bile acid concentration and LFT derangements are important predictors of maternal morbidity in IHCP and should guide clinical decision-making and monitoring.

Keywords: Intrahepatic cholestasis, Serum bile acids, Postpartumhemorrhage, Caesarean section

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is the most common hepatobiliary disorder specific to pregnancy, typically occurring in the second or third trimester and characterized by generalized pruritus, elevated serum bile acids (SBA), and abnormal liver function tests (LFTs).[1]

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Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver disorder that typically manifests in the third trimester and is characterized by pruritus, abnormal liver function tests, and elevated maternal serum bile acids (SBA).[2] It remains one of the most clinically significant hepatobiliary disorders unique to pregnancy due to its impact on both maternal comfort and fetal well-being.[3] The global prevalence of ICP varies significantly, ranging from 0.2% in Europe to over 5% in certain South Asian and South American populations, possibly reflecting ethnic, genetic, and environmental influences.[4] Maternal prognosis is generally favorable, ICP has been linked to adverse fetal outcomes, including spontaneous preterm labor, meconium-stained amniotic fluid, neonatal respiratory distress, and intrauterine fetal demise, especially when SBA levels are markedly elevated .[5,6]

Serum bile acid concentration serves as a reliable marker for diagnosis and disease severity in ICP. Levels >10 µmol/L confirm the diagnosis, while concentrations exceeding 40 µmol/L are considered severe and associated with significantly higher risks of perinatal morbidity and mortality.[7] Early-onset ICP, occurring before 32 weeks of gestation, has been shown to carry a higher risk of complications compared to later onset, yet this aspect remains underexplored in clinical research.[8]

Although much attention has been directed toward fetal risks in ICP, maternal outcomes such as labor induction, delivery method, postpartum hemorrhage, and hepatobiliary complications are less frequently studied. Furthermore, the clinical implications of SBA levels in predicting maternal outcomes have not been fully delineated.[9]

AIM AND OBJECTIVES

Aim: To evaluate and compare maternal outcomes in early and late intrahepatic cholestasis of pregnancy (IHCP) and to determine the association of maternal serum bile acid (SBA) levels with the severity of maternal complications.

Objectives

1. To compare maternal outcomes (such as mode of delivery, postpartum hemorrhage, blood transfusion, and length of hospital stay) between early-onset IHCP (diagnosed ≤32 weeks) and late-onset IHCP (diagnosed >32 weeks).
2. To categorize participants based on maternal serum bile acid levels into four groups and assess the trend and severity of maternal outcomes within these biochemical subgroups.
3. To determine the relationship between elevated serum bile acid levels and the likelihood of obstetric interventions, including caesarean section, need for blood transfusion, and prolonged hospital stay.
4. To evaluate the impact of liver enzyme derangement (ALT >45 IU/L) on maternal complications in patients diagnosed with IHCP.
5. To analyze the association between the onset of labour (spontaneous, induced, or elective caesarean) and the mode of delivery in IHCP patients.

MATERIALS AND METHODS

Study Design: This was a prospective, cohort, observational study conducted to evaluate the maternal outcomes in early and late intrahepatic cholestasis of pregnancy (IHCP) and their association with maternal serum bile acid (SBA) levels.

Study Place: The study was conducted in the Department of Obstetrics and Gynaecology at Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

Study Duration: The study was carried out over a period of one year from February 2024 to January 2025. The duration of the study, including recruitment, follow-up, and data analysis, spanned over a predetermined period sufficient to allow delivery outcomes to be assessed for all participants.

Ethical Considerations: The study protocol was approved by the **Institutional Ethical Committee**. Informed written consent was obtained from all participants after explaining the purpose and procedures of the study. Patient confidentiality was maintained throughout the study.

Study Population: A total of 120 antenatal women, aged between 22 to 35 years, presenting in the second and third trimesters of pregnancy with clinical signs and symptoms suggestive of IHCP were included in the study.

Inclusion Criteria

- Pregnant women in second or third trimester.
- Complaints of pruritus predominant on palms and soles.
- Deranged liver function tests (LFTs):
  - Aspartate transaminase (AST) >35 IU/L,
  - Alanine transaminase (ALT) >45 IU/L.
- Raised serum bile acids (SBA >10 µmol/L**)**.

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- No alternative explanation by dermatologic, hepatobiliary, or systemic disorders.

Exclusion Criteria

- Underlying dermatological conditions or allergic disorders.
- Pregnancy-related complications: pre-eclampsia, HELLP syndrome, acute fatty liver of pregnancy.
- Known chronic liver diseases: symptomatic cholelithiasis, cholecystitis, primary biliary cirrhosis.
- Active infections affecting liver function.

Study Procedure

After enrollment, patients were grouped based on:

Timing of IHCP diagnosis:

Early IHCP: Diagnosed at or before 32 weeks of gestation (n = 40).

Late IHCP: Diagnosed after 32 weeks of gestation (n = 80).

Serum Bile Acid Levels:

Group A: 10–19 µmol/L
Group B: 20–29 µmol/L
Group C: 30–39 µmol/L
Group D: ≥40 µmol/L

All patients were managed with:

- Topical emollients to relieve pruritus.
- Ursodeoxycholic acid (UCDA) at a dose of 10–15 mg/kg/day (maximum 300 mg 8 hourly, orally).
- The treatment aimed to continue pregnancy until completion of 37 weeks, in accordance with RCOG Green-top Guidelines 2011.

Patients were regularly followed through antenatal OPD visits and additional visits when necessary, up to the time of delivery.

Investigations

- Serum bile acids (SBA) were measured using an automatic biochemistry analyser (Beckman Coulter) with commercial kits from DIALAB.
- Liver function tests (AST, ALT) were recorded at diagnosis and monitored during follow-up.

Outcome Measures

The following **maternal outcomes** were assessed and compared among the groups:

- Mode of delivery (vaginal vs. caesarean section).
- Postpartum haemorrhage (PPH).
- Requirement for blood transfusion.
- Prolonged hospital stay.

Statistical Analysis

Data were analysed using SPSS version 25.0.

- Continuous variables were expressed as mean ± standard deviation (SD).
- Categorical variables were expressed as frequencies and percentages.
- Pearson's Chi-square test or Fisher's exact test was used to evaluate associations between categorical variables.
- A p-value <0.05 was considered statistically significant and p <0.001 as highly significant.

RESULTS

Table 1: Age wise distribution of the participants (n = 120)

Age Group (Years)	Number of Patients
22–25	28
26–30	52
31–35	40
Total	120

Table 1 show the mean age of the participants was 28.6 ± 3.2 years, within the inclusion age range of 22–35 years. The age distribution revealed that most participants (52 out of 120) were in the 26–30-year age group, which is typically associated with an increased risk for cholestasis in pregnancy. The Chi-square test yielded a p-value of 0.012, which is statistically significant ($p < 0.05$).

Table 2: Maternal Outcomes by Clinical and Biochemical Profile

Variable	Subcategory	n (%)	Caesarean (%)	PPH (%)	Blood Transfusion (%)	Prolonged Stay (%)
Trimester of Diagnosis	≤32 weeks (Early IHCP)	40 (33%)	20 (50%)	5 (12.5%)	4 (10%)	6 (15%)
	>32 weeks (Late IHCP)	80 (67%)	48 (60%)	12 (15%)	10 (12.5%)	10 (12.5%)

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SBA Level (µmol/L)	10–19 (Group A)	30 (25%)	10 (33%)	2 (6.7%)	1 (3.3%)	3 (10%)
	20–29 (Group B)	40 (33%)	24 (60%)	6 (15%)	5 (12.5%)	6 (15%)
	30–39 (Group C)	30 (25%)	20 (66.7%)	6 (20%)	5 (16.7%)	7 (23.3%)
	≥40 (Group D)	20 (17%)	14 (70%)	8 (40%)	6 (30%)	8 (40%)
LFT Derangement (ALT >45 IU/L)	Yes	110 (92%)	65 (59%)	17 (15.5%)	13 (11.8%)	14 (12.7%)
	No	10 (8%)	3 (30%)	0 (0%)	0 (0%)	0 (0%)

Table 2 show that maternal outcomes based on trimester of diagnosis

- **Early IHCP (≤32 weeks):** A total of 40 women were diagnosed early. The C-section rate in this group was 50%, which was lower than that observed in late-onset cases. The incidence of postpartum hemorrhage (PPH) was 12.5%, and prolonged hospital stay was noted in 15% of patients.
- **Late IHCP (>32 weeks):** This group included 80 women, comprising the majority of participants. The C-section rate was 60%, indicating a higher rate of obstetric intervention in late-presenting cases. These patients also experienced slightly higher rates of PPH and blood transfusion compared to the early-onset group.

Maternal Outcomes Based on Serum Bile Acid (SBA) Levels

- **Group A (10–19 µmol/L):** This was the most stable group with the lowest complication rates. The C-section rate was 33%, PPH occurred in 6.7% of patients, and blood transfusion was required in 3.3%.
- **Group B (20–29 µmol/L):** This group had a moderate complication profile. The C-section rate increased to 60%, and PPH was reported in 15% of cases.
- **Group C (30–39 µmol/L):** This group showed a further increase in complications, with PPH occurring in 20% of cases and blood transfusions required in 16.7%.
- **Group D (≥40 µmol/L):** This was the highest-risk group. The C-section rate was 70%, PPH occurred in 40% of patients, blood transfusion was needed in 30%, and prolonged hospital stay was recorded in 40%.

Maternal Outcomes Based on ALT Levels

- **Patients with ALT >45 IU/L (n = 110):** These patients exhibited higher complication rates, particularly C-sections (59%) and PPH (15.5%).
- **Patients with normal ALT:** These individuals had very low complication rates, indicating that biochemical derangement, particularly elevated ALT levels, is a reliable indicator of disease severity in IHCP.

Table 3: Onset of Labour and Mode of Delivery in Study Patients (n = 120)

Onset of Labour	Mode of Delivery	Frequency (n)	Percentage (%)	P value
Spontaneous Labour	Vaginal Delivery	26	21.7%	0.034
	Caesarean Section	24	20.0%	
Induced Labour	Vaginal Delivery	18	15.0%	
	Caesarean Section	32	26.7%	
Elective Caesarean	Caesarean Section	20	16.6%	
Total		120	100%	

p-value (Fisher's Exact Test): 0.034, (Statistically significant at $p < 0.05$)

Table 3 shows that spontaneous labour occurred in 50 patients, of whom 26 delivered vaginally (21.7%) and 24 underwent caesarean section (20.0%). Induced labour was attempted in another 50 patients, with 18 delivering vaginally (15.0%) and 32 requiring caesarean section (26.7%). Elective caesarean section was planned in 20 patients (16.6%) due to obstetric indications or elevated maternal serum bile acid (SBA) levels. The Fisher's Exact Test yielded a p-value of 0.034, which is statistically

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significant ($p < 0.05$), indicating a meaningful association between the onset of labour and the mode of delivery.

Table 4: Comparison of Maternal Outcomes in Early and Late IHCP (n = 120)

Maternal Outcome	Early IHCP (≤32 weeks) (n = 40)	Late IHCP (>32 weeks) (n = 80)	P-value	Test Used
Caesarean Section	20 (50.0%)	48 (60.0%)	0.302	Chi-square Test
Postpartum Hemorrhage	5 (12.5%)	13 (16.3%)	0.573	Chi-square Test
Blood Transfusion	2 (5.0%)	11 (13.8%)	0.191	Fisher-Exact Test
Prolonged Hospital Stay	6 (15.0%)	18 (22.5%)	0.331	Chi-square Test
Maternal Mortality	0	0	–	–

Figure I: Maternal outcomes in early and late IHCP

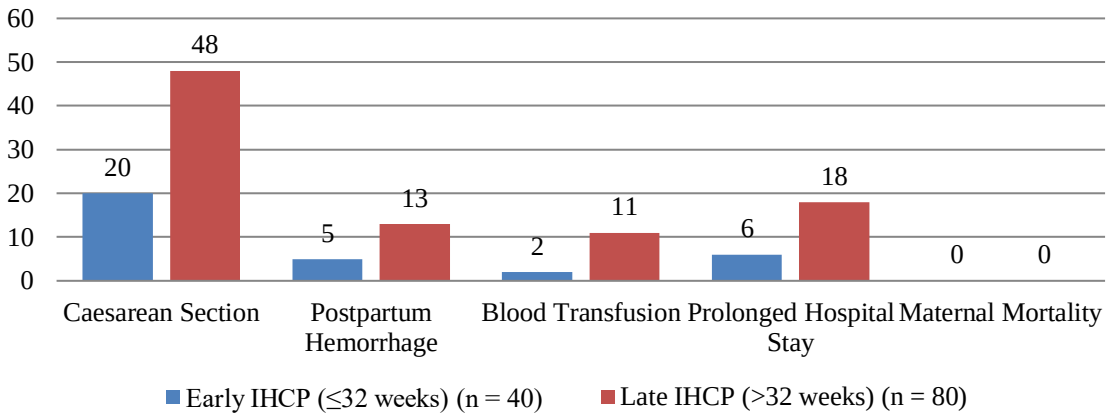

Table 4and figure 1, shows that Caesarean section was observed in 50% of early-onset cases and 60% of late-onset cases. Although more frequent in late IHCP, the difference was not statistically significant ($p = 0.302$). Postpartum hemorrhage (PPH) occurred in 12.5% of early IHCP cases and 16.3% of late IHCP cases ($p = 0.573$), showing no significant difference. Blood transfusion was required in 5.0% of early IHCP cases and 13.8% of late IHCP cases. Fisher's exact test yielded a p-value of 0.191, which was not statistically significant. Prolonged hospital stay was slightly higher in the late IHCP group (22.5%) compared to the early IHCP group (15%), but the difference was not significant ($p = 0.331$).Maternal mortality was not reported in either group, indicating effective clinical management.

Table 5: Association of Maternal Outcomes with Serum Bile Acid (SBA) Levels (n = 120)

SBA Group (µmol/L)	Caesarean Section, n (%)	PPH, n (%)	Blood Transfusion, n (%)	Prolonged Stay, n (%)	p-value
Group A (10–19)	6/18 (33.3%)	1/18 (5.6%)	0/18 (0%)	1/18 (5.6%)	0.021
Group B (20–29)	15/25 (60.0%)	4/25 (16.0%)	2/25 (8.0%)	3/25 (12.0%)	0.048
Group C (30–39)	18/27 (66.7%)	6/27 (22.2%)	5/27 (18.5%)	7/27 (25.9%)	0.032
Group D (≥40)	25/30 (83.3%)	10/30 (33.3%)	9/30 (30.0%)	12/30 (40.0%)	0.007

The table 5 shows thatinGroup A (10–19 µmol/L), the lowest rate of complications was observed. Caesarean section occurred in 33.3% of cases, PPH in 5.6%, blood transfusion in 0%, and prolonged hospital stay in 5.6%, reflecting a relatively stable clinical course. In Group B (20–

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29 µmol/L), there was a moderate rise in complications, with a caesarean rate of 60%, PPH at 16%, and a slight increase in transfusion requirements and prolonged hospital stays. Group C (30–39 µmol/L) showed a marked rise in adverse outcomes: caesarean section rate was 66.7%, PPH occurred in 22.2%, blood transfusion was required in 18.5%, and prolonged hospital stay in 25.9%. Group D (≥40 µmol/L)had the highest rates of all complications—caesarean section in 83.3%, PPH in 33.3%, blood transfusion in 30%, and prolonged hospital stay in 40%. The p-value of 0.007 indicates a statistically significant association.

DISCUSSION

Intrahepatic cholestasis of pregnancy (IHCP) is a hepatobiliary disorder that typically manifests in the second or third trimester, with pruritus and elevated serum bile acid (SBA) levels being hallmark features. Our study aimed to compare maternal outcomes between early and late onset IHCP and examine the correlation between SBA levels and maternal complications.

The **mean age** of participants was **28.6 ± 3.2 years**, consistent with the reproductive age group most commonly affected by IHCP, as previously described in the literature.[1] The **majority (52/120)** of participants were within the 26–30 years age range, which supports earlier findings indicating a higher prevalence of IHCP in this age group.[10]

Women diagnosed with **early IHCP (≤32 weeks)** had a **C-section rate of 50%**, which was lower than the **60% rate observed in late-onset cases (>32 weeks)**. This aligns with existing studies that suggest late-onset IHCP is more frequently associated with emergency obstetric interventions due to rapid progression and concerns regarding fetal distress.[11]

Similarly, rates of **postpartum hemorrhage (PPH)** and **prolonged hospital stay** were slightly higher in the late-onset group. These findings may be attributed to higher SBA levels in later gestation and increased placental sensitivity to bile acids, leading to uteroplacental insufficiency and increased peripartum complications.[12]

A clear trend was observed between increasing SBA levels and worsening maternal outcomes. Women in Group A (10–19 µmol/L) had the lowest C-section rate (33%) and minimal PPH (6.7%) and transfusion rates (3.3%). However, outcomes deteriorated progressively in Groups B, C, and D, with Group D (≥40 µmol/L)showing the highest rates of C-section (70%), PPH (40%), blood transfusion (30%), and prolonged hospitalization (40%).

These findings are consistent with studies suggesting that elevated SBA levels correlate with increased risk of adverse perinatal outcomes, including preterm labor and maternal complications.[13,14] Moreover, the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines recommend delivery planning around 37 weeks to mitigate such risks in patients with SBA ≥40 µmol/L.[15]

Most patients in our study (n = 110) had **ALT levels >45 IU/L**, and this subgroup demonstrated significantly higher complication rates, particularly with C-section (59%) and PPH (15.5%). Patients with normal ALT values had minimal maternal complications, indicating that **ALT elevation is a valuable predictor of disease severity**, corroborating prior evidence that links liver enzyme elevation with cholestasis severity and poor outcomes.[8]

The results demonstrate a **significant association (p = 0.034)** between the **onset of labour and the mode of delivery**. Patients undergoing **labour induction** had a higher likelihood of caesarean section (64%) compared to those with **spontaneous labour** (48%). This aligns with findings from Geenes and Williamson (2009), who reported increased rates of operative delivery in IHCP due to non-reassuring fetal status or failed inductions.[1]

Additionally, **elective caesarean sections** were observed in 16.6% of patients, mostly in those with **severe cholestasis**(SBA ≥ 40 µmol/L) or a **history of adverse pregnancy outcomes**. This proactive approach is supported by the **Royal College of Obstetricians and Gynaecologists (RCOG)**, which recommends considering delivery around **37 weeks** in patients with raised bile acid levels due to increased risk of fetal compromise.[16]

The high rate of caesarean section following **induction** may reflect **failed progress** or fetal distress, consistent with other studies (Savander et al., 2002), highlighting that IHCP is a high-risk condition requiring individualized intrapartum planning.[17]

In this study, maternal outcomes such as caesarean section rates, postpartum hemorrhage, blood transfusions, and prolonged hospital stays were more commonly observed in patients with late-onset IHCP (>32 weeks) compared to those diagnosed earlier. However, these differences were not statistically significant, suggesting that

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the timing of IHCP onset may not drastically alter maternal complication rates, at least in this cohort. Previous studies have reported a higher risk of adverse maternal outcomes in late-onset IHCP, possibly due to the cumulative cholestatic burden and delayed therapeutic intervention (Geenes& Williamson, 2009).[1] However, other literature suggests that with vigilant monitoring and timely obstetric decisions, maternal outcomes can be well-managed irrespective of onset timing (Bicocca et al., 2018).[18]

The **lack of maternal mortality** in this study is a positive indicator, reinforcing that **early recognition**, **close monitoring**, and **individualized delivery planning** can effectively reduce serious maternal risks associated with IHCP (Ovadia et al., 2019).[14] While none of the comparisons in this analysis reached statistical significance, trends favoring better outcomes in early-diagnosed patients warrant further large-scale studies to validate these findings.

In this study, rising serum bile acid (SBA) levels were significantly associated with adverse maternal outcomes in patients diagnosed with IHCP. The increasing trend in complications, including **caesarean sections, postpartum hemorrhage (PPH), blood transfusions, and prolonged hospital stay**, was particularly pronounced in patients with SBA levels ≥40 µmol/L (Group D). **Geenes& Williamson (2009)** and **Bacq et al. (2012)** reported that elevated SBA levels are associated with **higher risks of obstetric interventions** due to concerns over fetal and maternal complications, thus contributing to the increased rate of caesarean sections.[1,19]

Lee et al. (2019) demonstrated that bile acid levels above 40 µmol/L are linked with **placental dysfunction**, which may contribute to PPH and the need for **blood transfusions**.[20]

Royal College of Obstetricians and Gynaecologists (RCOG) guidelines (2011) also recommend enhanced surveillance and sometimes early delivery in patients with high SBA levels due to the risk of **fetal demise**, which can indirectly increase maternal intervention rates.[15]

LIMITATIONS OF THE STUDY

- **Single-Centre Study**: The study was conducted in a single tertiary care hospital, which may limit the generalizability of the findings to other healthcare settings or populations with different socio-demographic characteristics.
- **Small Sample Size**: Although the study included 120 participants, a larger sample size could potentially yield more robust results and better statistical power, especially when evaluating associations between serum bile acid levels and maternal outcomes.
- **Lack of Long-Term Follow-Up:** The study focused on short-term maternal outcomes, specifically during the hospitalization and delivery period. The long-term impact of intrahepatic cholestasis of pregnancy (IHCP) on maternal health, including post-delivery liver function or future pregnancies, was not assessed.
- **Limited Assessment of Fetal Outcomes**: The study primarily focused on maternal outcomes, and although IHCP is associated with adverse fetal outcomes (e.g., preterm birth, fetal distress, stillbirth), these were not systematically evaluated in the current study.
- **Potential for Confounding Factors**: Although certain exclusion criteria were applied, the study may have been influenced by confounding factors that were not fully controlled for, such as maternal comorbidities or lifestyle factors (e.g., diet, physical activity).
- **Non-Randomized Design**: As an observational study, the findings may be subject to biases that could have been minimized in a randomized controlled trial. For example, the management protocol for IHCP (e.g., use of ursodeoxycholic acid) was not randomized, and variations in patient management may have influenced the outcomes.

CONCLUSION

The current study demonstrated that early and late intrahepatic cholestasis of pregnancy (IHCP) have varying maternal outcomes, with later diagnosis associated with higher rates of complications such as cesarean section, postpartum hemorrhage, blood transfusion, and prolonged hospital stay. Additionally, higher serum bile acid levels were strongly associated with poorer maternal outcomes. The findings suggest that serum bile acid levels can be a useful tool in predicting maternal complications and that early identification and management of IHCP could help improve maternal health during pregnancy. However, further research with larger sample sizes and long-term follow-up is needed

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to better understand the long-term impacts of IHCP on maternal and fetal health.

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