Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2025.73848

Turk J Obstet Gynecol 2025;22(2):114-20

Is there a correlation between the severity of symptoms and vitamin D levels in pregnancy with hyperemesis gravidarum?

Hiperemezis gravidarumlu gebelerde semptomların şiddeti ile serum D vitamini düzeyleri arasında korelasyon var mı?

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Abstract

Objective: This study aimed to investigate the relationship between serum vitamin D levels and the severity of symptoms in individuals with hyperemesis gravidarum (HG).

Materials and Methods: A cohort of eighty patients exhibiting vomiting three or more times daily, positive ketones on complete urinalysis, and oral feeding difficulties were recruited. Symptom severity was assessed using the 8-question Rhodes index, categorizing patients into non-symptomatic, mild, moderate, and severe groups. Serum vitamin D levels were measured using venous blood samples; a deficiency was defined as less than 10 ng/mL, an insufficiency as 10-20 ng/mL, and a normal level as more than 20 ng/mL.

Results: The distribution of symptom severity revealed 14 (17.5%) with mild, 38 (47.5%) with moderate, and 28 (35%) with severe symptoms. Groups showed no significant differences in demographic or obstetric characteristics except for ketone positivity rates ($p<0.05$). There was a significant difference in vitamin D levels between the severity groups: mild symptoms (32.12±4.02 ng/mL), moderate symptoms (19.98±6.37 ng/mL), and severe symptoms (8.11±3.06 ng/mL) ($p<0.001$). Vitamin D and the Rhodes index mean score showed a significant negative relationship ($r=-0.844$, $p=0.001$). With 96.4% sensitivity and 89.5% specificity, receiver operating characteristic analysis showed that symptom intensity rose when blood vitamin D levels were less than 11.54 ng/mL.

Conclusion: These results highlight a negative relationship between the severity of HG symptoms and serum vitamin D levels. Screening pregnant women with nausea, vomiting, and severe symptoms for serum vitamin D deficiency is recommended. Appropriate pre-pregnancy treatment should be initiated for those deficient or insufficient in serum vitamin D to potentially alleviate HG symptom severity and frequency.

Keywords: Pregnancy, vitamin D, Rhodes index, vomiting

PRECIS: Using a 40 points questionnarie, we observed a negative correlation between the severity of HG and serum vitamin D levels.

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Received/Geliş Tarihi: 26.12.2024 **Accepted/Kabul Tarihi:** 29.03.2025 **Epub:** 15.04.2025 **Publication Date/Yayınlanma Tarihi:** 04.06.2025

Cite this article as: Bayramoğlu Tepe N, Bayramoğlu D, Gündüz R, Özcan HÇ, Taşdemir H, Güneyligil Kazaz T. Is there a correlation between the severity of symptoms and vitamin D levels in pregnancy with hyperemesis gravidarum?. Turk J Obstet Gynecol. 2025;22(2):114-20

Öz

Amaç: Bu çalışmanın amacı hiperemezis gravidarum (HG) hastalarının semptomlarının şiddeti ile serum D vitamini düzeyleri arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntemler: Günde 3 veya daha fazla sayıda kusma şikeyeti olan, yapılan tam idrar tetkikinde keton pozitifliği tespit edilen ve oral beslenme zorluğu bulunan 80 hasta çalışmaya dahil edildi. Hastalara, semptomlarının şiddetini belirlemek için 8 soruluk Rhode'nin indeks skorlama anketi uygulandı. Anket sonucunda 8 puanın altında olan hastalar semptomatik olmayan grup olarak görülürken, 9-18 puan arasında olanlar hafif, 19-32 puan arasında olanlar orta, 33-40 puan arasında olanlar şiddetli semptomatik grup olarak belirlendi. Tüm hastalardan serum D vitamini seviyesini belirlemek için 5 mL venöz kan örneği alındı. Serum D vitamin düzeyi <10 ng/mL olan hastalar eksiklik, 10-20 ng/mL arasında olanlar yetersizlik ve >20 ng/mL olanlar normal seviyede D vitaminine sahip grup olarak sınıflandırıldı.

Bulgular: Rhode'nin indeks skorlamasına göre, çalışmaya dahil edilen 80 hastanın 14'ü (%17,5) hafif, 38'i orta (%47,5), 28'i (%35) ağır semptomatik gruba dahil oldu. Gruplar arasında yaş, gebelik, doğum, abortus, yaşayan çocuk sayıları, gebelik haftaları ve vücut kitle indeksleri bakımından anlamlı farklılık yoktu. Hafif, orta ve ağır derecede semptomatik gruplarda keton pozitiflik oranları bakımından anlamlı farklılık saptandı (p<0,05). Gruplar arasında D vitamini düzeyleri bakımından anlamlı farklılık mevcuttu. Hafif semptomatik grupta D vitamini seviyesi 32,12±4,02 ng/mL, orta düzeyde semptomatik grupta 19,98±6,37 ng/mL ve ağır semptomatik grupta 8,11±3,06 ng/mL idi (p<0,001). Rhode'nin indeks skoru ile D vitamini arasında negatif yönde çok güçlü bir korelasyon saptandı (r=-0,844, p=0,001). Alıcı çalışma karakteristiği analizinde, serum D vitamini seviyesi <11,54 ng/mL olduğunda %96,4 duyarlılık ve %89,5 özgüllük ile, bulantı-kusma şiddet ve sıklığının arttığı izlendi.

Sonuç: Serum D vitamin seviyeleri ile HG semptomlarının şiddeti arasında negatif yönde güçlü bir ilişki vardır. Bu sonuçlarla,bulantı-kusması olup, ciddi semptom yaşayan gebelerde serum D vitamin düzeyinin araştırılmasının ve/veya gebelik öncesinden başlayarak, serum D vitamin düzeyleri bakımından eksiklik ve/veya yetersizlik seviyesinde değeri olan gebelerde uygun ilaçlarla tedavinin, HG semptomlarının şiddetini ve sıklığını azaltmada uygun bir yöntem olacağını düşünmekteyiz.

Anahtar Kelimeler: Gebelik, D vitamini, Rhodes indeks, kusma

Introduction

Hyperemesis gravidarum (HG) is a significant medical condition affecting approximately 1% of pregnant individuals, resulting in significant morbidity for both the mother and the fetus[1]. The etiology of HG remains unclear, with numerous theories having been proposed. Among these theories are psychological factors, hormonal changes, gastrointestinal dysmotility, and immunological dysregulation[2,3]. It is noteworthy that up to 80% of pregnant women experience some degree of nausea and vomiting; however, cases involving long-duration complaints are classified as HG. This condition manifests in 0.5-2% of all pregnancies[4]. The symptoms generally appear on the 5th or 6th day of pregnancy. It begins in the first weeks of pregnancy, reaches its peak in the 9th week, and continues from the 16th to the 20th week. It has been observed that the symptoms begin to disappear after the first week of pregnancy[5]. The severity of symptoms can range from mild to severe. While some pregnant women experience weight loss due to this condition, it can also lead to fluid, electrolyte, and acid-base imbalances, which may result in nutritional deficiency and necessitate hospitalization[6,7].

The body uses vitamin D as a well-known immunomodulator and anti-inflammatory. Numerous disorders affecting the reproductive system have been linked to vitamin D deficiency[8,9]. Sugito et al.[10] discovered that pregnant women with HG had higher blood levels of cell-free DNA. This disorder is thought to be caused by the mother's immune system overactivity and trophoblast destruction. Women with HG have been shown to have an active immune system. The etiopathogenesis of HG is believed to be significantly influenced by vitamin D, and deficiencies in this vitamin may contribute to immune regulatory issues and explain the immunological hypothesis of HG[11]. Teenagers sometimes suffer from vitamin D insufficiency. Low plasma concentrations are found in around 40% of African American women and 4% of non-Hispanic Caucasian women. Even in developed nations, pregnant women's vitamin D levels are concerning[12]. Overall, enhanced newborn calcium utilization results from vitamin D treatment in at-risk groups[13]. Initially, the number of vomiting episodes per day and the intensity of nausea were used to define the symptomatology of nausea and vomiting of pregnancy (NVP). However, Rhodes' description of the revolution in quantifying NVP symptomatology included the measurement of nausea, vomiting, and retching characteristics, and validated these in addition to the length and number of attacks[14]. Although the Rhodes score was created for nausea and vomiting secondary to cancer chemotherapy, it has been adapted for NVP in recent years[15,16].

The present study aimed to group pregnant women diagnosed with HG according to the severity of symptoms, and to reveal whether there is a difference in vitamin D levels between these groups. Thus, it was also aimed to initiate crucial studies on whether vitamin D can play an active role in both the etiology and treatment of severe nausea and vomiting, which is an important problem for pregnant women

Materials and Methods

Patients with nausea and vomiting complaints, three or more vomiting complaints per day, a full urine test showing ketone positivity, and difficulty with oral feeding, who applied to Gaziantep University Faculty of Medicine, Gynecology and Obstetrics Polyclinic between August 1, 2020, and February 1, 2021, were included in the study. The research involved eighty patients. The Faculty of Medicine Gaziantep University Clinical Research Ethics Committee granted approval for this

study, which was carried out in compliance with the Helsinki Declaration's criteria (approval number: 241/2020; date: 16.07.2020).

The following information was recorded for the research participants: age, body mass index (BMI), number of living children, weeks of gestation and ketone positive readings in a complete urine sample.

The study excluded pregnant women with trophoblastic illness, thyroid and gastrointestinal disorders before or during pregnancy, infections, multiple pregnancies, and drug use for any reason. After the patients were provided with the information they needed for the study, they completed the informed consent form.

The patients' serum vitamin D levels were measured using a 5 mL venous blood sample. Within two hours of withdrawal, the samples were centrifuged and kept at -20 °C until analysis. Serum vitamin D levels below 10 ng/mL were considered deficient, those between 10 and 20 ng/mL were considered insufficient, and those over 20 ng/mL were considered normal.

Rhodes Index

Each patient's level of nausea and vomiting was assessed using an 8-item Rhodes index. The Rhodes index's scoring methodology questioned patients if they had suffered from any pain in the previous 12 hours, and if they experienced symptoms such as nausea, vomiting, and retching, and how severe such symptoms were. The Rhodes index is a scoring system that allows the evaluation of both objective and subjective aspects of nausea and vomiting. In scoring, 1 point indicates the presence of minimal or no symptoms, while 5 points represent the most severe symptom. In the evaluation, a minimum of 8 points and a maximum of 40 points was considered. Patients who scored between 9 and 18 points reported mild nausea, and those who scored between 19 and 32 points reported moderate nausea. Those who scored between 33 and 40 points reported severe nausea, vomiting, retching, and pain, while patients with scores below 8 points did not report any of these symptoms. Three groups of patients were created based on this scoring: mild, moderate, and severe symptomatic categories.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether numerical variables conformed to a normal distribution. Three groups' normally distributed variables were compared using ANOVA and LSD tests, whereas three groups' non-normally distributed variables were compared using Kruskal-Wallis and Dunn tests. The cut-off point for vitamin D between the severe and mild hyperemesis groups was established using receiver operating characteristic (ROC) analysis. The analyses were conducted using MedCalc version 19.7.1 and SPSS version 22.0. A p-value of less than 0.05 was deemed significant.

Results

Of the 80 patients in the research, 14 (17.5%) were classified as mildly symptomatic, 38 (47.5%) as moderately symptomatic, and 28 (35%) as severely symptomatic, based on the Rhodes Index score. Age, pregnancy, birth, abortion, number of live children, gestational weeks, and BMI did not significantly differ across the groups (Table 1).

Ketone positive rates in the mild, moderate, and severe symptomatic groups varied significantly ($p<0.05$). Thirteen (61.9%) and eight (38.1%) of the 21 patients who had the highest ketone positivity (+4) in the whole urine study were classified as very symptomatic and moderately symptomatic, respectively.

The groups' variations in vitamin D levels were statistically significant. The mild symptomatic group had vitamin D levels of 32.12±4.02 ng/mL; the moderate symptomatic group had 19.98±6.37 ng/mL; and the severe symptomatic group had 8.11±3.06 ng/mL ($p<0.001$).

A very strong negative correlation was detected between the Rhodes index score and vitamin D level ($r=-0.844$, $p=0.001$). In the ROC analysis, it was observed that the frequency and severity of nausea and vomiting increased when the vitamin D level of the serum was <11.54 ng/mL (Figure 1).

There were 23 (28.75%) patients with vitamin D deficiency (<10 ng/mL) and 22 (27.5%) patients with insufficiency (10-20 ng/mL). Of the patients with vitamin D levels at the deficiency level, 2 were in the moderate symptomatic group and 21 were

Table 1. Demographic characteristics of the HG patients

	Mild (n=14)	Moderate (n=38)	Severe (n=28)	p
Age	27.5±6.28	26.74±5.22	28.11±6.27	0.635
Gravida	3.21±1.72	2.76±1.6	3.25±1.88	0.462
Number of pregnancies	1.57±1.09	1.26±1.11	1.5±1.29	0.575
Number of abortions	0.93±1.21	0.61±0.82	0.86±0.93	0.433
Number of living children	1.5±1.02	1.13±1.02	1.39±1.17	0.464
BMI	25.96±5.03	23.5±3.04	24.24±3.38	0.265
Gestational week	9.57±1.34	9.84±1.94	10.07±2.04	0.737

*: Significant at $p<0.05$ level, BMI: Body mass index, HG: Hyperemesis gravidarum

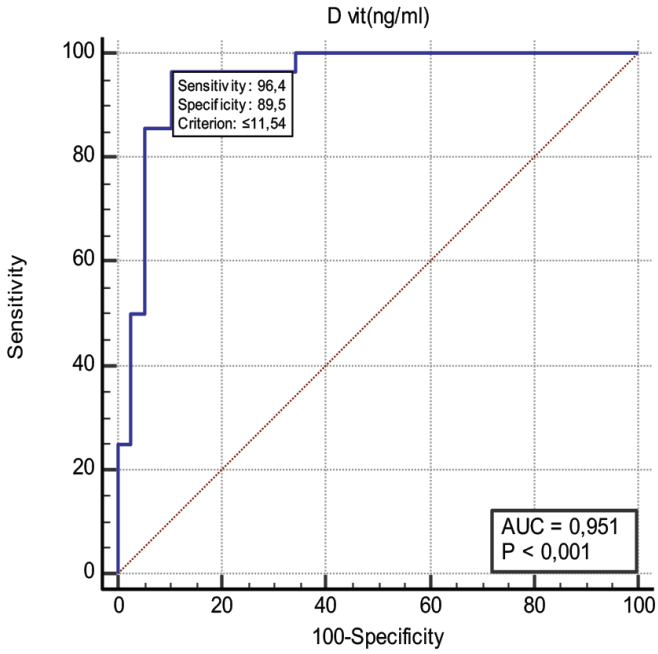

Figure 1. ROC analysis between the Rhodes index mean score and vitamin D level

ROC: Receiver operating characteristic

in the severe symptomatic group, while of the patients with another deficiency level, 15 were in the moderate symptomatic group and 7 were in the severe symptomatic group.

Discussion

Due to its anti-inflammatory and immune-modulating properties, vitamin D plays a significant role in a number of reproductive disorders. Many immune cells possess vitamin D receptors. By inhibiting T-helper cell cytokine release, vitamin D promotes embryonic immune adaptation[17]. The inflammatory response is suppressed, and the placenta is prevented from secreting pro-inflammatory cytokines. Vitamin D insufficiency may be linked to a number of adverse outcomes for both women and babies, including hypertension, intrauterine growth restriction, spontaneous abortion, and preterm delivery, according to recent studies[18,19].

Inflammation and immunological dysregulation have been proposed as key factors in the etiopathogenesis of HG[20,21]. Vitamin D is an essential component of the reproductive system, an immune modulator, and anti-inflammatory agent. Thus, in this prospective analysis, we evaluated the hypothesis that pregnant women with HG should have reduced vitamin D levels. To the best of our knowledge, this is the first study in the body of literature to use an objective scale to rate vitamin D levels and HG symptoms. Given that vitamin D is known to have a variety of roles in the reproductive system, this study suggests it may also have an impact on HG.

According to HG symptoms, we aimed to determine whether vitamin D levels varied across groups with mild, moderate, and severe symptoms. In contrast to previous research in the literature, we attempted to establish an objective symptom degree in our study by using the Rhodes index to score the intensity of symptoms and grading the responses provided by HG pregnant women. As a result, we separated the patients into three groups: those with mild symptoms, those with moderate symptoms, and those with severe symptoms. We found that the patients' vitamin D levels dramatically dropped as their symptom levels rose. In summary, we discovered a negative correlation between the intensity of HG symptoms and serum vitamin D levels. In light of these findings, it is recommended that future research explore the potential benefits of investigating serum vitamin D levels in pregnant women experiencing severe symptoms, including nausea and vomiting. This investigation should also include the administration of appropriate medications to women with serum vitamin D deficiency or insufficiency prior to becoming pregnant. The objective of this approach is to determine whether reducing the severity and frequency of HG symptoms in pregnant women can be effectively achieved.

While we did not assess serum vitamin D levels between pregnant women with HG and normal pregnant women without nausea and vomiting, in our study, our primary objective was to categorize patients based on their symptoms of HG and to ascertain vitamin D levels in each group. This approach would facilitate the interpretation of the severity of symptoms in relation to vitamin D levels. A critical next step is to determine whether vitamin D affects the etiopathogenesis of HG, or whether inflammation and the underlying cause of the disease lead to decreased vitamin D levels. Consequently, further studies investigating the relationship between vitamin D and HG in larger numbers of patients are needed. In designing these studies, it would be advantageous to categorize HG patients based on the severity of their symptoms using objective criteria and to establish a group that compares the vitamin D levels of these categories with the vitamin D levels of normal pregnant women. The exclusion of pregnant women who did not receive a HG diagnosis from our study could be regarded as a study limitation.

HG-related morbidities make it a significant medical concern. Fetomaternal morbidity rises, and metabolic and nutritional abnormalities linked to the severity of HG are prone to develop[22]. With over 59,000 hospital admissions annually, HG is the leading cause of hospitalization during the first part of pregnancy[23,24]. Over the course of pregnancy, HG causes consultations, ED visits, and hospitalizations[25-27]. According to conservative estimates, NVP cost the US economy more than $7 billion in 2012, with direct expenses of more than $1 billion[28]. Indirect costs include lost work and caregiver time. This total of more than $700 million is likely to be an underestimate, as not all applicable costs can be included.

In the present study, we observed a significant difference in vitamin D levels among the mild, moderate, and severe symptomatic groups. Furthermore, a direct correlation was identified between the decrease in vitamin D levels and the escalation in symptom severity among patients. The area under the curve analysis revealed that patients with serum vitamin D levels below 11.54 ng/ml exhibited a substantial increase in symptoms with 96% sensitivity and 89% specificity. In a study by Sahin et al.[29], serum 25OHD3 levels were found to be significantly lower in the severe HG group compared to the control group. The observed outcomes were attributed to inadequate calcium and vitamin D intake, a condition precipitated by symptoms such as nausea and vomiting. The existing literature documents deficiencies in thiamine, riboflavin, vitamin B6, vitamin A, retinal binding protein, and vitamin K in over 60% of these patients[28].

Vitamin D deficiency is prevalent among adolescents and particularly notable among African Americans, with approximately 40% of African Americans and 4% of non-Hispanic Caucasian women having low plasma concentrations of Vitamin D. The vitamin D status of pregnant women is also a concern, even in industrialized countries. Research has shown that moderately reduced 25(OH)D levels in late winter can lead to poor skeletal development and tooth mineralization in the fetus and newborn[12]. The use of vitamin D supplements in excess of the prescribed levels to avoid deficiency during pregnancy is not currently supported by any data[13]. Higher dosages of vitamin D supplementation, however, may be beneficial for pregnant women who have severe nausea and vomiting, according to our study and the study conducted by Sahin et al.[29].

Pregnant women are often advised to take a multivitamin that contains minerals before giving birth. If taken at least one month prior to pregnancy, this may lessen the frequency and severity of NVP[30]. Malnutrition and excessive electrolyte losses put women with HG at risk for nutritional deficiencies[31]. During pregnancy, vitamin D insufficiency, hypovitaminosis D, and inadequate sun exposure are prevalent[32,33]. Several studies have found that the Greek population has a significant frequency of vitamin D insufficiency and hypovitaminosis D, despite Greece being one of the sunniest nations in Europe[34]. A deficit prevalence of 23-90% was found in a comprehensive assessment of women in Mediterranean nations, including pregnant women[35]. This might have detrimental effects on the health of both the mother and the newborn. According to a study conducted in our nation, 8-61% of people were vitamin D deficient[36]. Similarly, in healthy pediatric age groups, research from throughout the world revealed that 7-68% had vitamin D deficiency and 19-61% had vitamin D insufficiency[37].

The ideal values of 25(OH)D are a matter of debate[38,39]. A 25(OH)D level below 20 ng/mL is regarded as a sign of vitamin D insufficiency. However, values between 20-30 ng/mL are deemed inadequate by the Endocrine Society and other expert organizations. Reaching concentrations beyond 40 ng/mL is advised by certain publications. Due to its possible role in fertility, there is now more evidence supporting the necessity of vitamin D both before and throughout pregnancy. Worldwide, vitamin D insufficiency is quite prevalent in pregnant women in every stage of pregnancy, according to several research studies[40-42].

The concentration of 25(OH)D in pregnant women has been found to be influenced by skin pigmentation, UV rays, and avoiding sun exposure due to cultural or religious beliefs. There is a significant risk of nutritional deficit in pregnant women experiencing winter pregnancy and obesity (BMI >30 kg/m^2)[43]. Pregnancy-related hypovitaminosis D is quite prevalent around the world[44]. Low vitamin D levels in pregnant Asian women were quite common, according to a study by Palacios et al.[45]. In India, 96% of the population; in China, 69%; in Kuwait, 70% to 83% of the population; in Pakistan, 72%; in Iran, 67%; and in Türkiye, 90% have the condition. The prevalence of vitamin D insufficiency is also very high. Research has demonstrated that within the Turkish population, 50% is affected, whereas in Pakistan, the figure stands at 45%. In Kuwait, the prevalence ranges from 38% to 41%, and in India, it has been documented as high as 60%. A recent review of 13 studies from seven countries found that the prevalence of vitamin D deficiency and insufficiency ranged from 39.4% to 76.5%. Vitamin D deficiency has been identified as a pervasive public health concern, impacting a substantial proportion of the global population. Notably, pregnant women are particularly vulnerable to this deficiency[46-49]. To benefit from the positive effects of vitamin D, it is recommended to maintain serum concentrations between 30 and 50 ng/mL[50-53]. In Türkiye, all women receive free vitamin D supplementation (1,200 IU/day) from early pregnancy until six months after delivery[54]. The global prevalence of vitamin D deficiency among pregnant women ranges from 20% to 40%, with figures ranging from 18.2% to 45.9% observed in Türkiye[55,56].

Study Limitations

The limited number of patients in each group and the exclusion of vitamin D levels in pregnant women without HG are two of the study's limitations. It is crucial, therefore, to establish a reference for research including pregnant women who do not have HG.

Conclusion

This study found significant differences in vitamin D concentrations among groups experiencing mild, moderate, and severe HG symptoms. According to the results, more severe HG symptoms are linked to lower vitamin D levels. Our study suggested that checking vitamin D levels before pregnancy and providing a routine replacement for patients with deficiency and insufficiency levels might help prevent severe HG symptoms. This can reduce hospitalizations and economic expenditures

related to this issue. HG patients cannot be treated on an outpatient basis and require long-term hospitalization.

Ethics

Ethics Committee Approval: The Faculty of Medicine Gaziantep University Clinical Research Ethics Committee granted approval for this study, which was carried out in compliance with the Helsinki Declaration's criteria (approval number: 241/2020; date: 16.07.2020).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.B.T., H.Ç.Ö., Concept: N.B.T., Design: N.B.T., D.B., Data Collection or Processing: N.B.T., R.G., H.T., Analysis or Interpretation: N.B.T., H.Ç.Ö., T.G.K., Literature Search: N.B.T., R.G., Writing: N.B.T., D.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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