

The relationship between low maternal serum 25-hydroxyvitamin D levels and gestational diabetes mellitus according to the severity of 25-hydroxyvitamin D deficiency

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OBJECTIVE: To assess the relationship between low maternal serum 25-hydroxyvitamin D levels and gestational diabetes mellitus in Turkish pregnant women according to the severity of 25-hydroxyvitamin D deficiency and assess intact parathyroid hormone levels in women with gestational diabetes mellitus and controls with low and sufficient 25-hydroxyvitamin D levels.

METHODS: We analyzed serum 25-hydroxyvitamin D and intact parathyroid hormone levels in 234 women with gestational diabetes mellitus and 168 controls. To define the deficiency status, 25-hydroxyvitamin D levels were further classified into severely deficient, deficient, insufficient and sufficient groups.

RESULTS: Women with gestational diabetes mellitus had significantly lower 25-hydroxyvitamin D levels compared to controls (30.8 ± 16.3 vs. 36.0 ± 16.2 nmol/L). However, when subgroups of 25-hydroxyvitamin D were analyzed, gestational diabetes mellitus was significantly more common only in women with severely deficient 25-hydroxyvitamin D levels. After adjusting for covariates, only severely deficient 25-hydroxyvitamin D levels were independently associated with an increased relative risk of gestational diabetes mellitus. The relative risk of gestational diabetes mellitus in women with insufficient and deficient 25-hydroxyvitamin D levels was not statistically significant. Intact parathyroid hormone concentrations were also significantly higher in women with gestational diabetes mellitus compared to the controls (45.3 ± 26.2 vs. 38.7 ± 27.6 pg/ml).

CONCLUSIONS: The results obtained from this study provide novel data indicating that only severely deficient maternal serum 25-hydroxyvitamin D levels are significantly associated with an elevated relative risk of gestational diabetes mellitus, even after adjusting for established risk factors of gestational diabetes mellitus.

KEYWORDS: Gestational Diabetes Mellitus; 25-hydroxyvitamin D; Parathyroid Hormone.

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INTRODUCTION

25-hydroxyvitamin D (25OHD) is well known for its function in maintaining calcium and phosphorus homeostasis. In addition to its classical actions, a growing body of evidence has linked 25OHD deficiency with an increased risk of cardiovascular disease, some infectious, malignant and autoimmune diseases and diabetes mellitus (DM) (1,2).

25OHD deficiency is common during pregnancy. Bodnar et al. demonstrated that 29.2% of Black and 5% of White

pregnant women residing in a northern United States city had 25OHD deficiency (3). The results of publications investigating the relationship between low maternal serum 25OHD levels and gestational diabetes mellitus (GDM) are controversial (4-7). Some of these publications suggested a relationship between 25OHD deficiency and GDM, while others failed to find such a relationship, despite an association between low 25OHD levels and insulin resistance during pregnancy (4-7). Although the results of all of these studies are interesting, none of these studies have addressed the relationship between low maternal serum 25OHD levels and GDM according to the severity of 25OHD deficiency.

Vitamin D and parathyroid hormone (PTH) are both responsible for maintaining extracellular calcium (Ca) homeostasis (8). Vitamin D contributes to intestinal Ca absorption, while low serum Ca levels stimulate PTH secretion from the parathyroid gland to increase the renal

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reabsorption of Ca and the resorption of Ca from bone (8). This condition is known as secondary hyperparathyroidism and has been suggested to increase the risk of DM (9-11).

However, previous studies investigating the relationship between low maternal serum 25OHD levels and GDM were limited by their inability to account for PTH levels. Therefore, this study was designed to assess the relationship between low maternal serum 25OHD levels and GDM according to the severity of 25OHD deficiency and assess PTH levels in women with GDM and controls with low and sufficient 25OHD levels in a large number of Turkish pregnant women with GDM and controls.

■ MATERIALS AND METHODS

This cross-sectional study was conducted at the diabetes out-patient clinic of the Sisli Etfal Training and Research Hospital. Four hundred and two consecutive pregnant women referred to our center for an oral glucose tolerance test (OGTT) between January 2010 and April 2011 were included in the study. All of the study participants were residing in Istanbul (41°00'N). According to the month of admission for OGTT, all of the participants were divided into spring-summer (May-October) and autumn-winter (November-April) groups. Pregnant women with pre-gestational diabetes, chronic disease or a history of consumption of drugs that interact with 25OHD metabolism and pregnant women with strict religious clothing were not included in the study. The study was designed in accordance with the Helsinki Declaration of 1975, informed consent was obtained from all participants, and the study was approved by the local ethics committee.

A 75 g OGTT was performed in all participants at 24-28 weeks' gestation. Plasma glucose levels (PGLs) were assessed immediately during OGTT using the glucose oxidase method. GDM was defined if at least one of the following diagnostic criteria was met: fasting, 1-hour or 2-hour PG levels ≥ 5.1 mmol/L, 10 mmol/L or 8.5 mmol/L, respectively (12).

Venous blood samples (20 mL) were also collected from each participant into plain (no additive) glass tubes on the day that the OGTT was performed (at 24-28 weeks' gestation) for the assessment of 25OHD and intact PTH (iPTH). Maternal serum 25OHD levels were measured using an electrochemiluminescence method (Roche Diagnostics GmbH, Mannheim, Germany), with inter-assay and intra-assay coefficients of variation (CVs) of 2.4 and 5.7%, respectively. To define the deficiency status, maternal serum levels of 25OHD were further classified into four groups: <12.5 nmol/L, severely deficient; 12.5-24.9 nmol/L, deficient; 25-49.9 nmol/L, insufficient; and ≥ 50 nmol/L, sufficient. Maternal serum iPTH levels were measured immediately after blood collection using a chemiluminescence immunoassay method (Roche Cobas, Roche Diagnostics GmbH, Mannheim, Germany), with a mean inter-assay CV of 6%. The experimental design of the study is presented in Figure 1.

Data regarding pre-pregnancy body mass index (BMI), parity, history of type 2 DM in first-degree relatives and the presence of GDM in previous pregnancies were obtained through one-on-one meetings with each participant and from antenatal visit records. BMI was calculated as the weight in kilograms divided by the height in meters squared.

■ STATISTICAL ANALYSIS

Data were analyzed using SPSS version 15.0.0 for Windows (SPSS Inc., Chicago, IL). Two-sided tests were used throughout. Categorical data were evaluated using a chi-square analysis or Pearson's correlation and Fisher's exact tests as appropriate. Student's t test and the Mann-Whitney U test were used to compare parametric quantitative and non-parametric data, respectively. Analysis of variance (ANOVA) was used to compare quantitative variables within groups, followed by post-hoc analyses for multiple comparisons. A logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs). GDM was included as a dependent variable in the model. Covariates included in the model as independent variables included maternal serum 25OHD, age, previous history of GDM, history of type 2 DM in first-degree relatives and pre-pregnancy BMI. Scale variables were presented as the mean \pm standard deviation (mean \pm SD). A *p*-value <0.05 was considered to be statistically significant.

■ RESULTS

The participants' characteristics and baseline biochemical features are summarized in Table 1. Women with GDM had a higher pre-pregnancy BMI, had higher parity, were more likely to have a history of GDM in previous pregnancies and a history of type 2 DM in first-degree relatives, and were older compared with controls. In the current study, 64 (15.9%) pregnant women were classified as severely 25OHD deficient, 79 (19.7%) as deficient, 196 (48.8%) as insufficient and 63 (15.7%) as sufficient. Of the study participants, 230 (57%) were admitted during the autumn-winter months and 172 (43%) during the spring-summer months. The maternal serum 25OHD levels were 28 ± 16.3 and 39 ± 14.4 nmol/L during the autumn-winter and spring-summer months, respectively ($p < 0.001$). As expected, severe 25OHD deficiency and 25OHD deficiency were significantly more common during the autumn-winter months than the spring-summer months ($p < 0.0001$ for both comparisons).

In this study, women with GDM had significantly lower 25OHD levels compared to controls (Table 1). However, when subgroups of 25OHD were analyzed, GDM was significantly more common only in pregnant women with severely deficient 25OHD levels compared to those with deficient, insufficient or sufficient 25OHD levels ($p < 0.0001$ for all comparisons). Nevertheless, the frequency of GDM was not significantly different when pregnant women with deficient 25OHD levels were compared with those with insufficient and sufficient 25OHD levels ($p = 0.89$ and $p = 0.14$, respectively) or when pregnant women with insufficient 25OHD levels were compared with those with sufficient 25OHD levels ($p = 0.10$). After adjusting for maternal age, previous history of GDM, history of type 2 DM in first-degree relatives and pre-pregnancy BMI, low maternal serum 25OHD levels were not associated with an increased relative risk of GDM when 25OHD was introduced as a single independent variable into the logistic regression analysis (OR = 1.01, 95% CI 1.003-1.03, $p = 0.14$). When subgroups of 25OHD were separately introduced into the model, the OR of GDM in women with insufficient and deficient 25OHD levels was also not statistically significant (OR = 1.46, 95% CI 1.27-2.74, $p = 0.23$, OR = 1.64, 95% CI

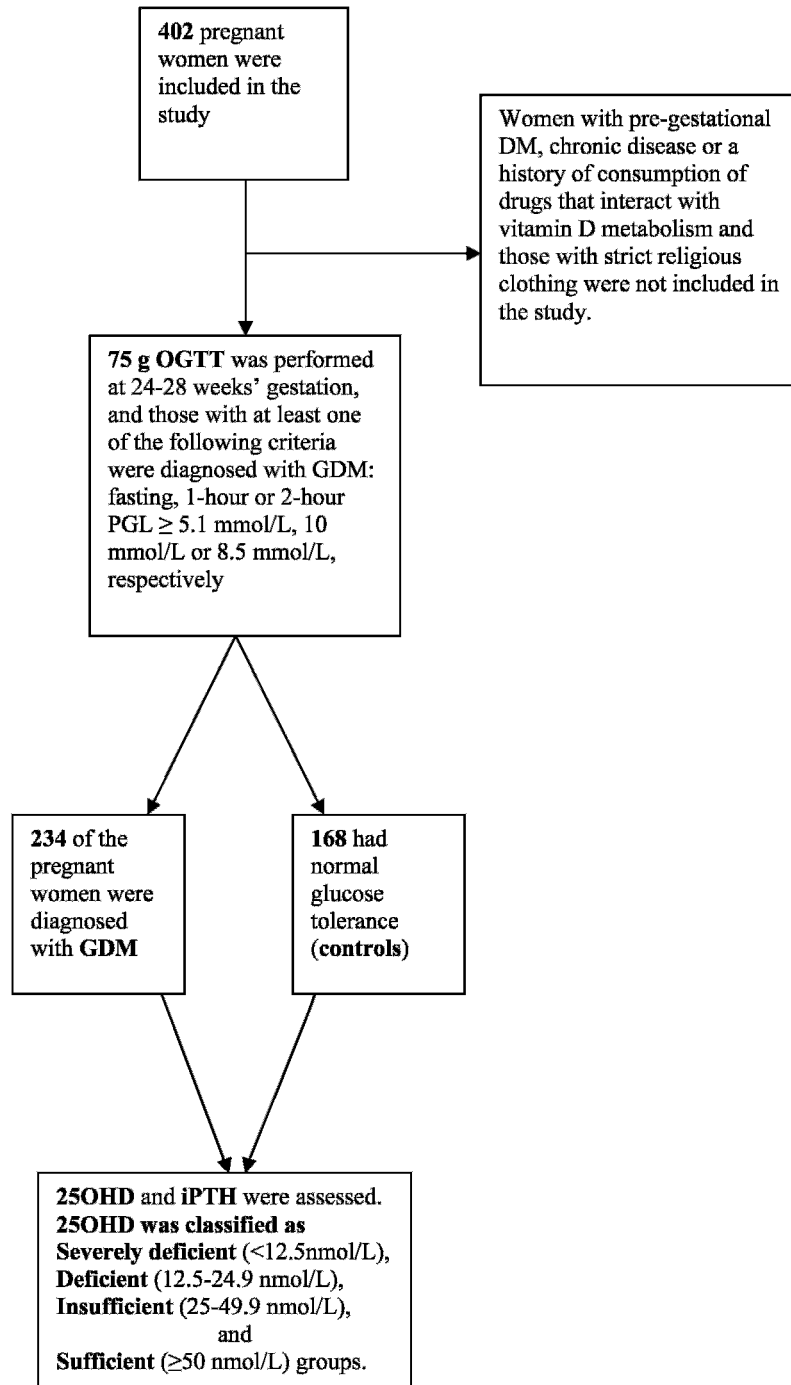


Figure 1 - Study experimental design. **DM**: diabetes mellitus, **GDM**: gestational diabetes mellitus, **OGTT**: oral glucose tolerance test, **PGL**: plasma glucose, **25OHD**: 25-hydroxyvitamin D, **iPTH**: intact parathyroid hormone.

1.26–3.43, $p=0.18$, respectively). However, after adjusting for all these factors, pregnant women classified as being severely deficient for 25OHD had a 3.9-fold increased relative risk of GDM compared to those with sufficient, insufficient and deficient 25OHD levels (OR = 3.95, 95% CI 1.68–9.25, $p=0.002$).

Likewise, as presented in Table 2, the fasting PGL was significantly higher in pregnant women with severely deficient 25OHD levels compared to those with deficient, insufficient and sufficient 25OHD levels ($p<0.0001$ for all

comparisons). An inverse correlation was also found between the fasting PGL and 25OHD levels ($r=-0.18$, $p<0.0001$). In addition, the inverse relationship between 25OHD and fasting PGL became more significant when the 25OHD level of women with severely deficient 25OHD levels was correlated with fasting PGL ($r=-0.28$, $p=0.024$). However, no relationship was found between 2-hour PGL and 25OHD levels ($r=-0.08$, $p=0.10$). An inverse correlation was also found between pre-pregnancy BMI and 25OHD levels ($r=-0.157$, $p=0.002$). Similar to GDM,



Table 1 - Clinical and baseline biochemical characteristics of the study participants.

	Women with GDM (n = 234)	Controls (n = 168)	p-value
Maternal age (years)	31.6 ± 6.0*	29.8 ± 5.2*	0.002
Pre-pregnancy BMI (kg/m ²)	26.7 ± 5.37*	24.2 ± 3.79*	<0.0001
Parity			
Multiparous	201 (85.9%)	102 (60.7%)	<0.0001
Primigravida	33 (14.1%)	66 (39.3%)	<0.0001
Previous history of GDM	46 (19.7%)	4 (2.4%)	<0.0001
Family history of type 2 DM	89 (38.0%)	28 (16.7%)	<0.0001
Gestational age [†] at OGTT	26.4 ± 1.5*	26.2 ± 1.5*	NS
Fasting PGL (mmol/L)	5.53 ± 0.75*	4.67 ± 0.31*	<0.0001
2-hour PGL (mmol/L)	10.3 ± 1.7*	7.05 ± 1.0*	<0.0001
25OHD (nmol/L)	30.8 ± 16.3*	36.0 ± 16.2*	0.002
Severely deficient (<12.5)	51 (21.8%)	13 (7.7%)	<0.0001
Deficient (12.5-24.9)	45 (19.2%)	34 (20.2%)	NS
Insufficient (25-49.9)	110 (47.0%)	86 (51.2%)	NS
Sufficient (≥50)	28 (12.0%)	35 (20.8%)	NS
iPTH (pg/ml)	45.3 ± 26.2*	38.7 ± 27.6*	0.016

25OHD: 25-hydroxyvitamin D, *: mean ± standard deviation.

[†]: weeks, BMI: body mass index, DM: diabetes mellitus, GDM: gestational diabetes mellitus, NS: non-significant, OGTT: oral glucose tolerance test, PGL: plasma glucose.

pre-pregnancy BMI was also significantly higher in pregnant women with severely deficient 25OHD levels compared to those with deficient, insufficient and sufficient 25OHD levels (Table 2). The inverse correlation between 25OHD and fasting PGL and BMI in the study participants is presented in Figures 2 A and B.

iPTH levels above the normal laboratory reference ranges (secondary hyperparathyroidism) were present in 26 (40.6%) of 64 pregnant women with severely deficient levels, 26 (32.9%) of 79 pregnant women with deficient levels, 6 (3%) of 196 pregnant women with insufficient levels and none of those with sufficient 25OHD levels. As expected, an inverse association was also found between iPTH and 25OHD levels ($r = -0.42, p < 0.0001$). However, no association was found between iPTH concentrations and fasting or 2-hour PGL ($r = 0.037, p = 0.45, r = -0.01, p = 0.83$, respectively). The inverse correlation between 25OHD and iPTH concentrations is presented in Figure 2 C, and the differences in fasting PGL, 2-hour PGL, pre-pregnancy BMI and iPTH concentrations between pregnant women with severely deficient levels and those with deficient, insufficient and sufficient 25OHD levels are summarized in Table 2.

DISCUSSION

As shown in Table 1, only 28 (12%) of 234 women with GDM and 35 (20.8%) of 168 controls had sufficient 25OHD levels, indicating a high prevalence of hypovitaminosis D during pregnancy. Moreover, 51% of women with GDM and 56% of those with normal glucose tolerance were taking a multivitamin supplement that contained 500 IU cholecalciferol. Considering the adverse effects of maternal vitamin D deficiency on offspring, such as neonatal hypocalcemia, seizure, impaired development and rickets (13,14), the high prevalence of hypovitaminosis D during pregnancy is a major public health problem, and vitamin D supplementation during pregnancy is of paramount importance.

In the current study, 25OHD levels were significantly lower in pregnant women with GDM compared to controls. However, when subgroups of 25OHD concentrations were analyzed, the difference between 25OHD levels in women with GDM and controls was only significant in pregnant women with severely deficient 25OHD levels, and only severely deficient maternal serum 25OHD levels were associated with an increased risk of GDM after controlling for established risk factors of GDM, including maternal age,

Table 2 - Differences in fasting and 2-hour PGL levels, pre-pregnancy BMI and iPTH concentrations between pregnant women with severely deficient 25OHD levels and those with deficient, insufficient and sufficient 25OHD levels (post-hoc analysis).

Serum 25OHD* status	Fasting PGL (mmol/L)	p-value	2-hour PGL (mmol/L)	p-value	Pre-pregnancy BMI (kg/m ²)	p-value	iPTH (pg/ml)	p-value
Severely Deficient	5.69 ± 0.76	<0.0001	9.50 ± 1.97	NS	27.97 ± 5.01	0.001	60.21 ± 29.91	NS
Deficient	5.04 ± 0.61		8.73 ± 2.24		24.88 ± 4.38		58.27 ± 40.92	
Severely Deficient	5.69 ± 0.76	<0.0001	9.50 ± 1.97	NS	27.97 ± 5.01	0.03	60.21 ± 29.91	<0.0001
Insufficient	5.14 ± 0.74		9.04 ± 2.23		25.91 ± 4.94		34.68 ± 13.94	
Severely deficient	5.69 ± 0.76	<0.0001	9.50 ± 1.97	NS	27.97 ± 5.01	0.001	60.21 ± 29.91	<0.0001
Sufficient	4.96 ± 0.61		8.46 ± 2.12		23.65 ± 4.45		29.38 ± 9.22	

* Adjusted for maternal age, previous history of GDM, family history of type 2 DM and pre-pregnancy BMI.

25OHD: 25-hydroxyvitamin D, BMI: body mass index, DM: diabetes mellitus, GDM: gestational diabetes mellitus, iPTH: intact parathyroid hormone, NS: non-significant, PGL: plasma glucose.

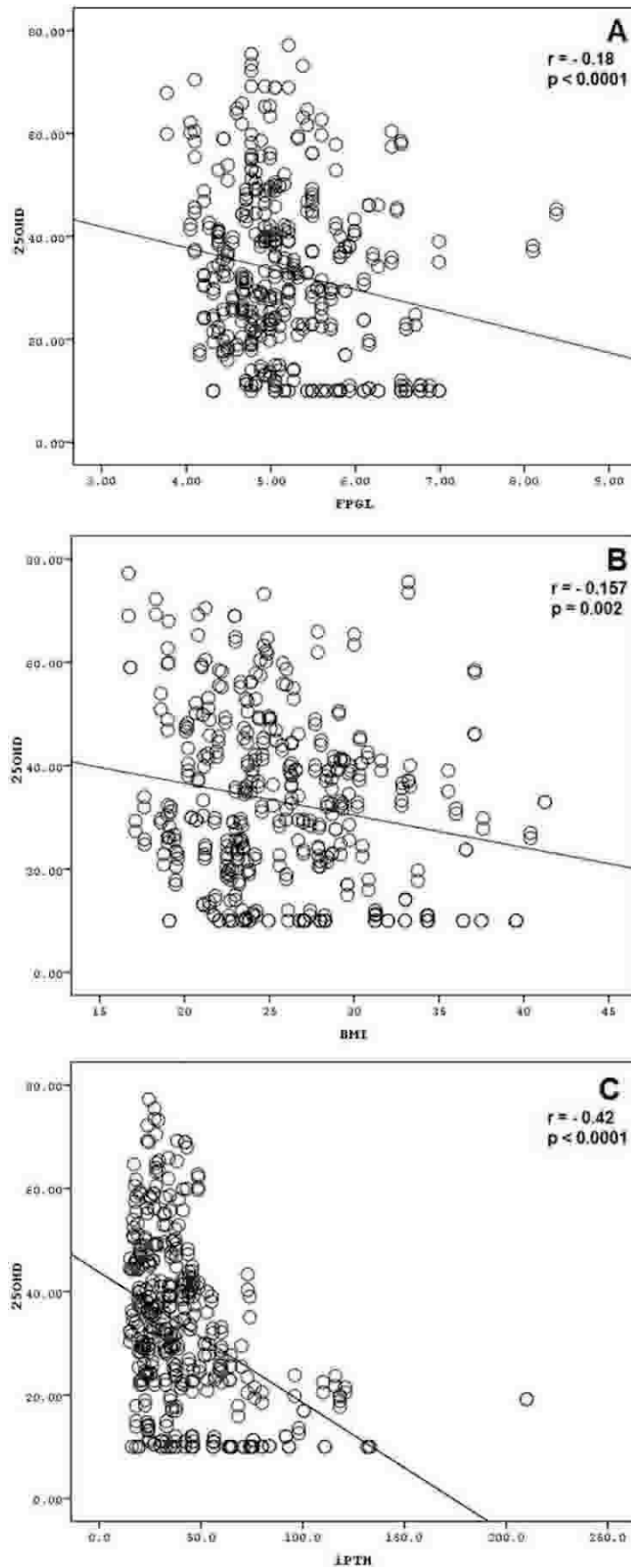


Figure 2 - The inverse correlation between 25OHD and the **A:** fasting PGL, **B:** BMI and **C:** iPTH concentrations of the study participants. **FPGI:** fasting plasma glucose (mmol/L), **25OHD:** 25-hydroxyvitamin D (nmol/L), **iPTH:** intact parathyroid hormone (pg/ml), **BMI:** pre-pregnancy body mass index (kg/m²).



a previous history of GDM, a history of type 2 DM in first-degree relatives and pre-pregnancy BMI. In accordance with previous results (5,15), we also found an inverse association between 25OHD and fasting PGL.

Evidence suggests that both type 2 DM and GDM have similar pathophysiological features characterized by two main metabolic defects: peripheral tissue resistance for insulin and insufficient secretion of insulin by pancreatic β cells to compensate for this peripheral tissue resistance (16,17). Evidence also suggests a role for vitamin D in maintaining normal glucose homeostasis (2). In both animal and human studies, an association was shown between low vitamin D levels and insulin resistance and impaired insulin secretion (16). Moreover, specific receptors for 1-25 (OH) $_2$ D $_3$ have been demonstrated in pancreatic β cells, indicating the possible role of vitamin D in the regulation of insulin secretion (19). In a study by Maghbooli et al., maternal serum 25OHD levels were inversely associated with homeostasis model assessment for insulin resistance (HOMA-IR), demonstrating that 25OHD deficiency may contribute to insulin resistance during pregnancy (4). However, the results of studies evaluating the association between 25OHD and GDM are controversial (4-7). Maghbooli et al. demonstrated that maternal serum levels of 25OHD during 24-28 weeks of pregnancy were significantly lower in women with GDM compared with controls (4). Clifton-Bligh et al. demonstrated an inverse association between maternal serum 25OHD levels and fasting blood glucose, although the association between 25OHD and GDM was not statistically significant (5). In a study performed in Indian pregnant women, no significant association was found between maternal serum levels of 25OHD and GDM risk (6). In a recent study, Makgoba et al. did not find an association between first trimester maternal serum 25OHD levels and subsequent GDM development (7). However, except for the study by Maghbooli et al., data regarding the severity of 25OHD deficiency in subjects included in these studies were insufficient. Therefore, the lack of an association between low maternal serum 25OHD levels and GDM in these studies may be due to the absence or very few numbers of pregnant women with severely deficient 25OHD levels.

In addition to type 2 DM and insulin resistance, obesity is a well-known risk factor for 25OHD deficiency (20-23). An analysis of the NHANES 2003-2004 data also demonstrated that 25OHD deficiency was highly prevalent in overweight and obese subjects (24). Although a few studies have found a relationship between pre-pregnancy BMI and low serum levels of 25OHD during pregnancy (25), the results from this study also suggest that a pre-pregnancy BMI >25 kg/m 2 is associated with severe 25OHD deficiency during the late second and third trimesters of pregnancy. In accordance with previous studies (26), this study also suggested that pre-pregnancy BMI was significantly higher in women with GDM compared with controls.

In the current study, iPTH levels were also significantly higher in pregnant women with severely deficient 25OHD levels compared to those with insufficient and sufficient 25OHD levels. Although no association was found between iPTH and fasting or 2-hour PGLs, iPTH concentrations were significantly higher in women with GDM compared to controls. Increased PTH levels, either primary or secondary to other disorders, have been shown to be associated with impaired glucose tolerance (2,27,28), decreased insulin

sensitivity and an increased risk of diabetes in glucose-tolerant subjects (9-11). Studies have suggested a two- to fourfold increased risk of diabetes in subjects with hyperparathyroidism (9-11). Therefore, in addition to severe 25OHD deficiency, high PTH concentrations may have an additional effect on glucose tolerance during pregnancy. However, further studies are needed to explain the putative role of high PTH concentrations on the pathogenesis of GDM.

As demonstrated in the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO), even a mild increase in fasting and 1-hour PGL corresponded to a significantly higher odds ratio for neonatal birth weight and cord blood c-peptide levels greater than the 90th percentile and caesarean delivery (29). Therefore, if appropriate therapy for severe 25OHD deficiency reduces the frequency or severity of GDM, this could have prominent public health significance.

An important limitation of our study was that maternal serum 25OHD levels were assessed by a single measurement during the late stage of pregnancy. Therefore, it may not reflect the maternal 25OHD status during the entire pregnancy. Another limitation was the cross-sectional design of this study; as such, we could not determine the neonatal outcomes of maternal 25OHD deficiency and also could not suggest any causal relationship.

In conclusion, the results obtained from this study provide novel data indicating that only severely deficient maternal serum 25OHD levels during pregnancy are significantly associated with an elevated relative risk of GDM, even after adjusting for established risk factors of GDM. As vitamin D deficiency is a worldwide public health problem and its severe deficiency during pregnancy may contribute to the development of GDM, the investigation of 25OHD deficiency during pregnancy and its appropriate replacement, particularly in patients with severely deficient levels, may contribute to the prevention of GDM. However, although several studies have suggested an association between 25OHD deficiency and DM, including GDM, more evidence is required to determine the effect of vitamin D on pancreatic β cells and peripheral insulin resistance.

■ AUTHOR CONTRIBUTIONS

Zuhur SS contributed to the study design, implementation, data analysis and preparation of the manuscript. Erol RS contributed to the study design and recruited and screened the patients. Kuzu I and Altuntaş Y contributed to the data analysis and preparation of the manuscript.

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