Original Article

Maternal and Fetal Outcome in Pregnancy Complicated by Intrahepatic Cholestasis of Pregnancy

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Abstract

Objective: To assess the maternal and fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP).
Methodology: This retrospective observational study was conducted from January 2020 to February 2023 at Naimat Begum Hamdard General Hospital, Karachi, Pakistan. All cases diagnosed with ICP during the second or third trimester, as documented in hospital records and characterized by pruritus, were included, regardless of maternal age or gestational age at diagnosis. Maternal outcomes assessed included mode of delivery, postpartum hemorrhage, resolution of itching within two days postpartum, and liver function test results. Fetal outcomes recorded included preterm birth, low birth weight, meconium-stained amniotic fluid, APGAR scores at 1 and 5 minutes, NICU admission, stillbirth, and neonatal death.
Results: Of the 76 patients, the median age was 27.5 (23.0-33.7) years. Forty-eight (63.2%) women with ICP delivered via cesarean section, 14 (18.4%) experienced postpartum hemorrhage, and 40 (52.6%) had persistent itching after delivery. Among neonates, 54 (71.1%) were born preterm, 43 (56.6%) had low birth weight, 18 (23.7%) had meconium-stained amniotic fluid, 23 (30.3%) had an APGAR score <7 at 1 minute, 8 (10.5%) had an APGAR score <7 at 5 minutes, 6 (7.9%) were admitted to the NICU, 4 (5.3%) were stillborn, and neonatal death occurred in 5 (6.6%) cases.
Conclusion: The study concludes that women with ICP have a higher incidence of cesarean section deliveries, postpartum hemorrhage, preterm births, low birth weight, and neonatal complications.
Keywords: Intrahepatic cholestasis of pregnancy, maternal outcome, fetal outcome, neonatal complications

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Introduction

Intrahepatic cholestasis of pregnancy (ICP), also referred to as obstetric cholestasis, is the most prevalent liver disorder uniquely associated with pregnancy.[1] It is characterized by pruritus and elevated serum bile acids, typically manifesting in the second or third trimester. The condition is believed to arise due to a combination of genetic, hormonal, and environmental factors that disrupt bile flow from the liver, leading to the accumulation of bile acids in the bloodstream. ICP presents a significant concern for both maternal and fetal health, as it is associated with an increased risk of adverse outcomes such as preterm labor, fetal distress, and stillbirth.[1,3] The estimated incidence of ICP varies widely, ranging from 0.2% to 6% globally, reflecting geographical, genetic, and diagnostic differences across populations.[1-4] Characterized by severe itching typically in the late second or early third trimester, ICP arises from a disruption in bile flow within the liver.[3] While the exact cause remains under investigation, hormonal changes during pregnancy, coupled with genetic predisposition, are believed to be key contributors.[1,5]

Beyond the significant discomfort experienced by the mother, ICP carries potential risks for both mother and

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fetus.[5] Studies have shown an association between ICP and an increased risk of complications such as preterm birth, meconium-stained amniotic fluid, fetal distress, and even stillbirth.[6,7] Understanding the full spectrum of maternal and fetal outcomes in ICP pregnancies is crucial for optimizing clinical management and improving perinatal health.[8]

The rationale of this study is to address the significant gap in the existing literature regarding ICP within the Pakistani population. While global studies have extensively documented the association between ICP and adverse maternal and fetal outcomes[9,10], there is a paucity of data specific to Pakistan, where unique genetic, environmental, and socio-economic factors may influence the disease's presentation and outcomes. By analyzing data from a cohort of pregnant women diagnosed with ICP in Pakistan, this study aims to evaluate the factors associated with adverse outcomes and explore strategies to mitigate these risks. This research seeks to contribute valuable insights that can inform clinical practices and improve pregnancy outcomes for mothers and babies affected by ICP in Pakistan.

Methodology

This retrospective observational study was conducted between January 2020 and February 2023 in Naimat Begum Hamdard General Hospital, Karachi, Pakistan. Informed consent was obtained from all participants before inclusion in the study. The study protocol was approved by the institutional review boards of Hamdard Hospital Karachi (Ref #: HCM&D/810/2023).

Data collection was based on hospital records, and the study included all cases of intrahepatic cholestasis of pregnancy (ICP) characterized by the development of pruritus during the second or third trimester. Inclusion criteria were independent of age and gestational status. Exclusion criteria included patients with chronic liver conditions, such as viral hepatitis B and C, autoimmune liver diseases (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis), symptomatic gallbladder disease (e.g., gallstones, cholecystitis), genetic liver disorders (e.g., Wilson's disease, alpha-1-antitrypsin deficiency), infections (e.g., cytomegalovirus, Epstein-Barr virus), or hypertensive disorders of pregnancy.

The sample size was estimated using Epi Info, based on a 95% confidence interval, a 5% margin of error, and a 5.2% reported frequency of postpartum hemorrhage. The calculated sample size was 76.

ICP was defined by the presence of pruritus without rash, primarily affecting the palms and soles, during the second or third trimester. Diagnosis was supported by elevated serum bile acids (>10 µmol/L) and/or elevated serum transaminases.

The study collected data on maternal characteristics, including age, parity, gravida, gestational diabetes mellitus, previous deliveries, history of pre-eclampsia, HELLP syndrome, and prior ICP. Baseline biochemical parameters included total bilirubin, direct and indirect bilirubin, serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), hemoglobin, and international normalized ratio (INR).

Maternal outcomes recorded included mode of delivery, postpartum hemorrhage (defined as blood loss ≥500 ml after vaginal delivery or ≥1000 ml after cesarean section), resolution of itching within two days postpartum, and liver function tests at the time of delivery. Fetal outcomes included preterm birth (delivery before 37 weeks), low birth weight (≤2500 grams), meconium-stained amniotic fluid, APGAR scores at 1 and 5 minutes, NICU admission, stillbirth (fetal death after 20 weeks gestation), and neonatal death.

Data analysis was conducted using SPSS version 24. Median values and interquartile ranges were calculated for quantitative variables, such as age and liver function test parameters. Frequencies and percentages were calculated for qualitative variables. Inferential statistics, including Chi-Square/Fisher Exact tests and Wilcoxon Sign Rank tests, were applied, with a significance level of $p \leq 0.05$.

Results

Of 76 patients, the median age of the patients was 27.5 (23.0-33.7) years. There were 43 (56.6%) patients with ≤28 years and 33 (43.4%) with >28 years of age. Primigravida was observed in 29 (38.2%), multigravida in 23 (30.3%), and grand multigravida in 24 (31.6%) patients. The history of pre-eclampsia was observed in 13 (17.1%) patients, HELLP in 7 (9.2%), ICP in 10 (13.2%), and GDM in 15 (19.7%) patients.

Maternal outcome showed that 48 (63.2%) had cesarean section delivery, 14 (18.4%) had post-partum

hemorrhage, and 40 (52.6%) had itching after delivery. Whereas fetal outcome showed that there were 54 (71.1%) preterm, 43 (56.6%) with low birth weight, 18 (23.7%) with meconium-stained amniotic fluid, 23 (30.3%) with APGAR score <7 at 1 min, 8 (10.5%) with APGAR score <7 at 5 mins, 6 (7.9%) had NICU admission, 4 (5.3%) had still birth, and neonatal death was observed in 5 (6.6%) neonates.

The comparison of maternal outcome with general characteristics of the patients showed that a significant association of mode of delivery was observed with age (p-value 0.020) and gravida (0.031). Whereas a significant association of post-partum hemorrhage was observed with gravida (p-value 0.008) and gestational diabetes (p-value 0.001). (Table I)

Significant associations were observed between maternal conditions and adverse fetal outcomes. Neonatal death was particularly higher in mothers with a history of pre-eclampsia, HELLP syndrome, and intrahepatic cholestasis of pregnancy (ICP). Additionally, low birth weight, meconium-stained amniotic fluid, and low APGAR scores at 1 and 5 minutes were significantly linked to specific maternal histories. These associations underscore the heightened risks for fetal complications in pregnancies complicated by these maternal conditions. Further details, including statistical values and the strength of these associations, are summarized in Table II.

A significant median difference of total bilirubin level (p-value <0.001), SGPT (p-value <0.001), SGOT (p-value <0.001), ALP (p-value <0.001), and GGT (p-value <0.001) were observed. (Table III)

Discussion

Intrahepatic cholestasis of pregnancy (ICP) is a significant obstetric condition that poses increased risks for both the mother and fetus. Its association with adverse outcomes, such as preterm birth and stillbirth, highlights the need for careful monitoring and management. The findings from this study contribute to the growing body of evidence on the impact of ICP, particularly in relation to neonatal outcomes, and reinforce the importance of targeted interventions to mitigate these risks. Maternal outcomes revealed a high rate of cesarean section delivery, post-partum hemorrhage, and persistent itching after delivery.

Table I: Comparison of maternal outcome with general characteristics of the patients. (n=76)

	Mode of delivery		PPH		Itching after delivery	
	C-Section (n=48)	NVD (n=28)	Yes (n=14)	No (n=62)	Yes (n=18)	No (n=58)
Age, years						
≤28	32 (74.4)	11 (25.6)	10 (23.3)	33 (76.7)	22 (51.2)	21 (48.8)
>28	16 (48.5)	17 (51.5)	4 (12.1)	29 (87.9)	18 (54.5)	15 (45.5)
p-value	0.020		0.215		0.770	
Gravida						
Primigravida	21 (72.4)	8 (27.6)	6 (20.7)	23 (79.3)	16 (55.2)	13 (44.8)
Multigravida	17 (73.9)	6 (26.1)	8 (34.8)	15 (65.2)	11 (47.8)	12 (52.2)
Grand Multigravida	10 (41.7)	14 (58.3)	0 (0)	24 (100)	13 (54.2)	11 (45.8)
p-value	0.031		0.008		0.856	
Past History of Preeclampsia						
Yes	8 (61.5)	5 (38.5)	4 (30.8)	9 (69.2)	8 (61.5)	5 (38.5)
No	40 (63.5)	23 (36.5)	10 (15.9)	53 (84.1)	32 (50.8)	31 (49.2)
p-value	>0.999		0.243		0.480	
Past History of HELLP						
Yes	2 (28.6)	5 (71.4)	2 (28.6)	5 (71.4)	2 (28.6)	5 (71.4)
No	46 (66.7)	23 (33.3)	12 (17.4)	57 (82.6)	38 (55.1)	31 (44.9)
p-value	0.093		0.606		0.246	
Past History of ICP						
Yes	3 (30.0)	7 (70.0)	2 (20.0)	8 (80.0)	5 (50.0)	5 (50.0)
No	45 (68.2)	21 (31.8)	12 (18.2)	54 (81.8)	35 (53.0)	31 (47.0)
p-value	0.032		>0.999		>0.999	
GDM						
Yes	10 (66.7)	5 (33.3)	8 (53.3)	7 (46.7)	8 (53.3)	7 (46.7)
No	38 (62.3)	23 (37.7)	6 (9.8)	55 (90.2)	32 (52.5)	29 (47.5)
p-value	0.753		0.001		0.952	

GDM: Gestational diabetes mellitus, HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets, ICP: Intrahepatic Cholestasis of Pregnancy, NVD: Normal vaginal delivery, PPH: Post partum hemorrhage

Table II: Comparison of fetal outcome with general characteristics of the patients (n=76)

	Neonatal Death		LBW		MSAF		APGAR <7 at 1 min		APGAR <7 at 5 min		NICU admission		Still Birth	
	Yes (n=05)	No (n=71)	Yes (n=43)	No (n=33)	Yes (n=18)	No (n=58)	Yes (n=23)	No (n=53)	Yes (n=8)	No (n=68)	Yes (n=6)	No (n=70)	Yes (n=4)	No (n=72)
Maternal Age, years														
≤28	0 (0)	43 (100)	23 (53.5)	20 (46.5)	12 (27.9)	31 (72.1)	14 (32.6)	29 (67.4)	6 (14.0)	37 (86.0)	2 (4.7)	41 (95.3)	0 (0)	43 (100)
>28	5 (15.2)	28 (84.8)	20 (60.6)	13 (39.4)	6 (18.2)	27 (81.8)	9 (27.3)	24 (72.7)	2 (6.1)	31 (93.9)	4 (12.1)	29 (87.9)	4 (12.1)	29 (87.9)
p-value	*0.013*		*0.535*		*0.323*		*0.619*		*0.454*		*0.394*		*0.032*	
Gravida history of mother														
Primigravida	2 (6.9)	27 (93.1)	15 (51.7)	14 (48.3)	6 (20.7)	23 (79.3)	6 (20.7)	23 (79.3)	4 (13.8)	25 (86.2)	4 (13.8)	25 (86.2)	0 (0)	29 (100)
Multigravida	0 (0)	23 (100)	11 (47.8)	12 (52.2)	12 (52.2)	11 (47.8)	14 (60.9)	9 (39.1)	4 (17.4)	19 (82.6)	2 (8.7)	21 (91.3)	2 (8.7)	21 (91.3)
Grand Multigravida	3 (12.5)	21 (87.5)	17 (70.8)	7 (29.2)	0 (0)	24 (100)	3 (12.5)	21 (87.5)	0 (0)	24 (100)	0 (0)	24 (100)	2 (8.3)	22 (91.7)
p-value	*0.224*		*0.225*		*<0.001*		*0.001*		*0.116*		*0.177*		*0.271*	
Maternal Past History of Preeclampsia														
Yes	5 (38.5)	8 (61.5)	7 (53.8)	6 (46.2)	4 (30.8)	9 (69.2)	2 (15.4)	11 (84.6)	2 (15.4)	11 (84.6)	4 (30.8)	9 (69.2)	4 (30.8)	9 (69.2)
No	0 (0)	63 (100)	36 (57.1)	27 (42.9)	14 (22.2)	49 (77.8)	21 (33.3)	42 (66.7)	6 (9.5)	57 (90.5)	2 (3.2)	61 (96.8)	0 (0)	63 (100)
p-value	*<0.001*		*0.827*		*0.493*		*0.322*		*0.619*		*0.007*		*<0.001*	
Maternal Past History of HELLP														
Yes	3 (42.9)	4 (57.1)	7 (100)	0 (0)	2 (28.6)	5 (71.4)	0 (0)	7 (100)	0 (0)	7 (100)	2 (28.6)	5 (71.4)	4 (57.1)	3 (42.9)
No	2 (2.9)	67 (97.1)	36 (52.2)	33 (47.8)	16 (23.2)	53 (76.8)	23 (33.3)	46 (66.7)	8 (11.6)	61 (88.4)	4 (5.8)	65 (94.2)	0 (0)	69 (100)
p-value	*<0.001*		*0.017*		*0.667*		*0.094*		*>0.999*		*0.092*		*<0.001*	
Maternal Past History of ICP														
Yes	3 (30.0)	7 (70.0)	9 (90.0)	1 (10.0)	2 (20.0)	8 (80.0)	1 (10.0)	9 (90.0)	0 (0)	10 (100)	2 (20.0)	8 (80.0)	4 (40.0)	6 (60.0)
No	2 (3.0)	64 (97.0)	34 (51.5)	32 (48.5)	16 (24.2)	50 (75.8)	22 (33.3)	44 (66.7)	8 (12.1)	58 (87.9)	4 (6.1)	62 (93.9)	0 (0)	66 (100)
p-value	*0.001*		*0.036*		*>0.999*		*0.266*		*0.587*		*0.176*		*<0.001*	
GDM in mother														
Yes	0 (0)	15 (100)	5 (33.3)	10 (66.7)	8 (53.3)	7 (46.7)	11 (73.3)	4 (26.7)	5 (33.3)	10 (66.7)	2 (13.3)	13 (86.7)	0 (0)	15 (100)
No	5 (8.2)	56 (91.8)	38 (62.3)	23 (37.7)	10 (16.4)	51 (83.6)	12 (19.7)	49 (80.3)	3 (4.9)	58 (95.1)	4 (6.6)	57 (93.4)	4 (6.6)	57 (93.4)
p-value	*0.576*		*0.043*		*0.005*		*<0.001*		*0.006*		*0.338*		*0.579*	

None of the variable was found significant preterm

APGAR: Appearance, Pulse, Grimace, Activity, and Respiration, LBW: Low Birth Weight, GDM: Gestational diabetes mellitus, HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets, ICP: Intrahepatic Cholestasis of Pregnancy, MSAF: Meconium-stained amniotic fluid

Table III: Median difference of laboratory parameters at baseline and post-delivery. (n=76)

	At Baseline	Post Delivery	
	median (IQR)	median (IQR)	p-value
Total Bilirubin	0.50 (0.27-0.83)	0.30 (0.30-0.47)	<0.001
Direct Bilirubin	0.19 (0.10-0.40)	0.20 (0.10-0.20)	0.055
SGPT	150 (98-249)	34 (28-84)	<0.001
SGOT	44 (40-73)	23 (15-36)	<0.001
ALP	220 (190-287)	68 (47-137)	<0.001
GGT	24 (20-52)	24 (18-30)	<0.001

IQR: Interquartile range

These findings are consistent with previous research indicating that ICP is associated with an increased risk of adverse maternal outcomes.[11-13] The high rate of cesarean section delivery in women with ICP may be attributed to obstetric complications such as fetal distress, meconium-stained amniotic fluid, and preterm birth, all of which are common in ICP.[11] Post-partum hemorrhage is also a known complication of ICP, possibly due to impaired liver function and coagulation abnormalities associated with the condition.[14]

The association between maternal age, gravida, and mode of delivery in the current study highlights the importance of obstetric management in women with ICP. According to the current study findings, older maternal age and higher gravidity were associated with an increased risk of cesarean section delivery, possibly due to increased obstetric complications in these populations. Similarly, the association between gravida and post-partum hemorrhage suggests that women with a higher number of pregnancies may be at increased risk of this complication. Somewhat similar findings were observed in previous studies as well.[11,12] Aftab et al reported that ICP has significant association with past obstetric cholestasis history, gestational diabetes, pre-eclampsia, and undergoing induction of labor.[11] Similarly, Wikström Shemer et al in their study reported that women with ICP are more at-risk for gestational diabetes and pre-eclampsia.[12] These findings emphasize the need for tailored obstetric care and vigilant monitoring in women with ICP, particularly those with advanced maternal age and higher gravidity, to mitigate the risk of cesarean delivery and other complications.

Fetal outcomes in this study revealed a high rate of preterm birth, low birth weight, meconium-stained amniotic fluid, and neonatal complications such as low APGAR scores, NICU admission, stillbirth, and neonatal death. These findings are consistent with previous studies highlighting the increased risk of adverse fetal outcomes in pregnancies complicated by ICP.[12-16] In a large epidemiological study, preterm delivery and low APGAR score (<7) at 5 minutes were found most common in women with ICP however, still birth was not found statistically significant.[12] Zecca et al in their study reported higher risk of respiratory distress syndrome in ICP newborns.[15]

The association between maternal history of pre-eclampsia, HELLP syndrome, and ICP with adverse fetal outcomes in the current study underscores the need for close monitoring and management of these high-risk pregnancies. Gestational diabetes also emerged as a significant risk factor for adverse fetal outcomes in women with ICP, highlighting the importance of glucose control in these patients.

Studies published from Pakistani population also showed similar findings. Shafqat et al reported that fetal distress, intrauterine growth restriction, meconium-stained liquor, intrauterine fetal demise, low birth weight babies, poor APGAR score and NICU admission were common perinatal outcome in women with ICP.[17] A considerably higher proportion of meconium-stained amniotic fluid and preterm deliveries were also found in a study conducted by Fahim et al.[18] Similar to the previous literature and the current study findings, Hafeez et al reported cesarean delivery, post-partum hemorrhage, and NICU admission as major outcome of ICP.[19] While Yazdani et al in their study recommended delivery between 37-38 weeks in ICP women for better fetal outcome.[20]

This retrospective study conducted in a private hospital in Karachi provides valuable insights into the maternal and fetal outcomes associated with ICP. However, several limitations should be considered when interpreting the findings. The retrospective design of the study limits its ability to establish causality between ICP and maternal and fetal outcomes. Additionally, being a single-center study, the findings may not be generalizable to the broader population. Furthermore, the study may not have included all relevant variables that could affect maternal and fetal outcomes in ICP. Future research should consider prospective, multi-center studies with more comprehensive data collection methods to further investigate the association between ICP and adverse outcomes, while also exploring potential risk factors and mechanisms underlying these outcomes.

Conclusion

The study highlights a high rate of cesarean section delivery, post-partum hemorrhage, preterm birth, low birth weight, and neonatal complications in women with ICP. This study provides valuable insights into the maternal and fetal outcomes associated with ICP, highlighting the need for close monitoring and management of these high-risk pregnancies. Further research is needed to elucidate the underlying mechanisms linking ICP to adverse outcomes and to develop optimal management strategies for these patients.

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