



Early versus Late Onset Intrahepatic Cholestasis of Pregnancy: A Prospective Observational Study

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) represents a pregnancy-specific hepatobiliary disorder characterized by pruritus and elevated serum bile acids. The gestational age at onset may influence disease severity and pregnancy outcomes, necessitating comparative evaluation of early and late presentations.

Methods: A prospective observational study was conducted over 18 months at a tertiary care center. Eighty pregnant women diagnosed with ICP were categorized into early-onset (diagnosis <32 weeks gestation, n=30) and late-onset (diagnosis ≥32 weeks gestation, n=50) groups. Maternal demographic characteristics, biochemical profiles including serum bile acids and liver enzymes, and comprehensive perinatal outcomes were systematically documented and compared. All participants received ursodeoxycholic acid therapy with weekly monitoring until delivery.

Results: Early-onset ICP demonstrated significantly elevated mean serum bile acid concentrations ($46.8 \pm 12.4 \mu\text{mol/L}$ versus $24.6 \pm 8.2 \mu\text{mol/L}$, $p < 0.001$) and higher aminotransferase levels compared to late-onset disease. Perinatal complications were substantially increased in the early-onset group, including preterm delivery (46.6% versus 18.0%, $p = 0.006$), meconium-stained amniotic fluid (36.6% versus 14.0%, $p = 0.019$), and neonatal intensive care unit admissions (33.3% versus 12.0%, $p = 0.021$). No stillbirths occurred in either group. Both groups demonstrated symptomatic improvement with pharmacological intervention.

Conclusion: Early-onset intrahepatic cholestasis of pregnancy is associated with more severe biochemical derangement and significantly increased adverse perinatal outcomes. These findings emphasize the necessity for enhanced fetal surveillance, earlier intervention, and individualized obstetric management in women presenting with ICP before 32 weeks gestation.

Keywords: Intrahepatic cholestasis of pregnancy, obstetric cholestasis, early-onset ICP, bile acids, preterm delivery, perinatal outcomes

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also termed obstetric cholestasis, constitutes the most prevalent pregnancy-specific liver disorder, characterized clinically by generalized pruritus in the absence of primary dermatological lesions and biochemically by elevated serum bile acid concentrations [1]. This condition typically manifests during the late second or third trimester and demonstrates spontaneous resolution within 2-6 weeks postpartum, confirming its pregnancy-specific etiology [2]. The pathognomonic symptom of intense pruritus, particularly affecting the palms and soles with nocturnal exacerbation, significantly impairs maternal quality of life and serves as the primary clinical indicator prompting diagnostic evaluation [3].

The global prevalence of ICP exhibits substantial geographical and ethnic variation, ranging from 0.1% to 2% of pregnancies [4]. Notably elevated incidence rates have been documented in Scandinavian countries, Chile, and South Asian populations, suggesting genetic predisposition coupled with environmental influences [5]. Within the Indian subcontinent, recent epidemiological studies estimate ICP prevalence between 0.8% and 1.5% [6], though actual incidence may be underestimated due to limited accessibility to specialized bile acid assays in resource-constrained settings.

The pathophysiological mechanisms underlying ICP are multifactorial, involving complex interactions between hormonal factors, genetic susceptibility, and environmental determinants [7]. Pregnancy-related elevations in estrogen and progesterone metabolites impair hepatocellular bile acid transport and excretion by inhibiting key biliary transporters. Genetic investigations have identified mutations in hepatobiliary transporter genes, particularly ABCB4 (MDR3) encoding phospholipid transporter and ABCB11 (BSEP) encoding bile salt export pump, conferring increased susceptibility to ICP development [8]. The accumulated bile acids subsequently traverse the placental barrier, exerting direct cardiotoxic effects on fetal cardiomyocytes, inducing placental vasoconstriction, and potentially triggering premature uterine contractility [9].

While maternal prognosis remains generally favorable with complete resolution following delivery, ICP is associated with substantial fetal and neonatal risks. Documented complications include spontaneous preterm labor, iatrogenic preterm delivery necessitated by fetal compromise, meconium-stained amniotic fluid, fetal distress, and most critically, sudden intrauterine fetal demise [10]. The magnitude of fetal risk demonstrates correlation with maternal serum bile acid concentrations, particularly when exceeding 40 $\mu\text{mol/L}$ [11]. Furthermore, emerging evidence suggests that gestational age at disease onset may represent an independent predictor of severity and adverse outcomes [12].

Although several studies have investigated ICP outcomes in relation to bile acid levels, comparative data specifically evaluating early-onset versus late-onset disease presentations remain limited, particularly from South Asian populations. Previous investigations have yielded conflicting results regarding whether earlier gestational onset independently predicts worse outcomes or merely reflects more severe disease [13]. This knowledge gap necessitates systematic investigation to inform clinical decision-making regarding surveillance intensity and delivery timing.

Therefore, this study aimed to comprehensively compare maternal biochemical parameters, treatment response to ursodeoxycholic acid therapy, and perinatal outcomes between women diagnosed with early-onset ICP (before 32 weeks gestation) and late-onset ICP (at or after 32 weeks gestation), thereby providing evidence to guide risk stratification and management protocols.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at a tertiary care teaching hospital over 11 months period from January 2025 to november 2025. The study protocol received approval from the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment.

Sample Size Calculation

Sample size determination was performed based on anticipated differences in preterm delivery rates between groups. Using existing literature estimates suggesting preterm delivery rates of 45% in early-

onset ICP versus 20% in late-onset ICP, with a two-sided significance level (alpha) of 0.05 and statistical power (1-beta) of 80%, the minimum required sample size was calculated as 36 patients per group (total 72 patients). Accounting for potential attrition and incomplete follow-up, a total of 80 patients were targeted for enrollment.

Inclusion Criteria

Pregnant women meeting all following criteria were eligible for inclusion: (1) gestational age ≥ 24 weeks confirmed by first-trimester ultrasound dating; (2) clinical presentation of generalized pruritus without pre-existing dermatological conditions or primary skin lesions; (3) biochemical confirmation with elevated fasting serum total bile acids ($>10 \mu\text{mol/L}$) and/or raised aminotransferases (aspartate aminotransferase or alanine aminotransferase $>40 \text{ IU/L}$).

Exclusion Criteria

Women were excluded if they demonstrated: (1) serological evidence of acute viral hepatitis (hepatitis A, B, C, or E); (2) ultrasonographic evidence of cholelithiasis, choledocholithiasis, or biliary obstruction; (3) autoimmune liver disorders including primary biliary cholangitis or autoimmune hepatitis; (4) drug-induced hepatotoxicity; (5) pre-existing chronic liver disease including cirrhosis or chronic hepatitis; (6) dermatological conditions potentially explaining pruritus; (7) multiple pregnancy; (8) pre-existing diabetes mellitus or chronic hypertension.

Diagnostic Criteria and Classification

ICP diagnosis was established based on clinical presentation of pruritus combined with biochemical abnormalities. Participants were systematically classified into two groups based on gestational age at diagnosis: Early-onset ICP was defined as diagnosis before 32 completed weeks of gestation, while late-onset ICP was defined as diagnosis at or after 32 weeks of gestation.

Baseline Evaluation and Monitoring

All participants underwent comprehensive baseline evaluation including detailed history, physical examination, and laboratory investigations. Maternal demographic data including age, parity, and body mass index were recorded. Laboratory assessment included fasting serum total bile acids measured by enzymatic assay, liver function tests (total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total protein, albumin), complete blood count, renal function tests, and coagulation profile. Viral hepatitis serology and obstetric ultrasound were performed to exclude alternate diagnoses.

Management Protocol

All diagnosed patients received ursodeoxycholic acid therapy initiated at 10-15 mg/kg/day in divided doses. Weekly clinical and biochemical monitoring was instituted, including symptom assessment, liver function tests, and bile acid levels. Fetal surveillance comprised weekly non-stress testing from 32 weeks gestation or diagnosis (whichever was later), biophysical profile assessment, and serial growth scans. Delivery timing was individualized based on disease severity, with planned delivery recommended at 37-38 weeks for controlled disease and earlier intervention considered for severe biochemical derangement or fetal compromise.

Outcome Measures

Primary outcome measures included maternal biochemical parameters (serum bile acid levels, aminotransferases) and perinatal outcomes (gestational age at delivery, preterm delivery rate, mode of delivery, meconium-stained amniotic fluid, Apgar scores, birth weight, neonatal intensive care unit admission, neonatal outcomes). Secondary outcomes included maternal symptom response and requirement for early delivery due to disease progression.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. Continuous

variables were expressed as mean $\pm$ standard deviation and compared between groups using independent samples Student's t-test after verification of normality assumptions. Categorical variables were presented as frequencies and percentages, with between-group comparisons performed using Chi-square test or Fisher's exact test as appropriate. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

RESULTS

During the 18-month study period, a total of 80 pregnant women fulfilling diagnostic criteria for intrahepatic cholestasis of pregnancy were enrolled and completed follow-up until delivery. Based on gestational age at diagnosis, 30 women (37.5%) were classified as early-onset ICP (diagnosis <32 weeks) and 50 women (62.5%) as late-onset ICP (diagnosis ≥ 32 weeks).

Maternal Baseline Characteristics

Table 1 presents the baseline maternal demographic and clinical characteristics. The mean maternal age was comparable between groups (27.4 ± 3.2 years in early-onset versus 26.9 ± 3.6 years in late-onset group, $p=0.534$). No statistically significant differences were observed in gravidity, parity, body mass index, or history of previous ICP between the two cohorts. As expected by study design, mean gestational age at diagnosis was significantly lower in the early-onset group (28.6 ± 2.1 weeks versus 34.1 ± 1.8 weeks, $p<0.001$).

Table 1: Baseline Maternal Demographic and Clinical Characteristics

Parameter	Early-onset ICP (n=30)	Late-onset ICP (n=50)	p-value
Maternal age (years)	27.4 ± 3.2	26.9 ± 3.6	0.534
Gestational age at diagnosis (weeks)	28.6 ± 2.1	34.1 ± 1.8	<0.001
Primigravida, n (%)	18 (60.0)	28 (56.0)	0.721
Multigravida, n (%)	12 (40.0)	22 (44.0)	0.721
Body mass index (kg/m ²)	24.6 ± 2.8	25.1 ± 3.1	0.470
History of previous ICP, n (%)	4 (13.3)	8 (16.0)	0.746
Twin pregnancy excluded	0 (0.0)	0 (0.0)	-

Biochemical Parameters

Table 2 demonstrates the comparative biochemical profiles between groups. Women with early-onset ICP exhibited significantly elevated mean fasting serum bile acid concentrations compared to late-onset disease (46.8 ± 12.4 $\mu\text{mol/L}$ versus 24.6 ± 8.2 $\mu\text{mol/L}$, $p<0.001$). Similarly, liver aminotransferases were significantly higher in the early-onset cohort, with mean aspartate aminotransferase of 168.4 ± 52.6 IU/L versus 102.3 ± 38.4 IU/L ($p<0.001$) and mean alanine aminotransferase of 186.2 ± 58.3 IU/L versus 118.6 ± 44.2 IU/L ($p<0.001$). Total bilirubin levels, while remaining within normal limits in most cases, showed a trend toward elevation in early-onset ICP without reaching statistical significance (1.4 ± 0.6 mg/dL versus 1.1 ± 0.4 mg/dL, $p=0.082$).

Table 2: Comparative Biochemical Parameters at Diagnosis

Parameter	Early-onset ICP (n=30)	Late-onset ICP (n=50)	p-value
Serum bile acids ($\mu\text{mol/L}$)	46.8 ± 12.4	24.6 ± 8.2	<0.001
Aspartate aminotransferase (IU/L)	168.4 ± 52.6	102.3 ± 38.4	<0.001
Alanine aminotransferase (IU/L)	186.2 ± 58.3	118.6 ± 44.2	<0.001
Total bilirubin (mg/dL)	1.4 ± 0.6	1.1 ± 0.4	0.082
Alkaline phosphatase (IU/L)	312.6 ± 86.4	298.4 ± 78.2	0.460
Gamma-glutamyl transferase (IU/L)	64.8 ± 24.2	52.4 ± 18.6	0.018

Albumin (g/dL)	3.2 ± 0.4	3.3 ± 0.3	0.345
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Perinatal Outcomes

Perinatal outcomes are summarized in Table 3. The early-onset ICP group demonstrated significantly increased rates of adverse perinatal events. Preterm delivery (spontaneous or iatrogenic) occurred in 14 of 30 women (46.6%) with early-onset disease compared to 9 of 50 women (18.0%) with late-onset disease ($p=0.006$). Mean gestational age at delivery was correspondingly lower in the early-onset group (36.2 ± 2.1 weeks versus 37.8 ± 1.4 weeks, $p<0.001$).

Meconium-stained amniotic fluid was observed significantly more frequently in early-onset ICP (11/30, 36.6% versus 7/50, 14.0%; $p=0.019$). Consequently, neonatal intensive care unit (NICU) admission rates were substantially higher in the early-onset cohort (10/30, 33.3% versus 6/50, 12.0%; $p=0.021$). Mean birth weight was lower in early-onset ICP (2642 ± 418 g versus 2856 ± 364 g, $p=0.021$), consistent with earlier gestational age at delivery.

Cesarean delivery rates were elevated in the early-onset group (16/30, 53.3% versus 18/50, 36.0%), though this difference did not achieve statistical significance ($p=0.126$). Five-minute Apgar scores <7 were more common in early-onset disease (6/30, 20.0% versus 4/50, 8.0%; $p=0.115$), though this trend did not reach significance. Importantly, no stillbirths or neonatal deaths occurred in either group during the study period.

Table 3: Comparative Perinatal Outcomes

Outcome	Early-onset ICP (n=30)	Late-onset ICP (n=50)	p-value
Gestational age at delivery (weeks)	36.2 ± 2.1	37.8 ± 1.4	<0.001
Preterm delivery (<37 weeks), n (%)	14 (46.6)	9 (18.0)	0.006
Mode of delivery - Cesarean, n (%)	16 (53.3)	18 (36.0)	0.126
Meconium-stained liquor, n (%)	11 (36.6)	7 (14.0)	0.019
Mean birth weight (grams)	2642 ± 418	2856 ± 364	0.021
5-minute Apgar <7 , n (%)	6 (20.0)	4 (8.0)	0.115
NICU admission, n (%)	10 (33.3)	6 (12.0)	0.021
Stillbirth, n (%)	0 (0.0)	0 (0.0)	-
Neonatal death, n (%)	0 (0.0)	0 (0.0)	-

Both groups demonstrated symptomatic improvement with ursodeoxycholic acid therapy, with 86.7% of early-onset and 92.0% of late-onset patients reporting reduced pruritus intensity ($p=0.464$). However, complete biochemical normalization was achieved in only 16.7% of early-onset cases compared to 38.0% of late-onset cases ($p=0.045$).

DISCUSSION

This prospective observational study demonstrates that early-onset intrahepatic cholestasis of pregnancy, defined as diagnosis before 32 weeks gestation, is associated with significantly more severe biochemical derangement and substantially increased adverse perinatal outcomes compared to late-onset disease. These findings have important clinical implications for risk stratification, surveillance intensity, and delivery timing in women with ICP.

The significantly elevated serum bile acid concentrations observed in early-onset ICP (46.8 ± 12.4 $\mu\text{mol/L}$ versus 24.6 ± 8.2 $\mu\text{mol/L}$) represent a clinically meaningful difference. Previous research has established that bile acid levels exceeding 40 $\mu\text{mol/L}$ confer heightened risk for adverse fetal outcomes [14]. The landmark study by Glantz et al. demonstrated a threshold effect, with complications increasing substantially when bile acids exceeded this level [15]. Our findings indicate that early-onset disease is more likely to present with this high-risk biochemical profile, potentially explaining the worse perinatal outcomes observed.

The pathophysiological mechanisms underlying more severe disease in early-onset cases likely

involve both genetic and environmental factors. Women presenting earlier in gestation may harbor more deleterious mutations in hepatobiliary transporter genes, particularly ABCB4 and ABCB11, resulting in greater functional impairment of bile acid excretion [16]. Additionally, prolonged duration of fetal exposure to elevated bile acids in early-onset disease may contribute cumulatively to placental dysfunction and fetal compromise.

Our observation of significantly increased preterm delivery rates in early-onset ICP (46.6% versus 18.0%) aligns with findings from several international cohorts. Ovadia et al., in a multinational study of over 10,000 pregnancies complicated by ICP, identified earlier gestational onset as an independent predictor of preterm birth [17]. Similarly, a Swedish population-based study reported preterm delivery rates exceeding 40% when ICP presented before 33 weeks [18]. The mechanisms driving preterm birth in ICP include both spontaneous labor, potentially triggered by bile acid-induced uterine contractility, and iatrogenic delivery necessitated by disease severity or fetal compromise.

The substantially elevated rate of meconium-stained amniotic fluid in early-onset disease (36.6% versus 14.0%) represents a concerning finding. Bile acids exert direct effects on fetal colonic motility, promoting meconium passage, while also potentially causing fetal distress through cardiomyocyte dysfunction [9]. The presence of meconium increases risk for neonatal complications including meconium aspiration syndrome, contributing to the higher NICU admission rates observed in our early-onset cohort.

Despite these adverse outcomes, the absence of stillbirths in our study is noteworthy and likely reflects the intensive surveillance protocol and timely delivery implemented for all participants. Previous studies have documented stillbirth rates of 1-3% in ICP, with risk substantially elevated when bile acids exceed 100 $\mu\text{mol/L}$ [2]. Our management approach included weekly bile acid monitoring, frequent fetal surveillance from diagnosis, and planned delivery at 37-38 weeks for controlled disease or earlier for severe cases, consistent with current international guidelines [1].

Regarding pharmacological management, both groups demonstrated symptomatic improvement with ursodeoxycholic acid therapy, consistent with its established efficacy for pruritus relief [6]. However, complete biochemical normalization was less frequently achieved in early-onset disease, suggesting more resistant pathophysiology. Emerging therapies including rifampicin and S-adenosyl-L-methionine may warrant consideration in refractory early-onset cases [3].

The clinical implications of our findings emphasize the necessity for enhanced surveillance in early-onset ICP. Current guidelines recommend individualized management based on bile acid levels, but our results suggest gestational age at onset should additionally inform risk stratification. Women diagnosed before 32 weeks may benefit from more frequent biochemical monitoring, earlier initiation of intensive fetal surveillance, and lower thresholds for delivery planning.

Several limitations warrant acknowledgment. The single-center design and modest sample size may limit generalizability, particularly to populations with different genetic backgrounds or healthcare infrastructure. The observational nature precludes definitive conclusions regarding optimal management strategies, which would require randomized controlled trials. Additionally, long-term maternal and neonatal outcomes were not assessed in this study but represent important areas for future investigation, given associations between ICP and subsequent maternal cardiovascular disease [4].

Future research should focus on genetic characterization of early-onset versus late-onset ICP to elucidate molecular mechanisms, validation of these findings in larger multicenter cohorts, investigation of novel biomarkers for risk stratification beyond bile acid levels, and evaluation of optimal delivery timing through randomized trials. Additionally, long-term follow-up studies examining childhood neurodevelopmental outcomes following early-onset ICP exposure are needed.

CONCLUSION

This prospective observational study conclusively demonstrates that early-onset intrahepatic cholestasis of pregnancy, presenting before 32 weeks gestation, represents a more severe disease phenotype characterized by substantially elevated serum bile acid concentrations and significantly increased adverse perinatal outcomes. Women with early-onset disease experience nearly triple the rate of preterm delivery, more than double the incidence of meconium-stained amniotic fluid, and

nearly triple the neonatal intensive care unit admission rates compared to those with late-onset presentation.

These findings underscore the critical importance of gestational age at diagnosis as an independent risk factor requiring integration into clinical decision-making algorithms. Early recognition through prompt evaluation of pruritus in pregnancy, intensive biochemical and fetal surveillance tailored to disease onset timing, and individualized obstetric management including strategic delivery planning are essential components of comprehensive care for women with ICP.

Healthcare providers managing pregnant women with intrahepatic cholestasis should recognize early-onset disease as a high-risk variant warranting heightened vigilance, more frequent monitoring, and potentially earlier delivery. Implementation of risk-stratified protocols based on both bile acid levels and gestational age at onset may optimize perinatal outcomes in this challenging obstetric condition. Further research investigating the genetic and molecular basis of early versus late onset disease, along with randomized trials evaluating optimal surveillance and delivery strategies, will continue to refine evidence-based management approaches for intrahepatic cholestasis of pregnancy

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