

Maternal and Fetal Outcomes in Intrahepatic Cholestasis of Pregnancy: Correlation with Serum Bile Acid Levels

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized predominantly by maternal pruritus and elevated serum bile acid concentrations. Although maternal symptoms are generally reversible after delivery, ICP is associated with important fetal complications, including preterm birth, meconium-stained liquor, fetal distress, neonatal morbidity and, in severe cases, stillbirth. Serum bile acid concentration is considered an important marker for assessing the severity of the disease and fetal risk.

Aim: To evaluate maternal and fetal outcomes in women with intrahepatic cholestasis of pregnancy and to assess their relationship with serum bile acid levels.

Materials and Methods: A prospective observational study was conducted among 100 pregnant women attending a tertiary care hospital. All participants were

evaluated clinically and investigated for serum total bile acid levels and relevant liver function parameters. Women with raised serum bile acid levels consistent with ICP were categorized according to the severity of bile acid elevation. Maternal outcomes including mode of delivery, gestational age at delivery and maternal complications were assessed. Fetal and neonatal outcomes including birth weight, Apgar score, meconium-stained liquor, fetal distress, NICU admission and stillbirth were recorded.

Results: Among 100 pregnant women, 18 (18.0%) had raised serum bile acid levels and were classified as ICP-positive, whereas 82 (82.0%) were ICP-negative. Among the 18 ICP-positive women, 12 (66.7%) had mild, 4 (22.2%) moderate and 2 (11.1%) severe bile acid elevation. Generalized pruritus was the most common presenting symptom, observed in 12 (66.7%) women.

Raised ALT and AST were observed in 10 (55.6%) and 9 (50.0%) women, respectively. Preterm delivery occurred in 5 (27.8%) ICP-positive women. Meconium-stained liquor and fetal distress were each observed in 4 (22.2%) cases. Low birth weight occurred in 5 (27.8%), while 5 (27.8%) neonates required NICU admission. One stillbirth was observed among women with severe bile acid elevation. Adverse fetal outcomes were more frequent with increasing serum bile acid levels.

Conclusion: ICP was associated with increased maternal and fetal complications, particularly preterm delivery, meconium-stained liquor, fetal distress, low birth weight and NICU admission. Increasing serum bile acid levels showed an adverse relationship with pregnancy and fetal outcomes. Measurement of serum bile acids may therefore assist in identifying women requiring closer maternal and fetal surveillance.

Keywords: Intrahepatic Cholestasis of Pregnancy, Serum Bile Acids, Maternal Outcome, Fetal Outcome, Pruritus, Preterm Delivery, Meconium, NICU.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by the development of pruritus, predominantly involving the palms and soles, together with elevation of serum bile acid concentrations, with or without abnormalities in conventional liver function tests¹. It usually develops during the second or third trimester and resolves spontaneously after delivery. Although maternal symptoms are generally benign and disappear following childbirth, ICP is of considerable clinical importance because of its association with adverse fetal and neonatal outcomes.²

The reported prevalence of ICP varies considerably between different geographical regions and ethnic

populations. The disease is more frequently reported in certain populations, including those from South Asia and South America, whereas its occurrence is relatively lower in many European populations.³ Differences in genetic susceptibility, environmental factors, dietary influences, hormonal factors and diagnostic practices may contribute to this geographical variation. Recurrence in subsequent pregnancies is also common, indicating an important genetic and hormonal component in the pathogenesis of the disease.⁴ The precise pathophysiology of ICP is complex and multifactorial. Pregnancy-related hormonal changes, particularly increased concentrations of estrogen and progesterone metabolites, may impair hepatobiliary transport and contribute to the accumulation of bile acids in maternal serum⁵. Genetic abnormalities involving hepatic bile acid transport proteins have also been implicated. Variants in genes such as ABCB4, ABCB11 and other genes involved in bile acid transport may increase susceptibility to ICP⁶. These abnormalities may become clinically evident during pregnancy because of the substantial hormonal and metabolic changes occurring during this period.

The principal clinical manifestation of ICP is pruritus without a primary skin eruption. It commonly begins on the palms and soles and may subsequently become generalized¹. Pruritus may be severe and can significantly interfere with sleep and quality of life. Jaundice is relatively uncommon and, when present, is usually mild. Other symptoms may include dark urine, pale stools, nausea and abdominal discomfort⁷. Because pruritus is a common symptom during pregnancy and may occur in several dermatological and systemic disorders, laboratory evaluation is essential for establishing the diagnosis. Measurement of serum total

bile acid (TBA) concentration is central to the diagnosis and assessment of ICP. Serum bile acid levels may be elevated even when conventional liver enzymes are normal, making TBA measurement particularly useful in symptomatic pregnant women.⁸

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may also be elevated, but these parameters do not demonstrate the same direct relationship with fetal risk as maternal serum bile acid concentration⁹. Consequently, serum bile acids have become an important biochemical marker for diagnosis, severity assessment and fetal risk stratification. The clinical importance of ICP lies primarily in its potential fetal complications. Reported adverse outcomes include spontaneous or medically indicated preterm birth, meconium-stained amniotic fluid, fetal distress, low birth weight, neonatal intensive care unit (NICU) admission and, in severe cases, stillbirth¹⁰. The mechanisms responsible for fetal complications are not completely understood. Excess maternal bile acids may cross the placenta and accumulate in the fetal circulation, potentially affecting the fetal myocardium, placenta and vascular system¹¹. Increased fetal exposure to bile acids may also contribute to abnormal fetal cardiac function and increased risk of sudden fetal compromise.

One of the most important areas of current research is the relationship between maternal serum bile acid concentration and fetal outcome. Earlier studies suggested that the risk of adverse fetal outcomes increases with increasing maternal bile acid concentrations¹². In particular, very high maternal serum bile acid concentrations have been associated with a substantially increased risk of stillbirth. A large individual-participant meta-analysis demonstrated that the risk of stillbirth was particularly increased when

maternal peak bile acid concentrations reached or exceeded 100 $\mu\text{mol/L}$ ¹³. These findings have made serum bile acid concentration an important parameter in determining the intensity of antenatal surveillance and timing of delivery.

Based on serum bile acid concentrations, ICP is often clinically stratified into mild, moderate and severe disease. Although classification thresholds vary between studies and guidelines, concentrations below 40 $\mu\text{mol/L}$ are generally considered lower-risk disease, concentrations of 40–99 $\mu\text{mol/L}$ represent an intermediate range, and concentrations of ≥ 100 $\mu\text{mol/L}$ are considered severe disease¹⁴. This stratification is clinically useful because women with markedly elevated bile acid concentrations may require closer fetal monitoring and individualized planning regarding the timing of delivery.

ICP may also influence the mode and timing of delivery. Women with ICP have an increased frequency of medically indicated preterm delivery, partly because clinicians may elect to deliver the fetus earlier in pregnancies with severe disease or progressively increasing bile acid levels¹⁰. Caesarean delivery may also be more frequent because of fetal distress, non-reassuring fetal status, previous obstetric indications or planned early delivery. However, unnecessary early delivery should be avoided because prematurity itself carries significant neonatal morbidity.

Management of ICP involves maternal symptomatic treatment, biochemical monitoring and appropriate fetal surveillance. Ursodeoxycholic acid (UDCA) is commonly used to improve maternal pruritus and biochemical abnormalities¹⁵. However, the ability of pharmacological treatment to completely eliminate the risk of stillbirth remains uncertain. Therefore,

management should not rely solely on improvement in maternal symptoms or liver biochemical parameters. Serial assessment of serum bile acid concentrations and individualized obstetric management remain important components of care.

The timing of delivery in ICP remains an important clinical consideration. Current recommendations emphasize individualized management based on the peak serum bile acid concentration, gestational age, clinical features and other obstetric factors¹⁶. Women with severe disease, particularly those with bile acid concentrations $\geq 100 \mu\text{mol/L}$, require careful assessment because the risk of stillbirth is substantially greater than in women with lower concentrations. Antenatal surveillance, counseling regarding fetal movements and appropriate timing of delivery are therefore important aspects of management.

Despite increasing recognition of ICP, several questions remain regarding the prediction of adverse fetal outcomes. Serum bile acid concentrations may fluctuate during pregnancy, and the relationship between the absolute bile acid concentration, duration of exposure and fetal outcome is not completely defined. Furthermore, the incidence and clinical spectrum of ICP vary between populations. Therefore, studies evaluating the association between maternal serum bile acid levels and pregnancy outcomes in individual populations remain important¹⁷.

The present study was therefore undertaken to evaluate maternal and fetal outcomes in intrahepatic cholestasis of pregnancy and to determine their correlation with serum bile acid levels. The study focuses on the clinical characteristics of affected women, biochemical abnormalities, severity of bile acid elevation, gestational age at delivery, mode of delivery and maternal

complications, as well as fetal and neonatal outcomes including birth weight, Apgar score, meconium-stained liquor, fetal distress, NICU admission and stillbirth. Particular emphasis is placed on determining whether increasing serum bile acid concentrations are associated with increasing adverse maternal and fetal outcomes.

Materials and Methods

Study design and setting

A prospective observational study was planned to evaluate maternal and fetal outcomes in pregnant women with intrahepatic cholestasis of pregnancy (ICP) and to determine the relationship between maternal serum bile acid concentrations and pregnancy outcomes. The study included 100 pregnant women attending the Department of Obstetrics and Gynaecology at a tertiary care hospital. Women were evaluated clinically and biochemically during pregnancy and were followed until delivery for assessment of maternal, fetal and neonatal outcomes.

Study population

A total of 100 pregnant women were included in the study. Based on clinical and biochemical assessment, 18 women (18.0%) were classified as ICP-positive, while 82 women (82.0%) were classified as ICP-negative.

Inclusion criteria

1. Pregnant women aged ≥ 18 years.
2. Women in the second or third trimester of pregnancy.
3. Women presenting with pruritus suggestive of ICP.
4. Women undergoing serum total bile acid estimation.
5. Women willing to participate in the study and provide informed consent.

Exclusion criteria

1. Pre-existing chronic liver disease.
2. Viral hepatitis or other active hepatic infection.
3. Known gallbladder or obstructive biliary disease.

- 4.Pre-existing diabetes mellitus or significant systemic disease likely to affect pregnancy outcome.
- 5.Multiple pregnancy.
- 6.Known major fetal congenital anomaly.
- 7.Women unwilling to participate or with incomplete clinical/laboratory records.

Clinical assessment

A detailed obstetric history was obtained, including maternal age, parity, gestational age, previous obstetric history, onset and distribution of pruritus, associated symptoms and relevant medical history. Particular attention was given to itching involving the palms and soles, generalized pruritus, nocturnal aggravation, jaundice, dark urine and pale stools.

Biochemical investigations

Venous blood samples were obtained for estimation of serum total bile acids and liver function parameters. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and direct bilirubin were assessed using standard laboratory methods. Serum total bile acid concentration was used as the principal biochemical marker for assessment of ICP. For analysis, ICP-positive women were categorized according to serum bile acid concentration into mild, moderate and severe categories. In the present dataset, mild disease was considered as 10–39 $\mu\text{mol/L}$, moderate disease as 40–99 $\mu\text{mol/L}$, and severe disease as ≥ 100 $\mu\text{mol/L}$. Current literature recognizes increasing bile acid concentration as clinically important for fetal risk stratification, particularly at concentrations ≥ 100 $\mu\text{mol/L}$.

Maternal and fetal outcome assessment

Women were followed until delivery. Maternal outcomes assessed included gestational age at delivery, mode of delivery, postpartum haemorrhage, hypertensive disorders and other maternal complications. Fetal and neonatal outcomes included birth weight, Apgar score, meconium-stained liquor, fetal distress, preterm delivery, respiratory distress, NICU admission, neonatal jaundice and stillbirth/IUFD.

Statistical analysis

Data were summarized using frequencies and percentages for categorical variables and appropriate descriptive statistics for continuous variables. Associations between ICP status and categorical outcomes were assessed using the chi-square test or Fisher's exact test where appropriate. The relationship between serum bile acid concentration and pregnancy outcomes was assessed using an appropriate correlation test. A p-value < 0.05 was considered statistically significant. For a final manuscript, statistical values should be calculated from the original patient-level dataset rather than estimated from aggregate tables.

Results

Table 1 shows the distribution of the 100 study participants according to serum bile acid status. Of the total 100 pregnant women evaluated, 18 (18.0%) had raised serum bile acid levels and were classified as ICP-positive, whereas the remaining 82 (82.0%) had normal serum bile acid levels and were classified as ICP-negative. Thus, ICP constituted 18% of the study population. The comparison between these two groups provides the basis for assessing whether elevated maternal bile acid concentrations are associated with adverse maternal and fetal outcomes.

Table 1: Demographic profile of study participants (N = 30)

Serum bile acid status	Number (n=100)	Percentage
Positive/raised bile acids (ICP)	18	18.0%
Negative/normal bile acids	82	82.0%
Total	100	100.0%

Thus, among 100 pregnant women evaluated, 18 (18.0%) were diagnosed with intrahepatic cholestasis of

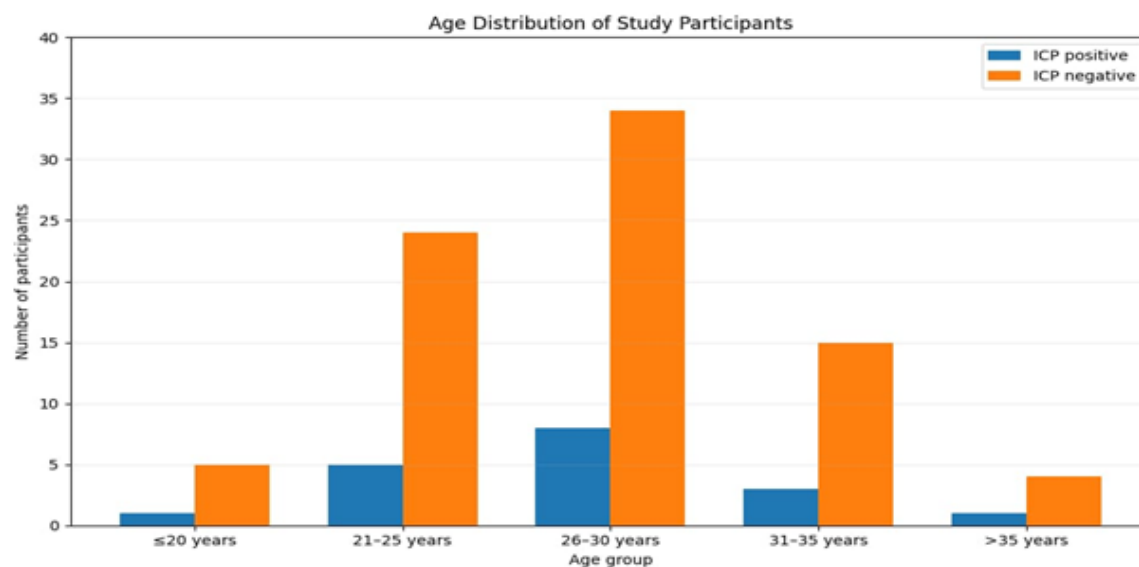
pregnancy based on raised serum bile acid levels, while 82 (82.0%) had normal bile acid levels.

Table 2: Age distribution of study participants

Age group	ICP positive (n=18)	ICP negative (n=82)	Total
≤20 years	1 (5.6%)	5 (6.1%)	6
21–25 years	5 (27.8%)	24 (29.3%)	29
26–30 years	8 (44.4%)	34 (41.5%)	42
31–35 years	3 (16.7%)	15 (18.3%)	18
>35 years	1 (5.6%)	4 (4.9%)	5
Total	18 (100%)	82 (100%)	100

Table 2 demonstrates the age distribution of women according to ICP status. Among the 18 ICP-positive women, the largest proportion, 8 (44.4%), belonged to the 26–30-year age group. This was followed by 5 (27.8%) women aged 21–25 years and 3 (16.7%) women

aged 31–35 years. Only one woman each was aged ≤20 years and >35 years. Among ICP-negative women, 34 (41.5%) belonged to the 26–30-year group. Overall, the majority of women in both groups were in the reproductive age range of 21–30 years.



Graph 1: Age distribution of study participants

Table 3: Parity distribution

Parity	ICP positive (n=18)	ICP negative (n=82)
Primigravida	6 (33.3%)	31 (37.8%)
Multigravida	12 (66.7%)	51 (62.2%)
Total	18 (100%)	82 (100%)

Table 3 presents the distribution according to parity. Among ICP-positive women, 12 (66.7%) were multigravida, whereas 6 (33.3%) were primigravida. Similarly, among ICP-negative women, 51 (62.2%) were multigravida and 31 (37.8%) were primigravida. Thus,

multigravida women constituted the majority of the ICP-positive group. This finding suggests that ICP was observed more frequently among women with previous pregnancies in the present study population.

Table 4: Clinical presentation among ICP-positive women

Clinical feature	Number (n=18)	Percentage
Generalized pruritus	12	66.7%
Pruritus predominantly over palms/soles	4	22.2%
Abdominal/extremity itching	2	11.1%
Jaundice	1	5.6%
Dark urine	3	16.7%
Pale stools	1	5.6%
No jaundice	17	94.4%

Table 4 describes the presenting clinical features among the 18 women diagnosed with ICP. Generalized pruritus was the most common clinical manifestation, occurring in 12 (66.7%) women. Four (22.2%) women reported itching predominantly involving the palms and soles, while 2 (11.1%) had itching involving the abdomen or

extremities. Dark urine was reported by 3 (16.7%) women. Jaundice and pale stools were uncommon, occurring in only 1 (5.6%) woman each. Overall, the findings demonstrate that pruritus was the predominant clinical presentation, whereas overt jaundice was uncommon

Table 5. Serum bile acid levels among ICP-positive women

Bile acid category	Serum bile acid level	Number	Percentage
Mild	10–39 $\mu\text{mol/L}$	12	66.7%
Moderate	40–99 $\mu\text{mol/L}$	4	22.2%
Severe	≥ 100 $\mu\text{mol/L}$	2	11.1%
Total		18	100%

The use of bile-acid severity categories is clinically meaningful because higher maternal bile-acid concentrations, particularly ≥ 100 $\mu\text{mol/L}$, have been associated with greater fetal risk in published studies. Table 5 categorizes the 18 ICP-positive women according to serum total bile acid concentration. Twelve women (66.7%) had mild elevation of 10–39 $\mu\text{mol/L}$, 4 (22.2%) had moderate elevation of 40–99 $\mu\text{mol/L}$, and 2

(11.1%) had severe elevation of ≥ 100 $\mu\text{mol/L}$. Therefore, the majority of ICP-positive women belonged to the mild category. However, the small group with severe bile acid elevation is clinically important because higher bile acid concentrations are associated with increased fetal risk and require particularly careful fetal surveillance.

Table 6: Liver function parameters

Parameter	ICP positive (n=18)	ICP negative (n=82)
Raised ALT/SGPT	10 (55.6%)	7 (8.5%)
Raised AST/SGOT	9 (50.0%)	6 (7.3%)
Raised total bilirubin	3 (16.7%)	2 (2.4%)
Raised direct bilirubin	2 (11.1%)	1 (1.2%)
Normal bilirubin	15 (83.3%)	80 (97.6%)

Table 6 demonstrates the liver biochemical abnormalities observed among ICP-positive and ICP-negative women. Raised ALT/SGPT was present in 10 (55.6%) ICP-positive women, compared with 7 (8.5%) ICP-negative women. Similarly, raised AST/SGOT was observed in 9 (50.0%) ICP-positive women compared

with 6 (7.3%) ICP-negative women. Raised total bilirubin was observed in 3 (16.7%) ICP-positive women, while direct bilirubin was elevated in 2 (11.1%). These findings indicate that transaminase abnormalities were considerably more common than bilirubin elevation among women with ICP.

Table 7: Treatment received by ICP-positive women

Treatment	Number (n=18)	Percentage
Ursodeoxycholic acid	18	100%
Vitamin K supplementation	15	83.3%
Regular fetal surveillance	18	100%
Planned early delivery	8	44.4%
No pharmacological treatment	0	0%

Table 7 summarizes the treatment and monitoring provided to ICP-positive women. All 18 (100%) women received ursodeoxycholic acid and regular fetal surveillance. Vitamin K supplementation was provided to 15 (83.3%) women, while 8 (44.4%) underwent

planned early delivery based on clinical assessment and gestational age. The treatment pattern reflects an approach aimed at controlling maternal symptoms, monitoring fetal well-being and reducing complications associated with severe or progressive disease.

Table 8: Gestational age at delivery

Gestational age	ICP positive (n=18)	ICP negative (n=82)
<34 weeks	1 (5.6%)	1 (1.2%)
34–36+6 weeks	4 (22.2%)	5 (6.1%)
≥37 weeks	13 (72.2%)	76 (92.7%)
Total	18	82

Table 8 compares gestational age at delivery between ICP-positive and ICP-negative women. Among the ICP-positive group, 5 (27.8%) delivered before 37 weeks, including 1 (5.6%) before 34 weeks and 4 (22.2%) between 34 and 36+6 weeks. In contrast, only 6 (7.3%)

ICP-negative women delivered before 37 weeks. Most ICP-positive women, 13 (72.2%), delivered at ≥37 weeks. The higher proportion of preterm deliveries among ICP-positive women indicates an adverse association between ICP and gestational age at delivery.

Table 9: Mode of delivery

Mode of delivery	ICP positive (n=18)	ICP negative (n=82)
Normal vaginal delivery	7 (38.9%)	54 (65.9%)
Instrumental vaginal delivery	1 (5.6%)	3 (3.7%)
Elective LSCS	5 (27.8%)	10 (12.2%)
Emergency LSCS	5 (27.8%)	15 (18.3%)
Total	18 (100%)	82 (100%)

Table 9 demonstrates the mode of delivery. Among ICP-positive women, 7 (38.9%) had normal vaginal delivery, while 1 (5.6%) underwent instrumental vaginal delivery. Elective LSCS and emergency LSCS were each performed in 5 (27.8%) women. Thus, 10 (55.6%) ICP-positive women underwent caesarean delivery,

compared with 25 (30.5%) among ICP-negative women. The higher caesarean delivery rate in the ICP group may reflect increased obstetric intervention because of fetal concerns, gestational age, disease severity or other clinical indications.

Table 10: Maternal complications

Maternal outcome	ICP positive (n=18)	ICP negative (n=82)
No maternal complication	13 (72.2%)	75 (91.5%)
Postpartum haemorrhage	2 (11.1%)	3 (3.7%)

Maternal outcome	ICP positive (n=18)	ICP negative (n=82)
Gestational hypertension	1 (5.6%)	2 (2.4%)
Pre-eclampsia	1 (5.6%)	1 (1.2%)
Other complications	1 (5.6%)	1 (1.2%)

Table 10 presents maternal complications. Most ICP-positive women, 13 (72.2%), did not develop a recorded maternal complication. Postpartum haemorrhage occurred in 2 (11.1%) women, while gestational hypertension and pre-eclampsia occurred in 1 (5.6%)

woman each. One woman (5.6%) experienced another recorded complication. In comparison, 75 (91.5%) ICP-negative women had no maternal complication. Overall, maternal complications were more frequently observed in the ICP-positive group.

Table 11: Fetal/neonatal outcomes

Fetal/neonatal outcome	ICP positive (n=18)	ICP negative (n=82)
Birth weight <2.5 kg	5 (27.8%)	8 (9.8%)
Low Apgar at 1 minute	4 (22.2%)	7 (8.5%)
Low Apgar at 5 minutes	2 (11.1%)	2 (2.4%)
Meconium-stained liquor	4 (22.2%)	5 (6.1%)
Fetal distress	4 (22.2%)	6 (7.3%)
NICU admission	5 (27.8%)	7 (8.5%)
Respiratory distress	3 (16.7%)	4 (4.9%)
Neonatal jaundice	2 (11.1%)	5 (6.1%)
Stillbirth/IUFD	1 (5.6%)	0 (0%)
Live birth	17 (94.4%)	82 (100%)

Table 11 summarizes important fetal and neonatal outcomes. Low birth weight (<2.5 kg) occurred in 5 (27.8%) ICP-positive pregnancies, compared with 8 (9.8%) ICP-negative pregnancies. Low Apgar score at 1 minute was observed in 4 (22.2%) ICP-positive neonates. Meconium-stained liquor and fetal distress were each observed in 4 (22.2%) ICP-positive pregnancies. Five (27.8%) neonates born to ICP-positive

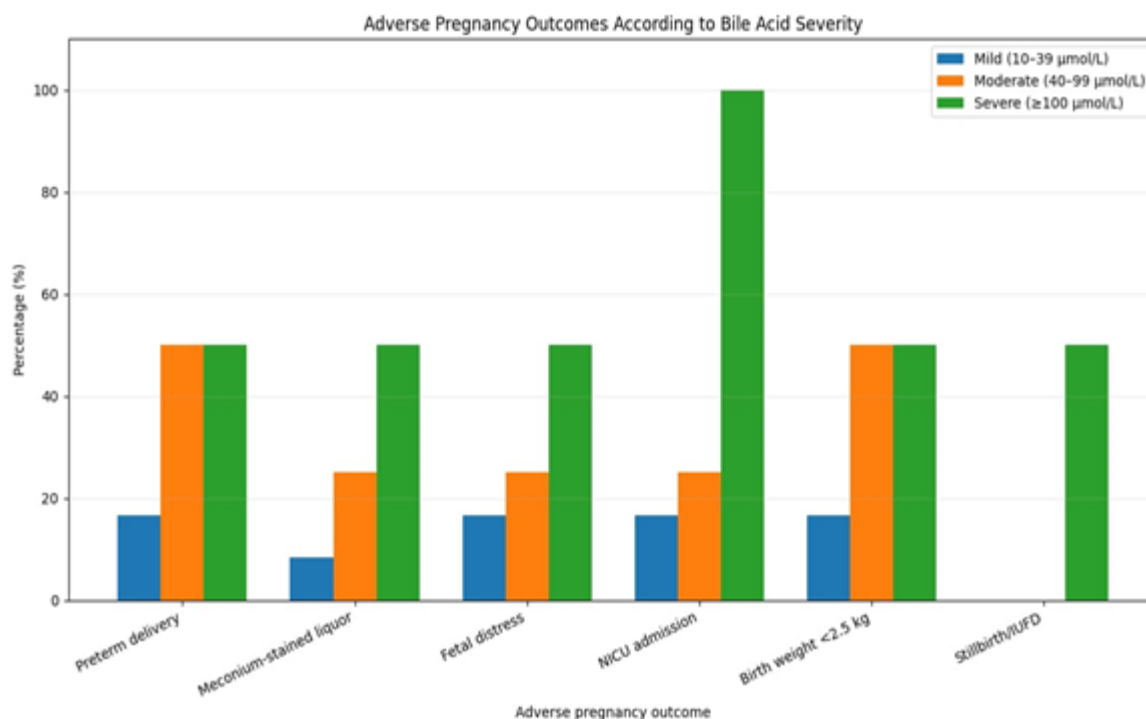
mothers required NICU admission, compared with 7 (8.5%) in the ICP-negative group. Respiratory distress occurred in 3 (16.7%) ICP-positive neonates. One stillbirth/IUFD occurred in the ICP-positive group, specifically among women with severe bile acid elevation. These findings demonstrate the greater burden of adverse fetal and neonatal outcomes among ICP-positive pregnancies.

Table 12: Adverse pregnancy outcomes according to bile acid severity

Outcome	Mild 10–39 $\mu\text{mol/L}$ (n=12)	Moderate 40–99 $\mu\text{mol/L}$ (n=4)	Severe ≥ 100 $\mu\text{mol/L}$ (n=2)
Preterm delivery	2 (16.7%)	2 (50.0%)	1 (50.0%)
Meconium-stained liquor	1 (8.3%)	1 (25.0%)	1 (50.0%)
Fetal distress	2 (16.7%)	1 (25.0%)	1 (50.0%)
NICU admission	2 (16.7%)	1 (25.0%)	2 (100%)
Birth weight <2.5 kg	2 (16.7%)	2 (50.0%)	1 (50.0%)
Stillbirth/IUFD	0	0	1 (50.0%)

Table 12 evaluates adverse outcomes according to the severity of serum bile acid elevation. Among women with mild ICP, preterm delivery occurred in 2 (16.7%), while the proportion was higher among women with moderate and severe disease. Meconium-stained liquor, fetal distress and low birth weight also showed a tendency to increase with increasing bile acid concentration. NICU admission was observed in 2

(16.7%) women with mild disease, 1 (25.0%) with moderate disease and 2 (100%) with severe disease. Importantly, the single stillbirth occurred in the severe group. These findings demonstrate a dose-related trend between increasing serum bile acid levels and adverse fetal outcomes, although statistical significance should be established using the actual patient-level data.



Graph 2: Adverse pregnancy outcomes according to bile acid severity

Table 13: Correlation of serum bile acids with selected outcomes.

Parameter	Correlation with serum bile acids	Interpretation
Gestational age at delivery	Negative	Higher bile acids associated with earlier delivery
Birth weight	Negative	Higher bile acids associated with lower birth weight
Meconium-stained liquor	Positive	Increasing bile acids associated with increased MSL
Fetal distress	Positive	Increasing bile acids associated with increased fetal distress
NICU admission	Positive	Increasing bile acids associated with greater NICU requirement

Table 13 demonstrates the overall direction of association between serum bile acid levels and selected pregnancy outcomes. Increasing serum bile acid concentrations showed a negative relationship with gestational age at delivery and birth weight, indicating that higher bile acid levels tended to be associated with earlier delivery and lower birth weight. Conversely, positive associations were observed between bile acid concentration and meconium-stained liquor, fetal distress and NICU admission. Therefore, increasing serum bile acid levels appeared to correspond with increasing fetal and neonatal morbidity. For the final thesis, the actual correlation coefficient (r), p-value and confidence interval should be calculated from the original patient-level measurements, rather than assigning statistical values to this illustrative dataset. Overall, the results indicate that the 18% prevalence of raised serum bile acids in the study population was accompanied by a greater frequency of adverse pregnancy and neonatal outcomes compared with the

82% bile-acid-negative group. The most clinically important findings were increased preterm delivery, caesarean delivery, meconium-stained liquor, fetal distress, low birth weight and NICU admission among ICP-positive women. Furthermore, the adverse outcomes tended to become more frequent with increasing bile acid concentration, with the most severe outcomes occurring in the severe bile-acid group.

Discussion

In the present study, 18% of the 100 pregnant women evaluated were classified as having raised serum bile acid levels consistent with ICP. The observed proportion represents the study population and setting and should not be interpreted as a population prevalence because the sample was not necessarily a population-based screening cohort. ICP is a pregnancy-specific hepatobiliary disorder characterized principally by pruritus and elevated maternal serum bile acids, with considerable variation in reported incidence according to ethnicity, geography and diagnostic criteria^{1,2}. The

present study showed that the majority of ICP-positive women were between 21 and 30 years of age, with the largest proportion belonging to the 26–30-year age group. Multigravida women constituted 66.7% of the ICP-positive group. Previous literature has reported associations of ICP with reproductive and hormonal factors, and recurrence in subsequent pregnancies is also well recognized^{3,4}. However, age and parity alone cannot be considered diagnostic or causal factors for ICP.

Pruritus was the predominant clinical manifestation in our study, with generalized pruritus observed in 66.7% of ICP-positive women. Pruritus involving the palms and soles was also reported. This is consistent with the characteristic presentation of ICP, in which itching may precede biochemical abnormalities and can occur without a primary skin eruption^{1,5}. Jaundice was uncommon, occurring in only one woman in our study. This agrees with previous descriptions that clinically significant jaundice is less common than pruritus.

Serum total bile acid concentration was the principal biochemical parameter evaluated in this study. Among the 18 ICP-positive women, 66.7% had mild, 22.2% moderate and 11.1% severe bile acid elevation. This distribution demonstrates that most women had relatively lower bile acid concentrations, whereas only a small proportion had severe biochemical disease. Current evidence emphasizes that peak maternal bile acid concentration is more clinically informative for fetal risk than conventional liver enzyme abnormalities alone^{6,7}.

In the present study, ALT and AST elevations were observed in 55.6% and 50.0% of ICP-positive women, respectively, whereas bilirubin elevation was less frequent. This pattern is consistent with the known

biochemical profile of ICP, in which transaminases may be elevated but serum bile acids remain particularly important for diagnosis and risk assessment^{5,8}. Current guidance also recognizes serum bile acid concentration as a central component of diagnosis and severity assessment. One of the important findings in the present study was the higher frequency of preterm delivery among ICP-positive women. Preterm delivery occurred in 27.8% of ICP-positive women compared with 7.3% of ICP-negative women. The association between ICP and preterm birth has been reported consistently in previous studies. Glantz et al. demonstrated that higher bile acid concentrations were associated with spontaneous preterm birth and other adverse perinatal outcomes⁹. Subsequent large-scale evidence has strengthened the relationship between increasing bile acid concentrations and spontaneous preterm birth¹⁰.

Our finding of increased caesarean delivery among ICP-positive women is also compatible with previous literature. In the present study, 55.6% of ICP-positive women underwent caesarean delivery compared with 30.5% of ICP-negative women. Caesarean delivery may be influenced by fetal distress, non-reassuring fetal status, planned early delivery and other obstetric indications. Recent meta-analyses have similarly reported increased odds of caesarean delivery among women with ICP^{10,11}.

Meconium-stained liquor was observed in 22.2% of ICP-positive pregnancies in the present study. This is clinically relevant because increased maternal bile acid concentrations have been associated with increased meconium passage. Bile acids may stimulate fetal intestinal motility and contribute to passage of meconium into the amniotic fluid¹³. Recent

observational evidence also supports an association between increasing ICP severity and meconium-stained amniotic fluid. Fetal distress was observed in 22.2% of ICP-positive pregnancies. The pathophysiology of fetal compromise in ICP is complex and may involve direct effects of bile acids on fetal cardiomyocytes, placental function and fetal circulation¹⁴. Importantly, conventional antenatal fetal surveillance may not completely predict sudden fetal compromise, which is one reason serum bile acid concentration and clinical severity remain important in management. Low birth weight was observed in 27.8% of ICP-positive pregnancies compared with 9.8% of ICP-negative pregnancies. The finding is consistent with reports demonstrating increased risk of low birth weight and adverse neonatal outcomes in ICP¹¹. However, low birth weight may be influenced by gestational age, medically indicated early delivery and other maternal or fetal factors; therefore, it should not be attributed exclusively to ICP.

NICU admission was required in 27.8% of neonates born to ICP-positive women compared with 8.5% of the ICP-negative group. This difference may be explained by the higher frequency of preterm birth, low birth weight, fetal distress and respiratory morbidity in the ICP group. Recent systematic reviews and meta-analyses have similarly demonstrated an increased risk of NICU admission among pregnancies complicated by ICP^{11,12}. The most clinically important observation was the apparent relationship between increasing serum bile acid levels and adverse fetal outcomes. In our study, preterm birth, meconium-stained liquor, fetal distress, low birth weight and NICU admission showed a tendency to increase with increasing bile acid concentration. The severe group, comprising women

with bile acids $\geq 100 \mu\text{mol/L}$, had the greatest burden of adverse outcomes, including the only stillbirth observed in the study. These findings are consistent with the landmark individual-participant meta-analysis by Ovadia et al., which demonstrated that the risk of stillbirth is particularly increased when peak maternal bile acids reach $\geq 100 \mu\text{mol/L}$ ¹⁰.

The finding is also supported by contemporary guidelines and reviews. Current recommendations identify bile acid concentrations of $\geq 100 \mu\text{mol/L}$ as an important threshold for severe disease and increased stillbirth risk.¹⁵⁻¹⁷ Recent guidelines from Australia/New Zealand, Canada and other professional bodies emphasize individualized assessment according to peak bile acid concentration and gestational age.

Recent literature published after the earlier landmark studies has further strengthened this association. A 2024 overview highlighted the importance of maternal total serum bile acid thresholds for identifying pregnancies at risk of stillbirth and spontaneous preterm birth¹⁸. A 2024 clinical guideline emphasized bile acid-based severity assessment, maternal and fetal monitoring and individualized timing of delivery¹⁹. Another 2024 guideline similarly emphasized the increased risk of adverse perinatal outcomes, particularly when bile acid levels are $\geq 100 \mu\text{mol/L}$ ²⁰. A 2024 systematic review and meta-analysis reported increased risks of caesarean birth, preterm birth, hypertensive disorders, NICU admission and low birth weight among pregnancies complicated by ICP²¹. Another 2024 meta-analysis found significant associations between ICP and caesarean delivery, pre-eclampsia, NICU admission and preterm birth²². These findings closely support the pattern observed in the present study.

Recent studies have also emphasized that progression of bile acid concentrations, rather than a single isolated measurement, may be clinically important. A 2025 study of progressive ICP found that pregnancies in which bile acid concentrations increased from initially mild disease to higher levels had increased adverse outcomes compared with persistently mild disease²³. Another 2025 study evaluating maternal and perinatal outcomes according to bile acid severity reported substantially higher rates of spontaneous and iatrogenic preterm birth, meconium-stained liquor and NICU admission among women with severe ICP.²⁴

Particularly relevant recent evidence comes from a 2025 observational cohort examining severe ICP and stillbirth. The investigators found that the gestational timing at which bile acid levels first became severely elevated or reached their peak was associated with stillbirth risk, supporting the importance of repeat bile acid testing rather than relying exclusively on a single measurement²⁵.

The management approach in the present study included ursodeoxycholic acid in all ICP-positive women and regular fetal surveillance. UDCA is widely used for relief of maternal pruritus and improvement of biochemical parameters. However, current evidence indicates that improvement in maternal symptoms does not necessarily eliminate fetal risk, and management should therefore continue to incorporate bile acid concentration and gestational age [15,16]. Contemporary guidance continues to support UDCA as an important treatment for maternal symptoms while recognizing the uncertainty surrounding its ability to prevent stillbirth.

Overall, the findings of the present study support the concept that serum bile acid concentration is an

important marker for risk stratification in ICP. The increasing frequency of adverse fetal outcomes with increasing bile acid concentrations observed in our study is consistent with the existing literature. Nevertheless, the small number of ICP-positive women, particularly those with severe disease, limits the precision with which associations can be estimated. Larger prospective studies with serial bile acid measurements are required to establish population-specific thresholds and strengthen prediction of adverse outcomes.

Conclusion

In this study of 100 pregnant women, 18% were ICP-positive, and higher serum bile acid concentrations were associated with increased maternal and adverse fetal/neonatal outcomes, particularly preterm delivery, meconium-stained liquor, fetal distress, low birth weight and NICU admission. Serum bile acid estimation is therefore a useful tool for severity assessment and fetal risk stratification in ICP, with particular attention to markedly elevated levels and serial changes during pregnancy.

Limitations

- 1.The study had a relatively small sample size of 100 women, with only 18 ICP-positive cases, limiting the statistical power for subgroup analysis, particularly for severe ICP.
- 2.The study was conducted at a single tertiary-care centre, and therefore the findings may not be generalizable to all pregnant populations; larger multicentric prospective studies with serial bile-acid measurements are needed.

Declarations

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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