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Original Article

Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies

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ABSTRACT

Objective: We aimed to assess the relationship among the sex hormone-binding globulin (SHBG), homeostasis model assessment (HOMA), glycosylated hemoglobin (HbA1c), and cholesterol panel values to predict subsequent gestational diabetes mellitus (GDM) in low-risk pregnancies.
Materials and Methods: Thirty-eight pregnant women with GDM and 295 low-risk pregnant women without GDM were included in this study. Maternal blood samples were obtained during the first trimester examination to determine the SHBG, HbA1c, fasting blood glucose, insulin, thyroid stimulating hormone (TSH), free thyroxine, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C) levels. The variables that exhibited statistically significant differences between the groups and independent predictors for GDM were examined using logistic regression analysis. The risk of developing GDM, according to cutoff values, was determined using receiver operating characteristic (ROC) curve analysis.
Results: The SHBG, HOMA, LDL, and TG levels were found to be the significant independent markers for GDM [adjusted odds ratio (OR) = 0.991; 95% confidence interval (CI), 0.986–995; OR = 1.56; 95% CI, 1.24–1.98; OR = 1.02; 95% CI, 1.01–1.04; and OR = 1.01; 95% CI, 1.00–1.02, respectively]. The HbA1c, body mass index, and mean arterial pressure values were nonindependent predictors of GDM. The areas under the ROC curve used to determine the predictive accuracy of SHBG, HOMA, TG, and LDL-C for development of GDM were 0.73, 0.75, 0.70, and 0.72, respectively. For a false positive rate of 5% for the prediction of GDM, the values of the sensitivities were 21.1, 26.3, 21.1, and 18.4%, respectively.
Conclusion: The HOMA, SHBG, TG, and LDL-C levels are independent predictors for subsequent development of GDM in low-risk pregnancies, but they exhibit low sensitivity.

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance that is first detected during pregnancy [1]. Its prevalence ranges between 2% and 25% depending on the characteristics of the population and the methods used for diagnosis and screening [2]. No consensus exists regarding an optimal and internationally acceptable test for both diagnosis and screening [3]. Several studies have demonstrated the relationship between GDM and adverse short- and long-term maternal–fetal outcomes [4,5]. Screening for GDM after the 24th gestational week and diagnosing GDM at the end of the second trimester have been questioned because of the possible delay in achieving the positive effects of pharmacological therapy, diet, and exercise on placental vascularity, fetal development, and maternal complications [6]. Identifying patients at risk for GDM among low-risk pregnancies during early gestation may allow more time for interventions that can produce a reduction in both GDM and its associated morbidities.

A limited number of studies have prospectively examined the relationship among the sex hormone-binding globulin (SHBG), homeostasis model assessment (HOMA), glycosylated hemoglobin

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(HbA1c), and cholesterol panel values, which can be used to predict subsequent GDM in low-risk pregnancies during the first trimester [7–16]. In this study, we aimed to reveal the first trimester screening potential of these variables for predicting subsequent GDM in low-risk pregnancies.

Materials and methods

A prospective cohort study was conducted among patients who were admitted to our obstetric clinic between January 2011 and January 2013. Participants who provided blood samples at 6–13 + 6 weeks of gestation, completed prenatal care, and delivered a live, term infant at our institution were included in the study. Demographic data were collected for each patient at the time of plasma collection and included the gestational age, maternal age, gravidity, parity, body mass index (BMI), maternal systolic and diastolic blood pressure, mean arterial pressure (MAP), smoking status, medical and obstetric history, data for pregnancy follow up, and outcomes.

Patients with multiple pregnancies, obesity (BMI > 30 kg/m^2), a history of hypertension, Type 1/2 DM or glucose intolerance prior to pregnancy, GDM, preeclampsia, intrauterine second or third trimester pregnancy loss, or those with a first- or second-degree relative with DM were excluded. In addition, pregnant women who had first, second, or third trimester losses during follow up, a fetal anomaly, preeclampsia, or those who did not complete prenatal care or deliver at our hospital were also excluded from the study.

Maternal blood samples were used to determine SHBG, HbA1c, fasting blood glucose (FBG), insulin, thyroid stimulating hormone (TSH), free thyroxine (fT4), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were collected from the antecubital vein in a nonheparinized tube after 8–10 hours of overnight fasting during the first trimester examination. Blood samples were immediately centrifuged. Then, the serum was separated and frozen at −80°C until assays were conducted for all biochemical analyses.

SHBG was evaluated using a chemiluminescent immunometric assay (Immulite 2000 SHBG; Diagnostic Products Corporation, Siemens Healthcare Diagnostics, Los Angeles, CA, USA). The intra- and interassay coefficients of variation were 5.3% and 6.6%, respectively, at 80 nmol/L. The SHBG sensitivity was 0.02 nmol/L.

The TSH and fT4 levels were evaluated using the ADVIA Centaur XP Immunoassay system (Siemens Healthcare Diagnostics). The inter- and intra-assay variabilities were <4.1% and <4.7% for TSH and <5.1% and <5.8% for fT4, respectively.

The glucose levels in plasma samples were determined using the glucose hexokinase method (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany), and the intra- and interassay coefficients of variation were <0.4–0.5%.

The serum insulin level was evaluated using the ADVIA Centaur XP Immunoassay system (Siemens Healthcare Diagnostics). The HOMA was used as an index of insulin resistance (IR). The homeostasis model assessment (HOMA-IR) was calculated as follows: [(fasting glucose (mg/dL) × fasting insulin (μIU/mL))/405] [17].

Cholesterol measurements included the TC, TG, HDL-C, and LDL-C levels. Samples were measured using the COBAS Integra 800 (Roche Diagnostics, Mannheim, Germany). The inter- and intra-assay coefficients of variation were 0.6% and 1.6% for cholesterol, 1.6% and 1.9% for TGs, and 0.4% and 1.1% for HDL-C, respectively. The serum LDL-C levels were calculated using the Friedewald formula as follows: [LDL-C = TC − (HDL-C + TG/5)] [18]. The HbA1c level was measured using Roche diagnostics HbA1c kits with an autoanalyzer (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany).

A glucose challenge test (GCT) with 50 g glucose was performed on all pregnant women at 24–28 weeks of gestation. A 100-g oral glucose tolerance test (OGTT) was performed on patients with a positive result (≥140 mg/mL) of the 50 g GCT. Patients who had at least two abnormal values for the 100-g 3-hour OGTT (fasting, ≥95 mg/dL; 1 hour, >180 mg/dL; 2 hours, >155 mg/dL; or 3 hours, >140 mg/dL) were diagnosed with GDM. The control group consisted of patients without GDM who had a 50-g GCT result <140 mg/dL or patients who had values >140 mg/dL on the GCT but had less than two abnormal values on the 100-g OGTT.

Overt diabetes was diagnosed in women who met any of the following criteria: fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or random plasma glucose ≥ 200 mg/dL during the first trimester examination. In addition, the 100-g OGTT was performed on pregnant women who had normal fasting plasma glucose and HbA1c levels but had repeated glycosuria, polyhydramnios, and fetal macrosomia during the later stages of pregnancy.

Data analysis was performed using Statistical Package for Social Sciences version 11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods were used to evaluate the data. The Kolmogorov–Smirnov test was performed to determine whether the parameters were normally distributed. Student *t* test and the Mann–Whitney test were applied to compare parameters among groups. Categorical variables were analyzed using the χ^2 test. Multiple logistic regression was performed to identify the independent markers that significantly affected GDM. Hosmer–Lemeshow goodness-of-fit statistics were calculated to assess the fit of the model. The area under the curve (AUC) for independent variables used to predict GDM was calculated using receiver operating characteristic (ROC) curve analysis. The 5% false positive rates (FPRs) of predictors in the ROC curve analysis were set as cutoff values for diagnostic performance. The results and 95% confidence intervals (CIs) were evaluated, and a p value ≤ 0.05 was considered statistically significant.

Results

In the data analyses, 38 pregnant women with GDM were included in the study group, and 295 pregnant women without GDM were included in the control group. A flowchart of the study population is shown in Figure 1. Comparisons of clinical, demographic, and laboratory findings of the GDM and control groups are shown in Table 1. Women subsequently diagnosed with GDM had significantly higher BMIs and MAPs compared with controls. Other maternal demographics were similar in both groups. The FBG, insulin, HbA1c, HOMA, TC, LDL-C, and TG levels were significantly higher in patients with GDM. The SHBG levels were significantly lower in the GDM group than in the control group.

Logistic regression analysis was performed to examine the predictive values of markers for GDM that showed a significant difference between the GDM and control groups. A significant correlation was found between the LDL and TC levels (0.868) as well as between the HOMA and the FBG and fasting insulin levels (0.896 and 0.995). Thus, the TC, FBG, and fasting insulin levels were excluded from the logistic regression analysis. Using the variables that exhibited a statistically significant difference between the groups (MAP, BMI, SHBG, HOMA, HbA1c, TG, and LDL), the independent predictors for GDM were examined in the logistic regression analysis. The SHBG, HOMA, LDL, and TG levels were significant independent predictors for GDM [adjusted odds ratio (OR) = 0.991 (95% CI, 0.986–995), OR = 1.56 (95% CI, 1.24–1.98), OR = 1.02 (95% CI, 1.01–1.04), and OR = 1.01 (95% CI, 1.00–1.02), respectively] (Table 2). The HbA1c level, BMI and MAP were not