



## COMPARISON OF MATERNAL SERUM VITAMIN D LEVELS IN PREECLAMPTIC AND HEALTHY PREGNANT WOMEN

### PREEKLAMPTİK VE SAĞLIKLI GEBE KADINLARDA MATERNAL SERUM D VİTAMİNİ DÜZEYLERİNİN KARŞILAŞTIRILMASI

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#### Research Article

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#### Abstract

This study aimed to examine the levels of 25 hydroxy vitamin D (25-OH D) in preeclampsia and normotensive pregnant groups. A total of 70 pregnant women who came to the Health Sciences University, Istanbul Gaziosmanpaşa Training and Research Hospital for delivery at 35-40 weeks of gestation were included in the study. The study group consisted of 35 preeclamptic (n=35) and 35 normotensive (n=35) pregnant women. Demographic, obstetric, and laboratory results of the two groups were compared in terms of 25-OH D levels. There was no statistically significant difference with the control group in terms of maternal age, gestational age at birth, gravidity, parity, number of abortions and living children, and BMI ( $p>0.05$ ). When the mean diastolic blood pressure and systolic blood pressure of the groups were compared, the mean blood pressure of the individuals in the preeclamptic group was found to be statistically and significantly higher than the mean systolic and diastolic blood pressure of the individuals in the control group ( $p<0.05$ ). When the groups were compared in terms of LFT (ALT, AST), proteinuria in urine, and platelet levels in blood, no statistically significant difference was found between the groups. Vitamin D levels were found to be statistically significantly lower in preeclamptic pregnancies compared to normotensive pregnancies. Low maternal vitamin D levels may play a role in the etiology of essential hypertension and preeclampsia, and more comprehensive research is needed on the

potential positive effects of additional vitamin D supplementation.

**Keywords:** Complications, Hypertension, Preeclampsia, Pregnancy, Vitamin D.

#### Öz

Bu çalışma, preeklamptik ve normotansif gebelerde 25-hidroksi vitamin D (25-OH D) düzeylerini incelemeyi amaçlamaktadır. Çalışmaya, Sağlık Bilimleri Üniversitesi İstanbul Gaziosmanpaşa Eğitim ve Araştırma Hastanesi'nde 35-40. gebelik haftalarında doğum yapmak üzere başvuran toplam 70 gebe kadın dahil edilmiştir. Çalışma grubu, 35 preeklamptik (n=35) ve 35 normotansif (n=35) gebeden oluşmaktadır. Her iki grubun demografik, obstetrik ve laboratuvar verileri 25-OH D düzeyleri açısından karşılaştırılmıştır. Anne yaşı, doğumdaki gebelik haftası, gravide, parite, düşük ve yaşayan çocuk sayısı ile beden kitle indeksi açısından kontrol grubu ile preeklamptik grup arasında istatistiksel olarak anlamlı bir fark bulunmamıştır ( $p>0.05$ ). Grupların ortalama diyastolik ve sistolik kan basıncı karşılaştırıldığında, preeklamptik gruptaki bireylerin ortalama kan basıncı değerleri, kontrol grubundakilere kıyasla istatistiksel olarak anlamlı düzeyde daha yüksek bulunmuştur ( $p<0.05$ ). ALT, AST gibi karaciğer fonksiyon testleri, idrarda proteinüri ve kandaki trombosit düzeyleri açısından gruplar arasında anlamlı bir fark saptanmamıştır. Ancak, vitamin D düzeyleri preeklamptik gebelerde normotansif gebelere kıyasla istatistiksel olarak anlamlı şekilde daha düşük bulunmuştur. Düşük

maternal vitamin D düzeylerinin esansiyel hipertansiyon ve preeklampsi etiyolojisinde rol oynayabileceği düşünülmektedir. Bu nedenle, ek vitamin D takviyesinin potansiyel olumlu etkilerini değerlendirmek üzere daha kapsamlı çalışmalarla ihtiyaç vardır.

**Anahtar Kelimeler:** Komplikasyonlar, Hipertansiyon, Preeklampsi, Gebelik, Vitamin D.

## 1. Introduction

Preeclampsia is one of the leading causes of maternal and fetal mortality and morbidity, despite advances in the field of obstetrics. Although the exact cause of preeclampsia is unknown, it complicates 5-8% of nulliparous women and 2-3% of all pregnancies (Sibai et al., 2005). Hypertension during pregnancy can manifest as gestational hypertension, preeclampsia, or eclampsia. Numerous markers that could be significant in predicting preeclampsia have been investigated, and the changes in maternal 25-hydroxyvitamin D levels throughout the trimesters of pregnancy have been evaluated in many studies (Baker et al., 2010). During pregnancy and lactation, changes occur in most vitamins and minerals. Deficiencies in some of these vitamins and minerals are thought to be responsible for a range of conditions, from maternal bone mineral loss to preeclampsia.

Vitamin D plays a crucial role in preventing calcium malabsorption and mitigating bone loss. Upon reviewing clinical studies concerning the relationship between Vitamin D and pregnancy outcomes, it has been suggested that Vitamin D deficiency may be associated with an elevated risk of preeclampsia, gestational diabetes, low birth weight, preterm birth, cesarean delivery, and infectious diseases. However, it has been emphasized that further randomized controlled trials are necessary to substantiate these associations. Recent studies have demonstrated a link between Vitamin D and hypertension. The renin-angiotensin system is well recognized for its significant role in the regulation of blood pressure. It has been established that Vitamin D deficiency directly influences the renin-angiotensin system, consequently increasing the risk of hypertension (Urrutia & Thorp, 2012). 25-OH D possesses essential roles in implantation and placentation, in addition to its angiogenic and anti-inflammatory properties. Certain studies have indicated that elevated levels of 25-OH D may offer protection against preeclampsia. In this context, it has been proposed that severe 25-OH D deficiency, characterized by levels below 10 ng/ml, may heighten the risk of preeclampsia and eclampsia during pregnancy (Rammos et al., 2008). Recommendations regarding screening and mineral and vitamin supplementation in pregnant women remain a subject of debate. The aim of this study was

to investigate the relationship between 25-OH D levels in preeclamptic and normotensive pregnant women.

## 2. Material and Methods

This study was conducted following decision number 67, dated 08/06/2022, by the Local Ethics Committee of the University of Health Sciences, Istanbul Gaziosmanpasa Training and Research Hospital. Each patient participating in the study was informed, and only those who provided informed consent by signing the participation form were included in the study.

The study was carried out with 70 pregnant women who presented to the Gynecology and Obstetrics Clinic of Gaziosmanpasa Training and Research Hospital for pregnancy follow-up. Pregnant women who had regularly used 25-OH D during pregnancy were excluded from the study. Based on their diagnosis, the participants were divided into two groups: normotensive pregnant women (n=35) (Group 1) and preeclamptic pregnant women (n=35) (Group 2). The demographic and laboratory results, as well as 25-OH D levels, were compared between the two groups.

The diagnosis of preeclampsia was made according to the criteria outlined in the American College of Obstetricians and Gynecologists (ACOG-2013) guidelines on hypertension during pregnancy. Preeclampsia is defined as a condition in which arterial blood pressure is equal to or exceeds 140 mmHg systolic and/or 90 mmHg diastolic in two separate measurements taken at least four hours apart, occurring after the 20th week of pregnancy, in conjunction with proteinuria—measured as 300 mg/dl or more per 24-hour urine collection, or a dipstick reading of 1+ or higher (8). The normotensive group included pregnant women whose blood pressure was normal before pregnancy (systolic/diastolic <120/80 mmHg). Pregnant women diagnosed with essential hypertension, characterized by elevated blood pressure prior to pregnancy (systolic >140 mmHg and diastolic >90 mmHg), were categorized into the essential hypertensive group.

The study cohort comprised pregnant women aged 18 to 40 years who presented to the Department of Obstetrics and Gynecology between 35 and 40 weeks of gestation. Participants with a history of metabolic diseases, thyroid disorders, uterine anomalies, multiple pregnancies, pregnancies achieved through assisted reproductive techniques, known genetic and structural anomalies in fetuses, intrauterine growth restriction, pregestational and gestational diabetes, membrane rupture, chorioamnionitis, fetal tachycardia, or unexplained fever were excluded from the study.

The control group consisted of healthy pregnant women who delivered between the 35th and 40th weeks of gestation without any medical conditions or

adverse obstetric features (such as a history of diabetes, hypertension, obesity, or thyroid disorders). Clinical parameters assessed included age, body mass index, gestational age, gravidity, history of abortion, neonatal weight, and Apgar scores at 1 and 5 minutes.

**2.1. Laboratory analysis**

In the literature, various threshold values such as 15, 20, and 30 ng/ml have been observed for the diagnosis of 25-OH D deficiency. Based on a series of biomarkers, a minimum serum concentration of 20 ng/ml has been considered desirable. Consequently, deficiency is now defined as a serum level of 20 ng/ml, which has also been utilized as the cutoff value in this study (Holick et al., 2011).

**2.2. Statistical analysis**

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were

expressed as standard deviations and means for numerical variables. The Kolmogorov-Smirnov test was employed to assess the normal distribution of variables, while the Mann-Whitney U test was used for subgroup comparisons. For categorical variables, the Pearson Chi-Square test was applied. A p-value of <0.05 was considered statistically significant.

**3. Results and/or Discussion**

Comparisons of sociodemographic and clinical data between the groups are presented in Table 1. No significant differences were observed for age, body mass index, gravidity, parity, number of abortions, gestational week, birth weight, and Apgar scores when compared to the control group (p>0.05). The comparison of laboratory values between the groups is displayed in Table 2.

**Table 1.** Comparison of Sociodemographic and Clinical Data Between Groups

Variables	Normotensive n=35	Preeclampsia n=35	P
Age (years)	29.17 ± 6.75	28.82 ± 7.53	0.842
BMI (kg/m <sup>2</sup> )	27.89± 4.05	27.02 ± 4.16	0.337
Gravidity (n)	2.77 ± 1.73	2.82 ± 2.09	0.7
Parity (n)	2.00 ± 1.23	2.02 ± 1.33	0.921
Abortus (n)	0.77 ± 1.03	0.74 ± 1.06	0.825
Gestational Week (week)	36.62 ± 2.46	36.51 ± 2.57	0.902
Birth Weight (g)	2982.71 ± 624.56	2911 ± 714.84	0.778
APGAR score	13.00 ± 5.63	14.05 ± 8.37	0.713

BMI: Body mass index, kg: kilogram, g: gram, p<0.005 was considered statistically significant

**Table 2.** Comparison of laboratory values of groups

Variables	Normotensive n=35	Preeclampsia n=35	P
AST(IU/L)	28.49±46.2	33.97 ± 37.26	0.704
ALT(IU/L)	26.2±51	27.6 ± 34.61	0.094
Platelet (10 <sup>3</sup> IU/L)	198.45±56.54	193.11 ± 67.11	0.315
Proteinuria median (min-max)	1 (0-3)	2 (0-4)	0.241
25-OH D(ng/mL)	14.69 ± 9.10	10.2 ± 7.82	0.009

AST: Aspartate Aminotransferase, ALT: Alanine aminotransferase, 25-OH D: 25-hydroxyvitamin D

While Vitamin D levels were significantly lower in the groups (p<0.05), NLO (non-lactate oxidase) values were higher in the preeclamptic and preterm groups compared to the control group (p<0.05). When comparing the average systolic blood pressure between the groups, the average blood pressure of individuals in the preeclamptic group was found to be statistically significantly higher than that of individuals in the other group. Similarly, when comparing the average diastolic blood pressure, individuals in the preeclamptic group exhibited a

statistically significantly higher average diastolic blood pressure than those in the other group. When the groups were compared in terms of LFT (ALT, AST), blood platelets, and proteinuria in urine, no statistically significant difference was found between the groups. When compared in terms of 25-OH D, a statistically significant difference was found between the groups. Preeclampsia remains one of the leading causes of maternal and fetal morbidity and mortality, despite advancements in the field of obstetrics. Numerous studies are being conducted to enable the early

detection of the disease, based on various events believed to be involved in the pathophysiology of preeclampsia. Among these, measurements of serum calcium, phosphorus, and 25-hydroxyvitamin D levels are included. During pregnancy, 25-OH D deficiency, as well as calcium and phosphorus deficiency, are significant concerning fetal and maternal outcomes. One study investigating the relationship between 25-OH D deficiency and placentation has demonstrated that 25-OH D plays a critical role in the development of vascular pathologies (Novakovic et al., 2009). In a study conducted in Sweden by Linnea Bärebring et al., published in 2016, which examined the relationship between preeclampsia, blood pressure changes, and 25-OH D levels in 1,834 pregnant women, preeclampsia developed in 80 of the women who underwent blood pressure monitoring throughout all three trimesters. In this study, the 25-OH D levels of the women in the first trimester were not associated with preeclampsia. However, a negative correlation was observed between preeclampsia and 25-OH D concentrations in the third trimester. Thus, it was concluded that vitamin D levels in early pregnancy may not play a significant role in placental development and consequently the onset of preeclampsia; however, an increase of at least 30 nmol/L in 25-OH D levels during pregnancy could potentially prevent the development of preeclampsia (Bärebring et al., 2016). Haugen et al., based on recent data indicating low vitamin D levels in preeclamptic nulliparous women, found that pregnant women with dietary vitamin D intake levels of 15-20 µg/day had a 27% lower incidence of preeclampsia compared to those receiving lower doses of vitamin D (Haugen et al., 2009). Additionally, a study conducted by Andersen et al. noted that increased plasma concentrations of 25-OH D were associated with a reduced risk of hypertension (Andersen et al., 2015). It has been stated that placental dysfunction or insufficiency, abnormal angiogenesis, and systemic inflammation, along with hypertension, may contribute to an increased risk of preeclampsia through biological and molecular pathways involving vitamin D (Andersen et al., 2015; Wei et al., 2012). In a study comparing women with preeclampsia to those without, it was found that levels of 25(OH) D vitamin were lower in cases of preeclampsia. Consequently, it has been suggested that vitamin D supplementation in the early stages of pregnancy may help prevent the risk of preeclampsia (Bodnar et al., 2007). A high prevalence of preeclampsia has been observed among women with 25-OH D deficiency, and studies have demonstrated that 25-OH D supplementation during pregnancy results in a reduction in the incidence of preeclampsia (Andersen et al., 2015; Baker et al., 2010; Bodnar et al., 2007; Haugen et al., 2009; Pedersen et al., 1984; Wei et al., 2012). In our study, a

significant relationship was found between 25-OH D levels and preeclampsia. The prevalence of deficiency and insufficiency of 25-OH D was significantly higher in preeclamptic women compared to healthy pregnant women, and serum levels of 25-OH D were significantly lower.

Our study demonstrated a high prevalence of 25-OH D deficiency among pregnant women. Considering the entire study population, the frequency of women with adequate 25-OH D levels was only 15.7%. The rates of deficiency and insufficiency were 64.3% and 20%, respectively, which are concerningly high. The causes of deficiency and insufficiency among pregnant women may include inadequate exposure to sunlight, lack of supplementation of foods with 25-OH D, and a deficiency in knowledge and awareness. It is evident that there is a need for awareness projects among healthcare professionals and at the community level regarding this issue within the framework of maternal and child health.

The low serum concentrations among preeclamptic women may indicate the underlying role of 25-OH D deficiency in the pathogenesis of the disease. The women in the control group were of similar age, had similar numbers of pregnancies, births, and miscarriages, were non-smokers, had no history of preeclampsia, were from the same geographic region, and were evaluated in the same time period as preeclamptic women, thus eliminating the effects of many other factors that could have an effect on preeclampsia. This finding aligns with similar studies conducted in various geographical regions worldwide and demonstrates that 25-OH D levels are significantly lower in preeclamptic women compared to healthy pregnant women. Sadin et al. reported a prevalence of 25-OH D deficiency of 60% among preeclamptic women in their study conducted in Iran, whereas the same prevalence in the control group was only 10%. Despite receiving similar amounts of 25-OH D supplementation, they reported that serum 25-OH D concentrations were significantly lower in preeclamptic women (Sadin et al., 2015). Bakacak et al. demonstrated that 25-OH D levels are lower in both preeclamptic and eclamptic patients compared to healthy normotensive pregnant women (Bakacak et al., 2015). Gholami et al. showed that the average serum 25-OH D level in healthy pregnant women was significantly higher than that in women with preeclampsia (Gholami et al., 2022). Richard et al. reported that the median 25-OH D level in preeclamptic women was lower than that in the control group (Richard et al., 2020). They also indicated that women with 25-OH D deficiency (at the threshold of 20 ng/mL) had a higher likelihood of developing preeclampsia (Andersen et al., 2015; Bodnar et al., 2007; Haugen et al., 2009; Wei et al., 2012). Although there are variations among studies

regarding design, the diagnosis of 25-OH D deficiency/insufficiency, timing of sample collection for 25-OH D, and criteria for diagnosing preeclampsia, all these findings point to a relationship between 25-OH D and preeclampsia. This study further confirms this relationship among women in our country.

Baker et al. demonstrated a correlation between midgestational levels of 25-OH D and the severity of preeclampsia, indicating that as 25-OH D levels decreased, the severity of preeclampsia increased (Baker et al., 2010). Additionally, levels of parathyroid hormone, calcitonin, and 1-25 dihydroxyvitamin D3 did not show significant changes in patients with preeclampsia compared to those with normal pregnancies (Pedersen et al., 1984). In another study, no significant relationship was found between maternal serum calcium and 25-OH D levels during the first trimester and the development of preeclampsia (Perçin & Kurtoğlu, 2011). Similarly, Bodnar et al. reported that serum 25-OH D levels in preeclamptic women during early pregnancy were lower compared to the control group, noting that a decrease of 5 nmol/L doubled the risk of preeclampsia (Bodnar et al., 2007). However, in our study, no significant relationship was detected between 25-OH D levels and the development of preeclampsia when comparing normotensive pregnant women.

Another aspect to consider in the relationship between vitamin D and preeclampsia is whether there is a correlation between the severity of the disease and 25-OH D levels. Singla et al. reported that all women with prodromal symptoms of eclampsia or who developed eclampsia had 25-OH D levels of less than 20 ng/mL. However, due to the predominance of 25-OH D deficiency in their study population, drawing definitive conclusions is challenging. The average serum 25-OH D levels did not show significant differences between women with and without eclampsia (Singla et al., 2015). Similarly, in this study, no significant differences in 25-OH D levels or the prevalence of deficiency/insufficiency were observed between women with mild and severe preeclampsia. These findings suggest that while 25-OH D may play a preventive role, once preeclampsia manifests, it may not be effective in altering the disease course or controlling its severity. The course of the disease is determined by various factors, including the individual's biological system, levels of oxidative stress, inflammatory mediators, vascular endothelial damage, and immune responses. Conversely, a study conducted in Turkey reported an average 25-OH D level of  $10.99 \pm 2.91$  in women with mild preeclampsia, indicating significantly higher levels compared to those with severe preeclampsia and HELLP syndrome (Aslan et al., 2022). These varying results underscore the need for larger sample studies

focusing on the role of 25-OH D in the severity of preeclampsia.

When the controversial results of studies supporting the relationship between 25-OH D and preeclampsia and reporting no evidence for this relationship are evaluated and when current meta-analyses are taken into account, in the light of our current knowledge and evidence, it is thought that 25-OH D deficiency may be a risk factor for preeclamptic disease and supports the importance of antenatal monitoring and support, especially in pregnant women. To clarify these contentious findings, it is necessary and prudent to conduct multicenter, large-sample national studies within individual populations. Such research could significantly contribute to the development of a national management algorithm.

Our study has some limitations. Due to its single-center design, regional characteristics cannot be overlooked, and the results may not be generalizable. The absence of eclamptic cases and the low number of severe preeclampsia cases limit the ability to conduct a definitive analysis of the relationship between disease severity and 25-OH D levels. On the other hand, being one of the studies conducted among women in our country is important for the national knowledge pool and has facilitated the addition of some regional evidence to the literature.

#### 4. Conclusion

In this study, we investigated how 25-OH D levels varied between preeclamptic and control groups consisting of normotensive individuals. Statistical analyses revealed a significant difference in 25-OH D levels between the groups. In most of the studies conducted to date for the early diagnosis and prevention of preeclampsia, it has been stated that low gestational 25-OH D levels may be significant in predicting the disease. However, further research with larger sample sizes is warranted.

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