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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

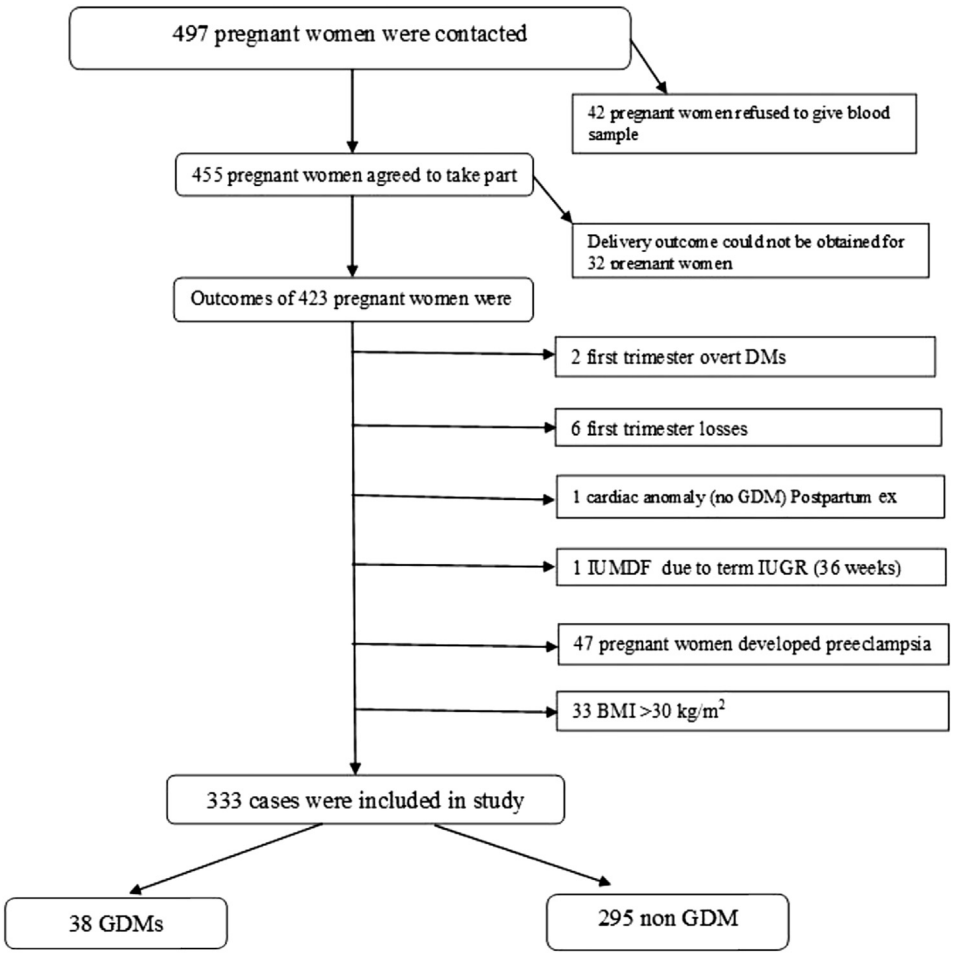

Figure 1. Flowchart of the study population. BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; IUGR = intrauterine growth restriction; IUMDF = in utero mort de fetus.

independent predictors. The model fit was confirmed by the Hosmer–Lemeshow test ($p = 0.477$) (Nagelkerke $R^2 = 0.41$).

The predictive accuracy of the HOMA, SHBG, TG, and LDL-C values as markers for GDM was determined by ROC curve analysis [AUC = 0.75 (95% CI, 0.67–0.83), AUC = 0.73 (95% CI, 0.65–0.82), AUC = 0.70 (95% CI, 0.60–0.79), and AUC = 0.72 (95% CI, 0.62–0.81), respectively] (Figure 2). The cutoff values for a 5% FPR, as well as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for predicting GDM are shown in Table 3. When 5.3 was used as a cutoff value for HOMA to predict subsequent GDM, the sensitivity, specificity, PPV, and NPV were 26.3%, 94.9%, 40%, and 90.9%, respectively. When 141 nmol/L was used as a cutoff value for the SHBG level to predict subsequent GDM, the sensitivity, specificity, PPV, and NPV were 21.1%, 94.9%, 34.8%, and 90.3%, respectively. When 129.6 mmol/L was used as a cutoff value for the LDL-C level, the sensitivity, specificity, PPV, and NPV were 18.4%, 94.9%, 33.3%, and 89.7%, respectively. When 182 mmol/L was used as a cutoff value for the TG level, the sensitivity, specificity, PPV, and NPV were 21.1%, 94.9%, 36.4%, and 89.7%, respectively.

Discussion

Identifying women with GDM is important during early pregnancy to minimize maternal and neonatal morbidity. Two-step (50-g GCT ± 100-g OGTT) and one-step (75-g OGTT) approaches are widely used for the diagnosis of GDM throughout the world, but these methods are more complicated, unpleasant, and costly. Thus, alternative diagnostic tests have been the subject of recent studies. The objective of our study was to define an optimal candidate marker during the first trimester for the prediction of GDM. The present study showed that the HOMA, SHBG, TG, and LDL-C levels are independent risk factors for the subsequent development of GDM during early pregnancy in low-risk pregnant women, irrespective of the confounding variables and hormones that may affect these markers (fT3, fT4, TSH).

Our study reported that first trimester HOMA-IR values were independent predictors for the development of GDM in logistic regression analysis, and the HOMA-IR value was found to be a better marker (AUC = 0.75; 95% CI, 0.67–0.83) than the other factors. We found that the +LR was 5.2 for the diagnosis of GDM, and when 5.3 was used as a cutoff for the HOMA-IR value, the sensitivity, specificity, PPV, and NPV were 26.3%, 94.9%, 40%, and 90.9%, respectively. Smirnakis et al [7] detected borderline significance in the multivariate analysis for risk of subsequent GDM for increased HOMA-IR values at gestational weeks 16–18, independent of other variables that are known to be associated with GDM. Ozcimen et al [8] determined the risk of GDM using the HOMA-IR value during the first trimester and found that a value of >2.60 appeared to be a good predictor of GDM. Interestingly, a HOMA-IR value of >2.60 had a sensitivity of 100%, specificity of 94%, PPV of 82%, and NPV of 100% for the diagnosis of GDM [8]. According to their study, the HOMA-IR was a unique test for the diagnosis of GDM. In our study,

Table 1
Comparison of clinical, demographic, and laboratory characteristics of gestational diabetes mellitus and control groups.

Variables	GDM group Mean ± SD or *n* (%) *N* = 38	Control group Mean ± SD or *n* (%) *N* = 295	*p*
Baseline characteristics			
Mean age (y)	28.6 ± 4.6	27.8 ± 4.7	0.278
Mean body mass index (kg/m^2)	24.9 ± 2.8	23.3 ± 2.9	0.001*
GA at fasting serum sampling (wk)	10.5 ± 2.7	10.8 ± 2.7	0.462
Nulliparous (%)	16 (42.1%)	110 (37.3%)	0.564
Gravida	1.9 ± 0.9	1.7 ± 1.1	0.081
Parity	0.5 ± 0.8	0.4 ± 0.7	0.427
Mean arterial blood pressure (mmHg)	84.3 ± 9.4	81.3 ± 7.7	0.032*
Systolic blood pressure (mmHg)	110.4 ± 11.3	106.9 ± 9.8	0.041*
Diastolic blood pressure (mmHg)	71.2 ± 9.9	68.6 ± 8.1	0.067*
Smoking status yes (%)	10 (26.3%)	74 (25.1%)	0.869
Laboratory characteristics			
Fasting glucose (mg/dL)	89.9 ± 8.9	84.3 ± 7.8	<0.001*
Fasting insulin (μU/dL)	17.8 ± 8.9	10.9 ± 6.6	<0.001*
Insulin resistance index (HOMA-IR)	4.04 ± 2.2	2.3 ± 1.5	<0.001*
50 g PGL (mg/dL)	169.3 ± 25.7	110.1 ± 19.9	<0.001*
100 g fasting PGL (mg/dL)	86.6 ± 28.8	92.0 ± 14.1	0.364
100 g 1 h PGL (mg/dL)	172.1 ± 57.7	151.7 ± 21.4	0.078
100 g 2 h PGL (mg/dL)	145.1 ± 49.6	127.8 ± 17.9	0.081
100 g 3 h PGL (mg/dL)	114.1 ± 39.7	108.1 ± 17.1	0.461
Glycosylated hemoglobin (HbA1c) (%)	5.5 ± 0.3	5.3 ± 0.2	<0.001*
Sex hormone-binding globulin (nmol/L)	195.7 ± 97.7	281.3 ± 92.6	<0.001*
Thyroid-stimulating hormone (TSH) (μU/mL)	2.0 ± 2.8	1.7 ± 1.2	0.202
Free thyroxine (fT4) (ng/dL)	1.2 ± 0.3	1.2 ± 0.2	0.863
Total cholesterol (TC) (mmol/L)	194.0 ± 39.2	171.8 ± 32.8	<0.001*
High density lipoprotein cholesterol (HDL-C) (mmol/L)	63.3 ± 13.0	68.2 ± 16.3	0.078
Low density lipoprotein cholesterol (LDL-C) (mmol/L)	107.2 ± 29.6	86.7 ± 24.6	<0.001*
Triglyceride (TG) (mmol/L)	144.9 ± 65.9	105.8 ± 39.6	<0.001*

HOMA-IR = Fasting glucose (mg/dL) × Fasting insulin (uIU/mL)/405.
* Significant differences ($p < 0.05$) of Student *t* test, and in cases of non-normally distributed variables Mann–Whitney for continuous variables. Categorical variables were analyzed using chi-square test.
GA = gestational age; GDM = gestational diabetes mellitus; HOMA-IR = homeostasis model assessment of insulin resistance; PGL = plasma glucose level; SD = standard deviation.

we found that the mean HOMA-IR values were 4.04 ± 2.2 in women with GDM and 2.3 ± 1.5 in the control group. Similarly, Smirnakis et al [7] reported HOMA-IR values of 3.5 ± 2.5 in the GDM group and 2.0 ± 1.3 in the control group. Ozcimen et al [8] reported that the mean HOMA-IR values were 4.7 ± 3.9 in women with GDM and 1.3 ± 0.6 in women without GDM. The range of HOMA-IR values was wide in women with GDM and narrow in women without GDM, which was a possible reason for the high sensitivity and PPV.

Another marker, SHBG, is a glycoprotein secreted by the liver that binds to sex steroids in circulation [9]. Thadhani et al [10] were the first group to report that pregnant women with low SHBG levels during the first trimester had a high risk of developing subsequent GDM. They also emphasized that evaluation during the first trimester is important because the difference in IR between women with abnormal and normal glucose tolerance diminishes as the pregnancy progresses [10]. Smirnakis et al [7] reported that the mean SHBG levels were 185.1 ± 105.1 nmol/L in women with GDM and 255.6 ± 92.1 nmol/L in the control group, and that SHBG appeared to be the optimal marker to predict subsequent GDM during the first trimester. In the present study, the mean SHBG levels were 195.7 ± 97.7 nmol/L in women with GDM and 281.3 ± 92.6 nmol/L in the control group, and decreased SHBG levels were independent predictors for GDM in the low-risk pregnancy group during early pregnancy. We also reported that an SHBG value of ≥141 nmol/L (with a 5% FPR) had a sensitivity of 21.1%, PPV of 34.8%, and NPV of 90.3% for predicting subsequent development of GDM (AUC = 0.73; 95% CI, 0.65–0.82). Caglar et al [11] evaluated the predictive value of SHBG for the diagnosis of GDM at 13–16 weeks of gestation and reported an AUC of 0.675 (95% CI, 0.555–0.795) by ROC analysis. The cutoff value of 97.47 exhibited the greatest sensitivity and PPV in this evaluation. Similar to our study results, these authors reported that the SHBG threshold of 97.47 nmol/L (approximately 15% FPR) had a sensitivity of 46.7%, specificity of 84.1%, PPV of 58.3%, and NPV of 76.8%.

Thadhani et al [10] noted that when a SHBG value of 175 nmol/L was used as a cutoff value, a twofold increased risk of GDM (OR = 2.2; 95% CI, 1.1–4.5) was detected compared with the control group. We found that an SHBG value of ≥141 nmol/L resulted in a 4.5-fold increased risk of GDM, whereas McElduff et al [12] reported that the SHBG serum concentration could not predict the presence of GDM, and no difference was detected between SHBG concentrations of pregnant women receiving or not receiving insulin therapy. Nanda et al [13] found that adiponectin and SHBG levels were lower in patients who developed GDM than in the control group, and they reported that the detection rate for GDM

Table 2
Results of logistic regression analyses for prediction of gestational diabetes mellitus.

Variables	Odds ratio	95% Confidence interval (lower–upper)
Body mass index	1.07	0.93–1.23
Mean arterial blood pressure	1.03	0.98–1.09
Glycosylated hemoglobin	1.11	0.22–5.57
Insulin resistance index	1.56	1.24–1.98*
Sex hormone-binding globulin	0.991	0.986–0.995*
Low density lipoprotein cholesterol	1.02	1.01–1.04*
Triglyceride	1.01	1.00–1.02*

Model is adjusted for maternal age, first trimester body mass index and mean arterial pressure.
* Significant differences ($p < 0.05$).

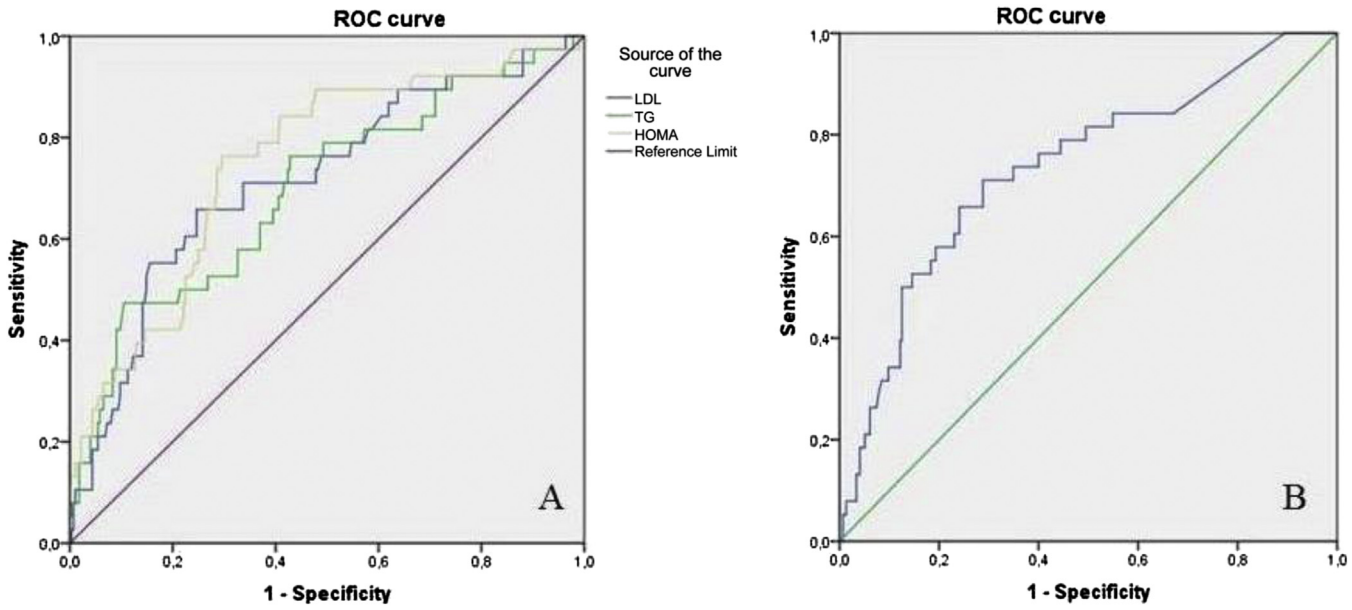

Figure 2. (A) Receiver–operator curve (ROC) showing the predictive probabilities of first-trimester HOMA, LDL-C, and TG levels for gestational diabetes mellitus. (B) Receiver–operator curve showing the predictive probabilities of first-trimester sex hormone-binding globulin levels for gestational diabetes mellitus. HOMA = homeostasis model assessment; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Table 3
Univariate receiver–operator curve analysis for the predictive accuracy of each marker for gestational diabetes mellitus at a fixed false-positive rate of 5%.

	ROC area (95% CI)	Cutoff value	Sens	Spec	NPV	PPV	+LR	−LR	OR (95% CI)
HOMA	0.75 (0.67–0.83)	≥5.3	26.3	94.9	90.9	40	5.2	1.3	6.88 (2.98–15.87)
SHBG	0.73 (0.65–0.82)	≥141	21.1	94.9	90.3	34.8	4.1	1.2	4.44 (1.84–10.75)
LDL-C	0.72 (0.62–0.81)	≥129.6	18.4	94.9	89.4	33.3	3.6	1.2	4.23 (1.59–11.25)
TG	0.70 (0.60–0.79)	≥182	21.1	94.9	89.7	36.4	4.1	1.2	4.99 (1.94–12.87)

CI = confidence interval; HOMA = homeostasis model assessment; LDL-C = low-density lipoprotein cholesterol; +(LR) = positive likelihood ratio; −(LR) = negative likelihood ratio; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; ROC = receiver operating characteristic; sens = sensitivity; SHBG = sex hormone-binding globulin; spec = specificity; TG = triglyceride.

increased to 74.1% when these factors were combined with maternal risk factors. Furthermore, they emphasized that the detection rate increased to 65% (with a 20% FPR) when these biochemical markers were combined with maternal risk factors in pregnant women without a history of GDM [13].

This study also determined that the lipid profile, maternal serum LDL-C level, and TG level are independent risk factors for the prediction of GDM during early pregnancy in patients included in the low-risk group. We reported that an LDL-C level of ≥129.6 mmol/L (5% FPR) had a sensitivity of 18.4% and a PPV of 33.3%, whereas a TG level of ≥182 mmol/L (5% FPR) had a sensitivity of 21.1% and a PPV of 36.4% for predicting subsequent GDM. We also detected a fivefold increased risk for GDM. Enquobahrie et al [14] reported a 3.5-fold increased risk for GDM in women with elevated serum TG levels during the 13th gestational week using a TG level cutoff value of ≥137 mg/dL after adjusting for prepregnancy adiposity and other factors. They also observed that each 20-mg/dL increment was associated with a 10% increase in the risk of GDM. However, they did not determine a significant relationship between the risk of GDM and the plasma concentrations of other lipids (TC, HDL-C, and LDL-C) [14]. In contrast, Vitoratos et al [15] found no significant difference between the GDM and non-GDM groups in terms of serum TC, TG, and LDL-C levels.

Although the current study detected a significant difference between the HbA1c levels in subsequent GDM and non-GDM groups, the HbA1c level was not found to be an independent predictor of GDM. Agarwall et al [16] reported that a threshold value of 5.5% for HbA1c resulted in a sensitivity of 82.1% and NPV of 83.3%, whereas a threshold value of 7.5% yielded a specificity of 95.8% and a PPV of 28.6% for GDM in high-risk pregnancies. A high FPR was found for the HbA1c threshold that produced an acceptable sensitivity, which resulted in more healthy women undergoing an OGTT. Similar to our results, the HbA1c level was found to be an unfavorable screening test for GDM [16].

To our knowledge, this is the only study in the literature that includes such strict criteria for the selection of a low-risk group. As mentioned previously, whereas the HOMA value, SHBG level, and lipid profiles during early pregnancy have been suggested as markers to select patients at risk for subsequent GDM (especially for a high-risk pregnancy group), our study demonstrated that these markers are not sufficient to predict GDM in a low-risk pregnancy group with a low sensitivity and high specificity.

In conclusion, we determined that the HOMA, SHBG, TG, and LDL-C levels during the first trimester are independent risk factors for GDM, but they have a low sensitivity and PPV.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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