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Prevalence of Gestational Diabetes Mellitus in Women Presenting with Intrahepatic Cholestasis of Pregnancy

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A B S T R A C T

Objective: The objective of this study is to evaluate the prevalence and associated factors of GDM in women who present with ICP.

Methodology: This observational study was conducted retrospectively over a period of three years from January 2021 to December 2023 in Fazaia Postgraduate medical institute Islamabad. Medical records of all the women who diagnosed with ICP during their second or third trimester were reviewed. ICP was diagnosed based on pruritus without rash and elevated serum total bile acids (>10 µmol/L). Women with pre-existing diabetes, chronic liver disease, multiple gestations, or other metabolic disorders were excluded. GDM was diagnosis was made on the basis of International Association of Diabetes and Pregnancy Study Groups criteria using a 75-g oral glucose tolerance test at 24–28 weeks of gestation. Logistic regression analysis was performed to identify independent predictors.

Results: There were 1,370 women with ICP in total. The mean age of the mothers was 29.4 ± 4.7 years. The prevalence of GDM was 22.8% (n=312). GDM was significantly more frequent in women with moderate-to-severe ICP (33.7% vs 17.6%; p<0.001). The mean levels of serum bile acid (48.5 ± 34.7 vs 21.4 ± 15.2 µmol/L; p<0.001) were significantly higher in women with GDM. Elevated bile acids (AOR 2.21), maternal age >30 years (AOR 1.58), and BMI ≥25 kg/m² (AOR 1.83) were independent predictors.

Conclusion: GDM is prevalent in ICP-affected women and has a strong relationship with increased BMI, advanced maternal age, and elevated bile acids. Early screening and targeted management are recommended.

Key Words: Intrahepatic cholestasis of pregnancy, Gestational diabetes mellitus, Serum bile acids, Body mass index.

Introduction

ICP is a liver disease specific to pregnancy, defined by a lack of bile circulation within the liver, leading to the increase of serum bile acid in the mother, which may be accompanied by severe pruritus. ICP manifests itself in the second or third trimester and normally disappears after birth.[1,2] The international incidence of ICP is very vagrant with a minimum of less than 1% among certain populations and up to 25% in selected high risk areas, including South Asia and South America, due to genetic, environmental, and hormonal factors.[1,3] The pathogenesis of ICP has also been associated with estrogen and progesterone metabolism, especially in genetically predisposed persons.[4,5] Although the symptoms of maternal origin are typically self-limiting, the condition poses serious risks to the health of the fetus.[1,4]

Gestational diabetes mellitus (GDM), which is intolerance to glucose discovered first during pregnancy, is one of the least famous metabolic problems of pregnancy.[6] Globally, it is estimated that GDM occurs in 14-17% of pregnancies, although the rate differs depending on the region, the maternal age, the prevalence of obesity and ethnicity.[7,8] GDM has been linked to unfavorable maternal complications, including higher rates of cesarean birth, preeclampsia, and type 2 diabetes mellitus in the future and neonatal adverse outcomes.[6,8,14] The increased prevalence of obesity and the delayed age at conception among mothers have contributed to the increasing burden of GDM in the world.[7,15]

ICP and GDM were initially accepted as different pregnancy complications, but there are new studies that indicate that both have a strong correlation. In the meta-analysis of more than 17,000 cases of ICP, it was noted that women with ICP are more likely to develop GDM than those pregnancies without ICP (OR 2.28; 95% CI 1.693.07).[5] According to the Retrospective cohort studies, the GDM prevalence rate among women with ICP varies between 13.6% to over 27% compared to the general obstetric population, which is much higher.[7,8] The incident of early-onset of ICP, especially, seems to predispose later GDM and therefore temporal aspects in disease development have high importance.[9]

The pathways connecting ICP and GDM are not completely clear and might also encompass the modulation of metabolic pathways through bile acid.[10] The dysregulation of FXR has been linked with the defective glucose homeostasis, decreased sensitivity to insulin, and the occurrence of gestational hyperglycemia.[11] Inherited factors such as genetic deficiencies in the transportation of bile acids and metabolic routes could also be the cause of common susceptibility to both ICP and GDM.[12]

A number of studies focus on maternal risk factors in the co-occurrence of ICP and GDM. The most common and independent risk factors for GDM among women with ICP are high body mass index, advanced maternal age, excessive weight gain during pregnancy, family history of diabetes type 2, and the use of assisted reproductive technologies. These probably contribute to the physiological insulin resistance of pregnancy making one prone to hyperglycemia in the presence of bile acid dysregulation. Thus, ICP can be a predetermined sign of the metabolic weakness, and that can be monitored and intervened beforehand.[7,14]

Intrahepatic cholestasis of pregnancy is the major hepatic disease that can predispose the women to metabolic disorders such as gestational diabetes mellitus. New evidence suggests that women with ICP are significantly more likely to develop GDM compared to the general obstetric population and the prevalence rates vary between 13.6% and 27%.[15,7,8] High serum bile acids, especially when early or severe ICP is present, seem to be a contributor to persist with impaired glucose metabolism through conjugations with nuclear receptors and membrane receptors which control insulin sensitivity.[6,16] Intrahepatic cholestasis of pregnancy has been increasingly linked with metabolic disturbances, yet its association with gestational diabetes mellitus remains insufficiently explored in many populations. Determining the prevalence and risk factors of GDM in women with ICP may help guide early screening and targeted management to improve maternal outcomes.

Methodology

This research was done as a Retrospective Quasi-Experimental Design in a tertiary care hospital Fazaia Postgraduate medical institute Islamabad. during three years, between January 2021 to December 2023. Hospital medical records, such as outpatient clinic record and inpatient admission record were evaluated to identify women diagnosed with Intrahepatic Cholestasis of Pregnancy (ICP) during the second or third trimester. ICP diagnosis was made according to clinical presentation of pruritus without rash, and laboratory diagnosis of High Serum Total Bile Acids greater than 10 μmol/L with or without abnormal liver function tests. Women who had pre-existing diabetes, chronic liver disease, multiple pregnancies and other metabolic disorders were excluded. Gestational diabetes mellitus (GDM) was diagnosed using the 75-gram oral glucose tolerance test (OGTT) during weeks 24–28 of pregnancy in accordance with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) standards, and confirmed by the world health organization guidelines. The patient records were reviewed and the demographic data, obstetric history, body mass index (BMI), gestational age at the diagnosis of ICP, serum bile acid levels, and OGTT results were included in a structured database to be analyzed. Data were compared to find out the rates of GDM in women with ICP and examine how the severity of cholestasis, bile acid levels, and maternal features are associated. Both inferential analysis and descriptive statistics, such as frequency tables, mean, and standard deviation, were used in the statistical study. For qualitative data, the chi-square test was utilized, and for quantitative data, the independent sample t-test. The univariate and multivariate logistic regression models were used to assess the possible risk factors for GDM. A P-value of less than 0.05 was considered significant.

Results

A total of 1,370 women diagnosed with intrahepatic cholestasis of pregnancy (ICP) were included in the analysis.

Table I shows that the mean mother age was 29.4 ± 4.7 years and the mean gestational age was 32.1 ± 2.5 weeks at the time of ICP diagnosis. The mean pre-pregnancy BMI was 26.3 ± 3.8 kg/m². Regarding disease severity, 952 (69.5%) women had mild ICP (serum total bile acids <40 μmol/L), whereas 418 (30.5%) had moderate-to-severe ICP (≥40 μmol/L). Overall, 312 women were diagnosed with gestational diabetes mellitus (GDM), yielding a prevalence of 22.8% in this cohort.

The comparison of women with and without GDM is shown in (Table II). Women with moderate-to-severe ICP had a considerably higher proportion of GDM than those with mild ICP (33.7% vs 17.6%; p < 0.001). Women with GDM had significantly higher mean blood total bile acid (TBA) levels than those without (48.5 ± 34.7 μmol/L vs 21.4 ± 15.2 μmol/L; p <0.001), which shows a clear positive association between bile acid concentration and the prevalence of GDM.

Table I: Demographic and Clinical Characteristics of Women with ICP (n = 1370)

Variables	Mean ± SD / n (%)
Maternal age (years)	29.4 ± 4.7

Table-II: Comparison of Serum Total Bile Acid Levels and ICP Severity Between Groups

Variable	GDM (n = 312)	No GDM (n = 1058)	p-value
ICP Severity			
Mild (<40 μmol/L)	168 (17.6)	784 (82.4)	<0.001
Moderate-to-Severe (≥40 μmol/L)	141 (33.7)	277 (66.3)	
Serum TBA (μmol/L)			
Mean ± SD	48.5 ± 34.7	21.4 ± 15.2	<0.001
Pre-pregnancy BMI (kg/m²)		26.3 ± 3.8	
Gestational age at ICP diagnosis (weeks)		32.1 ± 2.5	
Mild ICP (<40 μmol/L)		952 (69.5%)	
Moderate-to-Severe ICP (≥40 μmol/L)		418 (30.5%)	
Gestational Diabetes Mellitus		312 (22.8%)	

Univariate logistic regression analysis (Table III) demonstrated that elevated serum bile acids (≥40 μmol/L), maternal age >30 years, and pre-pregnancy BMI ≥25 kg/m² were significantly associated with GDM. Women with serum TBA ≥40 μmol/L had 2.32 times higher odds of developing GDM (95% CI: 1.78–3.04; p <0.001). Similarly, maternal age >30 years was associated with 1.74-fold increased odds (95% CI: 1.32–2.29; p <0.001), and pre-pregnancy BMI ≥25 kg/m² showed 1.96-fold increased odds of GDM (95% CI: 1.49–2.58; p <0.001).

Table III: Univariate Logistic Regression Analysis for Predictors of GDM.

Variables	Crude OR	95% CI	p-value
Serum TBA ≥40 μmol/L	2.32	1.78–3.04	<0.001
Maternal age >30 years	1.74	1.32–2.29	<0.001
Pre-pregnancy BMI ≥25 kg/m²	1.96	1.49–2.58	<0.001

On multivariate logistic regression analysis (Table-IV), after adjusting for potential confounders, serum TBA ≥40 μmol/L remained the strongest independent predictor of GDM (Adjusted OR 2.21; 95% CI: 1.66–2.94; p <0.001). Maternal age >30 years (Adjusted OR 1.58; 95% CI: 1.18–2.12; p = 0.002) and pre-pregnancy BMI ≥25 kg/m² (Adjusted OR 1.83; 95% CI: 1.37–2.44; p <0.001) also remained statistically significant independent risk factors.

Table IV: Multivariate Logistic Regression Analysis for Independent Predictors of GDM

Variables	Adjusted OR	95% CI	p-value
Serum TBA ≥40 μmol/L	2.21	1.66–2.94	<0.001
Maternal age >30 years	1.58	1.18–2.12	0.002
Pre-pregnancy BMI ≥25 kg/m²	1.83	1.37–2.44	<0.001

Discussion

The findings of the current study that indicate 22.8% of women with Intrahepatic Cholestasis of Pregnancy (ICP) also had Gestational Diabetes Mellitus (GDM) are in line with the ever increasing literature that indicated a substantial correlation between the two pregnancy complications. Large meta-analysis has shown that ICP is also linked to the significantly higher risk of GDM, and pooled odds ratios indicate more than a two-fold increased risk over women without ICP.[16,17] Such an association is probably due to overlapping metabolic malregulation and not coincidental occurrence of two independent conditions.

One of the main factors in the interpretation of this relationship is the role of bile acid metabolism that is essentially disturbed in ICP. The levels of serum total bile acid (TBA) which determine the degree of cholestasis, have been reported to be markedly higher in pregnant women who become GDM in subsequent pregnancies than in women who remain normoglycemic especially at the early stages of pregnancy before an individual is diagnosed to have glucose intolerance.[18] In addition, meta analytical data show that both moderate and severe ICP are linked with increased prevalence of GDM relative to mild disease and enhances the dose response hypothesis that bile acid load is linked to metabolic risk.[18]

Bile acids can communicate via nuclear and membrane receptors, such as the farnesoid X receptor (FXR) and Takeda G protein coupled receptor 5 (TGR5), influencing glucose and lipid metabolism. The impairment of these signaling pathways in ICP can be one of the factors that cause the disruption of insulin sensitivity and glucose regulation, and predisposes individuals to GDM.[19]

The bile acid-mediated mechanism is not the only factor that increases the chance of developing GDM in the ICP environment. Maternal metabolic risk factors, including advanced age, high body mass index (BMI), and excessive weight gain during pregnancy, also play a significant role. We also found such risk profiles with a significant association between higher BMI and GDM incidence among ICP patients, and this has been reported by other researchers, and is evidence that ICP might be able to show metabolic vulnerability that develops during pregnancy. The co-existence of these processes underscores the multi-factoriality of the GDM pathogenesis of cholestatic pregnancies.[3,18]

The findings of the current research revealed that the incidence of gestational diabetes mellitus (GDM) was 22.8%, which meant that almost in every four women with ICP, one experienced GDM. Notably, women with moderate-to-severe ICP (serum bile acids 40 μmol/L and above) had a high probability of GDM compared to those with mild disease (33.7% vs 17.6%; $p<0.001$). Women with GDM also had markedly higher mean serum bile acid levels (48.5 ± 34.7 μmol/L vs 21.4 ± 15.2 μmol/L; $p<0.001$). On multivariate analysis, high levels of bile acids (AOR 2.21), maternal age (>30 years) (AOR 1.58) and pre-pregnancy BMI (25 kg/m²) (AOR 1.83) were independent predictors of GDM, which underscored the interaction between the severity of cholestasis and the metabolic risk.

The results are aligned with the already published data indicating an association between ICP and GDM. In a meta-analysis, Arafa and Dong found that women with ICP were over two times more likely to develop GDM than controls (pooled OR 2.19).[19] Likewise, Martineau et al. reported that GDM was significantly more prevalent in women with ICP and suggested that bile acid dysregulation could drive the changes in glucose metabolism during pregnancy.[20] The results of our study, especially the high correlations between bile acids ≥40 μmol/L and GDM are in the same scale with these studies.

Recent data has also highlighted the metabolic effect of bile acids. In a recent study, Li X et al. found that a high level of maternal serum bile acid was linked to a higher risk of GDM particularly when measured at a time when routine glucose screening had not been made.[21] This association is supported by the substantially increased mean bile acid in our GDM group, and indicates a potential dose-response effect between the severity of cholestasis and the inability to regulate glucose levels.

Nonetheless, there have been inconsistent results of some studies. In a large study, Yan Y, et al. found that despite common coexistence of GDM and ICP, there was no significant difference in glucose metabolism parameters in ICP-GDM and ICP alone, indicating the heterogeneity of the metabolic profiles.[22] Likewise, Axelsen SM, et al. did not identify a statistically significant difference in the prevalence of GDM in the ICP and non-ICP groups in their hospital-based study.[23]

Conclusion

The findings of this study revealed that gestational diabetes mellitus is very common in women who have intrahepatic cholestasis of pregnancy with one quarter of the cases having the condition. High levels of serum bile acids, maternal age with over 30 years and high pre-pregnancy BMI were found to be the significant independent predictors of GDM. The close relationship between moderate to severe ICP and glucose intolerance highlights the importance of comprehensive and active screening of GDM in this high-risk population. Early diagnosis and interdisciplinary care can be used to maximize maternal outcomes and minimize possible metabolic complications during pregnancy.

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