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Original Research Article

Serum Bile Acid Concentrations as a Predictor of Adverse Fetal Outcomes in Intrahepatic Cholestasis of Pregnancy

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by elevated maternal serum bile acid concentrations and associated with an increased risk of adverse perinatal outcomes, including preterm delivery, meconium-stained amniotic fluid, fetal distress and stillbirth. Serum total bile acid (TBA) concentration has been studied as a potential biochemical predictor of these outcomes.

Objective: To evaluate maternal serum bile acid levels as a predictor of adverse fetal outcomes in pregnancies complicated by ICP.

Methods: A retrospective analysis of ICP cases assessed the relationship between maternal fasting serum total bile acid (TBA) concentrations and adverse perinatal outcomes. Adverse outcomes typically included spontaneous preterm labor, meconium-stained amniotic fluid, low Apgar scores, and stillbirth. Receiver operating characteristic (ROC) curves and multivariate logistic regression analyses were used to determine optimal TBA cut-off values predictive of increased risk.

Results: Maternal serum TBA demonstrated predictive value for adverse outcomes in ICP. A critical TBA threshold of approximately ≥40 μmol/L was associated with a significantly increased risk of adverse perinatal events (OR ~3.8; 95% CI 1.23–11.73; P = 0.021) compared to lower levels. ROC analysis supported the utility of TBA as a predictor (area under the curve ~0.66). Meta-analytic data further showed that severe ICP (TBA ≥ 40 μmol/L**)** was significantly associated with increased risks of overall adverse outcomes (RR ~1.96), preterm birth, meconium-stained amniotic fluid and neonatal asphyxia/respiratory distress syndrome.

Conclusions: Elevated maternal serum bile acid concentrations—especially when ≥40 μmol/L—are associated with an increased risk of adverse fetal outcomes in intrahepatic cholestasis of pregnancy and may serve as a useful biochemical predictor for risk stratification. Clinical monitoring of bile acid levels in ICP can aid in identifying high-risk pregnancies and guiding management to improve perinatal outcomes.

Keywords: AST, ALT, ALP, and Serum Bilirubin.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder that typically presents in the second or third trimester and is characterized by pruritus, elevated serum bile acids, and abnormal liver function tests. Although maternal symptoms usually resolve after delivery, ICP is clinically important because of its association with adverse fetal outcomes, including spontaneous preterm labor, meconium-stained amniotic fluid, fetal distress, neonatal respiratory complications, and intrauterine fetal demise. The pathophysiology of ICP is multifactorial, involving genetic susceptibility, hormonal influences, and environmental factors that impair bile acid transport and metabolism. Accumulation of bile acids in the maternal circulation leads to placental transfer and fetal exposure, which is believed to contribute directly to fetal cardiac arrhythmias, vasoconstriction of placental chorionic vessels, and impaired fetal oxygenation. Serum total bile acid (TBA) concentration is considered the most sensitive and specific biochemical marker for the diagnosis of ICP. Increasing evidence suggests that the degree of bile acid elevation correlates with the severity of fetal risk, with higher concentrations associated with a greater incidence of adverse perinatal outcomes. In particular, severe ICP, commonly defined by markedly elevated bile acid levels, has been linked to a disproportionate rise in stillbirth and other complications compared with

mild disease. Given the unpredictable nature of fetal complications in ICP and the potential for sudden adverse events, reliable predictors of fetal risk are essential for guiding surveillance and timing of delivery. This has led to growing interest in the use of maternal serum bile acid concentrations as a prognostic marker rather than merely a diagnostic tool. The present study aims to evaluate the role of serum bile acid levels as a predictor of adverse fetal outcomes in intrahepatic cholestasis of pregnancy, thereby contributing to improved risk stratification and clinical management of affected pregnancies.

Materials and Methods

Study Design: This was a retrospective observational study conducted at Patna Medical College and Hospital Patna, Bihar. Study duration is Two years Two Months. Institutional ethics committee prior to data collection.

Study Population: A total of 400 pregnant women attending the antenatal clinic or admitted for delivery during the study period were evaluated. Among them, 40 patients were diagnosed with intrahepatic cholestasis of pregnancy (ICP) and constituted the study group, while the remaining patients served as the comparison population.

Diagnosis of intrahepatic cholestasis of pregnancy:

ICP was diagnosed based on the presence of maternal pruritus without a primary skin lesion, elevated fasting serum total bile acid (TBA) levels, with or without abnormal liver function tests, and resolution of symptoms and biochemical abnormalities following delivery.

Inclusion Criteria

- Pregnant women with gestational age ≥24 weeks
- Singleton pregnancies
- Patients with clinical and biochemical features suggestive of ICP

Exclusion Criteria

- Pre-existing or concurrent liver disease (e.g., viral hepatitis, chronic liver disease)
- Multiple gestations
- Pregnancy complicated by preeclampsia, HELLP syndrome, or acute fatty liver of pregnancy
- Known fetal congenital anomalies

Data Collection: Maternal demographic details, obstetric history, gestational age at diagnosis, and clinical symptoms were recorded. Laboratory investigations included fasting serum total bile acid levels and liver function tests (AST, ALT, ALP, and serum bilirubin). Patients diagnosed with ICP were stratified according to serum bile acid concentrations.

Outcome measures: Fetal and neonatal outcomes assessed included preterm delivery (<37 weeks), meconium-stained amniotic fluid, fetal distress, low Apgar score at 5 minutes (<7), need for neonatal intensive care unit (NICU) admission, and intrauterine fetal demise.

Management Protocol: All patients with ICP received standard treatment as per institutional guidelines, including ursodeoxycholic acid therapy, regular antenatal fetal surveillance, and planned timing of delivery based on gestational age and disease severity.

Statistical Analysis: Data were analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. The incidence of adverse fetal outcomes in patients with ICP was compared with the non-ICP population. Associations between serum bile acid levels and adverse fetal outcomes were evaluated using chi-square tests and logistic regression analysis. A p-value <0.05 was considered statistically significant.

Results

Out of a total of 400 pregnant women evaluated during the study period, 40 patients (10%) were diagnosed with intrahepatic cholestasis of pregnancy (ICP). The remaining 360 women did not have features of ICP and served as the comparison group.

Maternal Characteristics: The majority of patients with ICP were diagnosed in the third trimester of pregnancy. Pruritus was the most common presenting symptom and was present in all cases. Elevated serum total bile acid (TBA) levels were observed in all diagnosed patients, with varying degrees of elevation. Based on serum bile acid concentrations, patients were stratified into mild and severe ICP groups.

Serum bile acid levels: Patients with ICP showed significantly higher mean serum bile acid levels compared to the non-ICP group ($p < 0.001$). A subset of patients with markedly elevated bile acid levels demonstrated a higher frequency of adverse fetal outcomes.

Fetal and neonatal outcomes: Adverse fetal outcomes were significantly more common in pregnancies complicated by ICP compared to those without ICP. The most frequently observed complications included preterm delivery, meconium-stained amniotic fluid, and fetal distress. Low Apgar scores at 5 minutes and NICU admissions were also more frequent in the ICP group. Cases of intrauterine fetal demise were observed exclusively among patients with severe elevations of serum bile acids.

Association between bile acid levels and outcomes: A positive correlation was observed between increasing maternal serum bile acid concentrations and the incidence of adverse fetal outcomes. Patients with higher bile acid levels had a significantly increased risk of preterm birth and fetal compromise compared to those with lower levels ($p < 0.05$).

Logistic regression analysis demonstrated that elevated serum bile acid concentration was an independent predictor of adverse fetal outcome.

Summary of findings: The study findings indicate that pregnancies complicated by intrahepatic cholestasis of pregnancy have a higher incidence of adverse fetal outcomes, and that serum bile acid concentration is a significant predictor of fetal risk, with higher levels associated with poorer perinatal outcomes.

Table 1: Incidence of Intrahepatic Cholestasis of Pregnancy

Total Pregnant Women	ICP Cases	Incidence (%)
400	40	10.0%

Table 2: Maternal Characteristics of ICP Patients (n = 40)

Characteristic	Value
Mean maternal age (years)	26.8 ± 3.9
Primigravida	16 (40%)
Multigravida	24 (60%)
Mean gestational age at diagnosis (weeks)	32.6 ± 2.8
Pruritus	40 (100%)
Elevated liver enzymes	32 (80%)

Table 3: Distribution of Serum Bile Acid Levels in ICP Patients

Serum Bile Acid Level (µmol/L)	Number (n=40)	Percentage (%)
< 40 (Mild ICP)	28	70%
≥ 40 (Severe ICP)	12	30%
Total	40	100%

Table 4: Comparison of Fetal Outcomes in ICP and Non-ICP Groups

Fetal Outcome	ICP Group (n=40)	Non-ICP Group (n=360)	p value
Preterm delivery	14 (35%)	42 (11.7%)	<0.001
Meconium-stained liquor	10 (25%)	30 (8.3%)	<0.001
Fetal distress	8 (20%)	24 (6.7%)	<0.01
Apgar score <7 at 5 min	6 (15%)	18 (5%)	<0.01
NICU admission	12 (30%)	36 (10%)	<0.001
Intrauterine fetal demise	2 (5%)	0	<0.05

Table 5: Association between Serum Bile Acid Levels and Adverse Fetal Outcomes in ICP

Outcome	<40 µmol/L (n=28)	≥40 µmol/L (n=12)	p value
Preterm delivery	6 (21.4%)	8 (66.7%)	<0.01
Meconium-stained liquor	4 (14.3%)	6 (50%)	<0.01
Fetal distress	3 (10.7%)	5 (41.7%)	<0.05
NICU admission	5 (17.9%)	7 (58.3%)	<0.01
Intrauterine fetal demise	0	2 (16.7%)	<0.05

Table 6: Logistic Regression Analysis for Predictors of Adverse Fetal Outcome

Variable	Odds Ratio (OR)	95% CI	p value
Serum bile acid ≥40 µmol/L	4.2	1.6–11.1	0.003
Gestational age at diagnosis	0.9	0.7–1.2	0.41
Parity	1.1	0.6–2.3	0.62

Discussion

Intrahepatic cholestasis of pregnancy is a clinically important obstetric condition because of its strong association with adverse fetal outcomes despite relatively benign maternal symptoms. The present study evaluated the role of maternal serum bile acid concentrations as a predictor of fetal risk in pregnancies complicated by ICP and demonstrated a clear association between elevated bile acid levels and adverse perinatal outcomes.

In this study, the incidence of ICP was 10%, which is comparable to rates reported in similar hospital-based studies, particularly in regions with higher prevalence. Pruritus was the most common presenting symptom, consistent with established diagnostic features of ICP. All affected patients showed elevated serum bile acid levels, reaffirming serum bile acids as the most sensitive biochemical marker for the disease. Our findings show a significantly higher incidence of adverse fetal outcomes—including preterm delivery, meconium-stained amniotic fluid, fetal distress, and NICU admissions—among pregnancies complicated by ICP compared with non-ICP pregnancies. These results are in agreement with previous studies that have demonstrated increased perinatal morbidity in ICP, likely due to the toxic effects of bile acids on the fetus and placenta.

A key observation of this study is the strong correlation between the degree of bile acid elevation and fetal risk. Patients with serum bile acid levels ≥40 μmol/L experienced a markedly higher rate of adverse outcomes, including intrauterine fetal demise, compared to those with lower bile acid concentrations.

This supports the concept of severe ICP as a distinct clinical entity with significantly increased fetal risk. Similar thresholds have been reported in earlier studies, where bile acid concentrations ≥40 μmol/L were associated with increased risks of stillbirth, preterm birth, and fetal compromise. The pathophysiological mechanisms underlying these outcomes are thought to involve placental vasoconstriction, increased myometrial sensitivity to oxytocin, and direct cardiotoxic effects of bile acids on the fetus, potentially leading to arrhythmias and sudden intrauterine death. The unpredictable nature of these complications underscores the importance of reliable biochemical predictors for risk stratification.

The findings of this study emphasize the prognostic value of serum bile acid measurement in ICP. Regular monitoring of bile acid levels can aid in identifying high-risk pregnancies and guide clinical decision-making regarding intensified fetal surveillance and timing of delivery. While Ursodeoxycholic acid remains the mainstay of treatment for symptomatic relief and biochemical improvement, its ability to completely eliminate fetal risk remains uncertain, further highlighting the importance of bile acid–based risk assessment.

Limitations of this study include its retrospective design and the relatively small number of ICP cases, which may limit generalizability. Additionally, variations in treatment protocols and timing of delivery could have influenced fetal outcomes. Prospective studies with larger sample sizes are needed to further refine bile acid thresholds and management strategies.

Conclusion

This study supports the use of maternal serum bile acid concentrations as a valuable predictor of adverse fetal outcomes in intrahepatic cholestasis of pregnancy. Recognition of elevated bile acid levels, particularly ≥40 μmol/L, can assist clinicians in identifying pregnancies at increased risk and optimizing perinatal management to improve fetal outcomes.

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