Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1438323

Severe vitamin D deficiency is associated with increased risk of first trimester miscarriage in the Eastern Black Sea region of Türkiye

Doğu Karadeniz Bölgesinde şiddetli D vitamini eksikliğinin ilk trimester düşük riski ile ilişkisi

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ABSTRACT

Aim: To measure 25-hydroxyvitamin D (25(OH)D) serum concentration among pregnant women in the first trimester and its association with first-trimester pregnancy loss in the Eastern Black Sea region of Türkiye.

Materials and Methods: In this retrospective, cross-sectional study, we collected health records of pregnant women attending prenatal care at our department between March 2020 and December 2020. Serum 25 (OH)D levels were measured in the first trimester, and the patient's characteristics and the course of the pregnancy were analyzed. We investigated the association between maternal vitamin D deficiency and the risk of subsequent miscarriage.

Results: The final analysis included 246 pregnant women, with 50 (20.3%) had a miscarriage in the first-timester. The prevalence of vitamin D deficiency was high in the group, with 78.5% of the study group having serum levels of 25(OH)D<20 ng/ml. The mean 25(OH)D concentration was 13.3±5.7 ng/ml in the miscarriage group, 15.5±6.4 ng/ml for control group. The miscarriage group had a statistically older maternal age, higher parity.and higher rate of severe vit D deficiency. Logistic regression showed that only severe vit D deficiency was associated with miscarriage.

Conclusion: We found high rates of vitamin D deficiency in this region among pregnant women in the first trimester. Severe Vitamin D deficiency was associated with an increased risk of first-trimester miscarriage. These findings suggest that a more aggressive approach for sufficient vitamin D supplementation may be considered in this region.

Keywords: 25-hydroxyvitamin D, miscarriage, pregnancy, spontaneous abortion, first trimester

ÖZ

Amaç: Türkiye'nin Doğu Karadeniz bölgesinde ilk trimesterda gebelerde 25-hidroksivitamin D (25(OH)D) serum konsantrasyonunu ve bunun ilk trimester gebelik kaybıyla ilişkisini değerlendirmek

Gereçler ve Yöntem: Bu retrospektif, kesitsel çalışmada, Mart -Aralık 2020 tarihleri arasında hastanemiz antenatal gebe takip polikliniğinde değerlendirilen gebe kadınların sağlık kayıtları toplandı. İlk trimesterda ölçülen serum 25 (OH)D düzeyleri, hastaların demografik özellikleri ve gebelik seyri not edildi. Maternal vit D eksikliği ile ilk trimester düşük riski arasındaki ilişki incelendi.

Bulgular: Çalışmaya 246 hamile hasta dahil edildi. Hastaların 50'si (%20,3) ilk trimesterda düşük yaptı. Tüm grupta vitamin D eksikliği prevalansı yüksekti; çalışma grubunun %78,5'inin serum düzeyleri 25(OH)D<20 ng/ml idi. Düşük yapan grupta ortalama 25(OH)D konsantrasyonu 13,3±5,7 ng/ml iken, kontrol grubunda 15,5±6,4 ng/ml idi. Düşük yapan grupta istatistiksel olarak anne yaşı daha yüksek, parite sayısı daha fazla, şiddetli D vitamini eksikliği insidansı daha yüksekti. Çok değişkenli analiz, şiddetli D vitamini eksikliğinin ilk trimester düşük riski ile ilişkili olduğunu gösterdi.

Sonuç: Bu bölgede ilk trimesterda gebelerde vitamin D eksikliğinin yüksek olduğu saptandı. Şiddetli D vitamini eksikliği, ilk trimesterde düşük yapma riskinin artmasıyla ilişkili idi. Bu bulgular, bu bölgede yeterli D vitamini takviyesi için daha agresif bir yaklaşımın düşünülebileceğini düşündürmektedir.

Anahtar Kelimeler: 25-hidroksivitamin D, gebelik, spontan düşük, ilk trimester, gebelik kaybı

Cite as: Bezirganoglu Altuntas N, Baki Yıldırım S, Bayoglu Tekin Y. Severe vitamin D deficiency is associated with increased risk of first trimester miscarriage in the Eastern Black Sea region of Türkiye. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):285–290.

Geliş/Received: 16.02.2024 • **Kabul/Accepted:** 29.03.2024

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Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Miscarriage is one of the most common adverse outcomes of pregnancy, with significant pregnancy losses occurring within the first trimester. Several studies report that the prevalence of miscarriage ranges between 12% and 21% (1,2). While miscarriage is attributed to multiple factors, including maternal infections, uterine anomalies, thrombophilias, and chromosomal abnormalities, acquired or environmental factors are also believed to contribute significantly as preventable risk factors (3,4).

Vitamin D is crucial in regulating calcium and phosphorus levels and bone mineralization (5). Moreover, reproductive tissues, such as the human placenta, endometrium, and ovaries, also express vitamin D receptors and 1α-hydroxylase, which are involved in vitamin D metabolism (6). Studies have shown that vitamin D regulates implantation, cytokine production, and the immune response to infection during pregnancy (7,8). Considering its potential role in modulating human reproductive processes, vitamin D deficiency is a significant concern, particularly for pregnant women and those planning pregnancy who are at increased risk. Vitamin D deficiency is shown to be more prevalent among women experiencing major reproductive and obstetric complications like preeclampsia, gestational diabetes, and preterm birth (9,10). However, the impact of vitamin D deficiency and insufficiency on first-trimester pregnancy loss remains less clear.

Vitamin D deficiency may play a role in the pathophysiology of miscarriage due to its potential importance as a regulator of trophoblast invasion in early pregnancy (11). Moreover, vitamin D can directly regulate HOX10, which is crucial for embryo implantation (12). Low serum levels of 25(OH)D may lead to a concurrent decrease in placental 1,25(OH)2D and subsequent placental dysregulation (13). Several studies have found an association between low levels of vitamin D and an increased risk of miscarriage in various populations (13-15). However, studies examining the relationship between vitamin D levels and pregnancy loss in the Black Sea region of Türkiye are lacking.

The objective of this study is to assess the vitamin D levels of pregnant women in the first trimester and determine whether these levels are associated with an increased risk of miscarriage in the Black Sea region of Türkiye.

MATERIALS AND METHODS

This retrospective, cross-sectional study was conducted between March 2020 and December 2020 at the Department of Obstetrics and Gynecology of the Kanuni Training and Research Hospital, Trabzon, Türkiye. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the hospital (E1-20–602). All pregnant women attending the outpatient clinic of the hospital who were carrying singleton fetuses at 7-14 week gestation by first day of the last menstrual period were considered eligible for inclusion in the study. Patients with a history of previous miscarriage, diagnosed uterine anomalies, thyroid dysfunction, autoimmune disorders, preexisting chronic diseases, diabetes mellitus (type 1 or 2), severe hepatic and liver disease, positive serology for intrauterine infection, chromosomal abnormalities, congenital anomalies or those who had been prescribed hormonal and antiepilectic medication, that might effect vitamin D metabolism, within the last three months were excluded. Multiple pregnancies were also excluded. The geographical coordinates for Trabzon province, situated on the North coast of Türkiye, are latitude 41°0’ N, longitude 39°43’ E, and altitude 49 m/161 feet,respectively.

Miscarriage was defined as a missed miscarriage, a complete or incomplete miscarriage, or a blighted ovum before 14 completed weeks of gestation. All cases of miscarriage were confirmed through transvaginal ultrasound. Controls were women with healthy liveborn babies without birth defects. Data on maternal characteristics included age, parity, pre-pregnancy weight, date of last menstrual period, smoking habits, outfit clotting style, and the time of blood collection were recorded. The season for blood collection was dichotomized into either May to October or November to April, representing the seasons of high and low 25(OH)D concentrations, respectively. Clothing was categorized as; wearing full cover-out fit style clothing, covering the whole body but leaving the hand and face exposed and uncovered women with exposed heads, arms, and legs.

During the study period, 294 pregnant patients were initially recruited. However, 48 patients were subsequently excluded from the study for various reasons. Among the exclusions, 21 patients did not continue follow-up at our institution, seven were diagnosed with twin gestations, four were using anti-convulsant medication, eight had a history of previous pregnancy loss, three were diagnosed with diabetes mellitus, three were diagnosed with uterine anomalies, one tested positive for intrauterine infection, and one had significant thyroid dysfunction. The final analysis included 246 pregnant patients with 50 cases of first-trimester miscarriage and 196 controls.

For each participant a fasting venous blood samples were collected using EDTA tubes and rotated for 5 minutes at 2500 rotations per minute. Plasma samples were then analyzed using the Beckman

Coulter Unicel Dx1600 immune analyzer, with the same branded kits, to measure levels of 25(OH) D. Due to the discrepancies in the definition of optimal serum levels of 25(OH)D in the literature, although some data suggest potential benefits for higher thresholds, we opted to consider serum concentrations of 25(OH) D >50 nmol/L (20 ng/mL) as sufficient. Mild to moderate deficiency was characterized by values between 30-50 nmol/L (12-19 ng/mL), while severe vitamin D deficiency was identified when levels <30 nmol/L (12 ng/mL) (16).

Statistical analysis

Data were analyzed using SPSS, version 25.0 (SPSS, Chicago, IL). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were described median and as percentages. Continuous variables were compared between groups by independent samples t tests for normally distributed variables and the Mann–Whitney U test for non–normally distributed variables. We dichotomized 25(OH)D levels by cutoff values of 20 ng/mL and 12 ng/mL. Multivariate linear regression analysis was performed to determine independent effects of 25(OH)D levels and covariates on first-trimester miscarriage. Entry into the multivariate model was conditional on p value of 0.2 in univariate analysis. Pearson correlation test was used where appropriate. For all statistical analyses, a p value ≤0.05 was considered significant.

RESULTS

A total of 246 pregnant patients were included in the analysis, including 50 patients who experienced first-trimester miscarriage (cases) and 80 pregnant women who delivered healthy liveborn babies (controls). The characteristics of the study population are summarized in Table 1. The miscarriage group had a higher maternal age and a higher rate of parity compared to healthy controls (p=0.013 and 0.011, respectively). The overall serum 25(OH)D level for the entire cohort was 14.6±6.2 ng/mL. The control group demonstrated a borderline significantly higher level of 25(OH) D compared to the miscarriage group (p=0.056). Table 2 shows the variations in serum 25(OH)D levels within the cohort. Vitamin

Table 1. General characteristics of the participants.

	Total cohort (n= 246)	Miscarriage (n=50)	No miscarriage (n=196)	*p* value[a]
Maternal Age (years), (SD)	30.46 ±5.26	31.88±5.07	29.53±5.16	0.013
Maternal BMI, kg/m^2, median (IQR)	23 (22-25)	24 (22-25)	23 (22-25)	0.67
Smoking in pregnancy, n (%)	10 (4.1)	2 (4)	8 (4.1)	0.97
Season of blood sample, n (%) Summer (May to October) Winter (November to April)	 91 (36.9) 155 (63.1)	 17 (34) 33 (66)	 74 (37.8) 122 (62.2)	0.85
Dressing outfit style, n(%) Covered Uncovered	 84 (34.2) 162 (65.8)	 18 (36) 32 (64)	 66 (33.6) 130 (66.3)	0.81
Parity, n(%) Nulliparous Paraous	 125 (50.8) 66 (49.2)	 16 (32) 34 (68)	 109 (55.7) 87 (44.3)	***0.011***

Plus-minus values are mean±standard deviation, SD: standard deviation, IQR: interquartile range , BMI: body mass index
[a] p<0.05 values were considered as significan

Table 2. Association of vitamin D deficiency and occurrence of miscarriage

	Total cohort (n= 246)	Miscarriage (n=50)	No miscarriage (n=196)	*p* value[a]
25 (OH)D level, (ng/mL), (SD)[b]	14.62±6.20	13.32 ±5.68	15.47±6.40	0.056
25(OH)D status, n (%) Sufficient (>20 ng/mL) Deficient (≤ 20 ng/mL)	 53 (21.5) 193 (78.5)	 9 (18) 41 (82)	 44 (22.4) 152 (77.5)	0.65
Severe vit D deficiency (<12 ng/ml)	72 (29.3)	24 (48)	48 (24.4)	0.03

[a] p<0.05 values were considered as significant
[b] 25 (OH)D : 25-hydroxyvitamin D, Plus-minus values are mean±standard deviation, SD: standard deviation

Table 3. Multivariate analysis of parameters associated with miscarriage.

Variables	Multivariate analysis (95% CI)	p value[a]
Age	0.916 (.830-1.010)	0.08
BMI	0.102 (.956-1.650)	0.11
Parity	0.508 (0.185-1.393)	0.18
Vit D level (ng/mL)	1.001 (0.919-1.090)	0.98
Severe vit D deficiency	3.764 (1.225-11.566)	0.02

[a] p<0.05 values were considered as significant, CI, confidence interval; OR, Odds ratio, BMI: body mass index

D deficiency was prevalent in 78.5% of the entire cohort, with no significant difference observed between the two groups (p=0.65). However, severe vitamin D deficiency was significantly higher in the miscarriage group (p=0.03), with 48% of pregnant women having miscarriage presenting severe vitamin D deficiency. Multivariate analysis revealed that severe vit D deficiency was an independent risk factor for first-trimester miscarriage. (adjusted OR=3.76, 95 %CI 1.22-11.56; p=0.02) (Table 3). Moreover, the incidence of severe vit D was statistically associated with miscarriage (r = 0.267, p = 0.003).

DISCUSSION

This retrospective, cross-sectional study is one of the first to investigate the vitamin D levels of pregnant women during the first trimester of pregnancy and the potential association between 25(OH) D serum concentrations and the risk of first-trimester miscarriage in the Eastern Black Sea region of Türkiye. Our findings showed that the prevalence of vitamin D deficiency is very high among pregnant women in this region, with 78.5% of the pregnant women being vitamin D deficient and 29.3% severely vitamin D deficient. Furthermore, our study indicates that there is a correlation between severe vitamin D deficiency and first-trimester miscarriage.

A miscarriage is generally defined as the loss of a pregnancy that occurs before the fetus reaches viability. It is a common occurrence and can have significant physical and psychological consequences for women. A recent review, which included data from nine studies totaling 4,638,974 pregnancies, found that the overall risk of miscarriage was 15.3% (95% CI 12.5–18.7) of all recognized pregnancies (2). The rate of spontaneous miscarriage varies across different countries and regions. For instance, a large study conducted in Israel revealed that as many as 43% of women reported experiencing one or more spontaneous miscarriages during the first trimester of pregnancy (17). Our findings are in line with the literature, as 20.3% of the participants in our cohort had a first-trimester miscarriage. Maternal age is shown to be the most important factor for first-trimester miscarriages, as the risk significantly increases in older ages (18). In our study, we observed that the miscarriage group had a statistically older maternal age and higher parity.

The American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics recommend supplementing 250–600 IU/day vitamin D3 during pregnancy as a standard (19,20). However; the prevalence of vitamin D deficiency appears to be increasing globally among women of reproductive age. A study involving pregnant Swiss women revealed that only 26.8% of participants had sufficient serum 25(OH)D levels (≥30 ng/mL) during the first trimester (21). Previous studies from Türkiye have also reported elevated rates of vitamin D deficiency in pregnant women, even during the summer months (22). A study conducted in the Black Sea Region found an even higher prevalence of vitamin D deficiency in this region, with 94.2% of pregnant patients having deficiency (23). Our findings support these results, with the majority of our patients also were vitamin D deficient. We conducted the study in both the winter and summer time zones. The skin synthesis of vitamin D3 should be expected to be even lower during the winter period (5). The majority of blood samples were taken in the winter (63.1%), potentially contributing to the prevalence of deficiency in our cohort. Although the testing period did not differ between the two groups (p=0.85), the mean serum 25(OH)D level of the entire cohort during the summer was 19.32±6.36 ng/mL, which still fell below the recommended threshold for sufficiency. Latitude and season significantly affect vitamin D3 production, particularly in regions above 35 degrees latitude, where the angle of the sun during winter limits ultraviolet ray exposure necessary for vitamin D3 synthesis (24). As our study center is situated around 41 degrees latitude, this may also contribute to lower 25(OH)D levels in our region. In our study, we observed that 34.2% of pregnant women in the entire cohort were wearing covered clothing. This suggests that clothing style may play a role on severity of vitamin D deficiency.

The elucidation of the immunomodulatory effects of 1,25(OH)2D has led to interest in the potential role of vitamin D in protecting against spontaneous abortion (11). This hypothesis is supported by ex vivo analyses demonstrating that 1,25(OH)2D can suppress inflammatory cytokine production by endometrial cells from women with unexplained recurrent spontaneous abortions. (25). Moreover, Özkan et al. found that serum and follicular fluid 25(OH)D concentrations are highly correlated, women with higher vitamin D level in their serum and folicular fluid are significantly more likely to achieve clinical pregnancy following in vitro fertilization (26). Considering these observations, the influence of maternal vitamin D status on miscarriage risk has been investigated in several cohorts (13-15). While some studies have reported an increased risk of subsequent miscarriage with maternal vitamin D insufficiency or deficiency, others have not found such an association (14,15,27). In our study, although the miscarriage group exhibited a higher rate of vitamin D deficiency, only severe deficiency (<12 ng/mL) was significantly associated with first-trimester miscarriage. It is plausible that the overall high prevalence of vitamin D deficiency in our study population could potentially diminish the predictive performance of serum 25(OH)D levels for miscarriage risk in the recent study. Moreover, discrepancies in findings across studies could be attributed to differences in population characteristics, sample sizes, and methodologies used to measure 25(OH)D levels.

Our study has several limitations. Firstly, it was conducted in a single unit with a relatively small sample size, which may limit the generalizability of the findings to broader populations. Secondly, we did not account for potential confounding variables such as dietary habits, vitamin supplementation,and folic acid levels when assessing the association between 25(OH)D and miscarriage. Previous studies have demonstrated a significant association between vitamin D levels and the severity of COVID-19 in pregnant women (28). However, our study did not assess the role of previous COVID-19 history in miscarriage. Furthermore, evaluating the underlying factors contributing to vitamin D deficiency was beyond the scope of this study.

In conclusion, our study revealed high rates of vitamin D deficiency among healthy women in the first trimester of pregnancy in this region, without any prior history of miscarriage. Importantly, we observed a significant association between severe vitamin D deficiency and miscarriage in this study population. These findings may show the potential protective role of vitamin D against miscarriage. Developing novel, more agressive supplementation strategies specific to this region may lead to improved maternal health outcomes.

Ethics Committee Aproval

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the hospital (E1-20–602).

Authors' Contributions

NBA and SBY were primarily responsible for protocol development and the analytic framework of the study, outcome assessment, and manuscript preparation. NBA had primary responsibility for reviewing the files, patient screening, enrollment, and data entry, and prepared the manuscript. YBT contributed to preparation and revision of the manuscript.

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