Proceedings S.Z.M.C. Vol: 40(1): pp. 64-69, 2026. *PSZMC-1016-40-1-2026*

ORIGINAL ARTICLE

Peri-natal complications of intrahepatic cholestasis in pregnancy and association with bile acid levels

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Received: Nov 30, 2025, **Accepted:** Mar 28, 2026, **Published:** 31 Mar, 2026.
DOI: https://doi.org/10.47489/szmc.v40i1.877
Data Availability: The corresponding author can provide access upon request.
Funding: No funding received
Competing Interests: No competing interest to declare.

Author Contributions:
QS, RI, AA, MS, AS, RAN:

- Each author made substantial contributions to the conception and design of the study or acquisition, analysis, and interpretation of data.
- All authors were involved in drafting the manuscript or critically revising it for important intellectual content.
- All authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work.

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is most common pregnancy related disorder of liver, characterized by increase serum bile acid levels, associated with number of fetal complications e.g. preterm delivery, stillbirth, meconium-stained amniotic fluid and neonatal respiratory distress syndrome.
Objective: This study aimed to determine the frequency of perinatal complications of intra-hepatic cholestasis of pregnancy and its association with serum bile acids level.
Method: This prospective cohort study was conducted at Department of Gastroenterology, Fatima Memorial Hospital, Lahore in 2024-25. In this study, 129 pregnant patients with diagnosis of intrahepatic cholestasis of pregnancy were included. Serum bile acid levels were measured at admission. Clinical outcomes i.e. still birth, preterm delivery, neonatal respiratory distress syndrome and low birth weight were analyzed using statistical package for social sciences (SPSS) v26.
Results: In 129 patients, the mean age of the patients was 27.29±3.43 years, 94(72.9%) developed intrahepatic cholestasis of pregnancy during their first pregnancy. Most of the patients delivered via cesarean section (70.5%). Still birth was observed in 8(6.2%) cases and preterm delivery in 38 (29.5%). Neonatal respiratory distress syndrome, and low birth weight was seen in 23(17.8%) and 22(17.1%) newborns respectively. APGAR <7 at 1 min and 5min was noticed in 40 (31%) and 22(17.1%) respectively. Higher levels of serum bile acids were associated with increased risk of neonatal complications i.e. still birth (OR 1.476, CI 95 %, p-value 0.05) and preterm (OR 1.524, CI 95 %, p-value 0.00) in these patients.
Conclusion: This study showed that ICP had significant impact on the outcome of pregnancy, with higher levels of serum bile acid leading to increased risk of preterm baby, still birth and APGAR <7 at 1 min and 5 min.
Keywords: intrahepatic cholestasis, pregnancy, still birth, neonatal respiratory distress syndrome

INTRODUCTION:

Intra hepatic cholestasis of pregnancy (ICP) also called cholestatic hepatosis or icterus gravidarum, is most common pregnancy related liver disease, characterized by pruritus that typically effective palms and soles due to raise serum bile acid levels [1]. While ICP classically presents in late second or third trimester of pregnancy, studies showed that it can manifest as early as the first trimester[1]. Global prevalence of ICP was reported between 0.1-2%, while in certain regions of America, higher incidence was cited (25%)[1][1,2]. Its prevalence in Pakistan was reported as 1.2-3.1% [3,4]. Females of age younger than 25 years and older than 35 years, high body mass index, insufficient pregnancy weight gain, with multi-fetal pregnancy, history of ICP in previous pregnancy, history of miscarriages, history of cholestectomy and hepatitis B and/or C infection with or without chronic liver disease are at increased risk of developing ICP [5,6].

After the delivery, symptoms of ICP are resolved completely and liver function returns to normal levels within 8 weeks post-partum [7]. Considering maternal health, there is higher risk of C section and ICP in the next pregnancy, but no long-term complication reported [8]. Fetal complications are more severe, include low birth weight, intrauterine death (IUD) or still birth, spontaneous preterm labor, respiratory distress of newborn and

meconium-stained amniotic fluid [1,4,5]. The exact mechanism of how bile acid levels in ICP leads to poor perinatal outcome is not fully understood. It was observed that higher bile acid peak levels were associated with higher rates of adverse perinatal outcomes with higher rates of intrauterine growth retardation and preterm delivery [7,8, 9]. Either these bile acid effect placental hormonal and transportational functions or had direct toxicity on the fetal heart leading to arrhythmias [6,10,11]. There is no specific toll recommended to predict the impact of ICP on fetal growth till date. High risk pregnancies i.e those with history of ICP and/or stillbirth and serum bile acid levels of more than 40 µmol/L, it is recommended to terminate pregnancy at 36 week of gestation, after given treatment for fetal lung maturity [6,12].

There is significant variation in the incidence of intrahepatic cholestasis of pregnancy and its related complications among pregnant patients. The relationship between the severity of ICP and maternal and neonatal complication is not well established in many settings. We aim to evaluate the association between serum bile acid levels and neonatal outcomes which will aid in risk stratification and guide clinical management in affected pregnancies'

METHODOLOGY: This was a prospective cohort study conducted at the department of Gastroenterology, Fatima Memorial Hospital, a tertiary care hospital, affiliated with FMH College of Medicine and dentistry, Lahore, after taking approval from ethical committee (IRB # FMH-18/03/2024-IRB-1371, dated May, 13th 2024). Among the pregnant females admitted in hospital, 129 cases of intrahepatic cholestasis of pregnancy from 30th April, 2024 to 30th October 2025 was included in the study. Diagnosis of ICP was based on presence of itching (pruritus), with elevated serum bile acid levels (> 10umol/L), alanine transaminase (ALT >45U/L) and aspartate transaminase (AST >40U/L) [7]. Pregnant ladies having other medical conditions like cardiovascular, renal, endocrine or autoimmune disorders, multi-fetal pregnancy, structural abnormality of liver on ultrasound, viral infections (hepatitis A, B, C, D, E or HIV), chronic liver disease and pregnancy related other disorders, e.g. HELLP syndrome and preeclampsia, were excluded from the study. Those who refused to give consent or failed to keep proper follow-ups were also excluded.

Sample size of 129 was calculated by using formula $n = \frac{z^2 \times P(1-P)}{d^2}$, (frequency of low birth weight in ICP 9.2%) [13]. with 95 %confidence level and margin of error 5%**.** Using non-probability, consecutive sampling cases were included in the study. These were further categorized into mild (≥10-39µmol/L), severe (≥40-99µmol/L) and very severe (≥100µmol/L) [6]. All the patients were followed till delivery and the outcomes were recorded. Data was entered and analyzed by SPSS-26. Frequencies and percentages were calculated for categorical variables e.g. obesity, mode of delivery, still birth, preterm delivery and neonatal respiratory distress syndrome, while mean and standard deviation of continuous variables i.e. age, and serum bile acid levels were determined. Chi square test was used to determine the significance of each variable. P-value ≤ 0.05 was considered significant.

RESULTS: Of the 129 patients, mean age of the patients was 27.29±3.43 years, 94(72.9%) develop intrahepatic cholestasis of pregnancy during their first pregnancy. Only 17.8 % pregnant lady were obese i.e. body mass index BMI >27.5 kg/m^2 as per Asian BMI classification. Most of the patients delivered via cesarean section (70.5%), cesarean was a preferred mode of delivery in females with 1st pregnancy (p-value 0.04). Still birth was observed in 8(6.2%) pregnant ladies with ICP. Meconium straining of amniotic fluid was observed in 36(27.9%) cases. Preterm delivery i.e. before completion of 37 weeks of gestation was observed in 38 (29.5%) patients. Neonatal respiratory distress syndrome, and low birth weight was seen in 23(17.8%) and 22(17.1%) newborns respectively. Considering the APGAR at 1 min, 40 (31%) newborns had score less than 7, while at 5 min, 22(17.1%) had score <7. Bile acid levels were moderately, severely and very severely high in 39(30.2%), 74(57.4%), and 16(12.4%) patients respectively. (Table 1)

Table 1: Demographic and clinical features of the ICP patients (n=129)

GENERAL CHARACTERS		
	Frequency	**Percentages %**
Age Groups		
18-24	32	24.8
25-33	90	69.8
34-40	7	5.4
Gravida		
Primary gravida	94	72.9
Multi gravida	35	27.1
Obesity	23	17.8
Mode of delivery		
SVD	38	29.5
Cesarean	91	70.5
Still birth	8	6.2
Preterm	38	29.5
Low birth weight (<2.5KG)	22	17.1
Respiratory distress syndrome	23	17.8
Meconium stained amniotic fluid	36	27.9
APGAR 1 (<7)	40	31
APGAR 5 (<7)	22	17.1
ICP on bases of bile acid levels (µmole/L**)**		
Moderate	39	30.2
Severe	74	57.4
Very severe	16	12.4

*ICP intrahepatic cholestasis of pregnancy, SVD spontaneous vaginal delivery, APGAR appearance, pulse, grimace, activity & respiration

The comparison of neonatal complications with general features of the patients, showed that low birth weight (<2.5 kg) was observed more commonly in younger females (<25 years age) (p- value 0.03), while other complications had no significant relationship with patient's age. Factors like age of patient, gravida and weight had no effect on serum bile acid levels. Neonatal complications are significantly associated with serum bile acid levels in patient of intrahepatic cholestasis of pregnancy (p-value <0.05), serum bile acid more than 100 µmole/L increase the risk of still birth (OR 1.476, CI 95 %, p-value 0.05) and preterm delivery (OR 1.524, CI 95 %, p-value 0.00) in these patients. (Table 2)

Table 2: Comparison of clinical features and neonatal complications with severity of serum bile acid levels

Clinical features		Bile acid levels (µmole/L) Mild (10-39)	Severe (40-99)	Very severe (>100)	p-value
Mode of delivery	**SVD**	10 (25.6%)	24 (32.4%)	4 (25.0%)	0.690*
(n=129)	**Cesarean**	29 (74.4%)	50 (67.6%)	12(75.0%)	
Gravida	**Primary**	27 (69.2%)	54 (73.0%)	13 (81.3%)	0.660*
(n=129)	**Multi**	12 (30.8%)	20 (27.0%)	3(18.8%)	
Obesity	**Yes**	4(10.3%)	17 (23.0%)	2(12.5%)	
(n=129)	**No**	35 (89.7%)	57 (77.0%)	14 (87.5%)	
Complications					
Still birth	**Yes**	0 (0%)	4(5.4%)	4(25.0%)	
(n=129)	**No**	39(100%)	71(94.6%)	13(81.3)	
Preterm	**Yes**	3(7.7%)	24(32.4%)	11(68.8%)	0.000*
(n=129)	**No**	36(92.3%)	50(67.6%)	5(31.3%)	
Low birth weight (<2.5kg)	**Yes**	8(20.5%)	12(16.2%)	2(12.5%)	
(n=129)	**No**	31(79.5%)	62(83.8%)	14(87.5%)	
Meconium strain amniotic fluid (n=129)	**Yes**	1(2.6%)	24(32.4%)	11(68.8%)	
	No	38(97.4%)	50(67.6%)	5(31.3%)	
APGAR 1 (<7)	**Yes**	7(17.9%)	28(40.0%)	5(41.7%)	0.001
(n=121)	**No**	32(82.1%)	42(60.0%)	7(58.3%)	
APGAR 5 (<7)	**Yes**	4(10.3%)	17(24.3%)	1(8.3%)	
(n=121)	**No**	35(89.7%)	53(75.7%)	11(91.7%)	
RDS	**Yes**	1(2.6%)	19(25.7%)	3(13.6%)	
	No	38(97.4%)	55(74.3%)	19(86.4%)	

*Chi-square test was applied, *Fisher Exact test was applied*

ICP intrahepatic cholestasis of pregnancy, SVD spontaneous vaginal delivery, RDS respiratory distress syndrome, APGAR appearance, pulse, grimace, activity & respiration.

DISCUSSION: Intrahepatic cholestasis of pregnancy is most common pregnancy related liver disease, effecting 3.1% pregnancies in Pakistan. Patients of ICP present with itching, usually in the 2nd and 3rd trimester of pregnancy with increase serum bile acid levels [3]. Though the symptoms of disease are resolved after delivery within 8 weeks with no significant residual effect on the mother health, but ICP was found to be associated with poor outcome in term of newborn health [5]. This study results revealed high rate of cesarean section delivery among the patients of ICP, thus having a significant effect on mother health. Cesarean section was significantly more common in primary gravida females (p-value 0.04). The results of previous local as well as international studies also showed increased risk of C-sections in ICP patients [7,13,14].

The finding of this study revealed that the ICP complicated pregnancies were associated with higher number of fetal related complications, including still birth, preterm delivery, low birth weight, meconium-stained amniotic fluid and neonatal respiratory distress syndrome. It was also seen that the APGAR score at 1 min and 5 min, to assess the fetal wellbeing was lower in significant number of newborns of ICP effected mothers. In a study at University Hospital of Messina, the perinatal complications e.g. preterm labor and meconium-stained amniotic fluid were associated with ICP effected pregnancies [7]. In a Swedish study, including 1.2 million pregnant females, it was found that preterm delivery and respiratory distress with low APGAR score had significantly common among pregnancy complicated by ICP [15]. All these studies emphasized that there is increased risk of adverse neonatal outcome in ICP complicated pregnancies.

A study conducted at Sargodha, Pakistan, also showed that increased incidence of respiratory distress of newborn, preterm birth, low birth weight and intrauterine death of the fetus in intrahepatic cholestasis of pregnancy [13]. The results of this study was similar to their results. Another study on Pakistani population by Shafqat et al reported that intrauterine fetal death, low birth weight babies, meconium-stained liquor, fetal respiratory distress and low APGAR score were frequent complications in women with ICP [16]. The results of our study were aligned to these studies.

In our study, it was found that all these complications were significantly associated with severity of cholestasis defined by serum bile acid levels, with many fold increase in number of complications with serum bile acid levels of more than 40 µmol/L. Roberta Granese et al also found that serum bile acid levels of >40 µmol/L in intrahepatic cholestasis of pregnancy increased the risk of feto-maternal complications[7]. In a recent study at Rawalpindi Teaching Hospital, Rawalpindi, it was found that very severe ICP i.e. serum bile acid levels >100 µmol/L significantly associated with intrauterine growth retardation and preterm delivery [12].

This prospective study conducted at a tertiary care hospital of Lahore provided a valuable insight of the fetal outcomes in the patients suffering from intrahepatic cholestasis of pregnancy and highlighted the importance of peak bile acid levels in these patients, but these results had few limitations. As it was a single center-based study, situated in a developed urban area, thus the findings can't be generalized to nationwide. Only the immediate post-delivery complications were noted in this study. Further study, preferably multi-centered to include both urban and rural population to determine a broader picture of the burden of ICP and its complication and to determine the risk factor of ICP and treatment benefit in preventing this neonatal complication are needed.

CONCLUSION: This study show ICP is associated with increased risk of adverse outcome i.e. intrauterine death, preterm delivery, low birth weight and respiratory distress especially in severe cases. Thus, all the patients should be closely monitor and carefully treated to prevent these complications. Further studies to determine better evidence and the mechanism behind these complications and treatment benefits is the need of time.

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