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PREVALENCE OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY AMONG PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific cholestatic disorder characterized principally by pruritus and elevated maternal serum bile acids. Gestational diabetes mellitus (GDM) is common and has been reported to coexist with ICP.

Objective: To determine the prevalence of ICP among pregnant women with GDM presenting to Memon Medical Institute Hospital, Karachi.

Methods: A descriptive cross-sectional study was conducted from 20 December 2022 to 20 June 2023. A total of 276 pregnant women aged 19–40 years, at ≥24 weeks of gestation, with GDM diagnosed using a 75-g oral glucose tolerance test according to ADA/IADPSG thresholds were enrolled by consecutive sampling. ICP was operationally defined as serum bile acids ≥10 μmol/L, at least two-fold elevation of AST and ALT, negative viral hepatitis serology, and normal abdominal ultrasonography. Associations with selected maternal characteristics were assessed using chi-square or Fisher's exact tests.

Results: Among 276 women with GDM, 22 had ICP, giving a prevalence of 8.0% (95% CI 5.3%–11.8%). Mean age was 31.40 ± 5.37 years, mean gestational age 26.28 ± 1.50 weeks, mean BMI 25.47 ± 2.04 kg/m², and mean serum bile acid level 6.65 ± 4.59 μmol/L. Previous ICP was reported by 29 (10.5%) women. ICP prevalence was higher among women with family income <100,000 PKR/month (10.3% vs 0%; p=0.003), BMI <23 kg/m² (21.2% vs 3.8%; p<0.001), multiparity (12.7% vs 0.9%; p<0.001), and previous ICP (48.3% vs 3.2%; p<0.001). Age, gestational age, and residence were not significantly associated with ICP.

Conclusion: ICP occurred in 8% of pregnant women with GDM in this tertiary-care cohort. A previous history of ICP showed the strongest observed association with ICP in the current pregnancy.

KEYWORDS: gestational diabetes mellitus; intrahepatic cholestasis of pregnancy; pregnancy; serum bile acids; obstetric cholestasis; prevalence

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also termed obstetric cholestasis, is a pregnancy-specific liver disorder characterized by pruritus and elevation of maternal serum bile acids, with biochemical abnormalities often involving liver enzymes. It is clinically important because maternal symptoms may coexist with adverse fetal outcomes, including preterm birth, meconium-stained amniotic fluid and, particularly at very high bile-acid concentrations, stillbirth. Its occurrence varies substantially between populations.1,11–17

Gestational diabetes mellitus (GDM) is glucose intolerance first recognized during pregnancy and is an increasingly important obstetric problem. It is associated with short- and long-term maternal and neonatal consequences and requires timely diagnosis and management.2–8,18–20

An association between ICP and GDM has been described. Majewska et al. reported a higher frequency of GDM among women with ICP and observed ICP in 5.77% of pregnancies complicated by GDM compared with 1.80% in pregnancies without GDM.9 A systematic review and meta-analysis reported a pooled odds ratio of 2.19 (95% CI 1.58–3.03) for the association between ICP and GDM, although substantial heterogeneity was present.10 Potential biological links include altered bile-acid signaling through the farnesoid X receptor and metabolic effects of cholestasis on lipid and glucose homeostasis.9,10

Data describing the frequency of ICP specifically among women with GDM remain limited in South Asian settings. This study therefore aimed to determine the prevalence of ICP among pregnant women with GDM attending a tertiary-care hospital in Karachi and to examine its relationship with selected demographic and obstetric characteristics.

MATERIALS AND METHODS

Study design and setting

This descriptive cross-sectional study was conducted in the inpatient Obstetrics and Gynecology Department of Memon Medical Institute Hospital, Karachi, from 20 December 2022 to 20 June 2023.

Sample size and sampling

The sample size was calculated using the WHO sample-size calculator, based on an expected ICP frequency of 6.94% among women with GDM, a 3% margin of error and a 95% confidence level, yielding 276 participants. Non-probability consecutive sampling was used.

Eligibility criteria

Women aged 19–40 years with gestational age ≥24 weeks and GDM diagnosed according to the study's operational definition were eligible, irrespective of parity or gravida. Women with multiple gestation, positive hepatitis A or E serology, unwillingness to participate, or pre-existing type 2 diabetes mellitus were excluded.

Diagnostic criteria

GDM was diagnosed using a standard 75-g oral glucose tolerance test: fasting plasma glucose ≥92 mg/dL, 1-hour glucose ≥180 mg/dL, or 2-hour glucose ≥153 mg/dL; one or more abnormal values qualified for diagnosis.8 For this dissertation-derived analysis, ICP was defined as serum bile acids ≥10 µmol/L together with at least a two-fold elevation of AST and ALT, negative viral hepatitis serology, and normal abdominal ultrasonography.

Data collection

After informed consent, age, residence, parity, gravida, gestational age, BMI, family monthly income and previous history of ICP were recorded. Serum liver function tests and serum bile acid levels were performed biweekly. Women developing findings compatible with ICP underwent viral hepatitis serology and liver ultrasonography. Clinical assessment was performed by a consultant gynecologist with at least two years of post-fellowship experience, and ultrasonography by a consultant radiologist.

Statistical analysis

Data were analyzed using SPSS version 25. The Shapiro–Wilk test assessed normality. Quantitative variables were summarized as mean ± standard deviation and categorical variables as frequencies and percentages. Associations between ICP and selected variables were evaluated using chi-square or Fisher's exact test. For this manuscript, exact Fisher's p values were recalculated from the dissertation's reported 2×2 cell counts where appropriate. A two-sided $p<0.05$ was considered significant.

RESULTS

A total of 276 pregnant women with GDM were included. Mean age was 31.40 ± 5.37 years (range 20–40), mean gestational age 26.28 ± 1.50 weeks (24–29), mean height 154.53 ± 1.92 cm, mean weight 60.82 ± 4.66 kg, mean BMI 25.47 ± 2.04 kg/m², mean family monthly income 71,286.23 ± 26,081.58 PKR, and mean serum bile acid level 6.65 ± 4.59 µmol/L. □filecite□turn0file0□L426-L430□

Urban residence was reported by 175 (63.4%) women and rural residence by 101 (36.6%). Multiparas and multigravidas each comprised 166 (60.1%) women. Previous ICP was reported in 29 (10.5%) participants. □filecite□turn1file1□L312-L313□

ICP in the current pregnancy was identified in 22 of 276 women, giving a prevalence of 8.0% (95% CI 5.3%–11.8%). □filecite□turn1file4□L626-L640□

Table 1. Baseline characteristics of the study population

Variable	N	Range	Mean ± SD
Age (years)	276	20–40	31.40 ± 5.37
Gestational age (weeks)	276	24–29	26.28 ± 1.50
Height (cm)	276	150–160	154.53 ± 1.92
Weight (kg)	276	50–65	60.82 ± 4.66
BMI (kg/m²)	276	21.60–28.00	25.47 ± 2.04
Family monthly income (PKR)	276	35,000–175,000	71,286.23 ± 26,081.58

Serum bile acids (μmol/L)	276	3–28	6.65 ± 4.59

Table 2. Distribution of demographic and obstetric characteristics

Characteristic	n	%
Rural residence	101	36.6
Urban residence	175	63.4
Primipara	110	39.9
Multipara	166	60.1
Primigravida	110	39.9
Multigravida	166	60.1
Previous ICP: Yes	29	10.5
Previous ICP: No	247	89.5

Table 3. Prevalence of ICP in the current pregnancy

ICP status	n	%
Yes	22	8.0
No	254	92.0
Total	276	100.0

Table 4. Association between ICP and selected maternal characteristics

Characteristic	Category	ICP n/N	Prevalence	Fisher's exact p
Age	<35 years	13/181	7.2%	0.493
Age	≥35 years	9/95	9.5%	
Gestational age	≤28 weeks	22/255	8.6%	0.391
Gestational age	≥29 weeks	0/21	0.0%	
Residence	Rural	7/101	6.9%	0.818
Residence	Urban	15/175	8.6%	
Family income	<100,000 PKR/month	22/213	10.3%	0.003
Family income	≥100,000 PKR/month	0/63	0.0%	
BMI	<23 kg/m²	14/66	21.2%	<0.001
BMI	≥23 kg/m²	8/210	3.8%	
Parity	Primipara	1/110	0.9%	<0.001
Parity	Multipara	21/166	12.7%	
Gravida	Primigravida	1/110	0.9%	<0.001
Gravida	Multigravida	21/166	12.7%	
Previous ICP	Yes	14/29	48.3%	<0.001
Previous ICP	No	8/247	3.2%	

Note: exact Fisher's p values were calculated from the dissertation's reported cell counts. The source dissertation records several statistically significant p values as 0.00; this manuscript reports <0.001 where appropriate.

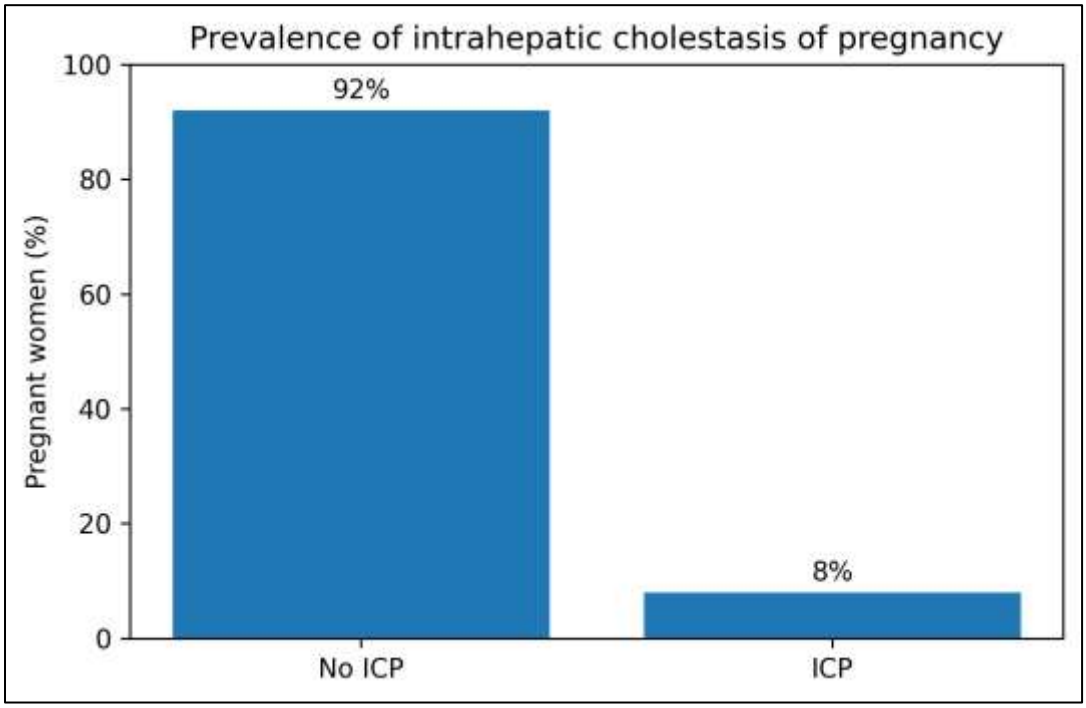

Figure 1. Distribution of ICP status among 276 pregnant women with GDM.

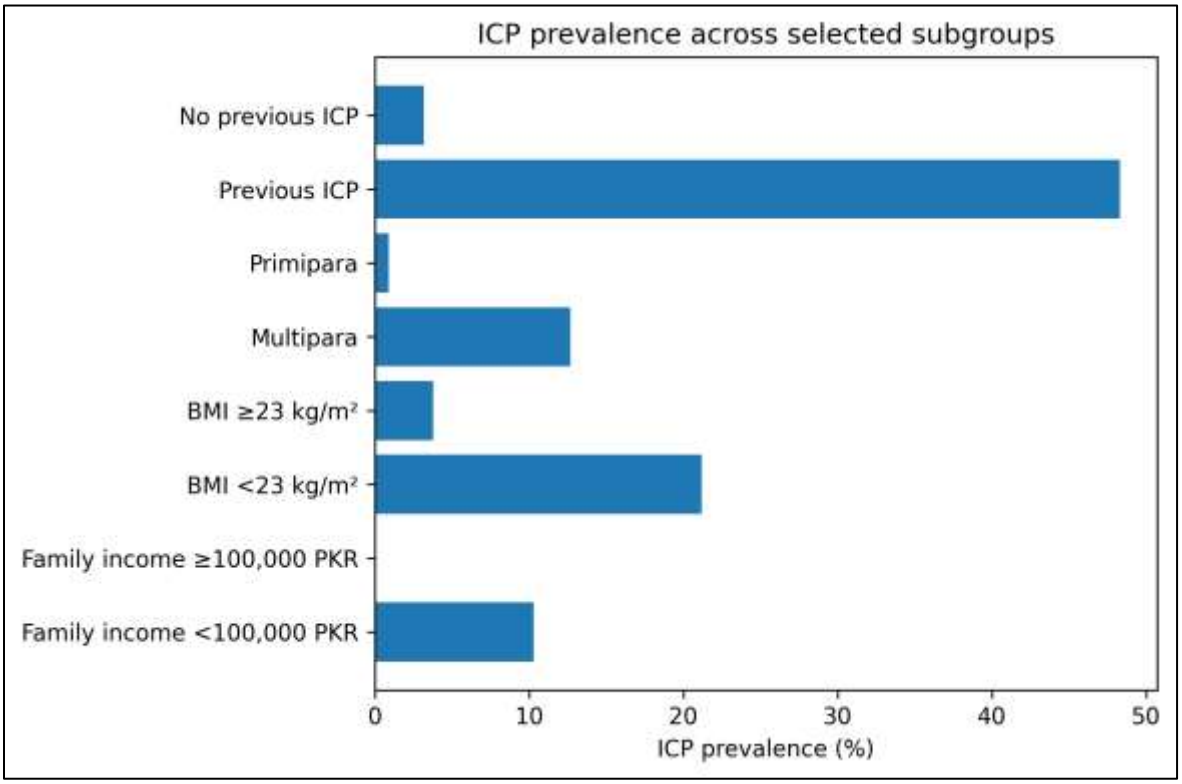

Figure 2. ICP prevalence across selected maternal subgroups.

DISCUSSION

This study found ICP in 22 of 276 pregnant women with GDM, corresponding to a prevalence of 8.0%. The observed frequency is broadly comparable with the 5.77% prevalence reported by Majewska et al. among pregnancies complicated by GDM.9 Differences may reflect population characteristics, diagnostic criteria, sampling strategy, and geographic variation.

The relationship between ICP and GDM has biological plausibility. Bile acids participate in metabolic signaling through receptors including FXR, which influences glucose and lipid metabolism. Altered bile-acid signaling and ICP-associated metabolic changes may therefore interact with insulin resistance.9,10

In this cohort, age, gestational age and residence were not significantly associated with ICP. The prevalence was 7.2% among women younger than 35 years and 9.5% among those aged 35 years or older. Similarly, ICP occurred in 8.6% of women enrolled at ≤28 weeks compared with none of those at ≥29 weeks; the latter subgroup was small, so the absence of cases should not be interpreted as evidence of protection.

ICP was more frequent among women with family income below 100,000 PKR/month (10.3% vs 0%, p=0.003). This should be interpreted cautiously because the higher-income group had no ICP events. Socioeconomic status may also represent unmeasured differences in nutrition, access to care and other exposures.

ICP was significantly more frequent among women with BMI <23 kg/m² than among those with BMI ≥23 kg/m² (21.2% vs 3.8%, p<0.001). This observation is counter to an intuitive expectation of greater metabolic clustering at higher BMI and may reflect the specific composition and categorization of this cohort. It should not be interpreted as a causal protective effect of higher BMI.

Multiparity and multigravida status were strongly associated with ICP, with prevalence of 12.7% compared with 0.9% among primiparas and primigravidas (p<0.001). The most striking association was previous ICP: 14 of 29 women with a previous history developed ICP again (48.3%), compared with 8 of 247 women without such a history (3.2%; p<0.001). This supports careful obstetric history-taking and heightened clinical vigilance in women with prior ICP.

Strengths include a defined sample size, consecutive recruitment, standardized GDM diagnostic thresholds, serial biochemical assessment, and confirmatory evaluation of suspected ICP. Limitations include the single-center design, non-probability sampling, small number of ICP events, cross-sectional design, absence of a non-GDM comparison group, and lack of multivariable adjustment. In addition, the dissertation's operational definition required simultaneous two-fold elevations of AST and ALT in addition to elevated bile acids, which may limit direct comparison with studies using other diagnostic definitions.

CONCLUSION

In this tertiary-care cohort, 8.0% of pregnant women with GDM met the dissertation's operational criteria for ICP. ICP was significantly associated with lower family income, BMI below 23 kg/m², multiparity, multigravida status, and particularly a previous history of ICP. Prospective multicenter studies using standardized contemporary diagnostic criteria and including a non-GDM comparison group are warranted.

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