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Assessment of the Relationship between Vitamin D Deficiency and the Development of Hyperemesis Gravidarum

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Abstract

Object: Hyperemesis gravidarum, the leading cause of hospitalization in the first trimester, is observed in 0.3% to 3.6% of all pregnant women worldwide. Vitamin D is a significant vitamin for human health, and vitamin D deficiency in the pregnant women population in Turkey is a common pathology. In this context, this study was carried out to assess the relationship between vitamin D deficiency and the development of hyperemesis gravidarum.

Methods: The population of this prospective, single-center, case-controlled study consisted of pregnant women diagnosed with hyperemesis gravidarum. In the end, 23 pregnant women with hyperemesis gravidarum were included in the patient group, and 30 healthy pregnant women with demographic characteristics that match those with hyperemesis gravidarum were included in the control group. The Vitamin D and hematocrit levels were compared between the two groups.

Results: There was no significant difference between the patient and control groups in the serum vitamin D ($p = 0.760$) and hematocrit ($p = 0.149$) levels. Overall, only 9 (17%) of the 53 pregnant women had sufficient (> 20 ng / ml) vitamin D. There was no significant difference between the patient and control groups in the number of patients with vitamin D deficiency.

Conclusion: The study findings did not indicate a correlation between vitamin D deficiency and hyperemesis gravidarum. Further large-scale studies are needed to establish the absence of a relationship between vitamin D deficiency and hyperemesis gravidarum. On the other hand, the fact that only 17% of the pregnant women who participated in this study had sufficient vitamin D revealed the need to emphasize using vitamin D supplements in pregnant women as early as possible in the first trimester.

Keywords: Hyperemesis gravidarum, nausea, pregnancy, vitamin D, vomiting

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INTRODUCTION

Hyperemesis gravidarum (HG) is a pregnancy complication characterized by severe nausea, vomiting, fluid-electrolyte imbalance, acid-base imbalance, malnutrition, and weight loss (1). HG is commonly diagnosed based on weight loss of more than 3 kg or 5% of the body weight compared to before pregnancy and continuous (more than three times a day) vomiting with ketonuria that cannot be attributed to any other condition (2,3). HG is observed in 0.3% to 3.6% of all pregnant women worldwide and is the leading cause of hospitalization in the first trimester (4-6). The factors that potentially play a role in the etiology of HG reportedly are psychogenic factors, hormonal factors, smoking-alcohol use, gastric passage, lower esophageal sphincter pressure, and genetic factors (7).

The most important hormone that plays a role in the etiology of HG is thought to be beta human chorionic gonadotropin (βhCG). βhCG levels, as the symptoms of HG, reach a maximum in the 12th week and then regress and plateau (8). However, symptoms of HG are more severe in pregnancies with high βhCG levels, such as molar pregnancy, pregnancies affected by Down's syndrome, and multiple pregnancies (9).

In a study evaluating patients with HG, a correlation was found between the severity of the HG symptoms and the βhCG levels (10). By regulating the production and release of IL and hCG, tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) produced by trophoblasts play an essential role in the etiology of HG (11). It was reported that pregnant women with HG had significantly lower type-1 helper (Th1)-to-type-2 helper (Th2) ratios than healthy pregnant women, and hormonal changes were implicated in this significant difference (12). HG is more prevalent in younger and first-time pregnant women, as well as those living in developed nations and urban areas, receiving estrogen-based treatment, and suffering from movement disorders and migraine (13). The adverse effects of HG on the fetus have not been clearly demonstrated. Then again, it is one of the most common causes of hospitalization during pregnancy, associated with maternal physical morbidity and negative psychological consequences (14).

Vitamin D is an essential vitamin for human health. A significant portion of the vitamin D in the body is synthesized endogenously in the skin by ultraviolet B (UVB) rays, whereas a small portion is taken with food. The vitamin

D3 synthesized in the skin turns into 25-hydroxy vitamin D in the liver, subsequently forming the primary form of vitamin D. This process, which has a half-life of 2 to 3 weeks, is considered in determining the vitamin D levels in the blood (15,16). Vitamin D deficiency in the pregnant population in Turkey is a common pathology. In a recent study, the incidence of vitamin D insufficiency in pregnant women was reported as high as 81.3% indifferent districts (17). The American College of Obstetricians and Gynecologists (ACOG) underlines that serum vitamin D levels of >30 ng/mL are required in pregnancy and recommends taking 1000-2000 IU vitamin D supplement daily in case of vitamin D insufficiency (18).

There are studies on the role of various factors in the etiopathogenesis of HG (19-23). For example, one study showed that βhCG levels increased as vitamin D levels decreased (24). It can be said that such studies indicate a possible mediating role of vitamin D in the etiopathogenesis of HG.

In view of the foregoing, this study was carried out to assess the relationship between vitamin D deficiency and the development of HG, one of the most common causes of hospitalization in the first trimester of pregnancy, significantly affecting the quality of life.

METHODS

Population and Sample

The population of this prospective, single-center, case-controlled study consisted of 53 pregnant women diagnosed with HG during the first 12 gestational weeks at Bakırköy Dr. Sadi Konuk Training and Research Hospital, Gynecology and Obstetrics Clinic between November 2019 and May 2020. The study protocol was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (23.12.2019/2019-25-03). Informed consent was obtained from all study participants. Participants' demographic and clinical data, i.e., their age, body mass index (BMI) values, pregnancy data, comorbidities, and the medications they have been using, were queried using a questionnaire form. 5 ml of venous blood samples were taken from all 53 cases, stored in tubes containing ethylene diamine tetra acetic acid (EDTA) solution, and sent to the biochemistry laboratory for analysis. To this end, first, the plasma in the samples was separated via centrifugation carried out at 3000 rpm for 5 minutes, and then the total vitamin D level was analyzed using UniCel DxI immunoassay kits (Beckman Coulter, Brea, CA, 92821, US) utilizing the paramagnetic particle-based chemiluminescence immunoassay method. In addition, a hematocrit test was requested for each patient, and their urine density and ketone positivity data were obtained from the results of the complete urinalysis and recorded. Consequently,

pregnant women with persistent (more than four times a day) vomiting with ketonuria and 5% or more weight loss compared to before the pregnancy were prediagnosed with HG were included in the patient group. Patients with multiple pregnancies, trophoblastic diseases, any systematic disease history (diabetes, hypertension, and thyroid diseases), psychiatric illness, inflammatory disease, antiemetics use, and patients that received any medical treatment with a potential effect on their hormone profile were excluded from the study. In the end, 23 pregnant women were included in the HG group. The results of the power analysis conducted based on literature data indicated that the minimum number of cases included in the study must be 52. Therefore, 30 healthy pregnant women with demographic characteristics that match the pregnant women with HG were included in the control group.

Statistical Analysis

Statistical analyses were carried out using the SPSS Statistics 17.0 (Statistical Package in the Social Sciences for Windows, Version 17.0, SPSS Inc., Chicago, IL, U.S., 2008), NCSS 11 (Number Cruncher Statistical System, version 11, NCSS LLC, Kaysville, Utah, US, 2016) and MedCalc 18 (MedCalc, version 18, MedCalc Software bv, Ostend, Belgium, 2018) software packages. Continuous variables were expressed as mean ± standard deviation and median and minimum-maximum values, whereas categorical variables were expressed as frequency and percentage values. Relationships between categorical variables were assessed using Pearson's chi-squared test. Independent samples t-test and Mann-Whitney U test were used to compare two groups with continuous independent variables determined to conform and not to conform to the normal distribution, respectively. The probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

RESULTS

The results of the study did not reveal any significant difference between the patient and control groups in terms of mean age, BMI value, gestational week, vitamin D level, and hematocrit value (p = 0.874, p = 0.552, p = 0.760, and p = 0.149, respectively) (Table 1).

Table 1. Distribution of participants' demographic and clinical characteristics by the patient and control groups

	Healthy Pregnant Women (Control Group)	**Pregnant Women with HG (Patient Group)**	
	Mean± SD Median (min.–max.)	**Mean±SD Median (min.–max.)**	***p*-value**
Age (year)	(n=30) 28.17±5.37	(n=23) 28.39±4.69	0.874
BMI (kg/m^2)	(n=30) 25.82±4.19	(n=23) 26.51±4.2	0.552
Gestational week (week)	(n=30) 11.98±1.93	(n=23) 12.01±2.63	0.962
Vitamin D level (ng/ml)	(n=30) 12.38 (7.19-28.36)	(n=23) 14.4 (5.7-53.13)	0.760*
Hematocrit (%)	(n=30) 34.9±2.35	(n=23) 35.91±2.56	0.149
Urine density (g/l)	(n=30) 1016±6.94	(n=23) 1022.13±9.55	0.009

Abbreviations: HG: Hyperemesis Gravidarum, SD: standard deviation, min.: minimum, max.: maximum, BMI: body-mass index
Student's t-test,
*: Mann-Whitney U test

On the other hand, there was a significant difference between the groups in urine density (p = 0.009) and ketone positivity in the urine. Only 17% of the 53 pregnant women who participated in this study had sufficient (> 20ng / ml) vitamin D.

DISCUSSION

Contrary to most studies available in the literature, which found a significant difference between pregnant women with HG and healthy pregnant women in vitamin D levels and attributed this difference to the weakened immune system of HG patients, no significant difference was found in vitamin D level between the patient and control groups included in this study.

Gürbüz et al., who found that vitamin D levels were significantly lower in cases with HG and in cases without HG (24), attributed this difference to the increase in gastric inflammation caused by vitamin D deficiency resulting in more severe complaints such as nausea and vomiting.

In contrast, in a prospective study that compared vitamin D and C-reactive protein (CRP) levels between 30 healthy cases and 30 HG cases, Yılmaz et al. found that the vitamin D levels were lower in the patient group than in the control group, yet this difference was not significant (25). The authors of the said study attributed the lack of significant difference between the patient and control groups in vitamin D levels to the relatively small size of their sample. In the results of our study, no significant difference was found between vitamin D levels in HG and healthy pregnant women, similar to the study of Yılmaz et al. However, unlike in our study, vitamin D levels were higher in the HG group than in healthy pregnant women.

A number of recent studies suggested a relationship between vitamin D deficiency and many maternal and fetal problems. In light of this information, this study was carried out based on the hypothesis that pregnant women with HG would have significantly lower 25 (OH) vitamin D levels compared to healthy pregnant women. However, the results of the study proved this hypothesis wrong.

It has been speculated that HG might be associated with elevated βhCG levels and excessive increase in cellular immunity (Th cells). Vitamin D, an immunomodulatory vitamin, regulates cellular immunity and has auxiliary effects on immune tolerance mechanisms during pregnancy. The relevant literature data, taken together with the results of this study, suggest that vitamin D deficiency cannot increase T-cellular immunity through the said mechanisms, thus that vitamin D deficiency cannot serve as a primary factor, yet may have a role secondary to elevated βhCG levels in the development of HG.

“Vitamin D Support Program for Pregnant Women” has been implemented in Turkey since 2011. Accordingly, pregnant women are

given 1200 IU / day of vitamin D orally starting from the second trimester till the end of the first six months of the lactation period. Nevertheless, vitamin D deficiency was detected in both patient and control groups included in this study. The fact that only 17% of the pregnant women who participated in this study had sufficient vitamin D revealed the need to monitor pregnant women closely and emphasize using vitamin D supplements in pregnant women as early as possible in the first trimester.

Limitations of the Study

The primary limitations of this study were its relatively small sample size and the fact that βhCG levels were not evaluated.

CONCLUSION

The etiology of HG has not been fully elucidated yet. There are conflicting results in the literature on the relationship between vitamin D deficiency and the development of HG. Then again, considering that vitamin D deficiency is common among pregnant women, they should be given vitamin D supplements as early as possible in the first trimester. Further large-scale studies are needed to corroborate the findings of this study and shed more light on the etiopathogenesis of HG.

Ethical Approval: Approval for the study was obtained from the Ethics Committee of University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (2019/25/03) and informed consents were obtained from the participants

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REFERENCES

1. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review [published correction appears in Hum Reprod Update. 2007 Mar-Apr;13(2):207]. Hum Reprod Update. 2005;11(5):527-539.
2. Goodwin TM. Hyperemesis gravidarum. Clin Obstet Gynecol. 1998;41(3):597-605.
3. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(3):695-703.
4. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol. 2013;20(2):e171-e183.

5. Fejzo, MS, Ingles SA, Wilson M, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol. 2008;141(1):13-17.
6. Gazmararian JA, Petersen R, Jamieson DJ, et al. Hospitalizations during pregnancy among managed care enrollees. Obstet Gynecol. 2002;100:94-100.
7. Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Pract. 2019;34(2):226-241.
8. Patil CL, Abrams ET, Steinmetz AR, Young SL. Appetite sensations and nausea and vomiting in pregnancy: an overview of the explanations. Ecol Food Nutr. 2012;51(5):394-417.
9. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 2010;363(16):1544-1550.
10. Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab. 1992;75(5):1333-1337.
11. Kaplan PB, Gücer F, Sayin NC, Yüksel M, Yüce MA, Yardim T. Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. Fertil Steril. 2003;79(3):498-502.
12. Yoneyama Y, Suzuki S, Sawa R, et al. The T-helper 1/T-helper 2 balance in peripheral blood of women with hyperemesis gravidarum. Am J Obstet Gynecol. 2002;187(6):1631-1635.
13. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Epidemiology of nausea and vomiting of pregnancy: prevalence, severity, determinants, and the importance of race/ethnicity. BMC Pregnancy Childbirth. 2009;9:26.
14. Bülbül M, Kaplanoğlu M, Arslan Yıldırım E, Yılmaz B. Hiperemezis Gravidarum. Arch Med Rev J. 2017;26(3):269-296.
15. Society of Endocrinology and Metabolism of Turkey. Osteoporosis and metabolic bone diseases diagnosis and treatment guide. 2018;119-127.
16. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc. 2013;88(7):720-755.
17. Ergür AT, Berberoğlu M, Atasay B, et al. Vitamin D deficiency in Turkish mothers and their neonates and in women of reproductive age. J Clin Res Pediatr Endocrinol. 2009;1(6):266-269.
18. Gür G, Abaci A, Köksoy AY, et al. Incidence of maternal vitamin D deficiency in a region of Ankara, Turkey: a preliminary study. Turk J Med Sci. 2014;44(4):616-623.
19. Fejzo MS, Fasching PA, Schneider MO, et al. Analysis of GDF15 and IGFBP7 in Hyperemesis Gravidarum Support Causality.

Geburtshilfe Frauenheilkd. 2019;79(4):382-388.

20. Özay ÖE, Özay AC. Inflammatory Markers in Hyperemesis Gravidarum. Eur Arch Med Res. 2021;37:27-31.
21. Kiran H, Rashmi N, Rajani H, Nandish M. Gestational Transient Thyrotoxicosis Associated with Hyperemesis Gravidarum. Glo J Med Phar Biomed U. 2021;16(1):1b-1b.
22. Ahmed Ahmed Shaheen AG, Wafa YAE-S, El-Omda FAE-A. Effect of high levels of human chorionic gonadotropin and estradiol on degree of hyperemesis gravidarum. Al-Azhar Int Med J. 2021;2(7):17-23.
23. Yıldırım E, Demir E. The relationship of hyperemesis gravidarum with sleep disorders, anxiety and depression. J Obstet Gynaecol. 2019;39(6):793-798.
24. Gürbüz T, Güngör ND, İyigün G, et al. Does the deficiency of 25-hydroxy vitamin D effect the placental peptides (free β-human chorionic gonadotropin and pregnancy-associated plasma protein A) levels? J Health Sci Adıyaman Uni. 2017;3(3):589-597.
25. Yılmaz S, Akdağ Cırık D, Demirtaş C, et al. Do vitamin D and high-sensitivity-C reactive protein levels differ in patients with hyperemesis gravidarum? A preliminary study. Turk J Obstet Gynecol. 2016;13(3):123-126.