PERINATAL JOURNAL

Original Article

Perinatal Journal 2022;30(2):136–143

Prediction of gestational diabetes mellitus in the first trimester: is it possible?

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Abstract

Objective: The aim of this study is to identify the first trimester markers that may be associated with gestational diabetes mellitus (GDM) and to evaluate whether those markers might be used for prediction of gestational diabetes or not.

Methods: Pregnant women between 11 and 14 weeks of gestation applying to the university hospital between August 2018 and March 2019 were included in the study. Body mass index calculation and blood tests including complete blood count, TSH, T3, T4, HbA1c, uric acid, CRP, procalcitonin, PAPP-A and β-hCG levels were done during assessment followed by 50 grams of glucose challenge test between the 24 and 28 weeks of gestation for each woman. Patients with positive results were further evaluated with a 3-hour, 100-g OGTT. According to the diagnostic test results, the relationship between biochemical markers during the first trimester, BMI and GDM was statistically analyzed.

Results: A hundred and eighty-two pregnant women participated in the study. Fifty-four women had positive glucose challenge test (GCT) results while 128 women had negative results. Pregnant women with positive GCT results underwent 3-hour, 100-g OGTT and, 24 pregnant women were diagnosed with GDM, while 158 pregnant women were considered healthy according to the results. There was no statistically significant difference between GDM and non-GDM groups in terms of age, height, TSH, T3, T4, β-hCG-mom, PAPP-A, PAPP-A-mom, uric acid and procalcitonin ($p>0.05$). The mean body weight, body mass index and HbA1c levels were higher and β-hCG levels were lower in the GDM group compared to the non-GDM group, and these findings were statistically significant ($p<0.001$).

Conclusion: The use of first trimester markers in GDM prediction seems to have no significance. There is a need for extensive, randomized studies with universal criteria.

Keywords: Gestational diabetes, pregnancy-induced gestational diabetes, oral glucose tolerance test.

Introduction

Gestational diabetes mellitus (GDM) is defined as a varying degree of carbohydrate intolerance beginning or first noticed during pregnancy. It is the most common medical complication of pregnancy that increases maternal and neonatal morbidity. Gestational diabetes prevalence varies from 1% to 6% in surveyed communities.[1] The prevalence in Turkey is between 4% and 10%.[2–4] Prevalence increases with increasing mean mother age and obesity rates.[5] The prediction and diagnosis of GDM are important both for existing pregnancy and health of the mother after pregnancy.

Gestational diabetes has been associated with an increased risk of some perinatal adverse outcome, gestational hypertension, polyhydramnios, macrosomia, birth traumas in mother and baby, operative delivery, perinatal mortality, fetal/neonatal hypertrophic cardiomyopathy, neonatal respiratory conditions and metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia, and polycythemia).[6–10] Both

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How to cite this article: Hansu İ, Hansu K, Balık Z, Özdemir H, Yücel N. Prediction of gestational diabetes mellitus in the first trimester: is it possible? Perinat J 2022;30(2):136–143. doi:10.2399/prn.22.0302004

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maternal and fetal complications may be reduced with early diagnosis and treatment of gestational diabetes.

GDM is diagnosed between the 24 and 28 weeks of gestation either by 75-g oral glucose tolerance test (OGTT) performed in a single time or by 50-g oral glucose screening test followed by 100-g OGTT if 50-g test is positive.[11] However, OGTT is a time-consuming, labor-intensive test that is often not well tolerated by pregnant women. It requires overnight fasting and sitting more than 3 hours and blood sample collection at least 3 times during the test. Approximately 10% of pregnant women cannot complete oral glucose tolerance test along with increasing nausea and vomiting during pregnancy.[12] Also diagnosing GDM after 24 weeks of gestation may cause prolonged exposure to intrauterine hyperglycemia and increased fetal growth, as well as an increase in cardiovascular risk of mother.[13–15]

Studies aimed at prediction and diagnosis of GDM during early stages of pregnancy have been increased in accordance with these evidences. However, there is no consensus on which test, or biochemical marker can be used for screening GDM in the early stages of pregnancy.

Specification of GDM-related markers in the early stages of pregnancy will be very beneficial to manage pregnant women at risk of GDM and in reducing diabetes-related complications. In this study, we aimed to identify the first trimester markers that may be associated with GDM and to evaluate if these markers may be used in predicting gestational diabetes.

Methods

This is a prospective study conducted in the Department of Obstetrics & Gynecology, School of Medicine, Kahramanmaraş Sütçü İmam University between August 2018 and March 2019. The study was approved by the Clinical Research Ethics Committee of School of Medicine of Kahramanmaraş Sütçü İmam University in 04.07.2018 with the decision number 2018/11-24. The study was conducted in accordance with the principles of Helsinki Declaration. Written informed consent was obtained from pregnant women participating in the study. Pregnant women aged 18–40 years old, between 11 and 14 weeks of gestation, applying to our clinic were included in the study. Pregnant women who had diabetes, chronic hypertension, systemic disease, and multiple pregnancies were excluded. Medical history, height and weight were recorded and BMI was calculated as kg/m^2. Then, blood samples were collected for complete blood count, thyrotropin (TSH), triiodothyronine (T3), thyroxine (T4), glycosylated hemoglobin (HbA1c), uric acid, C-reactive protein (CRP), procalcitonin and first trimester screening tests including pregnancy associated plasma protein-A (PAPP-A) and serum beta-human chorionic gonadotrophin (β-hCG) levels, and analyzed with COBAS-8000 (Roche Diagnotics, Basel, Switzerland) device and HbA1c was analyzed with Variant-2 (Bio-Rad Laboratories, Hercules, CA, USA) device. Results were recorded and filed. Pregnant women participating in the study were invited for gestational diabetes screening with 50-g glucose challenge test between 24 and 28 weeks of gestation. Plasma glucose level one hour after 50-g glucose challenge test was evaluated. Patients were considered positive if plasma glucose levels were above 135 mg/dL; if they were positive, 3-hour, 100-g OGTT was performed and results were evaluated according to Carpenter-Coustan criteria (fasting plasma glucose <95 mg/dl, first hour <180 mg/dl, second hour <155 mg/dl, third hour <140 mg/dl). Diagnostic test result was considered positive in pregnant women with at least 2 abnormal results. The patients were divided into two groups as positive and negative diagnostic test groups. The relationship between the first trimester biochemical markers, BMI and gestational diabetes was statistically evaluated.

Normal distribution of continuous variables was tested using Kolmogorov-Smirnov test. Levene's test was used for assessing homogeneity of variances. Descriptive statistics were expressed as mean ± standard deviation or median (interquartile range of distribution) for continuous numerical variables, and as number of cases and (%) for sortable variables. Significance of difference between groups was assessed with Student's t test in continuous variables which met parametric test assumptions while continuous variables which did not meet parametric test assumptions were analyzed with Mann-Whitney U test. Multivariate logistic regression analysis was used to identify the most predictive factors between glucose challenge test (GCT) negative and positive cases and, OGTT-negative and positive cases in GCT-positive group. Variables determined $p<0.25$ as a result of univariate statistical analyzes were included in the multivariate logistic regression model as candidate factors. In addition, odds ratio, 95% confidence interval and Wald statistics for each variable were calculated.

Data were analyzed using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) software package. A p-value less than 0.05 was considered statistically significant.

Results

A hundred and eighty-two pregnant women participated in the study. The participants were divided into two groups according to GCT results. GCT results were positive in 54 participants and negative in 128 participants. Glucose challenge test positive pregnant women received a 3-hour OGTT, and according to the results, 24 women were diagnosed with GDM while others were considered healthy.

There was no statistically significant difference between GCT-negative and GCT-positive groups in terms of age, height, thyroid function tests, β-hCG, PAPP-A, uric acid, procalcitonin and CRP (p>0.05). The mean body weight and body mass index were statistically significantly higher in GCT-positive group compared to GCT-negative group (p<0.001) (**Fig. 1**). HbA1c level was also significantly higher in GCT-positive group compared to GCT-negative group (p<0.001). Demographic, anthropometric and biochemical variables of the cases in OGTT-positive and negative groups were compared (**Table 1**). There was no statistically significant difference between OGTT-negative (non-GDM) and OGTT-positive (GDM) groups in terms of age, height, thyroid function tests, β-hCG-mom, PAPP-A, PAPP-A-mom, uric acid, procalcitonin and CRP (p>0.05). The mean body weight was significantly higher in OGTT-positive group compared to negative group (p<0.001). In addition, body mass index was significantly higher in OGTT-positive group in comparison with negative group (p<0.001) (**Fig. 2**). There was also a statistically significant difference in terms of body mass index distribution between groups, and body mass index of OGTT-positive group was categorized into a higher BMI group compared to those in negative group (p<0.001). The β-hCG level was significantly lower in OGTT-positive group compared to OGTT-negative group (p=0.041). HbA1c level was significantly higher in OGTT-positive group than the negative group (p<0.001).

According to the multivariate logistic regression analysis, the most determinant factor(s) in differentiating the GCT-negative and GCT-positive groups were determined (**Table 2**). Variables found to be p<0.25 as a result of univariate statistical analyzes were included in the multivariate logistic regression model as candidate risk factors. HbA1c was the most determinant factor in distinguishing between GCT-negative and GCT-posi-

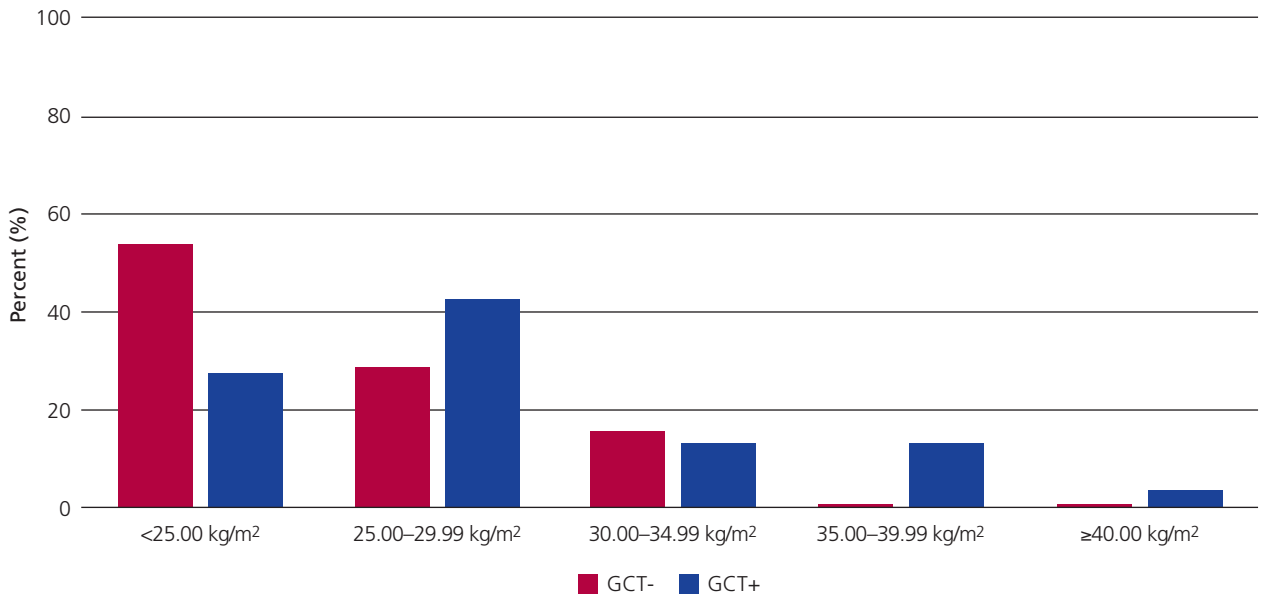

Fig. 1. Body mass index in GCT-positive group compared to GCT-negative group.

Table 1. Demographic characteristics, and anthropometric and biochemical measurements of OGTT-negative and positive groups.

	non-GDM (n=158)	GDM (n=24)	Total (n=182)	p-value
Age (years)	27.6±5.5	27.4±5.8	27.5±5.5	0.912*
Body weight (kg)	66.6±13.4	81.2±14.0	68.5±14.7	**<0.001***
Height (cm)	161.8±5.4	161.2±5.2	161.7±5.3	0.638*
BMI (kg/m²)	25.4±4.7	31.2±6.2	26.2±5.3	**<0.001***
BMI				**<0.001†**
<25.00 kg/m²	80 (50.6%)	4 (16.7%)	84 (46.2%)	
25.00–29.99 kg/m²	51 (32.3%)	9 (37.5%)	60 (33.0%)	
30.00–34.99 kg/m²	24 (15.2%)	3 (12.5%)	27 (14.8%)	
35.00–39.99 kg/m²	2 (1.3%)	6 (25.0%)	8 (4.4%)	
≥40.00 kg/m²	1 (0.6%)	2 (8.3%)	3 (1.6%)	
T3	3.0 (0.4)	3.1 (0.4)	3.0 (0.4)	0.312†
T4	1.2 (0.2)	1.1 (0.2)	1.2 (0.2)	0.283†
TSH	1.4 (1.4)	1.2 (1.0)	1.3 (1.4)	0.861†
β-hCG	31.1 (30.2)	23.0 (27.2)	30.7 (30.6)	**0.041†**
β-hCG (mom)	0.9 (0.7)	0.6 (0.8)	0.9 (0.7)	0.061†
PAPP-A	2.1 (1.8)	1.7 (2.0)	2.0 (1.9)	0.148†
PAPP-A (mom)	0.8 (0.5)	0.8 (0.6)	0.8 (0.5)	0.630†
HbA1c	5.1 (0.4)	5.3 (0.5)	5.1 (0.4)	**<0.001†**
Uric acid	3.1 (1.1)	3.1 (1.4)	3.1 (1.1)	0.768†
Procalcitonin	0.025±0.101	0.032±0.056	0.026±0.096	0.742*
CRP	5.8 (6.8)	8.0 (9.7)	6.1 (7.63)	0.394†

*Student's t test; †Mann-Whitney U test. **BMI:** body mass index.

tive groups. Independent of other factors, each 1-unit increase in HbA1c level increased the probability of being positive for GCT by 6.441 times (95% CI: 2.005–20.697) (p=0.002).When adjustments were made for other factors, BMI, which had a statistically significant effect previously, disappeared (p=0.124). According to multivariate logistic regression analysis, the most determining factor(s) in differentiating the group with negative OGTT results and the group with positive OGTT results among GCT-positive cases were determined (**Table 3**). Variables found to be p<0.25 as a result of univariate statistical analyzes were included in the multivariate logistic regression model as candidate risk factors. Body mass index was the most determinant factor in differentiating OGTT-negative and OGTT-positive groups. Independent of other factors, each 1 kg/m² increase in body mass index increased the probability of being positive for OGTT by 1.197 times statistically (95% CI: 1.049–1.367) (p=0.008).

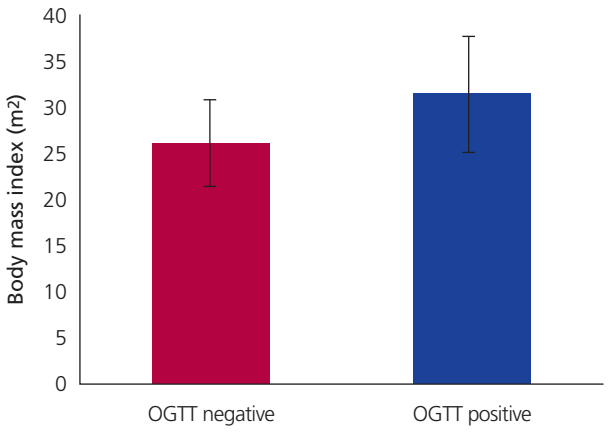

Fig. 2. Body mass index in OGTT-negative group compared to OGTT-positive group.

Discussion

It is known that body mass index before pregnancy has a critical role in development of GDM as well as insulin resistance and type 2 diabetes. Thirty metanalyses were analyzed in an umbrella review of observational studies conducted under by Giannakou in 2019 and it was deter-

Table 2. Determining the most determinant factors in differentiating GCT-negative and GCT-positive groups according to multivariate logistic regression analysis.

		95% CI			
	Odds ratio	Lower limit	Upper limit	Wald	p-value
BMI	1.058	0.985	1.137	2.367	0.124
β-hCG	0.993	0.977	1.009	0.706	0.401
HbA1c	6.441	2.005	20.697	9.782	**0.002**
CRP	1.011	0.965	1.059	0.212	0.645

BMI: body mass index.

mined that low or normal body mass index was the most important protective factor in development of GDM.[16] In our study, body mass index was the most determining factor in differentiating groups with positive and negative OGTT results. Our findings show that maternal body weight and body mass index have a major role in development of GDM similar to previous studies.

Both GDM and thyroid dysfunction are known to have an influence on pregnancy and pregnancy outcomes.[17,18] Although some studies revealed the relationship between thyroid dysfunction and GDM, no correlation has been shown in some other studies.[19–22] In a metanalysis performed by Toulis et al., pregnant women with subclinical hypothyroidism were found to have a 1.35-fold increase in the incidence of GDM compared to the control group (95% CI: 1.05–1.75).[19] In a retrospective study conducted by Shuai Yang et al., TSH and free T4 (fT4) levels were found to be significantly low in women diagnosed with GDM.[20] In our study, we did not find any statistically significant difference between groups in terms of thyroid function test.

PAPP-A produced by trophoblasts during pregnancy can be detected in maternal blood from the 28th day of pregnancy. In previous studies, PAPP-A was shown to play a role in the regulation of IGF. Considering the effect of IGF on glycemic control, the correlation between PAPP-A and glucose levels may be explained. However, existing studies are insufficient to fully explain the level of this correlation. In many studies, it was shown that pregnant women developing GDM had lower levels of serum PAPP-A and β-hCG during the first trimester compared to healthy pregnant women.[23–26] In a study conducted by Cheuk et al., it was found that PAPP-A mom and β-hCG mom values were not statistically significant in predicting GDM.[27] In another study, PAPP-A mom levels were lower in GDM patients compared to control group but there was no significant difference between groups in terms of β-hCG levels.[28] It is obvious that studies, conducted about predicting gestational diabetes with serum β-hCG and PAPP-A levels and the correlation between these markers in pregnant women with GDM, have different results from each other.[23–30] According to our study, PAPP-A and β-hCG, the first trimester screening markers, do not seem to be successful enough in predicting gestational diabetes.

The effect of HbA1c has been shown on pregnancy outcomes.[31] HbA1c is currently used for the diagnosis and follow-up of diabetes mellitus and it is an indicator

Table 3. According to multivariate logistic regression analysis, determining the most determinant factors in differentiating the group with negative OGTT results and the group with positive OGTT results among GCT-positive cases.

		95% CI			
	Odds ratio	Lower limit	Upper limit	Wald	p-value
BMI	1.197	1.049	1.367	7.083	**0.008**
T3	1.764	0.373	8.347	0.512	0.474
β-hCG	0.988	0.959	1.018	0.604	0.437
PAPP-A	0.934	0.589	1.480	0.085	0.771

BMI: body mass index.

of the mean glycemia level within last 2–3 months. In a study conducted by Kumru et al., HbA1c has been shown to have no predictive value for GDM.[32] Although the correlation between HbA1c and GDM was shown in the study of Agarwall et al., it was stated that HbA1c was not a useful marker in predicting GDM due to its high false-positive rate (using a value of HBA1c ≥7.5% to rule-in GDM; 15 (71.4%) of 21 patients over the threshold being false-positives).[33] In our study, there was a correlation between GDM and HbA1c as well, but using a threshold value of >5.5% to rule-in GDM; 7 (44.8%) of 16 patients over the threshold value being false-positives.

Uric acid is the final product of the oxidation step of purine catabolism. It is an important marker for predicting insulin resistance and metabolic syndrome development. In the study of Rasika et al., a linear relationship was found between high serum uric acid levels and increased risk of GDM.[34] In a study regarding the relationship between uric acid levels during the first trimester and GDM by Laughon et al., the relationship was shown between uric acid levels and GDM alike the study of Rasika et al.[35] However, it was reported that uric acid could not be used as a predictor of GDM in the study of Laughon et al. since it had a low positive-predictive value 9%, with a cut-off point of 3.6 mg/dL. Similar to our study, no correlation was found between uric acid and GDM in a prospective study with 112 pregnant women conducted by Güngör et al.[36] According to our study, uric acid level during the first trimester is not a useful marker in predicting GDM.

Wolf et al. compared the first trimester CRP levels between healthy pregnant women and pregnant women with GDM, and found that CRP levels were significantly higher in pregnant women with GDM.[37] However, CRP level may also increase during normal pregnancy. Although a correlation has been shown between CRP and GDM, a prediction interval could not be determined in the study. Similar to our study, no correlation was found between serum CRP level during the first trimester and GDM.[38] According to our study, serum CRP level is not a useful marker to be used for predicting GDM. We studied another inflammatory marker, procalcitonin, and we did not find any significant difference.

Our study has some limitations. The most important limitation of our study is the limited number of patients included; this small number has prevented us from performing subanalysis such as insulin requirements and evaluating pregnancy outcomes. The main strength is the prospective structure and the evaluation of several biochemical markers at the same time. Nevertheless, multicentered and prospective studies evaluating similar variables with large sample size are needed to determine the markers that can be used in prediction of GDM.

Conclusion

Body weight, BMI and HbA1c values were significantly higher in GDM group but the use of first trimester markers such as thyroid function tests, β-hCG, PAPP-A, uric acid, procalcitonin and CRP seems to have no significance in GDM prediction. There is a need for extensive, randomized studies with universal criteria.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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