Intrahepatic Cholestasis of Pregnancy is Associated with Gestational Diabetes Mellitus

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ABSTRACT

OBJECTIVES: Intrahepatic (also known as obstetric) cholestasis of pregnancy is one of the most frequently diagnosed conditions for pregnancy-specific hepatic disease. It has consistently been found to be related to adverse pregnancy outcomes. In recent studies, a relationship between Intrahepatic cholestasis of pregnancy and gestational diabetes mellitus was demonstrated. However, the association between serum total total bile acid evel in Intrahepatic cholestasis of pregnancy and gestational diabetes mellitus is not fully understood. This study aims to evaluate the association between serum total total bile acid levels in Intrahepatic cholestasis of pregnancy disease with gestational diabetes mellitus.

STUDY DESIGN: Eighty pregnant women diagnosed with Intrahepatic cholestasis of pregnancy and eighty healthy pregnant women as normal controls were included in the study. Their clinical characteristics and laboratory test results including liver function tests, glucose challenge tests, glucose tolerance tests, and fasting and postprandial total total bile acid levels were recorded. Cases with serumtotal total bile acid levels between 12-40 μmol/L were described as mild disease, >40 μmol/L was described as severe disease.

RESULTS: The mean 50-g glucose challenge tests value was significantly higher in pregnant women with Intrahepatic cholestasis of pregnancy compared to the healthy controls (128.7±28.2, 106.6±27.0; $p<0.0001$) and it was slightly higher in women with severe disease than women with mild disease (132.7±30.1, 125.5±26.5; $p=0.26$). The percent of gestational diabetes mellitus diagnosis with Intrahepatic cholestasis of pregnancy disease (11.25%) was higher than in healthy pregnant women (6.25%) but the difference was not found to be statistically significant ($p=0.187$) and it was similar in pregnant women with mild and severe disease (11.1%, 11.4%; $p=0.31$).

CONCLUSION: Our current study demonstrated that Intrahepatic cholestasis of pregnancy was not associated with gestational diabetes mellitus, also, we did not demonstrate a relationship of total total bile acid level with Intrahepatic cholestasis of pregnancy and gestational diabetes mellitus. It may be due to our study's small sample size. Further and well-designed studies with larger sample sizes are necessary to determine the relationship between gestational diabetes mellitus and Intrahepatic cholestasis of pregnancy and also the function of total total bile acid in the pathogenesis of gestational diabetes mellitus disease.

Keywords: Bile acid, Gestational diabetes mellitus, Intrahepatic cholestasis of pregnancy

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Introduction

Intrahepatic (or obstetric) cholestasis of pregnancy (ICP) is the leading cause of pregnancy-specific hepatic disorder. The incidence of ICP varies markedly among several reports, from as high as 5% in Chile to 0.7% in the UK (1). ICP is diagnosed with the elevation of serum aminotransferase concentration and/or elevation of fasting serum total bile acid (TBA) level accompanying pruritus. Pruritus, in particular, becomes symptomatic after the late second trimester of pregnancy and, itching worsens at night, influencing especially the palmar and plantar parts of the hands and feet (2). It resolves spontaneously approximately by four weeks postpartum.

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There are no factors that are well established in the etiopathogenesis of ICP. Genetic, hormonal, and environmental factors seem likely to play a role in the etiology of the ICP. Inadequate TBA homeostasis in the presence of physiological gestational alterations has been suspected as a reason for ICP (3).

Intrahepatic cholestasis of pregnancy has consistently been related to poor pregnancy outcomes-such as a higher rate of preterm birth, neonatal mortality, small for gestational age at birth and unexplained stillbirth (2,4). The risk of adverse pregnancy outcome is higher if fasting TBA concentration exceeds 40 μmol/L (5,6). In recent studies, it has also been demonstrated that ICP is related to gestational diabetes mellitus (GDM) (3,7), but to the best of our knowledge no one has investigated the association between TBA levels and GDM disease.

From the previous studies, we hypothesized the fact that ICP could have an association with an increased incidence of GDM as a result of the impaired bile homeostasis. In this study, we aimed to examine the relationship between serum TBA levels in ICP and GDM.

Material and Method

This case-control study was conducted between September 2015 and July 2016 at Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. Data were collected from patients' hospital records. This study was approved by our hospital ethics committee (approval number: 37) and the universal principles of the Helsinki Declaration were applied.

The hospital records of eighty consecutive pregnant women diagnosed with ICP were reached and 80 healthy pregnant women were included as a control group in the study. The two groups of pregnant women were matched according to the maternal age and body mass index (BMI). Pregnant women who had multiple pregnancies, drug use except for vitamins, any disease or viral infection that affected the liver and also those with a skin disease were not included in the study.

Diagnosis of ICP was made if a pregnant woman had generalized new onset persistent pruritus without skin lesions and laboratory results of TBAs exceeding 12 μmol/L and/or elevated liver enzymes in the absence of any identifiable liver disease. ICP group was also divided into two groups as mild and severe depending on the serum TBA levels. Diagnosis of severe disease was made with the serum levels of ≥40 mmol/L (1). All the pregnant women in the ICP group were hospitalized and tested for complete blood count (CBC), hepatic enzymes, and serology for hepatitis A, B and C virus for initial evaluation. All women who had ICP were evaluated with hepatic ultrasound examination to exclude other forms of hepatic disease. According to the American College of Obstetricians & Gynecologists guidelines, a 50 g oral glucose challenge test (50-g GCT) was applied to all participants between 24-28 weeks of gestation in both groups and blood glucose levels were measured 1 hour later. If the blood glucose level was above 140 mg/dL, a 100 g 3-h glucose tolerance test (GTT) was applied, diagnosis of GDM was confirmed if two of the blood glucose test results were above the following levels: fasting 95 mg/dL, 1-hour 180 mg/dL, 2-hour 155 mg/dL, 3-hour 140 mg/dL (8).

Patient demographic characteristics such as maternal age, gravity, parity, gestational week, BMI, and laboratory parameters including hepatic enzymes, fasting and postprandial TBA levels were recorded. Gestational age was determined according to The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) practice guidelines for the first trimester ultrasound (9). Gestational age at delivery, mean birthweight (BW), Neonatal Intensive Care Unit (NICU) admission requirement, meconium-stained amniotic fluid and Apgar score at the 5th minutes were recorded to evaluate the perinatal outcome.

Statistical Package for Social Sciences, Windows version 15.0 (SPSS, Chicago, IL, USA) was used to analyze the variables. The results of descriptive statistics were expressed as mean ± standard deviation and median (minimum-maximum) for numerical variables. The normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Parametric data were examined with independent two-sample t test and non-parametric data were compared using the Mann Whitney-U test. Categorical variables were expressed as number (percentage). Percentages were compared with the chi-square test. Associations between variables were evaluated using Pearson's correlation analyses. Logistic regression analyses were performed to calculate the odds ratios (OR) with a 95% confidence interval. A p value <0.05 indicates statistically significant differences.

Results

A total of 160 pregnant women (80 diagnosed with ICP and 80 patients as controls) were included in our study. Mean age was 27.4±5.1, mean BMI was 28.1±3.7, mean value of 50-g GCT was 117.5±29.6 and the percentage of GDM was 8.75% in our study population.

There were no statistically significant differences in terms of age, gravidity, parity, and BMI between two groups of pregnant women. Hepatic enzyme levels including mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly higher in the ICP group than the control group. Gestational age at birth and birthweight were lower in the ICP group than the control group (p=0.001 and p=0.016, respectively). Demographic data and laboratory test results of the two groups are presented in table I.

Also no significant differences were found regarding age, gravidity, parity and BMI between two ICP groups divided as mild and severe. Mean fasting and postprandial TBA levels

were significantly higher in the severe group than the mild group. Gestational age at birth and birthweight were lower in pregnant women with severe disease than those with the mild disease (p=0.001, p=0.016, respectively). Demographic information and laboratory parameters of the two ICP groups are shown in table II.

In this study population, the result of mean 50-g GCT was higher in pregnant women with ICP (128.7±28.2) compared to the healthy pregnant control group (106.6±27.0) (p=0.0001). The mean 50-g GCT value was slightly higher in women with severe disease than those with mild disease but the difference did not reach the significance level (132.7±30.1, 125.1±26.5, respectively; p=0.26) (Figure 1). Although the difference was not significant, GDM rates were higher in women with ICP compared to the healthy pregnant group (11.25%, 6.25%, respectively; p=0.187), (Table I). In addition, GDM rates were similar in pregnant women with mild and severe disease (11.1%, 11.4%, respectively; p=0.31) (Table II).

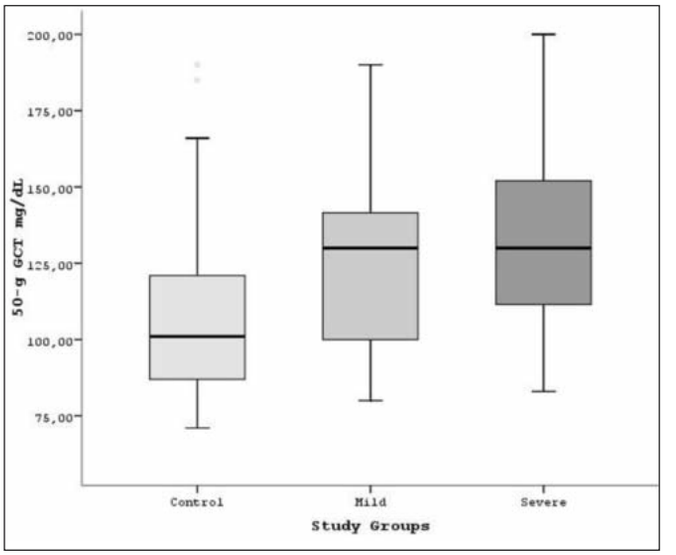

Figure 1: *Comparison of Mean 50 g GCT Levels between Study Groups.*

Table I: *Comparison of demographic and laboratory findings of intrahepatic cholestasis of pregnancy and control group*

Variables	ICP Group (n=80)	Control Group (n=80)	*p* value
Age (years)	27.6±5.0	27.2±5.2	0.62
Gravidity	2.0±1.2	2.3±1.5	0.14
Parity	0.5±0.7	0.6±1.0	0.44
BMI (kg/m²)	27.9±3.8	28.5±3.4	0.48
ALT (U/L)	138.0±115.7	14.2±7.7	0.0001
AST (U/l)	94.4±74.7	18.3±6.5	0.0003
Fasting TTBA (mmol/L)	40.2±42.4	-	-
Postprandial TTBA (mmol/L)	42.5±51.9	-	-
Gestational age at birth (week)	36.3±1.7	38.1±1.9	0.0004
Neonatal Birthweight (g)	2891.3±473.7	3141.4±481.7	0.001
FPG (mg/dL)	82.6±8.2	78.5±11.0	0.06
50-g GCT (mg/dL)	128.7±28.2	106.6±27.0	0.0001
Incidence of GDM, n (%)	9(11.25%)	5(6.25%)	0.187

Data expressed as mean±SD. ICP: Intrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TTBA: Total TBA, FPG: Fasting plasma glucose, GCT: Glucose challenge test, GDM: Gestational diabetes mellitus

Table II: *Comparison of demographic and laboratory findings of mild and severe intrahepatic cholestasis of pregnancy group*

Variables	Mild ICP Group (n=45)	Severe ICP Group (n=35)	*p* value
Age(years)	27.6±4.4	27.5±5.6	0.99
Gravidity	2.1±1.2	1.8±1.2	0.26
Parity	0.6±0.8	0.4±0.7	0.18
BMI (kg/m²)	28.5±3.5	27.9±3.8	0.48
ALT (U/L)	115.5±103.0	166.3±125.8	0.05
AST (U/L)	82.2±67.5	109.7±81.3	0.10
Fasting TBA (mmol/L)	22.3±9.1	67.9±69.9	0.0005
Postprandial TBA (mmol/L)	21.3±8.9	65.4±55.02	0.0001
Gestational age at birth (week)	36.9±1.2	35.6±2.0	0.001
Neonatal Birthweight (g)	2745.4±482.0	3008.7±438.1	0.016
FPG (mg/dL)	78.5±11.0	82.6±8.2	0.06
50-g GCT (mg/dL)	125.5±26.5	132.7±30.1	0.26
Incidence of GDM, n (%)	5 (11.1%)	4 (11.4%)	0.31

Data expressed as mean ± SD. BMI: Body mass index; ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TTBA: Total TBA, FPG: Fasting plasma glucose, GCT: Glucose challenge test, GDM: Gestational diabetes mellitus, ICP: Intrahepatic cholestasis of pregnancy

To evaluate a possible association between 50-g GCT value and TBA, ALT and AST levels in pregnant women with ICP, bivariate correlation analyses were used. In subgroup analyses of women with ICP, there was not any association between the 50-g GCT value and fasting TBA level (r=0.057, p=0.62) or postprandial TBA level (r=0.02, p=0.82). There was also no correlation between 50-g GCT value and ALT level (r=0.05, p=0.63) or AST level (r=0.07, p=0.51) in ICP pregnant women.

In the logistic regression model, although statistically not significant, ICP disease increased the risk of GDM 1.9- fold (95% CI: 0.71-3.31; p=0.24). Also the risk of positive screening rate in 50-g GCT increased 3.6-fold for ICP pregnant women (95% CI: 1.6-8; p=0.01).

Discussion

In the current study, we found that the mean 50-g GCT value was significantly higher in pregnant women with ICP than healthy pregnant controls. Although the percent of GDM diagnosis was higher in ICP pregnant women than controls and also in severe disease versus mild disease, the differences did not reach statistical significance. We found that while ICP disease insignificantly increases the risk of GDM by 1.9 fold, it significantly increased the risk of positive GDM screening by 3.6 fold.

The GDM definition is based on the glucose intolerance that is not overt before pregnancy and diagnosed second or third trimester during pregnancy (10) and the disease has important short term and long term effects on maternal and fetal well-being (11,12). GDM increases risks of perinatal complications and constitutes a risk for fetal macrosomia, shoulder dystocia and neonatal hypoglycemia (13). It is also demonstrated that women with a history of GDM have a high risk of developing dyslipidemia, obesity and insulin resistance as part of metabolic syndrome later in life (14,15). Due to the high risk for both the mother and fetus, its diagnosis and treatment during pregnancy should be managed accurately.

Different from our results, previous studies have reported an association between ICP and GDM (3,7). Wikström et al. (7) showed that pregnant women diagnosed with ICP tend to have GDM and large for gestational age infants at birth. More recently, Martineau et al. found that the incidence of GDM was higher in pregnancies with ICP and that this association increased more after the onset of cholestasis (3). We found that pregnant women with ICP had higher mean 50-g GCT values than the controls which is similar to the literature, however GDM rates were higher in pregnant women with ICP but this difference did not reach statistical significance in this study. The association between obesity and GDM is well known (16), however, in our study BMI was similar between the two groups.

BAs play an important role in dietary lipid absorption and cholesterol homeostasis. Also in recent animal modality studies it was demonstrated that BAs could take part in the regulation of glucose homeostasis by activating the cell surface and nuclear receptors as hormonal signaling molecules (17). As a primary BA receptor, FXR has a regulatory role in both glucose and cholesterol homeostasis (18). Gao et al. demonstrated that women with GDM have a significant increase in 8 BA species compared to the controls (19). Increased serum BA levels are a distinctive feature of ICP and it can be thought that GDM and ICP could share the same pathogenesis through BAs as the cornerstone. Nevertheless, the relationship between serum BA concentrations and metabolic syndrome or type 2 DM could not yet be demonstrated in humans (20). Although the diagnosis rate of GDM was found to be higher in the severe ICP group, in which the measurement of serum BA level was greater than 40 mmol compared to the mild group, we could not demonstrate a significant association between serum BA level and mean 50-g GCT value. To the best of our knowledge, our study is the first one in the literature that evaluated the relationship between BA levels and 50-g GCT value.

In many studies, it was demonstrated that ICP has an association with an increased risk of poor fetal and neonatal outcomes such as preterm delivery, fetal stress during labor, meconium-stained amniotic fluid, and intrauterine fetal death (5,21). Although severe ICP disease with serum TBA level >40mmoL/l has been shown to be associated with an increased risk of meconium-stained amniotic fluid, low APGAR scores and fetal intrauterine death in recent studies (5,21), optimal time for delivery and best predictors of the neonatal outcome before delivery are still unknown. Because of the increased rates of fetal death and postnatal complications, delivery before 37 weeks of pregnancy is usually recommended for these pregnancies (22). It's logical to found a statistically significant difference between ICP and healthy control group in terms of BW and gestational age at birth due to our policy of early delivery of ICP patients according to the recommendations in the literature.

Conclusion

In conclusion, our study showed that pregnant women with ICP had a higher incidence of GDM. But this difference did not reach statistical significance. Also, we could not find an association between TBA levels and serum 50-g GCT. Our results are not similar to the literature. It may be due to our small sample size. So, further and well-designed studies with larger sample sizes are necessary to determine the relationship between GDM and ICP and also the function of BA in the pathogenesis of GDM disease.

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