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ORIGINAL ARTICLE

Adverse Maternal and Fetal Outcomes in Intrahepatic Cholestasis of Pregnancy (ICP) among Women

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ABSTRACT

OBJECTIVE: To find out the adverse maternal and fetal outcomes in intrahepatic cholestasis of pregnancy (ICP)

METHODOLOGY: This study was conducted at PNS Shifa Hospital from October 2023 to March 2024. A cross-sectional study design was used, and the methodology was followed for this study. Ninety pregnant women with ICP were included. A predesigned proforma was used to document demographic, clinical, and laboratory information. The level of bile acids in serum was determined to confirm the diagnosis of ICP and severity (mild 19 – 39 µmol/L, moderate 40 – 99 µmol/L, and severe ≥100 µmol/L). We selected women in late pregnancy (Gestational Age≥28 weeks). Patients with fetal anomalies, dermatological cause of itching, chronic liver disease, viral hepatitis, HELLP syndrome, gallstone disease, biliary obstruction, acute fatty liver of pregnancy, coagulopathy and thrombocytopenia were excluded. We used We used SPSS o aanalyse

RESULTS: The average Age of patients was 26.31±4.80 years. Premature delivery (45.6%), emergency cesarean section (37.8%), elective cesarean section (31.4%), induction of labor (14.4%), PROM (8.9%) and placental complications (7.8%) were the most frequently reported adverse outcomes of the mother. Non-preferred outcomes in the fetus included low Apgar score (44.3%), admission to the NICU (44.3%), meconium-stained liquor (41.4%), low birth weight (34.1%), hyperbilirubinemia (4.5%) and two cases of intrauterine death (IUD).

CONCLUSION: ICP is correlated with severe maternal and fetal complications, especially during the late gestation period.

KEY WORDS: Intrahepatic cholestasis of pregnancy, obstetric cholestasis, maternal outcomes, fetal outcomes, bile acids, pregnancy complications.

INTRODUCTION

ICP, often referred to as obstetric cholestasis (OC), is the most common type of pregnancy-related liver disease. ICP usually occurs during the third trimester[1]. In this study, late pregnancy was defined as gestational Age ≥28 weeks. Although relatively uncommon, the possibility of a stillborn child causes anxiety and despair in the mother. ICP is defined as pruritus in the absence of skin rash and abnormal liver function tests (notably, changes in hepatic enzymes) in the absence of other causes and remission following/post-delivery[2]. We categorized disease severity by serum bile acid levels as mild (19-39 µmol/L), moderate (40-99 µmol/L), and severe (≥100 µmol/L). Obstetric cholestasis has been seen to be associated with poor pregnancy outcomes and fetal problems.

Previous investigation found an increase in spontaneous or iatrogenic premature birth, intrapartum fetal distress, meconium-stained liquor, abrupt intrauterine fetal death, caesarean section rates, neonatal intensive care unit admission, meconium aspiration, respiratory distress syndrome and postpartum hemorrhage[3]. The incidence of ICP varies from 0.1 to 15.6% and depends on geography, ethnicity, and environmental conditions. ICP risk factors include a history of the condition, either personal or familial, multiple pregnancies, cholelithiasis, in vitro fertilization, and infection with the hepatitis C virus[4]. The specific etiology of intrahepatic cholestasis of pregnancy (ICP) is unknown; however, environmental, genetic and hormonal variables are thought to be involved. The range of prevalence throughout the world shows that the illness is affected by the environment[5].

There is no specific prenatal monitoring of the fetus that can foretell sudden intrauterine fetal deaths. As a result, cessation of pregnancy is indicated around 36-37 weeks of gestation to reduce perinatal death with expectant treatment beyond this gestation[6]. ICP is more prevalent in twins and multiple babies, and it tends to occur in winter. Genesis and treatment of ICP are the subject of this review. In the United States (US), the frequency is between 0.3 and 5.6%; in Europe, it's between 0.5 and 1.5%, with the highest rates in Chile. Awareness initiatives about this disease have increased incidence in high-incidence areas due to increased case reporting[7]. Women with ICP were shown to have increased rates of moderate preterm birth and induced labour but favourable maternal and neonatal outcome[8]. Observational studies have identified an association between ICP and unfavorable pregnancy outcomes[9].

There is limited local data regarding maternal and fetal outcomes in intrahepatic cholestasis of pregnancy in the Pakistani population. This study aimed to address this gap and provide evidence to improve clinical management and risk stratification.

Intrahepatic Cholestasis of Pregnancy (ICP) presents serious morbidity and mortality concerns to both mothers and fetuses, especially after 36 weeks of gestation. This is the main reason for this study. The authors note a significant gap in the medical literature despite its clinical significance, noting that few local investigations have addressed these obstetric problems. To help general practitioners and obstetricians identify high-risk situations, this study was conducted to evaluate poor maternal and fetal outcomes in a tertiary care hospital. The project aims to identify these clinical patterns to improve perinatal care and ultimately reduce strain on Neonatal Intensive Care Units (NICUs).

METHODOLOGY

This cross-sectional study was conducted in the Department of Gastroenterology, P.N.S Shifa Hospital, Karachi, from October 2023 to March 2024. Assuming a prevalence of intrauterine fetal death in patients with intrahepatic cholestasis of 6.25%, once again, margin of error = 5% and confidence interval = 95%, we needed at least a sample size of 90.

Pregnancy clarification: we recruited only women in late pregnancy. The third trimester of pregnancy was considered late pregnancy (GA ≥28 weeks, confirmed by obstetric ultrasound).

Inclusion criteria included pregnant women aged 18-45 years, ≥28 weeks of gestation, any parity, booked status, raised bile acids and/or abnormal liver function tests suggestive of ICP, and willingness to provide written informed consent.

Exclusion criteria included women who had any chronic liver disease, hepatitis B or C, congenital liver disease, primary biliary cholangitis, primary sclerosing cholangitis, had any symptomatic gallstones, had biliary obstruction, cholecystitis, acute fatty liver of pregnancy, HELLP syndrome, had a congenital fetal abnormality, and had a chronic abnormality of the chorea.

This study was carried out after approval from the institutional ethical review committee (ERC/2023/GAS/66). Non-probability consecutive sampling was used. Eligible pregnant women were referred from the Department of Obstetrics and Gynecology to the Department of Gastroenterology and enrolled after written informed consent.

A general physical examination was performed. A predesigned proforma was used to document demographic, clinical, and laboratory parameters. The study included maternal Age, gestational Age at diagnosis, gestational Age at delivery, height, weight, body mass index (BMI), parity, mode of delivery, and history of ICP, history of diabetes mellitus, and history of hypertension.

Obstetric ultrasound was performed to confirm gestational Age, assess fetal well-being, and exclude fetal anomalies. Hepatobiliary ultrasound was performed to evaluate the liver and biliary tract, exclude gallstones or biliary obstruction, and assess for fatty liver/MASLD.

Investigations consisted of complete blood count, urine examination, liver function tests including elevated lactate dehydrogenase, direct and indirect bilirubin, elevated serum aspartate aminotransferase (AST), elevated serum alanine aminotransferase (ALT), elevated alkaline phosphatase (ALP), elevated serum bile acids, and urine routine microscopy.

We used serum bile acid levels to classify disease severity as mild (19-39 µmol/L), moderate (40-99 µmol/L), and severe (≥100 µmol/L). We added this classification for risk stratification and interpretation of maternal and fetal outcomes.

Because the mean BMI was 27.01 kg/m², indicating increased metabolic risk in an Asian population, we evaluated fatty liver/MASLD by hepatobiliary ultrasound. We documented it as a relevant comorbidity or confounder.

Maternal outcomes included preterm delivery, PROM, elective caesarean section, emergency caesarean section, PPH, and induction of labor. Fetal outcomes included low Apgar score, low birth weight, meconium-stained liquor, intrauterine death (IUD), NICU admission, and hyperbilirubinemia. We followed all women at 42 days postpartum to confirm resolution of symptoms and laboratory abnormalities.

RESULTS

The table shows descriptive statistics for the study population. (**Table I**).

Table I: Demographic and Clinical Characteristics of the Study Population (N=90)

Variables	Mean	SD*	Median	IQR
Age (Years)	26.31	4.80	25.5	7
Gestational Age at diagnosis (Weeks)	31.51	2.640	30	4
Gestational Age at delivery (Weeks)	36.43	2.427	37	2
Weight (kg)	63.14	7.118	62	8
Height (cm)	152.92	5.739	154	8
BMI (kg/m^2)	27.01	2.98	26.66	3.74
Parity	1.72	0.81	2	1

**SD standard deviation. § IQR Interquartile range*

The mean BMI of 27.01 kg/m² suggests a high risk of metabolic complications in this population, among whom hepatobiliary ultrasound-derived fatty liver/MASLD assessment was incorporated, and this should be considered when interpreting outcomes.
Table II summarizes the distribution of maternal and fetal outcomes in the study cohort.

Table II: History of Comorbidities and Adverse Outcomes in Women with ICP (N=90)

Variables	Frequency (n)	Percentage (%)
History of Intrahepatic Cholestasis		
Yes	27	30.0%
No	63	70.0%
History of Diabetes Mellitus		
Yes	15	16.7%
No	75	83.3%
History of Hypertension		
Yes	63	70.0%
No	27	30.0%
Maternal Outcomes		

Preterm Delivery	41	45.6%
Premature Rupture of Membranes (PROM)	8	8.9%
Emergency C-section	34	37.8%
Elective C-section	31	34.4%
Induction of Labor	13	14.4%
Postpartum Hemorrhage (PPH)	7	7.8%
Fetal Outcomes		
Low Apgar Score	39	44.3%
NICU Admission	39	44.3%
Meconium-stained Liquor	36	40%
Low Birth Weight	30	34.1%
Hyperbilirubinemia	4	4.4%
Intrauterine Death	2	2.2%

Of these, there were 63 patients (70.0%) with hypertension. This high frequency likely reflects recruitment of more severe cases at tertiary care centres specializing in high-risk obstetrics. The high-risk profile for hypertension is an important comorbidity and possible confounder; thus, adverse maternal and fetal outcomes should be interpreted in its context.

of examined maternal and fetal outcomes by maternal and fetal demographic and clinical characteristics. Mode of delivery significantly affected several outcomes: elective and emergency cesarean sections were more frequent among women delivering by cesarean ($p < 0.001$), and induction of labour was more frequent among women delivering by cesarean ($p = 0.016$). Primiparous women had a much higher rate of elective cesarean sections than did multiparous women ($p = 0.006$). Gestational Age at diagnosis showed no significant association with maternal and fetal outcomes, as no significant differences were found between groups. The results of these studies propose that cesarean delivery and parity had a significant impact on some of the results, whereas the results of other demographic factors such as residential status, maternal Age, and BMI did not have a significant impact (**Table III**)

Table III: Comparison of Adverse Outcomes by Parity and Mode of Delivery

Outcomes	Primiparous (n=43)	Multiparous (n=47)	P-Value	SVD (n=25)	CS (n=65)	P-Value
Preterm	20 (46.5%)	21 (44.7%)	0.862	9 (36.0%)	32 (49.2%)	0.259
PROM	5 (11.6%)	3 (6.4%)	0.382	0 (0.0%)	8 (12.3%)	0.10
Elective CS	21 (48.8%)	10 (21.3%)	0.006	0 (0.0%)	31 (47.7%)	0.0001
Emergency CS	15 (34.9%)	19 (40.4%)	0.588	0 (0.0%)	34 (52.3%)	0.0001
Low Apgar	17 (39.5%)	22 (46.8%)	0.488	10 (40.0%)	29 (46.0%)	0.642
NICU Admission	20 (46.5%)	19 (40.4%)	0.551	8 (32.0%)	31 (49.2%)	0.161

SVD: Spontaneous Vaginal Delivery; CS: Cesarean Section; P-values < 0.05 are considered statistically significant

DISCUSSION

Participants in this study had an average age of 26.31±4.80 years, indicating they were mostly young to middle-aged women. The fact that urban inhabitants (87%) outnumber rural people (13%) indicates that the study was conducted in an urban setting, which may reflect population distribution or the location of the healthcare institution. The majority of instances involved operative delivery (72.22%), which included cesarean sections, proving that a high number of newborns need medical intervention. Only 27.78% of the births were normal vaginal deliveries.
Preterm delivery (45.6%) emerges as the most common unfavorable outcome, which is worthy of attention because it could be directly related to the health and development of an infant. The rates of emergency C-sections (37.8%), elective C-sections (31.4%), induction of labor (14.4%) and premature rupture of membranes (PROM) (8.9%) indicate the vast spectrum of obstetric procedures and problems that existed across the research. In the research by ul Hassan G 2022[10], 35% and 33.33%, respectively, of women had dyslipidemia and disordered coagulation profile. A history of PROM was found in 73% of the investigated women. Other maternal outcomes, including PPH and surgical delivery, were reported in 10% and 75.5% of participants, respectively.
Ghimire SP 2016[11], conducted study in Nepal, during the study period, reported the frequency of adverse feto-maternal outcomes like, preterm birth (18.7%), Premature rupture of membrane PROM (10%), elective C-section (10%), emergency C-section (36.25%), postpartum hemorrhage (11.25%), Apgar score<7 at 5 minutes (13.75%), low birth weight (22.5%), meconium stained liquor (32.5%) and intrauterine fetal death (6.25%).
Another study revealed a 10% prevalence of ICP and maternal and fetal outcomes such as initiation of labor (45.3%), preterm delivery (36%), postpartum hemorrhage (14.7%), intrauterine fetal death (7.1%), low birth weight (27.1%), NICU admission (11.8%) and hyperbilirubinemia (30.6%)[6]. ICP is also related to fetal outcomes. Many unfavorable situations threaten the survival of the fetus in pregnancies with the risk of ICP. The large numbers of low Apgar scores (44.3%) and hospitalization in the neonatal unit (44.3%) in this study highlight that neonates in this group of patients are vulnerable, and this is thought to be related to premature birth or other problems. The occurrence of meconium-stained fluid (41.4%) and low birth weight (34.1%) indicates the problems of the utmost importance of ensuring optimum fetal health and development.
Williamson C 2014[12] found that fetal discomfort was the highest complaint linked to ICP. Tolunay HE et al.[13] published extensive data on the risk of MSL in mothers with ICP. Preterm births are a result of transfer of bile acids through placental transport receptors. Similarly, ICP during pregnancy could be the cause of LBW as well. Zhang Q 2022[14] found that Ursodeoxycholic acid had a good impact on the management of ICP during pregnancy and unfriendly fetal outcomes.
The stimulation of intestinal motility by bile acids in obstetric cholestasis is believed to contribute to the intrapartum fetal discomfort as well as the increased incidence of meconium-stained liquor[17]. In another study, we found a greater incidence of meconium-stained liquid (41.4%)[15]. However, another study found no pronounced incidence of meconium-stained liquid, which is associated with good prenatal visits and early management of Obstetric Cholestasis[13]. In our study, hyperbilirubinemia (4.5%) and intrauterine mortality (2 times) were found as other health issues in fetuses that mandate the attention of clinical practitioners and care. A recent

study by Sultana R 2009[17] found 6.67% of intrauterine fetal death. However, this is higher than a study in which the incidence of IUFD was only 3.1% [19].

Another study reported comparable results, with an incidence of meconium-stained liquid between 25% and 45%, preterm labor at 44%, and IUFD up to 5% [16]. There is some association between OCD and premature birth (spontaneous and induced), and also an increased risk of IUFD. The perinatal death rate secondary to obstetric cholestasis is 10.6/1000 live births[17]. Intrauterine fetal mortality is often very sudden and is apparently due to acute anoxia.

This cohort has significantly more hypertension (which can be discussed separately because it may have independent adverse effects on delivery, specifically as follows: preterm delivery, caesarean section, fetal distress, low Apgar score and admission to the NICU unit). Thus, adverse effects seen could be due to ICP alone. This discovery reinforces the necessity to request multidisciplinary evaluation (obstetric, hepatology and medical assessment) in pregnant women with ICP, particularly those with complicated pregnancies who are most likely to be referred to tertiary care centers.

CONCLUSION

In our study, pregnancy-related intrahepatic cholestasis seems to be rather prevalent. It was found to be responsible for a large percentage of perinatal and neonatal mortality, especially after 36 weeks of gestation. A comprehensive prospective investigation is needed to find out the clinical epidemiological pattern of this obstetric condition. In the meantime, it is of great importance to create awareness among the health staff involved in the care of pregnant women that pregnancy pruritus is a high-risk disease, one that demands vigilance of the fetus and rapid management to mitigate perinatal death significantly.

Limitations of Study and Recommendations:
This study has several limitations that should be recognized. The cross-sectional design precludes the determination of a causal relationship between intrahepatic cholestasis of pregnancy and the adverse outcomes observed. Second, the study was conducted at only one tertiary care centre in an urban environment, so it may not represent the entire population or healthcare settings in rural areas. The use of non-probability consecutive sampling also makes selection bias possible. Additionally, the study did not include a control group of healthy pregnant women for direct comparison. Although the main measures were statistically calculated, a sample size of 90 may not allow evaluation of rarer complications or subtle differences in certain subgroups. Future prospective, multicenter studies with larger cohorts and control groups are needed to define the clinical epidemiological patterns of this condition comprehensively.

Ethical permission: P.N.S Shifa Hospital, Karachi, Pakistan, IRB approval letter No. ERC/2023/GAS/66.
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AUTHOR CONTRIBUTION

Kumari P: Conceptualization, writing 1st draft, data Collection, data Interpretation and Analysis, Critical Revision and Approval of the final manuscript
Siddiqui H: Data analysis, Manuscript Revision and Formatting
Hafeez M: Conceptualization, Critical Revision and Approval of Final Manuscript
Abbasi A: Critical Revision and Approval of Final Manuscript
Afzal U: Critical Revision and Approval of Final Manuscript
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