



Evaluation of the Relationship Between 1st Trimester HbA1C, Fasting Blood Glucose, Thyroid Function Tests and Gestational Diabetes Mellitus

1. Trimester HbA1C, Açlık Kan Şekeri ve Tiroid Fonksiyon Testlerinin Gestasyonel Diabetes Mellitus ile İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to examine the relationship between gestational diabetes mellitus (GDM) and fasting blood glucose (FBG), thyroid function tests, and HbA1C values in the first trimester of healthy pregnant women who do not have DM and visit our gynecology and obstetrics polyclinic for regular checkups.

Methods: This retrospective study included pregnant patients who applied to the Karaman Training and Research Hospital, Clinic of Obstetrics and Gynecology between 01.08.2023 and 01.05.2024. The department applied statistical analyses using the Statistical Package for the Social Sciences (SPSS Inc., version 20.0; Chicago, IL). Statistical significance was set as $p < 0.05$.

Results: Our study included 78 patients: 59 (75.6%) were in the non-GDM group and 19 (24.4%) were in the GDM group. We calculated the under the curve as 0.912 (0.60-0.96) for 2nd trimester FBG at a cut-off value of 88 and 0.786 (0.37-0.93) for 2nd trimester HbA1C at a cut-off value of 5. We observed that both 2nd trimester FBG and 2nd trimester HbA1C significantly outperformed 1st-trimester FBG in predicting GDM ($p=0.00$, $p=0.04$). It was observed that 2nd-trimester FBG predicted GDM significantly better than 2nd-trimester HbA1C ($p=0.028$). Although no statistically significant difference was detected between 1st trimester HbA1C and 2nd trimester HbA1C in predicting GDM ($p=0.481$), it was observed that 2nd trimester FBG predicted GDM statistically significantly better than first trimester HbA1c ($p=0.004$).

Conclusion: First- and second-trimester HbA1c and FBG and oral glucose tolerance test (OGTT) values can predict gestational diabetes. HbA1C cannot be used instead of OGTT, but it is an important predictor.

Keywords: Gestational diabetes mellitus, fasting blood glucose, HbA1c, thyroid function test

ÖZ

Amaç: Çalışmamızın amacı, kadın hastalıkları ve doğum polikliniğimize düzenli kontrollerine gelen sağlıklı ve bilinen diabetes mellitus (DM) tanısı olmayan gebelerin birinci trimesterdeki açlık kan şekeri (AKŞ), tiroid fonksiyon testleri ve HbA1C değerlerinin gestasyonel DM (GDM) ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmamız retrospektif olarak planlanmış olup, Karaman Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne 01.08.2023-01.05.2024 tarihleri arasında başvuran gebe hastalar çalışmaya dahil edildi. İstatistiksel analizlerde SPSS Inc., versiyon 20.0; Chicago, IL kullanıldı. İstatistiksel anlamlılık $p < 0,05$ olarak kabul edildi.

Bulgular: Çalışmamızda toplam hasta sayısı 78 olup hastalarımızın 59'u (%75,6) GDM olmayan, 19'u (%24,4) ise GDM olan gruba dahildi. Hesaplanan eğri altında kalan alan değeri 2. trimester AKŞ için 88 kesim değerinde 0,912 (0,60-0,96), 2. trimester HbA1C için 5 kesim değerinde 0,786 (0,37-0,93) olarak hesaplandı. İkinci trimester AKŞ'nin ve 2. trimester HbA1C'nin 1. trimester AKŞ'ye göre GDM'si, istatistiksel anlamlı olarak daha iyi öngördüğü gözlemlendi ($p=0,00$, $p=0,04$). İkinci trimester AKŞ'nin 2. trimester HbA1C'ye göre ise GDM'si istatistiksel anlamlı olarak daha iyi öngördüğü gözlemlendi ($p=0,028$). İkinci trimester AKŞ'nin 1. trimester HbA1C'ye göre GDM'si istatistiksel anlamlı olarak daha iyi öngördüğü gözlemlendi ($p=0,004$).

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Sonuç: Birinci ve ikinci trimester HbA1C ile ikinci trimester FBG ve OGTT değerleri, gestasyonel diyabeti öngörebilmektedir. HbA1C, OGTT yerine kullanılamaz ama önemli bir prediktördür.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, açlık kan şekeri, HbA1c, tiroid fonksiyon testleri

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disease diagnosed during pregnancy (1,2). Although its prevalence has been gradually increasing, the average is 17.8% (9.3%-25.5%) (3). Mothers diagnosed with GDM have a higher risk of adverse birth outcomes, and their risk of being diagnosed with type 2 DM in later life increases by sevenfold (4-6). Important risk factors for GDM: body mass index >38.6 kg/m², fasting blood glucose (FBG) (rapid blood sugar) > 81 mg/dL, presence of polycystic ovary syndrome, and abdominal circumference >91.5 cm. The multiple coexistence of these risk factors significantly increases the incidence of GDM (7). Thyroid hormones are a group of hormones that are very important for both the mother and the fetus in maintaining current and long-term health (4). Thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroglobulin, and thyroid peroxidase antibody (anti-TPO) are the most commonly used tests to measure thyroid functions (4). Thyroid dysfunction is closely related to DM; While the prevalence of thyroid dysfunction increases in patients diagnosed with type 1 and 2 DM, the risk of type 2 DM also increases in people with thyroid dysfunction (4-7). Physiological changes are observed in thyroid function during pregnancy, and inadequate adaptation to these changes leads to thyroid dysfunction (8).

Glycosylated hemoglobin (HbA1C) is a test used for the diagnosis and follow-up of Type 2 diabetes. The HbA1C test reflects the average glucose concentration over the last two to three months. FBG and oral glucose tolerance test (OGTT) are instantaneous values. Fasting is not necessary for HbA1C analysis (7,9). The ADA has accepted an HbA1C level of ≥ 6.5 among the diagnostic criterion for diabetes (10). There are many studies in the literature that evaluate the relationship between thyroid function tests (TFT) (4-6) and HbA1C and GDM (11,12). However, there are a limited number of studies in which TFT, fast blood glucose (FBG), and HbA1C were evaluated together (13), and the first trimester (14), and comparisons of the first and second trimesters were investigated (15).

Aim

The primary aim of our study was to evaluate the relationship between GDM and TFT, FBG, and HbA1C values in the first trimester of pregnant women who are healthy and have no known diagnosis of DM and come to our gynecology and

obstetrics polyclinic for regular checkups. Our secondary aim was to compare the relationship between FBG, TFT and HbA1C values in the first and second trimesters with GDM.

METHODS

Study Design

Our study was planned retrospectively, and pregnant patients who applied to Karaman Training and Research Hospital, Clinic of Obstetrics and Gynecology between 01.08.2023 and 01.05.2024 were included in the study. This hospital is a high-volume regional hospital with intensive referrals. The instant study was carried out with the permission of Local Ethics Committee of the Karamanoğlu Mehmetbey University Faculty of Medicine (number: 06-2024/19, date: 30.05.2024).

Patient Population

Pregnant women with live singletons, over the age of 18, who regularly came for pregnancy follow-up, and whose last menstrual date was known were included in our study. Pregnant women with known type 1 and type 2 DM, multiple pregnancies, pregnancies with anomalies, pregnant women who did not accept OGTT screening or could not tolerate OGTT, pregnant women with comorbidities, and pregnancies that ended with abortion and baby death in the womb during their follow-up were not included in the study.

Data Collection

Obstetric information of pregnant women (gravide, parity, abortion), age, height, weight, examination findings, 1st and 2nd Trimester FBG, HbA1C, TFT, 75 gr. OGTT results were recorded by scanning the hospital database. In our study population, those diagnosed with gestational diabetes and those not diagnosed with gestational diabetes were recorded. The 1st trimester test results were obtained with data between the 6th and 13th weeks of pregnancy, and the 2nd trimester test results were obtained with data from the 24th and 28th weeks of pregnancy of the same pregnant women.

Diagnosis of GDM: GDM was diagnosed with routine examination and OGTT scan results. GDM was diagnosed with 75-g oral OGTT according to American Diabetes Association (ADA) criteria (10). Gestational diabetes was diagnosed when one of the following criteria was positive:

FBG: 92 mg/dL, 180 mg/dL in the 1st hour after OGTT, and 153 mg/dL in the 2nd hour after OGTT.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc., version 20.0; Chicago, IL) was used for statistical analyses applied to the department. Normal analysis of continuous data was performed using the Shapiro-Wilk test. Those with normal distribution were determined using Student's t-test. Those that did not conform to the normal distribution were evaluated using the Mann-Whitney test and Brunner Munzel test. The HbA1c, fasting blood sugar, and other hormonal parameters of pregnant women diagnosed with and without GDM were compared using the Mann-Whitney U test and Brunner Munzel test. A receiver operating characteristic (ROC) curve was created for gestational diabetes, and the area under the curve (AUC) values for individual variables were obtained. The AUC values of the parameters were calculated and tested mutually for significance using the DeLong quality test. Statistical significance was set as $p < 0.05$.

RESULTS

In our study, the total number of patients was 78, 59 (75.6%) of our patients were in the non-GDM group and 19 (24.4%) were in the GDM group. Considering the first trimester values, FBG was an average of 85.0 ± 6.3 mg/dL in the non-GDM group and 87.0 ± 6.6 mg/dL in the GDM group, and there was no statistically significant difference ($p = 0.245$). HbA1C was an average of $5.2 \pm 0.3\%$ in the non-GDM group and $5.4 \pm 0.3\%$ in the GDM group, and there was a statistically significant difference ($p = 0.002$). Free T3 (FT3) was 2.9 ± 0.4 ng/dL, and there was no statistically significant difference ($p = 0.458$). The average free T4 (FT4) level was 1.2 (1.1 to 1.2) ng/dL in both groups, and there was no statistically significant difference ($p = 0.514$). There was no significant difference between the two groups in terms of TPO and TG antibody status ($p = 0.813$, $p = 0.982$ respectively).

When the second trimester values were examined, the average FBG was 82.2 ± 5.8 mg/dL in the non-GDM group and 93.6 ± 6.2 mg/dL in the GDM group, and a statistically significant difference was found ($p < 0.001$). HbA1C was an average of $4.9 \pm 0.3\%$ in the non-GDM group and an average of $5.3 \pm 0.3\%$ in the GDM group. A statistically significant difference was also found for this parameter ($p < 0.001$). The average 2nd trimester FT3 was 3.0 ± 0.3 ng/dL in both groups, and there was no statistically significant difference ($p = 0.826$). The 2nd trimester FT4 was 1.0 ± 0.1 ng/dL on average in both groups, and there was no statistically significant difference ($p = 0.599$).

When the OGTT parameters were examined, the OGTT-FBG, 75 g OGTT 1st hour and 2nd hour values were statistically significantly higher in GDM patients (< 0.001 , < 0.001 , < 0.001 respectively). There were no statistically significant differences in terms of TSH values both in the low and high categories and between the alternative categories ($p = 0.135$, $p = 0.572$ in the 1st and 2nd Trimester, respectively).

The demographic data of our patients, the values of FBG, HbA1c, and TFT in the 1st and 2nd trimester, and the OGTT data are presented in Table 1.

Table 2 presents the AUC values of FBG and HbA1c in the first trimester. The cut-off value of 1st trimester HbA1C was statistically significant for the diagnosis of GDM, and the AUC was calculated as 0.740 (0.94-0.38) for HbA1C at a cut-off value of 5.2. AUC = 0.591 (0.33-0.81) for 1st trimester FBG at a cut-off value of 89.

Table 3 presents the AUC values of 2nd trimester FBG and 2nd trimester HbA1C. The cut-off value of 2nd trimester FBG and 2nd trimester HbA1C were statistically significant in the diagnosis of GDM, and the AUC values were 0.912 (0.60-0.96) for 2nd trimester FBG at a cut-off value of 88 and 0.786 (0.37-0.93) for 2nd trimester HbA1C at a cut-off value of 5.

AUC values were compared in Table 4, and the DeLong test was performed. Accordingly, it was observed that 2nd trimester FBG and 2nd trimester HbA1C predicted GDM statistically significantly better than 1st trimester fasting blood sugar ($p = 0.00$, $p = 0.04$). It was observed that 2nd trimester FBG predicted GDM significantly better than 2nd trimester HbA1C ($p = 0.028$). Although no statistically significant difference was detected between 1st trimester HbA1C and 2nd trimester HbA1C in terms of predicting GDM ($p = 0.481$); It was observed that 2nd trimester FBG predicted GDM statistically significantly better than the first trimester HbA1c ($p = 0.004$).

According to the ROC curve analysis, 1st and 2nd trimester HbA1C and 2nd trimester FBG and OGTT values showed strong performance in predicting gestational diabetes. Some parameters, such as age, showed lower predictive performance (Figure 1).

DISCUSSION

In our study, HbA1c was significantly higher in the GDM group in the first trimester. The cut-off value with the highest Youden index was 5.2, showing 89.47% sensitivity and 54.24% specificity in predicting gestational diabetes. The model demonstrated high prediction performance with an AUC value of 0.740. First trimester FBG showed 52.63% sensitivity and 66.1% specificity for predicting gestational

Table 1. Relationship between demographic characteristics, FBG, HbA1C, TFT, and gestational diabetes

	GDM (-)	GDM (+)	Total	p-value
Age (mean SD)	27.3 (5.4)	29.6 (5.0)	27.9 (5.4)	0.113
Size (mean SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.839
Weight (median IQR)	67.0 (57.5 to 74.0)	72.0 (60.0 to 81.0)	67.5 (58.2 to 76.0)	0.111
Gravida (mean SD)				
1	30 (50.8)	5 (26.3)	35 (44.9)	0.171
2	11 (18.6)	4 (21.1)	15 (19.2)	
3	10 (16.9)	6 (31.6)	16 (20.5)	
4	5 (8.5)	4 (21.1)	9 (11.5)	
5	3 (5.1)	0 (0.0)	3 (3.8)	
Chemical pregnancy (mean SD)	1 (1.7)	0 (0.0)	1 (1.3)	1.000
Abortion story (mean SD)				
0	45 (76.3)	15 (78.9)	60 (76.9)	0.481
1	8 (13.6)	4 (21.1)	12 (15.4)	
2	5 (8.5)	0 (0.0)	5 (6.4)	
3	1 (1.7)	0 (0.0)	1 (1.3)	
Curettage (mean SD)	1 (1.7)	0 (0.0)	1 (1.3)	1.000
Thyroglobulin (mean SD)	9 (15.3)	2 (10.5)	11 (14.1)	0.982
Thioperoxidase (mean SD)	9 (15.3)	4 (21.1)	13 (16.7)	0.813
1st trimester				
FBG (mg/dL) (mean SD)	85.0 (6.3)	87.0 (6.6)	85.5 (6.4)	0.245
HbA1C (%) (mean SD)	5.2 (0.3)	5.4 (0.3)	5.2 (0.3)	0.002
FT3 (ng/dL) (mean SD)	2.9 (0.4)	2.9 (0.4)	2.9 (0.4)	0.458
FT4 (ng/dL) (median IQR)	1.2 (1.1 to 1.3)	1.2 (1.2 to 1.2)	1.2 (1.1 to 1.2)	0.514
TSH (mIU/L) (median IQR)	1.3 (1.0 to 2.2)	1.0 (0.5 to 1.6)	1.2 (0.9 to 2.1)	0.135
2nd trimester				
FBG (mg/dL) (mean SD)	82.2 (5.8)	93.6 (6.2)	85.0 (7.7)	<0.001
HbA1C (%) (mean SD)	4.9 (0.3)	5.3 (0.3)	5.0 (0.3)	<0.001
FT3 (ng/dL) (mean SD)	3.0 (0.3)	3.0 (0.3)	3.0 (0.3)	0.826
FT4 (ng/dL) (mean SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.599
TSH level (mIU/L) (median IQR)	1.9 (1.5 to 2.7)	1.6 (1.2 to 3.1)	1.9 (1.4 to 2.8)	0.572
2.TR-75 OGTT-FBG (mean SD)	82.5 (5.9)	94.2 (5.8)	85.3 (7.7)	<0.001
75 OGTT, 1 st hour (mean SD)	125.4 (24.0)	159.8 (27.7)	133.8 (28.9)	<0.001
75 OGTT-2 nd hour (mean SD)	101.4 (17.2)	128.4 (29.1)	108.0 (23.6)	<0.001

GDM: Gestational diabetes mellitus, FBG: Fast blood glucose, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, OGTT: Oral glucose tolerance test

Table 2. Receiver operating characteristic analysis of 1st trimester FBG and HbA1C for the prediction of diagnosis

	Cut-off value	Sensitivity	Specificity	NPV%	PPV %	95% CI	Youden's index	AUC	p-value
1 st trimester FBG (mg/dL)	89	52.63%	66.1%	81.25%	33.3 %	33-81.25%	0.187	0.591	0.121
1 st trimester HbA1C (%)	5.2	89.47%	54.24%	94.12%	38.64%	38.64-94.12%	0.437	0.740	0.000

FBG: Fast blood glucose, NPV: Negative predictive value, PPV: Positive predictive value, AUC: Area under the curve, CI: Confidence interval

Table 3. Receiver operating characteristic analysis of 2nd trimester FBG and 2nd trimester HbA1C for the prediction of diagnosis

	Cut-off value	Sensitivity	Specificity	NPV%	PPV %	95% CI	Youden's index	AUC	P value
2 nd trimester FBG (mg/dL)	88	89.47%	81.36%	96%	60.71%	60.71-96%	0.708	0.912	0.000
2 nd trimester HbA1C (%)	5	89.47%	52.54%	93.94%	37.78%	37.78-93.94%	0.420	0.786	0.000

FBG: Fast blood glucose, NPV: Negative predictive value, PPV: Positive predictive value, AUC: Area under the curve, CI: Confidence interval

Table 4. AUC differences in 1st trimester FBG, 1st trimester HbA1C, 2nd trimester FBG, 2nd trimester HbA1C

	AUC 1	AUC 2	AUC difference	CI lower	CI upper	p (delong test)
1 st tr FBG vs. 1st tr HbA1C	0.591	0.740	0.149	0.34	0.041	0.124
1 st tr FBG vs. 2nd tr FBG	0.591	0.912	0.322	0.474	0.169	0.00
1 st tr FBG vs. 2nd tr HbA1C	0.591	0.786	0.196	0.382	0.009	0.04
1 st tr FBG vs. age	0.591	0.635	0.045	0.257	0.168	0.680
1 st tr HbA1C vs. 2nd tr FBG	0.740	0.912	0.172	0.289	0.055	0.004
1 st tr HbA1C vs. 2nd tr HbA1c	0.740	0.786	0.046	0.175	0.083	0.481
1 st tr HbA1C vs. age	0.740	0.635	0.105	0.074	0.284	0.251
2 nd tr FBG vs. 2nd tr HbA1C	0.912	0.786	0.126	0.014	0.238	0.028
2 nd tr FBG vs. age	0.912	0.635	0.277	0.117	0.437	0.001
2 nd tr HbA1C vs. age	0.786	0.635	0.151	0.017	0.319	0.077

tr: Trimester, FBG: Fast blood glucose, AUC: Area under the curve, CI: Confidence Interval, p<0.05, statistically significant

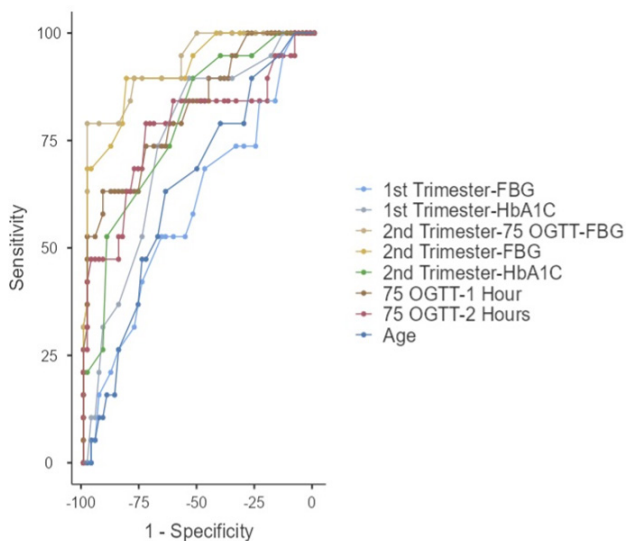


Figure 1. Receiver operating characteristic curves for the FBG, HbA1c, OGTT, and age for the prediction of GDM

FBG: Fasting blood glucose, OGTT: Glucose tolerance test, GDM: Gestational diabetes mellitus

diabetes. FBG demonstrated moderate predictive performance with an AUC of 0.591. Although the AUC difference between HbA1C and FBG was not significant, 1st trimester HbA1c was a strong parameter in predicting GDM based on the Youden index and AUC values. When 2nd trimester HbA1C and 2nd trimester FBG were examined, the

AUC value of HbA1C was 0.786, which was highly predictive of GDM. It is clear that FBG is a more powerful parameter for predicting GDM than HbA1C, with an AUC value of 0.912. The AUC difference was statistically significant.

As a result, especially 1st and 2nd trimester HbA1C and 2nd trimester FBG and OGTT values showed strong performance in predicting gestational diabetes. Although there are studies showing that age increases the incidence of GDM, no statistically significant relationship was found between age and GDM in our study (2). No statistically significant relationship was detected between TFT (TSH, FT3, FT4, TPO, thyroglobulin) and GDM in the first and second trimesters. Studies investigating the relationship between TFT and GDM and obtaining different results have taken place in the literature. In a retrospective study including more than 2,000 pregnant women, high FT4 was not observed in pregnant women who developed GDM; No significant relationship could be detected between TSH and GDM (4). In a study by Zhang et al. (5), the relationship between TSH concentrations and GDM was similar to that in our study. In another study evaluating the relationship between FT4 levels and GDM, high F4 levels were shown to predict GDM (6).

According to our study, although we found a clear superiority of FBG in the 2nd trimester, HbA1C level proved that it can strongly predict GDM in both the first and second

trimesters. HbA1c is expected to fall below normal values during pregnancy. This condition should also be taken into consideration in the relationship between GDM diagnosis and HbA1C level (7). Several studies have evaluated the relationship between HbA1C and FBG levels and GDM (8,9). In a retrospective study including 107 pregnant women, it was concluded that HbA1C and FBG could predict GDM, but TFT such as FT4 and TSH could not be used in the diagnosis of GDM, similar to our study (8). In a prospectively planned study, it was concluded that HbA1c in the first trimester could not be used instead of OGTT, and a statistically significant relationship was found between HbA1C and the risk of GDM development (9). In a meta-analysis evaluating OGTT and HbA1C tests performed in the second or third trimester of pregnancy, it was found that HbA1C could predict GDM with an AUC value >0.800 (11). In our study, OGTT FBG and OGTT 1st hour AUC values were higher than HbA1C. Therefore, according to our study, we cannot say that we can use HbA1C instead of OGTT. In a study investigating the relationship between HbA1C levels in the third trimester and GDM, it was determined that there was a statistically significant relationship between HbA1C and GDM, but since the AUC was less than 0.80, it was determined that HbA1C was not sufficient to predict GDM (12). In another study examining HbA1C and FBG values taken in the first trimester, the ability of HbA1C and FBG values to predict GDM was similar to that of our study (13). Again, a prospective observational study conducted in the first trimester determined that HbA1C could predict GDM (14).

The studies mostly consisted of data from specific trimesters. The comparison of data obtained in different trimesters, as in our study, has also begun to take place in the literature. In a study evaluating 45 patients diagnosed with GDM, HbA1C levels in both the first and second trimesters were statistically significantly higher in pregnant women diagnosed with GDM than in the control group, similar to our study (15). We also think that many pregnancy-related complications can be prevented using pre-pregnancy data. In a prospective study by Alwash et al. (16), pre-pregnancy FBG levels were associated with GDM. Pre-pregnancy HbA1C and TFT values will also contribute to the literature.

Study Limitations

Because our study was retrospective, data were obtained from the hospital data system. Our number of patients was limited to obtain detailed examinations and both trimester values of the patients.

CONCLUSION

First- and second-trimester HbA1c and FBG and OGTT values can predict gestational diabetes. HbA1C cannot be used instead of OGTT, but it is an important predictor. Second-trimester FBG is more powerful in predicting GDM than first- and second-trimester HbA1c and first-trimester FBG.

ETHICS

Ethics Committee Approval: The instant study was carried out with the permission of Local Ethics Committee of the Karamanoğlu Mehmetbey University Faculty of Medicine (number: 06-2024/19, date: 30.05.2024).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Ö.D., Concept: Ö.D., H.Ş.A., Design: Ö.D., H.Ş.A., S.K., Data Collection or Processing: Ö.D., Analysis or Interpretation: Ö.D., H.Ş.A., Literature Search: Ö.D., H.Ş.A., S.K., Writing: H.Ş.A.

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