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FIRST-TRIMESTER MATERNAL VITAMIN D LEVELS AND RISK FOR GESTATIONAL DIABETES MELLITUS

İLK TRİMESTER MATERNAL VİTAMİN D DÜZEYLERİ VE GESTASYONEL DİYABET RİSKİ

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Öz

Amaç: Vitamin D eksikliği; artmış advers gebelik sonuçları, fetal neonatal komplikasyonlar ve anne yenidoğanın ilerideki yaşamlarındaki ciddi sağlık sorunları ile ilişkilidir. Bununla birlikte maternal vitamin D statüsünün gestasyonel diyabet (GDM) riski ile ilişkisini araştıran çalışma sonuçları çelişkilidir. Bu çalışma retrospektif olarak maternal vitamin D düzeylerine göre GDM riskini değerlendirmeyi amaçlamaktadır.

Materyal ve Metot: Dışlama kriterleri uygulandıktan sonra 33 GDM ve 164 kontrol toplam 197 gebe kadın çalışmaya alındı. Vitamin D düzeylerine gebeliğin 11-14 haftaları arasında bakıldı. GDM tanısı gebeliğin 24-28 haftaları arasında 75 gram glukozla yapılan oral glukoz tolerans testi ile kondu.

Bulgular: GDM grubunda BMI non-GDM grubundan yüksekti (24,68 [21,72–27,64] kg/m^2 vs. 22,04 [20,51–24,73] kg/m^2, p = 0,004).). Vitamin D düzeyleri GDM grubunda non-GDM grubundan anlamlı olarak daha düşük bulundu (17,2 [15,6–19,2] nmol/L vs. 33,0 [31,2–35,0] nmol/L, p <0,001). Vitamin D eksikliği prevalansı GDM grubunda % 87,88 olup, D vitamini eksikliği GDM riskini 67,06 kat arttırmaktaydı (odds oranı 67,06, 95% güven aralığı 20,90–215,15, p <0,001).

Sonuç: Gebeliğin erken döneminde D vitamini eksikliği ile GDM gelişme riski arasında anlamlı bir ilişki saptanmıştır. Gebelik sırasında özellikle de ilk prenatal vizitte D vitamini eksikliğinin rutin olarak taranması GDM'nin ve GDM'nin anne ve yenidoğandaki olumsuz sonuçlarının daha iyi yönetilmesi bakımından yararlı olacaktır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, vitamin D eksikliği, gebelik, ilk trimester.

Abstract

Objectives: Vitamin D deficiency is linked to increased risk of adverse pregnancy outcomes, fetal and neonatal complications, as well as serious health consequences later in life for both mothers and offspring. However, studies on maternal vitamin D status and risk for gestational diabetes mellitus (GDM) are controversial. This study aimed to retrospectively evaluate the risk for GDM based on maternal serum vitamin D levels.

Materials and Methods: After applying the exclusion criteria, a total of 197 pregnant women, including 33 GDM cases and 164 controls, were enrolled in the study. Vitamin D levels were measured at 11–14 weeks of gestation. GDM was diagnosed by performing a 75-g oral glucose tolerance test between 24 and 28 weeks of gestation.

Results: BMI was higher in the GDM group than in the non-GDM group (24.68 [21.72–27.64] kg/m^2 vs. 22.04 [20.51–24.73] kg/m^2, p = 0.004). Vitamin D levels were significantly lower in the GDM group than in the non-GDM group (17.2 [15.6–19.2] nmol/L vs. 33.0 [31.2–35.0] nmol/L, p < 0.001). The prevalence of vitamin D deficiency was as high as 87.88% in the GDM group, with a 67.062-fold higher risk for GDM (odds ratio 67.062, 95% confidence interval 20.904–215.150, p < 0.001).

Conclusion: Insufficient vitamin D level in early pregnancy is significantly associated with GDM development. Routine screening for vitamin D deficiency during pregnancy, particularly at the first prenatal visit, may contribute to the identification and better management of GDM and its related adverse outcomes in mothers and offspring.

Keywords: Gestational diabetes mellitus, vitamin D deficiency, pregnancy, first trimester.

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Introduction

Gestational diabetes mellitus (GDM) is a condition characterized by variable severities of glucose intolerance that begins or is first recognized during pregnancy.[1] The prevalence of GDM ranges between 1% and 14% depending on ethnicity, race, and diagnostic criteria, and it increases in parallel with the substantial rise in the prevalence of overweight and obesity in women of childbearing age.[2] GDM is associated with both impaired insulin secretion and resistance, leading to maternal hyperglycemia and an elevated long-term and short-term risk of adverse pregnancy outcomes and fetal and neonatal complications.[3] GDM is also related to serious health consequences later in life for both mothers and their offspring, including obesity, metabolic syndrome, type 2 DM, and cardiovascular disorders.[4] Thus, it is crucial to identify the etio-pathological mechanisms leading to abnormal glycemic regulation in pregnancy, to enhance pre- and antenatal care and management, and to reduce the frequency of adverse pregnancy outcomes.

Vitamin D plays a neurohormone regulating role in cell proliferation and differentiation and bone and calcium–phosphate homeostasis and has a wide spectrum of effects as an antioxidant, anti-inflammatory, antifibrotic, and immunomodulatory agent.[5] Studies have reported that vitamin D deficiency is related to altered glucose metabolism through impaired pancreatic beta-cell function and mass, leading to insulin resistance.[6] Vitamin D deficiency was also shown as a risk factor for obesity and type 2 DM, especially in women of late reproductive age.[7] In addition, insufficiency and deficiency of vitamin D were common among pregnant women. Vitamin D deficiency in pregnant women has significant involvement in the health of the mother and life-long health status of her child, as it is linked to maternal and child infections, preterm delivery, preeclampsia, small for gestational age, and chronic diseases.[8] However, results of studies on maternal vitamin D status and risk for GDM are inconclusive and contradictory, which are mostly due to differences in population features, including ethnicity, geographic location, seasonal variations, gestational age in sampling, and diagnostic criteria for GDM.[9]

This study aimed to retrospectively determine first-trimester serum vitamin D levels in patients with GDM and to investigate the effects of vitamin D levels on the risk for GDM.

Materials and Methods

This retrospective single-center study was carried out from March 2014 to December 2020 in the Obstetrics and Gynecology Department of Bahçeşehir University Göztepe Medikal Park Hospital. A total of 197 women who presented to the outpatient obstetrics clinic for routine antenatal care between 11 and 14 weeks of gestation were included in the study. All participants had singleton pregnancies and had given blood samples for routine first-trimester screening. Women with known or clinically suspected type 1 and 2 DM, history of

GDM, preeclampsia, thyroid, parathyroid or adrenal diseases, alcohol use, smoking, metabolic bone or kidney disease, and hepatic failure and those taking medications that might affect glucose, calcium, and vitamin D metabolism were excluded from the study.

Pregnant women were divided into two groups based on the presence of GDM. GDM was diagnosed by performing a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[10] According to IADPSG recommendations, the diagnosis of GDM is confirmed if one of the following is met: fasting glucose level ≥92 mg/dL, 1-h glucose level ≥180 mg/dL, or 2-h glucose level ≥153 mg/dL.

Demographic characteristics, including age, weight, height, smoking, number of parity and gravidity, history of abortion and polycystic ovarian syndrome (PCOS), delivery type (vaginal or cesarean), and gestational complications (including atony uterine, bilateral hydronephrosis; placental detachment; early membrane rupture; hemolysis, elevated liver enzyme levels, and low platelet level syndrome; intrauterine growth restriction; cholestasis, placenta previa; pancreatitis; preeclampsia; Rh alloimmunization; and small gestational age) were retrospectively obtained from patients' file. Body mass index was calculated as body weight (kilograms) divided by the square of body height (meters). Clinical data of neonates, including weight, sex, gestational age, length of stay in the neonatal intensive care unit, and congenital abnormalities such as ventricular septal defect and cleft lip and palate, were also obtained from hospital records. Gestational age was evaluated according to the last menstruation date and first-trimester obstetric radiologic examination. Fetal anthropometric measurements (body weight) of the neonates were determined immediately after birth by hospital staff following the hospital quality control procedures.

Biochemical Analyses

Blood samples for 25-hydroxy (25-OH) vitamin D test were obtained from the antecubital vein after overnight fasting within 11–14 weeks of gestation. Blood samples were kept at room temperature for 30 min after collection and were centrifuged at 2000 g for 15 min to separate the serum. Serum 25-OH vitamin D levels were determined with chemiluminescent enzyme immunoassay on the UniCel DxI 800 (Beckman Coulter Inc., CA, USA). Serum 25-OH vitamin D level >50 nmol/L was considered as sufficient, 30–49.9 nmol/L insufficient, and <30 nmol/L deficient. Since vitamin D levels show seasonal variations, only patients whose blood samples were taken to evaluate vitamin D status during the summer season were included in the study.

An OGTT was conducted in all participants with a glucose load of 75 g after overnight fasting between 24 and 28 weeks of gestation. Serum glucose levels were measured at 0, 60, and 120 min after glucose intake. During OGTT, serum HbA1c levels were also measured in all participants. Serum glucose and HbA1c levels were determined by a photometric method using an Olympus AU 2700 autoanalyzer (Beckman Coulter Inc., CA,

USA). All blood samples were examined within <1 h after sampling. All biochemical analyses, which are routinely checked every day, were performed with the same analyzers in the central laboratory of our hospital, depending on the test type.

Statistical Analyses

Power analysis was performed using PASS 11 software. Using the mean values of Vitamin D from the study conducted by Vijay et al., the minimum sample size should be 32 with a power level of 0.80 and 0.05 alpha error. Data from the hospital records were entered in the SPSS Statistics version 26 software (IBM Corp., Armonk, NY, USA), where all statistical analyses were carried out. Histogram and Q-Q plots were used to determine whether variables are normally distributed. Data are expressed as mean ± standard deviation for normally distributed variables and as median (1^{st}–3^{rd} quartiles) for skewed variables. Categorical variables are reported as frequency (percentage). For continuous variables, the independent samples t-test was used to test the significance of differences between groups to normally distributed variables, and the Mann–Whitney U test was used to test the differences between groups in terms of skewed variables. The chi-square test or Fisher's exact test was used to test the differences between groups for categorical variables. Multiple logistic regression analysis (forward conditional method) was performed to determine significant risk factors of GDM, and $p < 0.05$ values were accepted as significant results.

Results

A total of 33 patients with GDM (GDM group) and 164 individuals without GDM (non-GDM group) were enrolled in the study. The mean age was 31.80 ± 3.98 years in the GDM group and 30.99 ± 3.92 years in the non-GDM group ($p = 0.278$). BMI values were higher in the GDM group than in the non-GDM group (24.68 [21.72–27.64] kg/m^2 vs. 22.04 [20.51–24.73] kg/m^2, $p = 0.004$). Smoking was present in 8 (24.24%) patients in the GDM group and 13 (7.93%) patients in the non-GDM group ($p = 0.011$). No significant differences in the number of parity and gravidity, history of abortion and PCOS, delivery type, and gestational complications were observed between the two groups (all, p > 0.05) (Table 1). Neonatal clinical data, including weight, sex, gestational age, length of stay in the neonatal intensive care unit, and congenital abnormality, were similar between the two groups (all, p > 0.05) (Table 1).

Vitamin D levels were significantly lower in the GDM group than in the non-GDM group (17.2 [15.6–19.2] nmol/L vs. 33.0 [31.2–35.0] nmol/L, $p < 0.001$) (Figure 1). The prevalence of vitamin D deficiency was as high as 87.88% in the GDM group compared with 9.76% in the non-GDM group ($p < 0.001$). Fasting blood glucose levels were higher (90 [87–96] mg/dL) in the GDM group than in the non-GDM group (82 [79–87) mg/dL; $p < 0.001$). The mean blood glucose levels with OGTT were 195.73 ± 25.66 mg/dL at 60 min and 154.03 ± 35.38

mg/dL at 120 min in the GDM group, which were significantly higher than that in the non-GDM group ($p < 0.001$). Serum HbA1c levels were 5.52 ± 0.25% in the GDM group and 5.21 ± 0.18 in the non-GDM group ($p < 0.001$). The biochemical characteristics of the participants are shown in Table 2.

Table 1. Demographic characteristics of participants and neonates

	Gestational Diabetes Mellitus		
	Present (n=33)	**Absent (n=164)**	***p* value**
Age (years)	31.80 ± 3.98	30.99 ± 3.92	0.278
Weight (kg)	65 (57 - 73)	60 (55 - 68)	**0.028**
Height (cm)	162.73 ± 5.27	164.30 ± 5.39	0.127
Body mass index (kg/m^2)	24.68 (21.72 - 27.64)	22.04 (20.51 - 24.73)	**0.004**
Smoking (*n*)	8 (24.24%)	13 (7.93%)	**0.011**
Gravidity			
1	24 (72.73%)	121 (73.78%)	0.971
2	7 (21.21%)	33 (20.12%)	
3	2 (6.06%)	9 (5.49%)	
4	0 (0%)	1 (0.61%)	
Parity			
0	28 (84.85%)	133 (81.10%)	0.701
1	5 (15.15%)	28 (17.07%)	
2	0 (0%)	3 (1.83%)	
The history of Aborts (*n*)			
0	29 (87.88%)	144 (87.8%)	0.148
1	2 (6.06%)	18 (10.98%)	
2	2 (6.06%)	2 (1.22%)	
The history of Polycystic ovarian syndrome (*n*)	12 (36.36%)	49 (29.88%)	0.597
Other gestational complications (*n*)	5 (15.15%)	20 (12.20%)	0.578
Type of delivery			
Vaginal	1 (3.03%)	15 (9.15%)	0.481
Cesarean section	32 (96.97%)	149 (90.85%)	
Weight at birth (g)	3260 (3150 - 3520)	3215 (3075 - 3395)	0.083
Gestational week at birth	39 (38 - 39)	39 (38 - 39)	0.219
Gender			
Boy (*n*)	18 (54.55%)	81 (49.39%)	0.727
Girl (*n*)	15 (45.45%)	83 (50.61%)	
The length of stay in neonatal intensive care unit (days)	1 (3.03%)	10 (6.10%)	0.695
Congenital abnormality (*n*)	1 (3.03%)	1 (0.61%)	0.308

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. A *p*-value of <0.05 was considered significant.

Moreover, multiple logistic regression analysis was performed to determine significant risk factors of GDM (Table 3). Patients with vitamin D deficiency (<30 nmol/L) have 67.062-fold higher risk for GDM than other patients (odds ratio [OR] 67.062, 95% confidence interval [CI] 20.904–215.150, $p < 0.001$). Other variables included in the model, namely, age ($p = 0.862$), gravidity ($p = 0.767$), BMI ($p = 0.061$), smoking status ($p = 0.063$), history of PCOS ($p = 0.525$), and sex of neonates ($p = 0.717$), were non-significant.

Table 2. Biochemical characteristics of participants

	Gestational Diabetes Mellitus		
	Present (n=33)	**Absent (n=164)**	***p***
Vitamin D (nmol/L)	17.2 (15.6 - 19.2)	33.0 (31.2 - 35.0)	**<0.001**
< 30 (*n*)	29 (87.88%)	16 (9.76%)	**<0.001**
≥ 30 (*n*)	4 (12.12%)	148 (90.24%)	
Fasting blood glucose (mg/dL)	90 (87 - 96)	82 (79 - 87)	**<0.001**
Blood glucose levels at 60 min with OGTT	195.73 ± 25.66	136.65 ± 25.87	**<0.001**
Blood glucose levels at 120 min with OGTT	154.03 ± 35.38	110.19 ± 19.57	**<0.001**
HbA1c (%)	5.52 ± 0.25	5.21 ± 0.18	**<0.001**

OGTT: Oral glucose tolerance test; HbA1c: Glycosylated hemoglobin. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. A *p*-value of <0.05 was considered significant.

Table 3. Significant risk factors of the gestational diabetes mellitus with multiple logistic regression analysis

	β coefficient	**Standard Error**	***p* value**	**Exp(β)**	**95.0% CI for Exp(β)**	
Vitamin D deficiency (< 30 nmol/L)	4.206	0.595	**<0.001**	67.062	20.904	215.150
Constant	-3.611	0.507	**<0.001**	0.027		

Dependent Variable: Gestational DM; Nagelkerke R2=0.575; Correct prediction=89.85%. CI: Confidence Interval

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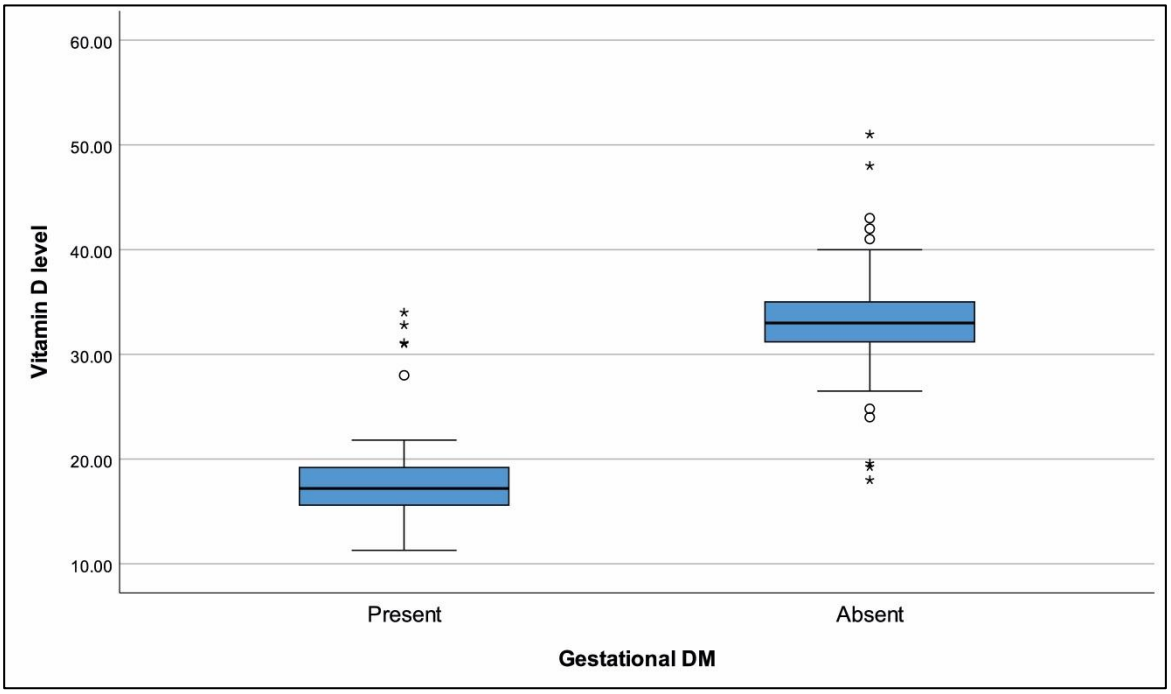

Figure 1. Vitamin D levels in pregnant women with regard to the presence of Gestational diabetes mellitus

Discussion

This study aimed to examine the relationship between maternal vitamin D levels in the first trimester and the risk for GDM. As main study findings, vitamin D levels were lower in women with GDM than in healthy individuals. In addition, the rate of first-trimester vitamin D deficiency was higher in patients with GDM, with a value of 87.88%. Moreover, the risk for GDM development was significantly higher among patients with vitamin D deficiency than among those without vitamin D deficiency. Finally, GDM was not associated with age, BMI, gravidity, smoking, and history of PCOS.

Vitamin D is a secosteroid with various biological effects on multiple mechanisms, including bone formation and mineralization, neuromuscular function, immunomodulatory functions, glucose homeostasis, and placental function.[11] A high prevalence of vitamin D deficiency among pregnant women has been reported.[12] Vitamin D deficiency has been associated with an elevated risk of adverse pregnancy outcomes such as placental implantation, preterm birth, preeclampsia, postpartum depression, maternal hypocalcemia, urinary tract infections, the cesarean section in mothers, as well as increased susceptibility to low-birth-weight, small for gestational age, respiratory diseases, autoimmune diseases, cardiovascular disease, and type 2 DM in neonates and offspring development.[13,14] However, the relationship between vitamin D level and GDM is still controversial. Some studies have demonstrated a relationship between vitamin D deficiency and GDM

development in pregnant women, but others reported no significant difference in healthy normoglycemic individuals. Savvidou et al. conducted a study with three groups of complicated pregnancies, including 50 patients with type 2 DM, 50 individuals without DM who subsequently delivered large-for-gestational-age neonates, and 100 women who subsequently developed GDM and 1000 healthy individuals without DM (control group), and they found no significant differences in the maternal serum vitamin D levels at 11–13^{+6} weeks of gestations in the three groups compared with the control group.[15] In a study of 25 patients with GDM and 208 healthy individuals, Ateş et al. showed that vitamin D levels at 11–14 weeks of gestation and prevalence of first-trimester vitamin D deficiency were comparable between the two groups.[16] Baker et al. did not find a relationship between maternal serum vitamin D levels at 11–14 weeks of pregnancy and GDM development in 60 patients with GDM and 120 ethnicity-matched healthy women from an overall cohort of 4225 pregnant women.[17] By contrast, Lacroix et al. evaluated 54 patients who subsequently developed GDM and 601 control participants and found that a low vitamin D level at the first trimester is an independent risk factor for GDM development.[18] Xu et al. demonstrated lower vitamin D levels at the first trimester in 101 women with GDM than in 726 healthy individuals.[19] Moreover, in their multivariate model analysis, vitamin D levels in the first and second quartiles were related to late development of GDM, and the risk for GDM increased by 24% and 48%, respectively. These differences may be explained by methodological issues, including study design, sample size, gestational age at sampling (first or second trimester), diagnostic criteria, the definition of vitamin D deficiency, and ethnic and genetic features of the participants.

In the present study, vitamin D levels were lower among patients with GDM than among women without GDM. Our results indicate that vitamin D may affect pancreatic beta-cell function and insulin sensitivity and secretion and that vitamin D deficiency may contribute to glucose intolerance during pregnancy. In addition, patients with vitamin D deficiency had a 67 times higher risk for GDM. Our results demonstrated that vitamin D levels at the first prenatal visit were related to an elevated risk of GDM. Various mechanisms may elucidate the observed relationship between vitamin D levels and risk for GDM. Vitamin D exhibits significant role in glucose homeostasis through different mechanisms. First, pregnancy has been an insulin-resistant condition with improved beta-cell function and proliferation that occurs in response to increased insulin secretory demand.[20] Beta cells exhibit vitamin D receptors, and studies have reported that vitamin D increases insulin sensitivity of target cells (i.e., adipose tissue, skeletal muscle, and liver) by increasing the insulin response to glucose transport.[21] Vitamin D also increases the function of beta cells and prevents them from deleterious immune attacks by acting on immune cells, including T cells, dendritic cells, and macrophages.[5] Furthermore, vitamin D promotes intestinal calcium absorption, while low serum calcium levels cause secondary hyperparathyroidism, which is independently related to abnormal glucose homeostasis during pregnancy.[22] Our results support the hypothesis that vitamin D deficiency was a risk factor for GDM. General screening for vitamin D deficiency during pregnancy, especially at the first prenatal visit, may contribute to the identification and management of GDM and its related adverse consequences in mothers and offspring. Previous studies have reported numerous

risk factors for GDM, including ethnicity, maternal age, history of GDM, high BMI, weight gain during pregnancy, multiparity, macrosomia, preeclampsia, family history of DM, history of abortion, and preterm delivery, and congenital anomalies.[23] In this study, although vitamin D deficiency was found to be the only risk factor for GDM, no relationship was observed between risk for GDM and age, BMI, gravidity, smoking, and history of PCOS. This may be related to the relatively small sample size, study design, lack of or uneven adjustments for confounding factors, and inclusion of a single ethnic group of patients. Further large-scale, well-designed prospective studies are warranted to identify risk factors and etiopathogenetic mechanisms on the onset and progression of GDM.

Some limitations should be considered. First, participants were recruited from a tertiary care hospital and from the Turkish pregnancy population and thus did not represent the general population. Second, data on clinical characteristics and vitamin D supplementation were obtained from the hospital data system, which could lead to under-or over-reporting. Third, as selection bias is also a concern in retrospective studies, it is difficult to control all potential covariates, and there may be unmeasured differences between the two study groups. Fourth, we did not provide information on dietary habits, lifestyle, sun exposure, use of fat-derived hormones, and other parameters that could theoretically affect vitamin D status. Fifth, serum vitamin D levels were evaluated by a single measurement during the early period of pregnancy, which did not allow for a time-integrated measure to demonstrate vitamin D status throughout pregnancy. Finally, the study uses a retrospective design, so we could not determine the effect of adequate vitamin D replacement on GDM and any causal relationship.

In conclusion, this retrospective analysis of first-trimester vitamin D levels in Turkish pregnant women demonstrated lower vitamin D levels in pregnant women with GDM than in healthy subjects. Moreover, the multiple regression analysis revealed that insufficient vitamin D level during pregnancy is associated with GDM. Thus, routine screening for vitamin D deficiency before and during early pregnancy may contribute to better management of the adverse outcomes associated with GDM in mothers and offspring.

Ethical considerations

All research procedures were evaluated and accepted by the Research Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (date: 13.01.2021, decision number: 2021/0007) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written informed consent was obtained from patients before they participated in this study.

Conflict of interest

The authors declare no conflict of interest.

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