The European Research Journal 2024;10(5):474-481 Original Article

DOI: https://doi.org/10.18621/eurj.1509016 *Obstetrics and Gynaecology*

Can first trimester vitamin D levels predict adverse maternal outcomes in patients who do not take vitamin D supplements?

Burcu Dinçgez[1], Gülten Özgen[1], Levent Özgen[2]

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye; [2]Department of Obstetrics and Gynecology, Uludağ University, Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Objectives: Vitamin D deficiency is claimed to be associated with adverse perinatal outcomes. Here, we aimed to compare adverse maternal outcomes according to vitamin D levels and determine the predictive role of first-trimester vitamin D for adverse maternal outcomes in patients not receiving vitamin D supplementation.

Methods: This study was designed as a retrospective study. A total of 232 patients were divided into three groups: vitamin D deficient (n=127), vitamin D insufficient (n=57), and vitamin D sufficient group (n=48). Then, the vitamin D deficiency group was divided into severe (n=72) and mild (n=55) vitamin D deficiency. Sociodemographic characteristics, first-trimester vitamin D levels, and adverse maternal outcomes such as gestational diabetes mellitus, preeclampsia, preterm birth, and intrauterine growth restriction were compared between the groups. The predictive role of first-trimester vitamin D levels for adverse maternal outcomes was evaluated by ROC analysis.

Results: Gestational diabetes was more common in the vitamin D deficient group than in the vitamin D insufficient group (P=0.024). However, preeclampsia, preterm delivery, and composite adverse outcomes were more common in the vitamin D deficient group than in the vitamin D sufficient group (P=0.044, P=0.008, and P=0.023, respectively). There was no difference in maternal outcomes between the mild and severe vitamin D deficiency groups. First-trimester vitamin D levels ≤19 ng/mL predicted adverse outcomes with 73.2% sensitivity and 49.2% specificity (AUC=0.630, P=0.006).

Conclusions: We recommend screening vitamin D levels in the first trimester, especially in high-risk groups, due to the increased incidence of adverse outcomes. We believe that more research is needed to clarify the relationship between vitamin D and adverse outcomes and the effect of supplementation on these outcomes.

Keywords: First trimester, maternal outcomes, supplementary nutrients, vitamin D

Micronutrients are essential for metabolic processes. Since metabolism becomes faster during pregnancy, pregnant women need more micronutrients and perinatal morbidities can easily occur in micronutrients deficiencies [1].

Vitamin D is a vital micronutrient for bones and calcium metabolism. Vitamin D plays an important role not only in calcium and bone metabolism, but also

Corresponding author: Burcu Dinçgez, MD., Assoc. Prof., Phone: +90 224 295 50 00, E-mail: burcumavis@gmail.com

How to cite this article: Dinçgez B, Özgen G, Özgen L. Can first trimester vitamin D levels predict adverse maternal outcomes in patients who do not take vitamin D supplements? Eur Res J. 2024;10(5):474-481. doi: 10.18621/eurj.1509016

Received: July 6, 2024
Accepted: August 4, 2024
Published Online: August 6, 2024

in immune regulation, fertility and perinatal well-being [2]. In the literature, increased tumor necrosis alfa, interferon gamma and interleukin-6 levels were shown in vitamin D deficiency [3]. In gynecological practice, vitamin D has been found to be associated with ovarian reserve, menopausal response, polycystic ovary syndrome, endometriosis, ovarian carcinoma and breast cancer [4, 5].

Recent studies have shown that vitamin D deficiency or insufficiency is associated with adverse obstetric outcomes such as preeclampsia, gestational diabetes mellitus (GDM), intrauterine fetal growth restriction (IUGR), preterm birth, increased cesarean section rates and placental abnormalities [1, 2, 6]. In the future life, it has been found to be associated with hyperactivity disorders, attention deficits, type 1 diabetes, and asthma [7-9]. However, this relationship is still under debate.

However, the synthesis of vitamin D is an easy procedure, low dietary intake, skin diseases affecting synthesis, low sun exposure, and malabsorption syndromes can lead to vitamin D deficiency [1]. The cut-off levels for diagnosis are controversial worldwide and vary depending on ethnicity. In general, vitamin D deficiency is considered for vitamin D levels below 20 ng/ml (50 nmol/L), and vitamin D insufficiency is considered for vitamin D levels between 20-30 ng/ml (50-75 nmol/L) [10]. Vitamin D deficiency is an increasing problem worldwide. A systematic review reported a prevalence of vitamin D deficiency as 46-87% in different regions of the world [11]. Due to this high prevalence, researchers have focused on investigating the effects of vitamin D deficiency and supplementation on perinatal outcomes.

In this study, we aimed to compare adverse maternal outcomes among groups with vitamin D deficiency, insufficiency, and sufficiency. The outcomes were then compared between groups with mild and severe vitamin D deficiency. Additionally, we aimed to determine the predictive role of first-trimester vitamin D for adverse maternal outcomes in patients not receiving vitamin D supplementation.

METHODS

This is a retrospective study performed at a university affiliated Training and Research Hospital between March 2022 and March 2024. The study was in accordance with Helsinki Declaration and it was approved by the local ethics committee (2024-TBEK 2024/06-10). Written informed consent was taken from all study participants for using data from medical records.

Study Population

A total of 589 patients who have first-trimester vitamin D levels were included in the study. Singleton pregnant women between 16 to 45 years old and having available perinatal records and first-trimester vitamin D levels were included in the study. Exclusion criteria were as follows: multiple pregnancies, missing medical records of pregnancy outcomes, using tobacco products, having systemic disease before pregnancy, and using drugs affecting vitamin D levels such as steroids and anti-epileptics. Also, we excluded patients who take vitamin D supplements during pregnancy to prevent changes in maternal pregnancy outcomes. After selected according to the inclusion and exclusion criteria, a total of 232 patients were analyzed. The participants were divided into three main groups: patients who have vitamin D levels below 20 ng/mL were accepted as vitamin D deficient group (n=127), patients who have vitamin D levels between 20 and 30 ng/mL were accepted as vitamin D insufficient group (n=57) and patients who have vitamin D levels above 30 ng/mL were accepted as vitamin D sufficient group (n=48). Then, the vitamin D deficient group was divided into two groups: patients who have vitamin D levels below 12 ng/mL were accepted as severe vitamin D deficiency (n=72) while vitamin D levels between 12 ng/mL and 20 ng/mL were accepted as mild vitamin D deficiency (n=55).

Sociodemographic features such as age, parity, gestational week, body mass index, presence of insurance, economic status, seasonal change, educational status, first-trimester vitamin D levels, adverse maternal outcomes such as GDM, preeclampsia, preterm birth, and IUGR were retrospectively screened and obtained from medical records.

Pregnant women were routinely screened for GDM by two-step protocol which means performing 100-gram oral glucose tolerance test (OGTT) after 50-gram OGTT screening value exceeds 140 mg/dl at the first hour. According to the Carpenter and Coustan criteria, GDM was established with two abnormal values of 95 mg/dl for fasting, 180 mg/dl for the first hour,

155 mg/dl for the second hour, and 140 mg/dl for the third hours in 100-gram OGTT [12]. Preterm birth was defined as a live birth before the 37th gestational week, while preeclampsia was defined as the existence of hypertension after 20th gestational week accompanied by proteinuria or systemic symptoms such as visual symptoms, pulmonary edema, headache, renal insufficiency, impaired liver function, and thrombocytopenia [13].

IUGR was diagnosed based on the following criteria: a) fetal abdominal circumference/estimated fetal weight <3rd percentile, b) changes in umbilical artery Doppler, c) fetal abdominal circumference/estimated fetal weight <10th percentile with mean pulsatility index >95th percentile or pulsatility index >95th percentile [14]. In our clinic, vitamin D levels are routinely measured between 9 am to 12 am by chemiluminescent microparticle immunoassay technique with ARCHITECT i2000SR immunoassay analyzer (Abbott Diagnostics).

Statistical Analysis

The normality of distribution was tested by the Shapiro Wilk test. Since the data were not normally distributed, the Kruskal-Wallis test was used for comparisons of continuous variables between 3 groups, while the Mann-Whitney U test was used for comparisons between 2 groups. Chi-square, Fisher's Exact,

Table 1. Sociodemographic features and maternal outcomes of three groups

	Vitamin D Deficienct Group (n=127)	Vitamin D Insufficient Group (n=57)	Vitamin D Sufficient Group (n=48)	P value
Age (years)	28 (18-42)	28 (18-43)	29.5 (18-40)	0.687
Parity (n)	1 (0-5)	1 (0-5)	0.5 (0-5)	0.600
Gestational week (week)	10 (5-14)	11 (5-14)	11 (6-14)	0.358
Body mass index (kg/m^2)	27 (21-36)	27 (24-36)	27 (23-36)	0.166
Presence of insurance, n (%)	115 (90.6)	53 (93)	47 (97.9)	0.269
Economic status, n (%)				0.794
Low	53 (41.7)	25 (43.9)	21 (43.8)	
Middle	68 (53.5)	27 (47.4)	25 (52.1)	
High	6 (4.7)	5 (8.8)	2 (4.2)	
Season, n (%)				0.987
Spring	30 (23.6)	12 (21.2)	10 (20.8)	
Summer	61 (48)	28 (49.1)	22 (45.8)	
Autumn	25 (19.7)	11 (19.3)	12 (25)	
Winter	11 (8.7)	6 (10.5)	4 (8.3)	
Educational status, n (%)				0.442
Illiterate	28 (22)	8 (14)	8 (16.7)	
Literate	99 (78)	49 (86)	40 (83.3)	
Gestational diabetes, n (%)	15 (11.8)	1 (1.8)	1 (2.1)	**0.017**
Preeclampsia, n (%)	16 (12.6)	2 (3.5)	1 (2.1)	**0.032**
Preterm birth, n (%)	22 (17.3)	5 (8.8)	1 (2.1)	**0.015**
IUGR, n (%)	7 (5.5)	1 (1.8)	1 (2.1)	0.365
Adverse maternal outcome, n (%)	30 (23.6)	7 (12.3)	4 (8.3)	**0.029**
Vitamin D level (ng/mL)	11 (4-19)	25 (21-27)	35.3 (31-45)	**<0.001**

Data are shown as median (minimum-maximum) or n (%). IUGR=Intrauterine growth restriction.

and Fisher Freeman Halton tests were performed for group comparison of categorical variables. Variables were given as median (minimum-maximum) values for continuous variables and frequency (percentages) for categorical variables. The predictive role of first-trimester vitamin D levels for adverse maternal outcomes was evaluated with ROC analysis. SPSS version 22.0 and MedCalc 18 statistical software were used for statistical analysis. A P-value ≤0.05 was accepted as statistically significant.

RESULTS

Gestational diabetes mellitus was detected in 7.3% (n=17) of the patients and preeclampsia 8.2% (n=19) of patients. A total of 28 pregnant women had preterm birth (12.1%). Intrauterine growth restriction was present in 3.9% (n=9) of the patients. Composite adverse maternal outcomes were detected in 17.7% (n=41) of all participants.

The sociodemographic features and maternal outcomes of the three groups are shown in Table 1. There were no significant differences among the three groups in terms of age, parity, gestational age, body mass index, insurance, economic status, seasonal variation, and educational status. As expected, maternal first-trimester vitamin D levels were significantly different among the three groups. When maternal outcomes were examined, the rates of GDM, preeclampsia, preterm birth and composite adverse outcomes were statistically different in at least one group. There was no difference among the groups in terms of IUGR rates.

Comparison of maternal outcomes between groups is demonstrated in Table 2. Gestational diabetes was significantly common in the vitamin D deficient group as compared to the vitamin D insufficient group while preeclampsia, preterm birth, and composite maternal adverse outcomes were more common in the vitamin D deficient group as compared to the vitamin D sufficient group.

Sociodemographic features and maternal outcomes of severe and mild vitamin D deficiency groups were presented in Table 3. No difference was detected between the severe and mild vitamin D deficiency group concerning age, parity, gestational week, body mass index, presence of insurance, economic status, seasonal change, and educational status. Furthermore, there was no statistically significant difference between the two groups according to maternal outcomes.

The predictive role of vitamin D for adverse maternal outcomes was evaluated by ROC analysis. ROC analysis revealed that first-trimester vitamin D levels ≤19 predicted adverse maternal outcomes with 73.2% sensitivity and 49.2% specificity (AUC=0.630, P=0.006) (Fig. 1).

DISCUSSION

Vitamin D deficiency has become a major health problem worldwide, especially among pregnant women. Current literature provides increasing data on the relationship between adverse perinatal outcomes and vitamin D deficiency [1, 2].

A systematic review in 2013 showed that vitamin D levels <20 ng/mL was associated with an increased risk of GDM, preeclampsia, small for gestational age, and preterm birth [6]. Contrary to this study, first-trimester vitamin D was not found to be associated with adverse perinatal outcomes in Malaysian women in 2020 [15]. This conflicting results may be due to the heterogenity of the study populations and different cut-off points for vitamin D deficiency. In the current study, maternal adverse outcomes were found to be

Table 2. Comparison of maternal outcomes between groups

	P_{1-2}	P_{1-3}	P_{2-3}
Gestational diabetes	**0.024**	0.073	1.000
Preeclampsia	0.055	**0.044**	1.000
Preterm birth	0.130	**0.008**	0.216
Maternal adverse outcome	0.076	**0.023**	0.511

Table 3. Sociodemographic features and maternal outcomes of severe and mild vitamin D deficiency groups

	Severe Vitamin D Deficiency (n=72)	Mild Vitamin D Deficiency (n=55)	P value
Age (years)	27 (18-42)	30 (18-40)	0.216
Parity (n)	1 (0-5)	1 (0-4)	0.449
Gestational week (week)	10 (5-14)	10 (6-14)	0.746
Body mass index (kg/m^2)	26.5 (21-36)	27 (23-36)	0.448
Presence of insurance, n (%)	64 (88.9)	51 (92.7)	0.464
Economic status, n (%)			0.195
Low	35 (48.6)	32.7)	
Middle	34 (47.2)	34 (61.8)	
High	3 (4.2)	3 (5.5)	
Season, n (%)			0.706
Spring	17 (23.6)	13 (23.6)	
Summer	34 (47.2)	27 (49.1)	
Autumn	13 (18.1)	12 (21.8)	
Winter	8 (11.1)	3 (5.5)	
Educational status, n (%)			0.608
Illiterate	18 (25)	10 (18.2)	
Literate	54 (75)	45 (81.8)	
Gestational diabetes, n (%)	10 (13.9)	5 (9.1)	0.406
Preeclampsia, n (%)	11 (15.3)	5 (9.1)	0.298
Preterm birth, n (%)	15 (20.8)	7 (12.7)	0.232
IUGR, n (%)	4 (5.6)	3 (5.5)	1.000
Adverse maternal outcome, n (%)	20 (27.8)	10 (18.2)	0.207
Vitamin D level (ng/mL)	9 (4-11)	18 (13-19)	**<0.001**

Data are shown as median (minimum-maximum) or n (%). IUGR=Intrauterine growth restriction.

higher in vitamin D deficient group as compared to vitamin D sufficient group. However, interestingly, no significant difference was detected between mild and severe vitamin D deficiency. Moreover, first-trimester vitamin D levels ≤19 ng/mL predicted adverse outcomes with 73.2% sensitivity and 49.2% specificity. Considering these results, it would be more logical to compare the outcomes for each adverse outcome than compositely.

The underlying mechanisms of the relationship between preeclampsia and vitamin D deficiency are not well recognized. Possible mechanisms include susceptibility to proinflammatory responses in the absence of vitamin D, oxidative stress, and endothelial dysfunction [16, 17]. Moreover, vitamin D receptors are present in fetal tissues and the placenta which plays role in the regulation of fetal growth and placental implantation [18]. In the literature, seasonal variations were shown in preeclampsia. This can be related to the vitamin D synthesis from sunlight [19, 20]. Bodnar *et al*. [21] reported that first-trimester vitamin D levels were significantly lower in patients who subsequently developed preeclampsia. There was a confusing point in the literature on the subject, which was

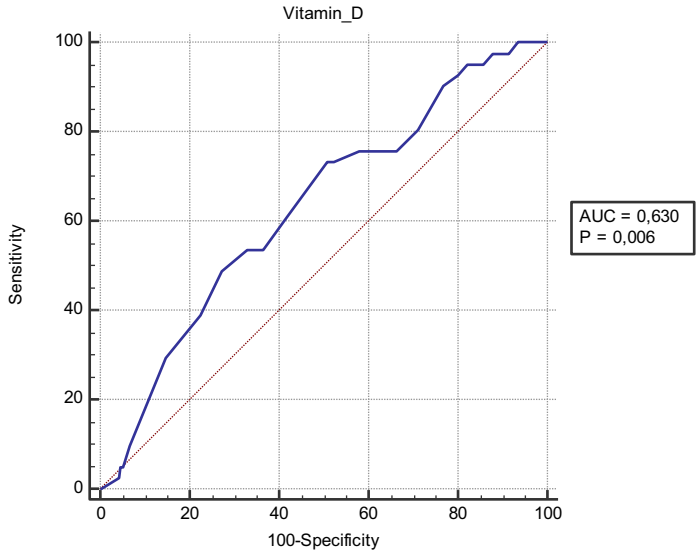

Fig. 1. The ROC analysis evaluating the predictive role of vitamin D for adverse maternal outcomes.

the role of vitamin D supplementation. A study from Norway has shown that taking vitamin D supplements reduces the risk of preeclampsia [22]. In our study, we first showed that the risk of preeclampsia is increased in vitamin D deficiency, independent of the severity of deficiency and supplementation. In contrast to these studies, Al-Shaikh *et al*. [23] revealed no association between low vitamin D levels and pregnancy-induced hypertension. This difference may be explained with confounding factors such as vitamin D sampling time, race, season, and diet. In addition to inflammation, oxidative stress and endothelial dysfunction; vitamin D receptor modulate pancreatic beta cell functions, stimulates insulin receptors, increase insulin sensitivity [24]. Consequently, vitamin D deficiency comes across with GDM in clinical practice. In a meta-analysis searching 22000 pregnant women, vitamin D deficiency was associated with increased GDM rates [25]. Similarly, a meta-analysis searching 16515 patients revealed that GDM risk increase by 45% in vitamin D deficiency [26]. Two meta-analyses searching the effects of supplementation claimed that supplementation improves pregnancy outcomes in women with GDM [27, 28]. In contrast to these studies, in a study of Abd Aziz *et al*. [15], no significant relationship was reported between vitamin D deficiency and GDM. Similarly, Ni *et al*. [13] found no correlation between vitamin D and GDM in unadjusted and adjusted models. In the present study, we found no difference between vitamin D deficiency and sufficient group while GDM was more prevalent in the vitamin D deficient group as compared to vitamin D insufficiency in pregnant women who do not take any supplementation. Similar to preeclampsia, the severity of the deficiency did not affect GDM rates.

Vitamin D regulates the production of inflammatory cytokines and reduces the response to pathogen organisms that cause bacterial vaginosis. It also plays a role in uterine relaxation via calcium metabolism. Impairment of these mechanisms results in preterm birth [29]. The association between vitamin D and preterm birth has conflicting results. A meta-analysis found that low vitamin D levels were associated with an increased rate of preterm birth [30]. A cohort study evaluating 2327 patients demonstrated that vitamin D levels <50 nmol/L significantly increase preterm birth [31]. Perez-Ferre *et al*. [32] showed that a cut-off value of 35 nmol/L predicted preterm birth with 66.7% sensitivity and 71% specificity. Similarly, in a study of Tahsin *et al*. [1] defining vitamin D deficiency as being below 30.25 nmol/L, low second-trimester vitamin D levels were related to increased preterm birth risk. The latest meta-analysis in 2024 showed that low vitamin D levels increase the risk of preterm birth [33]. Consistent with these findings, we found that vitamin D deficiency increases the risk of preterm birth. Con-

trary to this, other studies have not claimed this relationship [34-38]. A study searching 3465 pregnant women reported that there was no relation between vitamin D deficiency and preterm birth [39]. These conflicting results can be related to the different study populations having different nutrition habits, race, sunlight exposure, and vitamin D supplementation.

Limitations

The current study has several limitations. First, it has a retrospective design and a small sample size. Second, confounding factors such as nutritional status were not taken into account. Third, second, and third-trimester vitamin D levels were absent. Finally, neonatal and offspring outcomes were lacking.

CONCLUSION

Vitamin D deficiency is a common condition in pregnancy. Although the effect of supplementation has conflicting results, considering the high incidences of adverse maternal outcomes in vitamin D deficiency, it could be an appropriate strategy to screen vitamin D levels at first trimester and give supplementation for our population.

Authors' Contribution

Study Conception: BD, GÖ, LÖ; Study Design: BD, GÖ; Supervision: BD; Funding: LÖ; Materials: LÖ; Data Collection and/or Processing: BD, LÖ; Statistical Analysis and/or Data Interpretation: BD; Literature Review: GÖ, BD; Manuscript Preparation: BD, GÖ, LÖ and Critical Review: BD, GÖ.

Ethical Statement

This study was approved by local ethics committee of University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital (date: 12.06.2024 and number: 2024-TBEK 2024/06-10).

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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