Vitamin D Deficiency and Pregnancy Outcome: Does it Have a Role in Preeclampsia Etiology?

Vitamin D Eksikliği ve Gebelik: Preeklampsi Etyolojisinde Rolü Var Mıdır?

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Abstract

Objective: Vitamin D deficiency is higher in pregnancy and there is evidence of its relationship with various obstetric problems. The aim of our study was to investigate the association between preeclampsia and vitamin D levels in pregnancy.

Material and Method: This study included 1209 women. General characteristics, laboratory results, and obstetric outcomes were evaluated. As globally accepted vitamin D deficiency was determined as <20 ng/mL and we found a critical level of deficiency that is 8.335 ng/mL in ROC analyses.

Results: The patients' median age was 28 (17-45). The rate of labor induction needed was 11.9%. The cesarean section rate was 32.5%. The incidence of vitamin D deficiency was 81% (n:979). Gestational week (38.6 vs. 38.5), birth weight (3291 gr vs. 3248 gr), and head circumference (34.98 cm vs. 34.9 cm) were not different groups with regard to vitamin D deficiency (p: 0.145, p:0.184 and p:0.358, respectively). Besides, vitamin D deficiency was associated with the risk of labor induction and premature rupture of membranes in univariant analyses.

38 patients were diagnosed with preeclampsia. The diagnostic accuracy rate of level vitamin D level as 8.335 ng/mL was 76.1%. According to multivariate analysis 25-OH vitamin D level of 8.335 ng/mL (HR: 2.94; 95%CI: 2.04-4.22; P < 0.001) and nulliparity (HR: 2.05; 95%CI: 1.43-2.93; *p < 0.001*) were independent risk factors associated significantly with preeclampsia.

Conclusion: Low vitamin D levels were related to preeclampsia in our study. The association was stronger in lower levels. Vitamin D deficiency is observed quite frequently, and future studies will reveal supportive results for this health problem.

Keywords: 25-hydroxy vitamin D; Outcome; Preeclampsia; Pregnancy; Vitamin D eficiency

Özet

Amaç: Vitamin D eksikliği gebelikte daha sık görülmektedir ve çeşitli obstetrik rahatsızlıklarla ilişkisi olduğuna yönelik kanıtlar mevcuttur. Bu çalışma, gebelerde D vitamini seviyesi ile preeklampsi arasındaki ilişki olup olmadığını araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Çalışmaya 1209 kadın dahil edilmiştir. Genel karakteristikler, laboratuvar sonuçları ve obstetrik sonuçlar değerlendirilmiştir. Global olarak da kabul edilmiş olan <20ng/mL, vitamin D eksikliği olarak tanımlanmıştır. ROC eğrisi analizinde eksiklik için kritik düzey 8,335 ng/mL olarak tespit edilmiştir.

Bulgular: Hastaların ortanca yaşı 28 (17-45) idi. Hastaların %11,9'unda doğum indüksiyonu gerekmiştir. Sezaryen seksiyo oranı %32,5 idi. Hastaların %81'inde (n:979) vitamin D eksikliği tespit edilmiştir. Gestasyonel hafta (38,6 vs. 38,5), doğum ağırlığı (3291 gr vs. 3248gr) ve baş çevresi (34,98cm vs. 34,9cm) vitamin D eksikliği olmayan ve olan gruplarda benzerdi (sırasıyla p: 0,145; p:0,184 ve p:0,358). Buna ek olarak, tek değişkenli analizde vitamin D eksikliği olan grupta doğum indüksiyonu ve erken membran ruptürü daha yüksek oranda tespit edilmiştir. Otuz sekiz hasta preeklampsi tanısı almıştır. Vitamin D düzeyinin 8,335 ng/mL olarak tanısal doğruluk oranı %76,1 idi.

Çok değişkenli analizde, 8,335 ng/mL 25-OH vitamin D düzeyi (HR: 2,94; %95 GA: 2,04-4,22; p<0,001) ve nulliparitenin (HR: 2,05; %95 GA: 1,43-2,93; *p< 0,001*) preeklampsi için istatistiksel olarak anlamlı bağımsız risk faktörleri oldukları tespit edilmiştir.

Sonuç: Çalışmamızda azalmış vitamin D düzeyi preeklampsi ile ilişkili olarak bulunmuştur. İlişkinin vitamin D düzeyi düştükçe, arttığı gözlenmiştir. Vitamin D eksikliği oldukça sık izlenmektedir ve ileride yapılacak çalışmalar dünya genelinde izlenen bu sağlık sorununa destekleyici sonuçlar ortaya koyacaktır.

Anahtar Kelimeler: 25-hidroksi vitamin D; Gebelik; Preeklempsi; Sonuçlar; Vitamin D Eksikliği

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Introduction

Vitamin D has diverse functions in many organ systems and its deficiency is seen almost universally (1), therefore vitamin D deficiency (VDD) is a global health problem even in developed countries (2). Vitamin D plays important roles in implantation and placental development and has immunomodulatory and anti-inflammatory activities which makes it a vital nutrient in pregnancy, as well (3). Many studies have been administered to demonstrate an association between VDD and gestational complications such as low birth weight, gestational diabetes mellitus (GDM), or preeclampsia in the literature (4-6).

Vitamin D has some target receptors in decidua and trophoblasts (7) and therefore there is an increasing trend in investigating the association between preeclampsia and vitamin D levels. Most of these investigations found an association between low vitamin D levels and higher preeclampsia risk whereas few reported conflicting results (8-11).

Our objective was to research the VDD rates in pregnant patients and its effects on preeclampsia development, in our study.

Material and Method

This was a retrospective non-randomized study. The patients who continued their follow-up during their pregnancy and who gave birth between 2016-2019 in our hospital were included in the study. Patients' general characteristics such as age, parity, and laboratory parameters such as 25-hydroxy vitamin D (25-OH vit D) level, 75-g oral glucose tolerance test (OGTT), and obstetric outcome parameters such as birth weight, amniotic fluid index, presence of GDM, preeclampsia (PE), preterm birth or neonatal intensive care unit (ICU) need were retrospectively reviewed.

25-OH vit D level was tested in 1738 patients. The patients with lost follow-up, missing laboratory data, history of rheumatological conditions, hepatic or renal failure, GDM, hypertension, PE, eclampsia, drug addiction, alcohol consumption, or any long-term medical therapy were excluded. As a result, 1209 patients were involved in the study. The method of delivery, the need for labor induction for any reason, oligohydramnios, smoking status, and premature rupture of membranes (PROM) were recorded from patient records. Birth weight was evaluated according to gestational age.

VDD was defined as the level of 25-OH vit D below 20 ng/mL. Moreover, a receiver operating characteristic (ROC) curve was used to analyze the discriminative role of the 25-OH vit D level between the presence and absence of preeclampsia. The area under the curve was found significant and the point at which the sum of sensitivity and specificity reached the maximum was engaged as the best cut-off point. The cut-off point for 25-OH vit D was determined as 8.335ng/mL.

Data were analyzed by utilization of SPSS for Windows version 15.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using Fisher's exact test or chi-square test, as proper. Logistic regression analysis was used to appreciate independent factors affecting preeclampsia. Statistically, significance level was adjusted as $p<0.05$.

Results

The median age was 28 (17-45). Multiparous patients constituted 67.1% of patients (n: 811). The incidence of the need for labor induction, cesarean section, and vaginal

Table I. General characteristics of patients

	N	%
Age (years)		
<35	1012	83.7
≥35	197	16.3
Parity		
Nulliparous	398	32.9
Multiparous	811	67.1
Need of labor induction		
Present	144	11.9
Absent	1065	88.1
Delivery		
VD (Nulliparous)	293	24.2
VD (Multiparous)	523	43.3
Primary CS	147	12.2
Repeated CS	246	20.3
Vitamin D level		
Low	979	81.0
Normal	230	19.0
Smoking		
Present	22	1.8
Absent	1187	98.2

*VD : Vaginal Delivery, **CS : Cesarean Section

Table II. Obstetric properties of patients

Gestational Week at Delivery		
Term	1134	93.8
Preterm	75	5.2
Preeclampsia		
Present	38	3.1
Absent	1171	86.9
GDM		
Present	64	5.3
Absent	1145	94.7
SGA		
Present	82	6.8
Absent	1127	93.2
Oligohidramnios		
Present	87	7.2
Absent	1122	92.8
PROM		
Present	49	4.1
Absent	1160	95.9
Neonatal ICU Need		
Present	167	13.8
Absent	1042	86.2

GDM: Gestational Diabetes Melltius, SGA: Small for Gestational Age
PROM: Premature Rupture of Membranes, ICU: Intensive Care Unit

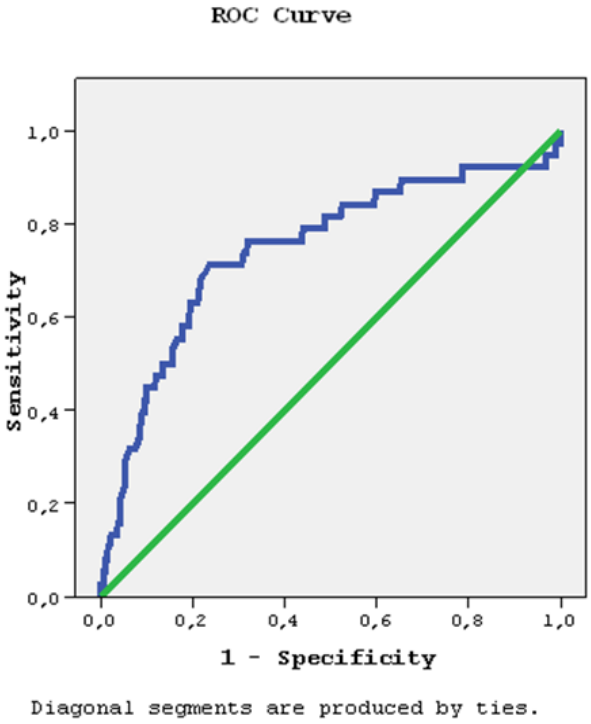
delivery were 11.9%, 32.5%, and 67.5%, respectively. The general characteristics of patients are indicated in Table I. Preeclampsia was diagnosed in 38 patients. The characteristics of the pregnancy outcome were summarized in table II.

The rate of VDD was 81% (n:979). The VDD rates according to the quarters of the year were 83.7%, 80.7%, 76.4%, and 84.5%, respectively and this showed significance, statistically (*p:0.033*). VDD did not affect the gestational week (38.6 vs. 38.5), birth weight (3291gr vs. 3248gr), and head circumference (34.98 cm vs. 34.9 cm) (p: 0.145, p:0.184 and p:0.358, respectively). Nevertheless, VDD was significantly related to the need for labor induction and PROM in univariate analyses. Table III shows the association between VDD and obstetric outcomes.

Most patients with preeclampsia (71.1%, n: 27 vs. n: 11) had VDD. The area under the ROC was calculated as statistically significant for the distinctive role of 25-OH vit D level for preeclampsia (AUC=0.745,95% CI: 0.653-0.837, $p < 0.001$) (Figure I). The optimal cut-off point for 25-OH vit D level predicting the presence of preeclampsia was determined as 8.335 ng/mL. The rate of sensitivity and specificity, positive, and negative predictive values were 71.0%, 76.4%, 91.1%, and 98.8%, respectively. The diagnostic precision rate was 76.1 % at this point. On multivariate analysis 25-OH vit D level of 8.335 ng/mL (HR: 2.94; 95%CI: 2.04-4.22; $p < 0.001$) and nulliparity (HR: 2.05; 95%CI: 1.43-2.93; $p < 0.001$) were independent factors significantly associated with preeclampsia. Factors related to the presence of preeclampsia based on univariate and multivariate analysis are listed in Table IV.

Table III. Vitamin D deficiency (<20 ng/mL) and Obstetric Outcome

	VDD (+)		VDD (-)		
	N	%	N	%	*p* value
GDM					
Present	51	5.2	13	5.7	0.787
Absent	928	94.8	217	94.3	
Need of Labor Induction					
Present	130	13.3	14	6.1	0.002
Absent	849	86.7	216	93.9	
Preterm Labor					
Present	59	6.0	16	7.0	0.599
Absent	920	94.0	214	93.0	
SGA					
Present	67	6.8	15	6.5	0.861
Absent	912	93.2	215	93.5	
Neonatal ICU need					
Present	135	13.8	32	13.9	0.961
Absent	844	86.2	198	86.1	
Oligohydramnios					
Present	71	7.3	16	7.0	0.504
Absent	809	92.7	214	93.0	
PROM					
Present	47	4.8	2	0.9	0.007
Absent	932	95.2	228	99.1	



Discussion

VDD in pregnancy is widespread and associated with adverse consequences in pregnancy (12). In prior studies, VDD was associated with preeclampsia (4). We investigated retrospectively the level of vitamin D in pregnancy and its relation with pregnancy in this study. The most prominent results of our study were the VDD's high incidence and its association with preeclampsia.

Foods constitute a smaller portion of Vitamin D source however it is primarily synthesized by the skin (13). It is converted to 25-OH vit D form which is the leading form of serum levels of vitamin D. Then it is activated by the kidney. It works through a nuclear steroid hormone receptor (13) and has multiple functions in different body parts. Besides the major function of bone metabolism, activated vitamin D has an important role in immune regulation (14-16). Decreased levels of vitamin D might have a role in immune anomalies (16). The abnormal inflammatory process in preeclampsia is well-known when compared to pregnancy without preeclampsia. It's an important mediator that can have a role in preeclampsia pathophysiology as its deficiency leads to defective placental implantation.

There are numerous studies focused on the relationship between vitamin D levels and preeclampsia. In a large case-control study, Serrano et al. compared 1013 preeclampsia patients with 1015 controls with regard to levels of vitamin D. Lower vitamin D levels were related to a twofold increased risk for preeclampsia in this study (4). In a recent meta-analysis, VDD was related to an increase in preeclampsia risk (8). Although, the protective effect of vitamin D supplementation has not been proved; studies are reporting the positive influence of vitamin D intake (10, 17).

VDD is defined as levels under 20 ng/mL and mostly this threshold was used in previous studies. Plenty of the patients in this study had VDD but this rate was still higher than the other studies reporting an association between preeclampsia

Table IV. Univariate and multivariate analyses of Presence of Preeclampsia – Chi-square and Logistic Regression Analyses

	Univariate Analysis					Multivariate Analysis		
	Preeclampsia (+)		Preeclampsia (-)					
	N	%	N	%	*p- value*	HR	95% CI	*p*-value
Age (year)								
<35	34	3.4	978	96.6	*0.328*			
≥35	4	2.0	193	98.0				
Vitamin D level								
<8.335	27	8.9%	277	91.1	*<.0001*	2.94	2.04-4.22	*<.0001*
≥8.335	11	1.2%	894	98.8				
GDM								
Present	2	3.1	62	96.9	*0.993*			
Absent	36	3.1	1109	96.9				
Parity								
Nulliparous	24	6.0	374	94	*<.0001*	2.05	1.43-2.93	*<.0001*
Multiparous	14	1.7	797	98.3				
Smoking								
Present	2	9.1	20	90.9	*0.107*			
Absent	36	3.0	1151	97.0				

and VDD. Therefore, we applied a ROC curve analysis to investigate if there is a better cut-off level of vitamin D for our patient group. And as a result, the lower level which had a stronger association with preeclampsia was found according to our analysis. This finding was in parallel with the results of a recently published meta-analysis by Akbari et. al. (8). They concluded that VDD (20 ng/mL) was associated with PE, however, this association was stronger up to 90% in the case of a lower cut-off (10.6 ng/mL).

There are many studies indicating a relationship between low vitamin D levels and poor obstetric outcomes and maternal or fetal complications (4, 8, 18, 19). No association was found with birth weight, preterm birth or gestational diabetes in our study and VDD was associated with in need for labor induction and a higher risk of PROM. Some of these results were in accordance and some had a conflict with the prior studies.

A recent Cochrane review indicated that vitamin D supplementation alone may probably reduce preeclampsia risk, gestational diabetes, low birth weight, and severe postpartum hemorrhage (20). Vitamin D supplementation has become widespread with increasing evidence of positive effects on pregnancy. Vitamin D supplementation approach has also entered the health policies of various countries including our country in recent years. Also, VDD incidence in our study points to a public health problem and may direct clinicians to evaluate the issue from a different perspective.

Standard follow-up, a substantial number of patients, and evaluation of other gestational characteristics are strengths of the study. On the other hand, retrospective design, and lack of power analysis may be limitations of the study.

Conclusion

The present study focused on the association between vitamin D levels and obstetric outcomes of pregnant patients focusing on preeclampsia and found an association between severe VDD and preeclampsia. We found no relation between VDD and GDM, preterm birth, or birth weight in contrast to previous studies. Based on the present findings, we think that additional prospective studies on the effect of vitamin D levels on preeclampsia and prospective randomized studies on the efficacy of supplementation or better identified threshold levels may contribute to the literature.

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