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The frequency of intrahepatic cholestasis of pregnancy among Pakistani women and its association with adverse maternal and neonatal outcomes; A cross sectional study at Agha khan university hospital

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ABSTRACT

OBJECTIVE

To determine the frequency of intrahepatic cholestasis of pregnancy among Pakistani women and to evaluate its maternal and neonatal outcomes in a tertiary care setting in Karachi.

METHODOLOGY

This cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Aga Khan University Hospital, Karachi, and included 186 pregnant women diagnosed with intrahepatic cholestasis of pregnancy. Data on maternal and neonatal outcomes such as preterm birth, meconium-stained liquor, and NICU admission were collected using a structured proforma. Statistical analysis was performed using SPSS version 26.0, applying Chi-square with $p \leq 0.05$ considered significant**.**

RESULTS

Among 186 Pakistani women with intrahepatic cholestasis of pregnancy, the mean age was 30.1±4.6 years, and 60.2% were multigravida. Elevated ALT (>35 IU/L) was found in 93.5% and raised bile acids in 87.1% of patients. Caesarean delivery occurred in 47.3%, GDM in 50.5%, and PPH in 16.7%. Foetal outcomes included preterm birth (29.6%), low birth weight (18.3%), and NICU admission (14.5%).

CONCLUSION

Intrahepatic cholestasis of pregnancy was found to be associated with significant maternal and neonatal complications. The most frequent maternal outcomes included gestational diabetes, caesarean delivery, and postpartum haemorrhage, while preterm birth, low birth weight, and NICU admission were the predominant neonatal outcomes. Early diagnosis, close biochemical monitoring, and timely obstetric intervention are essential to improve perinatal outcomes and reduce complications among affected Pakistani women.

KEYWORDS

Intrahepatic Cholestasis of Pregnancy, Maternal Outcomes, Neonatal Outcomes, Pregnancy Complications, Liver

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) constitutes a hepatobiliary disorder that manifests during gestation and is absent during the non-gestational phase, generally occurring in the latter stages of the second or third trimester. It manifests itself with severe itching (especially of the palms and soles), high bile acid and liver enzyme levels in the blood [1,2]. Despite the fact that the symptoms tend to disappear after the birth of the child, ICP has severe dangers on the unborn baby, and it may cause a lot of pain to the mother [3]. The prevalence of intrahepatic cholestasis of pregnancy (ICP) exhibits significant variability across geographical regions and diverse ethnic populations. On the international level, it is known to impact between 0.2% to 2% of all pregnancies, with greater prevalence being reported in women of the South Asian and South American descent [4,5]. Since the prevalence of ICP is relatively high in the Pakistani population, some hospital-based studies have been conducted to show a range of 2-3 percent [6,7].

The exact cause of ICP is not fully understood, but it appears to be the result of multiple interacting factors. Hormonal changes during pregnancy, especially increased levels of estrogen and progesterone, can interfere with bile acid transport. Genetic factors also play a role, as mutations in certain transporter genes such as ABCB4 (MDR3), ABCB11, and ATP8B1 have been linked to a higher risk of developing the condition [8,9]. Environmental influences and dietary deficiencies may further contribute to its occurrence in genetically predisposed women [10].

Clinically, ICP occurs with irritating itching with the potential of a major impact on sleep and quality of life. Mild jaundice may also develop in some women. Maternal outcome is generally favourable; however, ICP also involves various complications of the infant; preterm delivery, meconium-contaminated amniotic fluid, low Apgar readings and still birth [13]. There is a high risk of negative outcomes particularly stillbirth in case the level of maternal serum bile acid exceeds 100 µmol/L [14].

Despite ongoing research, information about the burden and outcomes of ICP in Pakistan remains limited. Most local studies have been small and have not fully explored both maternal and neonatal outcomes [6,7,15]. Generating local evidence is important for improving clinical awareness, guiding management, and reducing preventable perinatal complications.

Consequently, this investigation seeks to figure out the prevalence of intrahepatic cholestasis of pregnancy and to evaluate its concomitant neonatal outcomes within a tertiary healthcare environment. The results are anticipated to assist medical practitioners in the early identification of patients at risk and to formulate more efficacious strategies aimed at enhancing pregnancy outcomes for women impacted by this condition.

METHODOLOGY

This cross-sectional study was conducted in the Obstetrics and Gynaecology Department of the Aga Khan University Hospital (AKUH), Karachi, over a minimum duration of six months following institutional ethical approval (ERC #_____). Eligible participants were pregnant women aged 18–40 years with singleton gestations of ≥20 weeks. **Cases of intrahepatic cholestasis of pregnancy (ICP) were**

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diagnosed based on pruritus without rash and elevated serum bile acids (>10 µmol/L) in accordance with established clinical guidelines. A non-probability consecutive sampling technique was used to recruit 186 participants who met the eligibility criteria.

Exclusion criteria included multiple gestation; chronic hepatic diseases (hepatitis B/C, biliary cirrhosis, primary sclerosing cholangitis); symptomatic gallstone disease or cholecystitis; autoimmune hepatitis; acute hepatic infections; preeclampsia or eclampsia; shock or **ischemic hepatitis**; congestive hepatopathy; haemolytic anaemia; use of hepatotoxic or cholestasis-inducing medications (e.g., statins, acetaminophen, valproate, phenytoin, amiodarone); and malignancy.

Written informed consent was obtained from all participants, after which data were collected using a predesigned proforma. Variables included demographic characteristics, gestational age, clinical presentation (pruritus/jaundice), laboratory parameters (ALT, AST, total/direct bilirubin, total bile acids), and predefined maternal and neonatal outcomes. Maternal outcomes included postpartum haemorrhage (PPH) and mode of labour/delivery, while neonatal outcomes included preterm birth, stillbirth, meconium-stained liquor/aspiration, intrapartum fetal distress, Apgar score <7 at 5 minutes, neonatal respiratory distress syndrome (RDS), and neonatal intensive care unit (NICU) admission within 48 hours; each was recorded as present or absent. Potential confounders (maternal age, gestational age, BMI, and comorbid diabetes/hypertension) were also documented.

Data were analysed using SPSS version 26.0. Descriptive statistics summarized all variables, while associations between ICP and maternal/neonatal outcomes were evaluated using chi-square tests and logistic regression analyses, with $p < 0.05$ considered statistically significant.

RESULTS

Table 1 shows the demographic and baseline clinical characteristics of pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP). The mean age of the patients was **30.11±4.63 years**, ranging from 19 to 42 years, with the majority (44.09%) aged above 30 years. The mean gestational age at admission was **31.03±6.33 weeks**, and the mean gestational age at delivery was **36.74±1.64 weeks**. The mean height and weight of the participants were **157.72±5.06 cm** and **70.19±10.39 kg**, respectively, resulting in a mean BMI of **27.09±4.53 kg/m²**. Based on BMI classification, **45.70%** of women were overweight and **28.49%** were obese. Most patients were **multigravida (60.2%)**, while **18.82%** had a previous history of ICP.

Table 2 presents the laboratory findings of women with ICP. Elevated liver enzymes were commonly observed, with **93.55%** of patients having serum ALT levels above 35 IU/L (median 99 IU/L) and **91%** showing AST levels above 31 IU/L (median 77 IU/L). Total bilirubin levels were elevated in **2.7%** of the patients, while direct bilirubin was elevated in **49.5%**. Regarding total bile acids, **62.4%** of patients showed mild elevation, **8.1%** moderate, and **0.5%** severe elevation, whereas only **12.9%** remained within the normal range. These findings reflect the characteristic biochemical profile of cholestasis with predominant hepatic enzyme elevation and bile acid derangement.

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Table 3 shows the distribution of maternal outcomes among women with ICP. Caesarean section was performed in **47.31%** of cases, of which **31.72%** were emergency procedures and **15.59%** were elective. Spontaneous vaginal delivery occurred in **50%** of cases, while **2.69%** required instrumental assistance. Labor induction was common, accounting for **67.34%** of cases, compared to **32.65%** spontaneous onset. Among maternal complications, **gestational diabetes mellitus (50.54%)** was the most frequent, followed by **postpartum haemorrhage (16.67%)**, **pregnancy-induced hypertension (6.98%)**, and **anaemia (3.76%)**.

Table 4 demonstrates the foetal outcomes associated with obstetric cholestasis. **Preterm birth (<37 weeks)** occurred in **29.56%** of cases, while **18.3%** of neonates were of **low birth weight (<2.5 kg)**. **Small for gestational age (SGA)** and **intrapartum foetal distress (IFD)** were observed in **10.75%** of cases each. **NICU admissions** were required in **14.52%** of neonates, and **neonatal respiratory distress syndrome (RDS)** occurred in **9.14%**. A small proportion of neonates had **Apgar scores <7** at 1 minute (2.68%) and 5 minutes (1.61%), indicating mild perinatal compromise in some cases.

DISCUSSION

The present study evaluated the maternal and neonatal outcomes in women diagnosed with intrahepatic cholestasis of pregnancy (ICP) at a tertiary care hospital in Karachi. The results demonstrate that ICP is associated with substantial maternal morbidity and adverse perinatal outcomes, findings that are consistent with both local and international literature.

The mean maternal age in this study was 30.1±4.6 years, with most women being multigravida (60.2%). This finding concurs with the results of Shafqat et al. [1] and Smith and Rood [2], who observed that ICP commonly affects women in their late twenties to early thirties and tends to recur in subsequent pregnancies. The predominance of multigravidity may be attributed to cumulative hormonal exposure and hepatic sensitivity to oestrogen and progesterone during successive pregnancies [3].

The mean gestational age at admission and delivery in this study, 31 and 36.7 weeks respectively, closely aligns with previously reported ranges [1,4,6]. Ovadia et al. [4] demonstrated that ICP typically presents during the late second or third trimester when oestrogen levels peak, which is consistent with our findings. Similarly, Hafeez et al. [6] in Punjab reported that most cases of ICP are diagnosed between 30 and 36 weeks of gestation, emphasizing the hormonal basis of the disease.

Biochemical abnormalities were common in this cohort, with elevated ALT in 93.5 percent and raised bile acids in 87.1 percent of patients. These results are consistent with the hepatic dysfunction pattern described by Geenes and Williamson [3] and Reyes and Sjövall [5], who noted that increased bile acids and transaminases are hallmark features of ICP. Glantz et al. [12] and Brouwers et al. [14] also reported that elevated bile acid concentrations are directly related to adverse perinatal outcomes, including preterm birth and stillbirth. Our findings reinforce this biochemical association and suggest that even moderate elevations in bile acids warrant close foetal surveillance.

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Among maternal outcomes, caesarean section was the predominant mode of delivery (47.3 percent). This observation is in agreement with Akram et al. [7] and Kenyon et al. [11], who reported caesarean rates exceeding 45 percent among women with ICP. The higher caesarean rate in these studies, as in ours, likely reflects proactive obstetric management and a lower threshold for operative delivery in cases of foetal compromise. Gestational diabetes mellitus was observed in 50.5 percent of participants, which is similar to the findings of Hafeez et al. [6], indicating a possible metabolic link between ICP and insulin resistance related to hormonal and genetic factors [8,9].

Postpartum haemorrhage occurred in 16.7 percent of the participants, which aligns with previous studies showing frequencies between 14 and 20 percent [7,11]. This complication may be attributed to impaired vitamin K absorption and resulting coagulation disturbances in cholestatic pregnancies [10]. Although the overall maternal prognosis in ICP is generally favourable, these findings highlight the importance of vigilant antenatal monitoring, correction of coagulation abnormalities, and timely delivery to prevent complications.

Foetal outcomes in this study, including preterm birth (29.6 percent), low birth weight (18.3 percent), and NICU admission (14.5 percent), are similar to the findings of Rook et al. [13] and Brouwers et al. [14]. Ovadia et al. [4] demonstrated in their large meta-analysis that increasing maternal bile acid levels directly correlate with adverse neonatal outcomes such as spontaneous preterm labour, meconium-stained liquor, and foetal distress. Likewise, Jamsheed et al. [15] reported a 31 percent rate of preterm birth and 17 percent NICU admissions in ICP pregnancies, findings nearly identical to the present study. The relatively low incidence of low Apgar scores in our data suggests that timely intervention and delivery planning may reduce perinatal compromise, supporting the importance of active management strategies as reported by Kenyon et al. [11].

Collectively, the results of this study confirm that ICP remains a clinically significant obstetric condition associated with notable maternal and neonatal risks. The high prevalence of biochemical abnormalities, gestational diabetes, and operative deliveries in this cohort reflects the need for enhanced screening and standardized management. Compared with Western populations, the higher frequency of adverse outcomes observed in South Asian women may be explained by differences in genetics, nutrition, and delayed access to specialized care [6,15].

In conclusion, this study reinforces the evidence that intrahepatic cholestasis of pregnancy is associated with significant maternal and perinatal complications. Regular biochemical screening for liver enzymes and bile acids, combined with early diagnosis, close foetal surveillance, and timely delivery, can markedly improve pregnancy outcomes. Future multicentric studies exploring therapeutic interventions such as ursodeoxycholic acid and their impact on bile acid levels and perinatal morbidity are recommended to further strengthen local evidence and guide clinical practice.

CONCLUSION

Intrahepatic cholestasis of pregnancy was found to be associated with significant maternal and neonatal complications. The most frequent maternal outcomes included gestational diabetes, caesarean delivery,

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and postpartum haemorrhage, while preterm birth, low birth weight, and NICU admission were the predominant neonatal outcomes. Early diagnosis, close biochemical monitoring, and timely obstetric intervention are essential to improve perinatal outcomes and reduce complications among affected Pakistani women.

Table 1: Demographic characteristics of the ICP patients (n=186)

Variables	**Mean ± SD/ Frequency**	**Range / Percentage**
Age (Years)	30.11±4.63	Range: 19-42
Age groups (Years)		
≤25	29	15.59%
26-30	75	40.32%
>30	82	44.09%
Gestational age at admission	31.03±6.33	Range: 20-38
Gestational age	36.74±1.64	Range: 29-39
Height (cm)	157.72±5.06	Range: 144-173
Weight (kg)	70.19±10.39	Range: 44-106
BMI (kg/m^2)	27.09±4.53	Range: 18.8-46.3
BMI Category		
Normal	48	52.81%
Overweight	85	45.70%
Obese	53	28.49%
Gravida		
Primigravida	74	39.8%
Multigravida	112	60.2%
Previous history of ICP	35	18.82%

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Table 2: Laboratory Investigation of Pregnant Women with Obstetric Cholestasis

Laboratory Parameter	**Frequency (%)**	**Median [IQR]**	**Range (Min-Max)**
ALT (IU/L) **[n=186]**		99 [118]	14-1149
≤ 35	12(6.45%)		
>35	174(93.55%)		
AST (IU/L) **[n=111]**		77[87]	21-669
<31	10(9%)		
>31	101(91%)		
Total Bilirubin (mg/dL) **[n=110]**		0.40[0.43]	0.10-4.9
≤1.2	105(56.5%)		
>1.2	5(2.7%)		
Direct Bilirubin (mg/dL) **[n=111]**		0.20[0.30]	0.10-3.6
≤0.20	56(50.5%)		
>0.20	55(49.5%)		
Total Bile Acid (umol/L) **[n=156]**		12.3[16.98]	1.3-111
Normal	24(12.9%)		
Mild	116(62.4%)		
Moderate	15(8.1%)		
Severe	1(0.5%)		

ALT=Serum Alanine Aminotransferase; AST=Serum Aspartate Aminotransferase

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Table 3: Frequency of Maternal Outcomes in Obstetric Cholestasis (n=186)

Maternal outcome	**Frequency**	**Percentage**
Mode of delivery		
Caesarean Section	88	47.31%
• Elective	29	15.59%
• Emergency	59	31.72%
Instrument	5	2.69%
SVD	93	50%
Type of Labour (n=147)		
Induced	99	67.34%
Spontaneous	48	32.65%
Associated Complications		
Gestational Diabetic Mellitus (GDM)	94	50.54%

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Chronic Hypertension	4	2.15%
Pregnancy-Induced Hypertension	13	6.98%
Hypothyroidism	9	4.84%
Anaemia	7	3.76%
Postpartum Haemorrhage (PPH)	31	16.67%
Meconium-Stained Liquor (MSL)	7	3.76%

Table 3: Frequency of Foetal Outcomes in Obstetric Cholestasis (N=186)

Foetal outcome	**Frequency**	**Percentage**
Preterm (GA<37 weeks)	55	29.56%
Meconium Aspiration (MAS)	02	1.08%
Low Birth Weight (<2.5kg)	34	18.3%
Small for gestational age (SGA)	20	10.75%

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Intrapartum Foetal Distress (IFD)	20	10.75%
Apgar score <7 at 1min	05	2.68%
Apgar score <7 at 5min	03	1.61%
NICU Admission	27	14.52%
Neonatal RDS	17	9.14%

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