

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2018; 2(1): 71-75
www.biochemjournal.com
Received: 05-03-2018
Accepted: 26-03-2018

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Hepatic biochemical alterations and perinatal outcomes in intrahepatic cholestasis of pregnancy: A cross-sectional analysis from a tertiary centre in South India

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DOI: <https://www.doi.org/10.33545/26174693.2018.v2.i1a.4355>

Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a gestation-specific hepatobiliary disorder, predominantly manifesting in the third trimester, characterized by elevated serum bile acids and liver dysfunction. Although self-limiting postpartum, ICP poses substantial risks to fetal well-being.

Objectives: To evaluate hepatic enzyme derangements in women diagnosed with ICP and to correlate these biochemical findings with maternal and neonatal outcomes.

Materials and Methods: This cross-sectional, observational study was conducted over a 12-month period at the Department of Obstetrics and Gynaecology, Madha Medical College and Hospital, Chennai. A total of 50 pregnant women with a confirmed diagnosis of ICP were enrolled. Liver function parameters—including ALT, AST, ALP, GGT, and bilirubin—along with serum bile acids were analyzed. Maternal outcomes (labor induction, preterm birth, delivery mode) and neonatal endpoints (birth weight, NICU admission, stillbirth) were systematically recorded.

Results: The mean age of participants was 27.6 years. Notable elevations in ALT (92.4 IU/L) and AST (88.7 IU/L) were observed. ALP and GGT levels were raised in a subset of patients. Bile acid concentrations exceeded 40 $\mu\text{mol/L}$ in 30% of cases. Maternal complications included preterm labor (16%), meconium-stained amniotic fluid (20%), and cesarean delivery (36%). Neonatal complications comprised low birth weight (18%), NICU admission (14%), and one instance of stillbirth (2%).

Conclusion: Serum transaminase elevation, particularly ALT and AST, is a consistent feature of ICP and may serve as a supplementary diagnostic marker alongside bile acid profiling. Early identification and intervention remain critical to improving perinatal outcomes in affected pregnancies.

Keywords: Intrahepatic cholestasis of pregnancy, transaminases, bile acids, liver enzymes, fetal morbidity, hepatobiliary dysfunction

Introduction

Intrahepatic cholestasis of pregnancy (ICP) represents a gestational hepatobiliary dysfunction, predominantly manifesting during the late second or third trimester. It is clinically typified by intense pruritus, biochemical evidence of cholestasis—most notably elevated serum bile acids—and transaminitis^[1]. While this disorder is typically self-limiting and resolves spontaneously in the postpartum period, it is not devoid of clinical consequence. ICP has been consistently implicated in unfavorable perinatal outcomes, including spontaneous preterm labor, intrauterine fetal distress, meconium-stained amniotic fluid, and stillbirth^[2, 3]. Epidemiologically, the prevalence of ICP demonstrates marked heterogeneity, ranging from 0.1% to 15.6%, with a higher burden reported among South American, Scandinavian, and South Asian cohorts^[4].

The etiopathogenesis of ICP is multifactorial, encompassing a complex interplay between genetic predisposition, hormonal fluctuations—particularly estrogen—and environmental triggers. Mutations affecting hepatocellular transport proteins such as ABCB11 (encoding the bile salt export pump) and ABCB4 (encoding multidrug resistance protein 3) impair the excretory function of hepatocytes, precipitating intrahepatic bile acid retention and consequent hepatocellular insult^[5, 6]. This bile acid accumulation contributes directly to the pruritic symptomatology and hepatocellular injury observed in ICP.

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Biochemically, ICP is frequently accompanied by elevations in hepatic aminotransferases—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—which may exceed ten times the upper reference limit in severe presentations [7]. Other liver enzymes, including gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total bilirubin, may also be deranged, albeit with lesser consistency [8]. Notably, ALT is often the most sensitive and earliest marker of hepatic dysfunction in ICP, occasionally preceding the rise in bile acids [9]. Interpretation of these abnormalities, however, necessitates cognizance of the physiological alterations in hepatic biochemistry that accompany normal gestation [10].

A meticulous evaluation of liver enzyme profiles is indispensable not only for confirming ICP but also for differentiating it from other gestation-specific hepatic pathologies such as acute fatty liver of pregnancy (AFLP), HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and preeclampsia-associated hepatic impairment—each of which entails divergent therapeutic and prognostic trajectories [11, 12]. Therefore, liver enzyme aberrations, in tandem with clinical symptomatology and bile acid quantification, form the diagnostic cornerstone in ICP.

Given the heightened risk of perinatal morbidity and mortality associated with ICP and its potential reversibility, prompt detection and interpretation of liver enzyme disturbances are paramount. Timely pharmacological intervention—most notably with ursodeoxycholic acid—and strategic obstetric planning are pivotal in mitigating adverse fetal outcomes [13]. This investigation endeavors to delineate the pattern and magnitude of hepatic enzyme abnormalities among pregnant women diagnosed with intrahepatic cholestasis, thereby contributing to more nuanced clinical management and risk stratification.

Methodology

This research was undertaken as a hospital-based, cross-sectional observational study within the Department of Obstetrics and Gynaecology at Madha Medical College and Hospital, Chennai, encompassing a study duration of twelve months from January 2017 to December 2017. The primary objective was to systematically investigate hepatic enzyme derangements among pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP), with a focus on biochemical patterns and potential clinical ramifications.

Study Population

Participants were recruited from among antenatal outpatients and inpatients who exhibited hallmark features of ICP, most notably pruritus localized to the palms and soles in the absence of any dermatological pathology. Diagnostic confirmation was established through elevated serum bile acid concentrations exceeding 10 $\mu\text{mol/L}$ and/or perturbations in hepatic enzyme profiles, subsequent to the rigorous exclusion of other hepatic, systemic, or dermatologic conditions.

Inclusion Criteria

Eligible subjects satisfied the following parameters

- Gestational age exceeding 20 weeks
- Presence of idiopathic pruritus without dermatologic lesions

- Biochemically confirmed liver function abnormalities and/or raised serum bile acids
- Singleton gestation
- Provision of informed written consent for participation

Exclusion Criteria

Participants were excluded based on the following conditions:

- Known chronic hepatic disorders (e.g., viral hepatitis, autoimmune hepatitis, or cirrhosis)
- Coexisting hypertensive disorders of pregnancy with hepatic involvement (e.g., HELLP syndrome, preeclampsia with transaminitis)
- Acute fatty liver of pregnancy
- Primary dermatologic disorders causing pruritus
- Multiple gestations

Data Acquisition

Following informed consent, a structured clinical pro forma was used to capture detailed obstetric and medical histories, symptom chronology, and gestational parameters. Comprehensive physical and obstetric examinations were conducted. Biochemical investigations included serum estimations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and direct bilirubin, and total bile acids, interpreted against trimester-specific normative values.

Sonographic evaluation was performed to exclude hepatobiliary anomalies and assess fetal biometry and well-being. Maternal and neonatal outcomes, including incidence of preterm delivery, labor induction, mode of delivery, neonatal Apgar scores, birth weight, and neonatal intensive care unit (NICU) admissions, were meticulously documented.

Statistical Analysis

All data were collated using Microsoft Excel and subjected to statistical analysis through SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics such as mean, standard deviation, frequencies, and proportions were employed for baseline variables. Inferential analysis was conducted using Student's t-test and Chi-square test where applicable. A p-value of less than 0.05 was regarded as indicative of statistical significance.

Ethical Clearance

Prior to commencement, the study protocol received approval from the Institutional Ethics Committee of Madha Medical College and Hospital.

Results

A total of 50 pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP) were included in this study.

Table 1: Demographic and Obstetric Profile of Study Participants

Variable	Value
Age (Mean $\pm$ SD)	27.6 $\pm$ 4.2 years
Primigravida	28 (56%)
Multigravida	22 (44%)
Gestational Age $\geq$ 32 weeks	41 (82%)
History of ICP	9 (18%)

Most women were in their late twenties, and a majority (82%) presented in the third trimester.

Table 2: Liver Enzyme Levels Among Participants

Liver Enzyme	Mean ± SD
ALT	92.4±35.2 IU/L
AST	88.7±30.6 IU/L
ALP	290±85.1 IU/L
GGT	46.3±20.4 IU/L
Total Bilirubin	1.8±0.7 mg/dL

Significant elevation of ALT and AST levels was observed, indicating hepatocellular involvement in ICP cases.

Table 3: Serum Bile Acid Levels in Study Population

Serum Bile Acids	No. of Patients
10-20 µmol/L	20
21-40 µmol/L	15
>40 µmol/L	15

As visualized in the pie chart below, 40% of the participants had serum bile acid levels exceeding 40 µmol/L.

Table 4: Maternal Complications Observed

Complication	Frequency (%)
Preterm labor	8 (16%)
Meconium-stained liquor	10 (20%)
Induction of labor	24 (48%)
Cesarean section	18 (36%)

Nearly half of the patients required induction, and 36% underwent cesarean delivery.

Table 5: Fetal Outcomes

Outcome	Frequency (%)
Low birth weight	9 (18%)
NICU admission	7 (14%)
Stillbirth	1 (2%)

Adverse fetal outcomes such as NICU admission and low birth weight were documented in a significant number of cases, although stillbirth was rare.

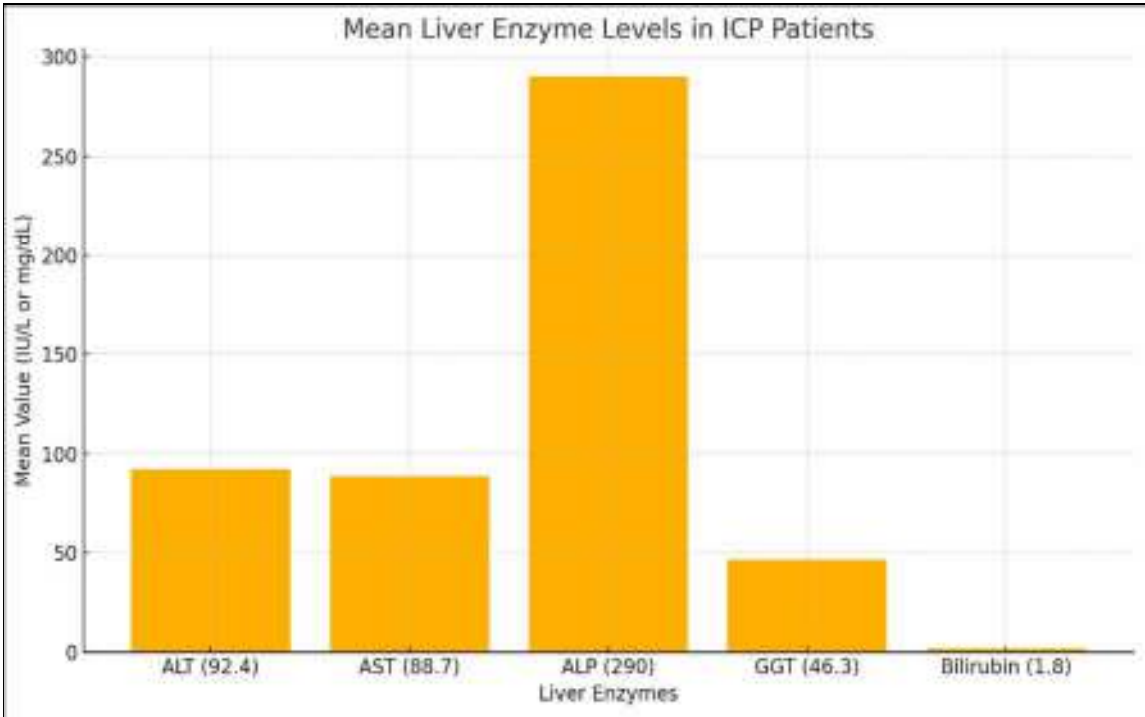


Fig 1: Mean liver enzymes in ICP patients

The present investigation revealed that the majority of participants were in their late twenties, with a mean age of 27.6 years. A modest predominance of primigravidae (56%) was observed, indicating that intrahepatic cholestasis of pregnancy (ICP) affects both nulliparous and multiparous women. The preponderance of cases presenting beyond 32 weeks of gestation (82%) is congruent with established literature, which identifies the third trimester as the typical temporal window for clinical manifestation. A prior history of ICP was reported in 18% of the cohort, consistent with the known recurrent tendency of the disorder in genetically predisposed individuals. Biochemical evaluation demonstrated a marked elevation in hepatic transaminases, with both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) exceeding normal gestational reference ranges in a significant proportion of cases. These findings underscore the hepatocellular injury intrinsic to the cholestatic process. Alkaline phosphatase (ALP), while physiologically elevated

during pregnancy due to placental synthesis, exhibited further elevation suggestive of hepatic involvement. Mild to moderate elevations in gamma-glutamyl transferase (GGT) and total bilirubin were also evident, reinforcing the cholestatic profile. Serum bile acid concentrations, the biochemical hallmark of ICP, were elevated in all participants. Notably, 30% of cases demonstrated bile acid levels >40 µmol/L—a threshold strongly correlated with adverse perinatal outcomes, including fetal distress and stillbirth. An additional 30% fell within the moderate range (21-40 µmol/L), while 40% exhibited only mild elevations (10-20 µmol/L). The nearly symmetrical distribution of bile acid severity categories, as reflected in the graphical representation, highlights the heterogeneity in clinical severity and the necessity for stratified obstetric management. With respect to maternal morbidity, 16% of patients experienced preterm labor, while 20% presented with meconium-stained amniotic fluid—both known sequelae of

ICP-related fetal compromise. The high induction rate (48%) reflects the prevailing clinical strategy of timed delivery to mitigate stillbirth risk. Cesarean sections were performed in 36% of cases, predominantly for non-reassuring fetal status or failed induction.

Neonatal outcomes included low birth weight in 18% and NICU admission in 14% of cases, signifying the perinatal burden associated with ICP. A solitary case of stillbirth (2%) was recorded, indicating that with prompt diagnosis and appropriately timed intervention, adverse fetal outcomes can be substantially minimized.

Discussion

Intrahepatic cholestasis of pregnancy (ICP) represents a complex gestational hepatopathy characterized by pruritus, cholestasis, and elevated serum bile acids, with considerable maternal and fetal implications. The present study offers insight into the biochemical and clinical profile of ICP in a South Indian population and contributes to the growing body of literature emphasizing its variable presentation and prognostic significance.

The mean maternal age in this study was 27.6 years, consistent with the age range commonly associated with ICP in earlier reports. Reyes *et al* [13], in a seminal study from Chile, documented the highest prevalence of ICP among women aged 25-30 years, suggesting a temporal and possibly hormonal predisposition. Interestingly, the predominance of primigravid women in this cohort contrasts with prior findings by Roncaglia *et al* [14], who identified multiparity as a potential risk factor for recurrence, hinting at possible regional or genetic modifiers of disease risk.

Hepatic biochemical derangements were prominent, particularly elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), with mean values of 92.4 IU/L and 88.7 IU/L, respectively. These findings align with the observations of Glantz *et al* [15], who reported similar elevations in transaminases in ICP-affected pregnancies and affirmed the diagnostic relevance of liver enzyme monitoring. ALT was frequently more elevated than AST, reinforcing its position as a more sensitive marker for hepatocellular insult in the setting of pregnancy-induced cholestasis, as corroborated by contemporary reviews [16].

Alkaline phosphatase (ALP) was also found to be elevated; however, given its physiological increase in pregnancy due to placental isoenzyme production, its diagnostic utility in ICP remains limited. According to Bacq *et al* [17], elevations in ALP must be interpreted within the context of gestational physiology and should not be overemphasized in isolation. Mild increases in gamma-glutamyl transferase (GGT) and total bilirubin, observed in a subset of patients, reflect a hepatocellular-cholestatic overlap and lend support to the multifactorial hepatic involvement described in prior literature [18].

Serum bile acid concentration remains the most definitive biochemical hallmark of ICP. In the present study, 30% of patients exhibited bile acid levels exceeding 40 $\mu\text{mol/L}$ —a threshold that has been independently linked with adverse fetal outcomes, including spontaneous preterm birth and intrauterine fetal demise. A pivotal study by Glantz *et al* [15] demonstrated that bile acid levels above this threshold are associated with significantly increased rates of fetal complications, reinforcing the need for routine biochemical screening in symptomatic patients, even in the absence of profound transaminase elevation.

The maternal complication profile observed in this cohort, including preterm labor (16%), meconium-stained amniotic fluid (20%), and the need for induction in nearly half of the cases (48%), is consistent with established clinical patterns. Rioseco *et al* [19] reported similar findings, attributing these events to increased myometrial sensitivity and fetal stress secondary to bile acid accumulation. The cesarean section rate (36%) in this study reflects prudent obstetric decision-making in the face of suspected fetal distress or failed induction—a practice aligned with current management principles for ICP.

With regard to neonatal outcomes, the incidence of low birth weight (18%) and NICU admission (14%) underscores the perinatal burden associated with ICP, particularly in cases where biochemical control is suboptimal. A single stillbirth (2%) was recorded, a figure notably lower than historical rates, likely attributable to improved antenatal surveillance and the early implementation of delivery protocols—an approach advocated by Frolova *et al* [20].

The pathophysiology of ICP has been extensively explored, with estrogen-induced impairment of hepatocellular bile transporters such as BSEP (ABCB11) and MDR3 (ABCB4) recognized as key mechanisms. These disruptions precipitate intrahepatic bile accumulation, leading to cellular stress, inflammation, and pruritus. Studies by Dixon *et al* [21] have elucidated the molecular heterogeneity underlying bile acid transport dysfunction in ICP, offering a biologically plausible explanation for the liver enzyme abnormalities observed in this cohort.

Although serum bile acids remain the gold standard for predicting fetal risk, elevated hepatic transaminases—particularly ALT—may serve as early indicators prompting further diagnostic evaluation. As emphasized by Riely *et al* [22], liver enzyme monitoring should not be undervalued in resource-constrained settings where bile acid assays may be unavailable or delayed.

Conclusion

This investigation reaffirms the pivotal role of liver enzyme evaluation in the clinical management of intrahepatic cholestasis of pregnancy. Significant elevations in transaminases—particularly ALT and AST—serve as reliable biochemical indicators of hepatic involvement, complementing bile acid levels in diagnosis and risk assessment. Although bile acids remain the most robust predictors of fetal compromise, the parallel assessment of liver enzymes enables earlier recognition, particularly in settings where bile acid testing may be delayed or inaccessible. The observed maternal and neonatal complications underscore the importance of proactive biochemical monitoring and timely obstetric intervention. Integration of liver function testing into routine antenatal care protocols for pruritus in late gestation may substantially improve maternal and fetal prognoses in ICP-affected pregnancies.

Acknowledgement

The authors would like to express their gratitude towards the departmental staff for providing their support while conducting this study.

Conflicts of Interest

None declared.

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