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Evaluation of Maternal Serum 25-Hydroxyvitamin D Levels in Patients with Hyperemesis Gravidarum at Early Gestational Weeks

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ABSTRACT

Aim: The aim of this study was to compare vitamin D levels between pregnant women with hyperemesis gravidarum before 12 weeks of gestation and healthy pregnant women at similar ages.

Methods: Sixty pregnancies with hyperemesis gravidarum and 60 age compatible healthy pregnancies applied to our facility were included in the study. Demographic characteristics, maternal thyroid function tests and 25-Hydroxyvitamin D levels were evaluated. Student t test was used for the variables with normal distribution and Mann-Whitney U test was used to analyze the variables without normal distribution.

Results: Only one pregnant woman had normal vitamin D levels (>30ng/ml), whereas 71 patients had deficiency (10-30 ng/ml), and 48 had severe deficiency (<10 ng/ml). The mean vitamin D level of the total 120 pregnancies was 11.9±5.00 ng/ml (9.92±3.67 ng/ml in case group, 13.88±5.38 ng/ml in control group). The mean value of vitamin D was found to be significantly lower in hyperemesis gravidarum. 45% (n=27) of the pregnant women had vitamin D deficiency, whereas 55% (n=33) of them had severe deficiency. Free T3 and T4 levels were significantly higher than the control group, and thyroid-stimulating hormone level was significantly lower.

Conclusion: Vitamin D levels of pregnant women with hyperemesis gravidarum were significantly lower. Vitamin D deficiency should be considered in patients with hyperemesis gravidarum.

Keywords: pregnancy, hyperemesis gravidarum, Vitamin D deficiency

Hiperemezis Gravidarumu Olan Hastalarda Erken Gebelik Haftalarında Maternal Serum 25-Hidroksivitamin D Düzeylerinin Değerlendirilmesi

ÖZ

Amaç: Oniki hafta altı hiperemezis gravidarum tanılı gebeler ve benzer yaş aralığındaki sağlıklı gebeler arasında vitamin D düzeylerini karşılaştırmayı ve hiperemezis gravidarum etiyolojisinde serum vitamin D düzeyinin yerini saptamayı amaçladık.

Yöntem: Hiperemezis gravidarum tanısı konulan, 18-40 yaş arası 60 gebe ve kontrol grubu olarak benzer yaş grubundan 60 sağlıklı gebe çalışma kapsamına alındı. Gebelerin yaşı, gebelik haftası, kaçıncı gebeliği olduğu, demografik özellikleri, vücut kitle indeksleri, hastaneye yatış anındaki veya başvurusundaki tiroid fonksiyon testleri ve 25-Hidroksivitamin D düzeyi incelendi.

Bulgular: D vitamini düzeyi normal olan (>30 ng/ml) 1, eksiklik olan (10-30 ng/ml) 71, şiddetli eksik olan (<10 ng/ml) 48 gebe saptamıştır. Hiperemezis gravidarum tanısı alan bireylerin vitamin D ortalama değeri istatistiksel olarak anlamlı derecede düşük bulunmuştur. Hiperemezis gravidarum tanısı alan %55 (n=33) gebede D vitamini düzeyinde şiddetli eksiklik saptanırken, %45 (n=27) gebede D vitamini düzeyinde eksiklik saptanmıştır. Hiperemezis gravidarum tanısı alan bireylerin vitamin D düzeyinde şiddetli eksiklik istatistiksel olarak anlamlı derecede yüksektir. Hasta grubunda serbest T3 ve T4 değeri kontrol grubuna göre anlamlı derecede yüksek, tiroid stimulan hormon düzeyi ise anlamlı derecede düşük bulunmuştur.

Sonuç: Bu sonuçlar ile, hiperemezis gravidarum tanılı hastalarda, daha erken haftalarda vitamin D düzeyine bakılması ve eksiklik saptananlarda daha erken dönemde vitamin D replasmanı önerilmesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: gebelik, hiperemezis gravidarum, Vitamin D eksikliği

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Introduction

Approximately 50-70% of pregnant women have nausea and vomiting (1). This situation peaks at the ninth week of pregnancy and usually begins to decrease spontaneously. However, in 20% of the cases, nausea and vomiting can continue until the end of pregnancy. The nausea and vomiting that do not affect daily life are called gravidarum and this condition is not considered pathological (2). Hyperemesis gravidarum (HG) means excessive nausea and vomiting followed by dehydration, ketonuria, fluid electrolyte disturbance and loss of more than 5% of body weight and it affects 0.5-2% of pregnancies that last more than three days (3). In addition to these symptoms, Wernicke's encephalopathy, chronic protein-calorie malnutrition, late wound healing and immunosuppression can occur (4). HG ranks second in terms of the causes of hospitalization in pregnant women (3). The etiopathogenesis of hyperemesis gravidarum has not been fully elucidated to date. It has been suggested that hormonal, immunological, psychological factors and gastrointestinal motility disorders may have a role in the pathogenesis, however, there is no consensus and the studies are ongoing (5). In addition, there are multiple risk factors such as increased β-hCG and steroid levels, multiple pregnancies, increased body mass index, trophoblastic diseases, hyperemesis gravidarum in previous pregnancies, nulliparity, Helicobacter pylori infection and vitamin deficiency (6,7). Vitamin D inhibits calcium malabsorption and reduces bone loss. When clinical studies of vitamin D and pregnancy outcomes are examined, it was found that it may be associated with increased risk of preeclampsia, gestational diabetes, low birth weight, preterm labor, hyperemesis gravidarum, caesarean section and infectious diseases. It was determined that for more precise results, a randomized controlled study should be performed.

The aim of this study was to compare the vitamin D levels of pregnant women who were diagnosed with hyperemesis gravidarum before 12 weeks of pregnancy and the healthy pregnant women at a similar age range and to determine the serum vitamin D level in the etiology of hyperemesis gravidarum.

Methods

The study group consisted of 60 healthy pregnant women who met the criteria and who were admitted with hyperemesis gravidarum in our hospital between 2016-2018. The control group consisted of healthy pregnant women who had less than 12 weeks of gestational age and had no ketone in the urine, nausea or vomiting. According to our protocol, for post-diagnostic surveillance all hospitalized patients with symptoms were considered valid at the time of the first visit and their follow-up hospitalizations were not included in the study. In HG, 2+ ketone was considered to be significant (8). In both groups, age groups were matched and appropriate patient groups were formed. Some information about the patients such as the age, gestational week, number of pregnancies, presence of additional diseases, demographic characteristics, body mass index, biochemical findings at the time of admission (thyroid function tests and 25-Hydroxyvitamin D level) were used in the study. According to serum 25-Hydroxyvitamin D (25 (OH) D) status, the levels were grouped as follows: the vitamin D levels above 30 ng/ml were defined as normal, those between 30-10 ng/ml were defined as deficiency and those below 10 ng/ml were defined as severely deficiency (9).

The patients who were at 12 weeks of gestation and were admitted to the hospital for the first time with nausea and vomiting were included in the study. In these patients, the nausea and vomiting might have been caused by non-infectious, hormonal, gastrointestinal, psychiatric and non-fetal congenital malformations.

Patients with obstetric or medical complications, patients previously admitted with hyperemesis gravidarum, women with multiple pregnancies, major uterine anomaly, acute or chronic inflammatory diseases, systemic diseases, infectious diseases, history of hyperemesis gravidarum in previous pregnancy, stillbirth, major or minor pregnant complicated by fetus with fetus, pregnancies with chromosomal anomalies, abortus imminence and

abortus incipiens, pregnant women with renal and inflammatory bowel diseases and diseases that may cause enteropathy, pregnant women with diabetes mellitus and patients with a history of drug use affecting the autoimmune system (Azathioprine, cyclosporine A, cyclophosphamide, quinine, TNF-alpha blockers, etc.) were excluded from the study. Patients who smoke were also excluded from the study. Patients with maternal tachycardia (100 beats/min and maternal fever >38°C) were also excluded. Blood samples were taken from the volunteers at least 8 hours after fasting with gel and clot activator tubes (BD Vacutainer SST II Advance, 5 mL, 13x100 mm, catalog number 367955, Becton Dickinson, NJ, USA). After waiting 10 min at room temperature, the blood was separated from the serum by centrifugation. Hemolytic, icteric or lipemic samples were excluded from the study. 25 (OH) D measurements were performed on the Advia Centaur XP analyzer (Siemens Healthineers, Erlangen, Germany) by using the chemiluminescence immunoassay test method (15). Free T3 (fT3), Free T4 (fT4), Thyroid-stimulating hormone (TSH) levels were measured by chemiluminescence method in DXI 800 (Beckman Coulter Inc., Brea, CA, USA). The study was approved by the Ethics Committee of Tepecik Training and Research Hospital of Health Sciences University. The signed consent form of those who want to participate in the study which is in accordance with the criteria were included in the study.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) package was used in the analysis of the collected data. Continuous data were given as Mean ± Standard Deviation. Categorical data were given as percentage (%). Shapiro Wilk's test was used to investigate the suitability of the data to normal distribution. In comparison of groups that are not normally distributed, Mann-Whitney U test was used for the cases with two groups and Kruskal-Wallis H test was used for the cases with three or more groups. Spearman correlation coefficients were calculated for variables that did not conform to normal distribution to determine the direction and magnitude of the correlation between variables. Pearson's Chi-Square and Pearson's Exact Chi-Square analyzes were used to analysis of the cross-tables. A p value of <0.05 was considered as the criterion for statistical significance.

Results

A total of 120 pregnant women who were examined in our hospital were included in the study. Of these women, 60 had a diagnosis of HG (cases) and 60 were age compatible healthy pregnancies anthropometric measurements, some sociodemographic characteristics, serum 25 (OH) D3 levels and thyroid function findings were evaluated. There was no significant difference between the groups in terms of maternal age, gravidity, parity, number of abortions, gestational age, number of children, educational status and financial status ($p>0.05$). The mean body mass index (BMI) of the case group was statistically significantly lower ($p=0.02$).

The study included one pregnant woman with normal vitamin D levels (> 30 ng/ml), 71 with deficiency levels (10-30 ng/ml) and 48 with severely deficiency levels (<10 ng/ml). The mean vitamin D levels of the pregnant women was 11.9±5.00. The mean vitamin D level of the patients in the case group was 9.92±3.67 and 13.88±5.38 in the control group. Vitamin D mean values were significantly lower in the case group ($p<0.001$). When vitamin D levels were compared according to age groups, no significant difference was found between the case and the control groups ($p>0.05$). There was a significant difference between the two groups in terms of vitamin D levels (severely deficiency, deficiency, normal) ($p=0.001$). It was statistically significant that vitamin D levels were found to be severely deficient in patients with HG ($p=0.001$). There was no statistically significant difference in mean age and height between vitamin D levels and severe deficiency ($p>0.05$).

When the levels of fT3, fT4 and TSH were compared between the two groups, fT3 and fT4 values were found to be significantly higher than the control group as expected. When the mean values of thyroid function levels were compared according to vitamin D

levels in the patient group diagnosed with HG, there was no statistically significant difference between the two groups, although the mean TSH levels were lower in patients with severely deficiency vitamin D levels (p>0.05).

Table 1. Clinical characteristics of the study and control population

Variable		Study Group (n=60)	Control Group (n=60)	P value
Maternal age (years)		28.57 ±5.90	28.65 ±6.38	0.524
BMI (kg/m2)		23.38 ±2.84	25.33 ±4.04	0.002
Obstetric history	Gravidity	1 (1–3)	1 (1–2)	0.177
	Parity	0 (0-4)	0 (0-4)	0.451
	Number of abortions	0 (0-1)	0 (0–1)	0.139
	Live	0 (0-4)	0 (0-4)	0.254
Gestational age (weeks)		8,2±2.21 (6-12)	8.4±2.36 (6-12)	0.454
School	Primary	23	31	0.447
	Secondary	30	24	
	University	7	6	
Wage	Min. wage in 500 dollars	33	31	0.482
	Min. wage in 1000 dollars	15	18	
	Min. wage in 1500 dollars	12	11	
Age groups	18-24	20	20	0.993
	25-29	10	11	
	30-34	17	17	
	35-40	13	12	
Vitamin D		9.92±3.67	13.88±5.38	**<0.001**
TSH		1.18±1.20	1.66±1.43	**0.007**
ST4		1.06±0.39	0.97±1.17	**<0.001**
ST3		3.27±0.75	3.98±3.48	**0.003**

Data are presented as mean T standard deviation, median (interquartile range), and n (%), where indicated, based on two-tailed Students' t-test, Mann–Whitney U test. A P value of <0.05 was considered as statistically significant.
Abbreviations: BMI: body mass index; TSH,Thyroid Stimulating Hormone; ST4, free thyroxine; ST3, triiodothyronine

Table 2. Evaluation of demographic data and comparing the level of education, income and levels of fT3, fT4 and TSH

		Severe deficiency (n=33)	*Deficiency* (n=27)	P value
Maternal age (years)		29.85±5.37	27.00±6.22	0.070
Lenght (cm)		162.12±6.10	159.74±6.37	0.190
Weight (kg)		62.39±6.16	58.22±8.02	**0.016**
BMI (kg/m2)		23.79±2.54	22.87±3.15	0.397
School	Primary	14 (42.4%)	9 (33.3%)	0.810
	Secondary	15 (45.4%)	15 (55.5%)	
	University	4 (12.1%)	3 (11.1%)	
Wage	Min. wage in 500 dollars	23 (69.7%)	19 (70.4%)	0.175
	Min. wage in 1000 dollars	7 (21.2%)	2 (7.4%)	
	Min. wage in 1500 dollars	3 (9.1%)	6 (22.2%)	
Gestational age (weeks)	6	4 (12.1%)	4 (14.8%)	0.995
	7	5 (15.2%)	4 (14.8%)	
	8	5 (15.2%)	6 (22.2%)	
	9	5 (15.2%)	3 (11.1%)	
	10	5 (15.2%)	4 (14.8%)	
	11	6 (18.2%)	4 (14.8%)	
	12	3 (9.1%)	2 (7.4%)	
Gravidity	1	5 (15.2%)	10 (37.0%)	0.250
	2	9 (27.3%)	6 (22.2%)	
	3	12 (36.4%)	8 (29.6%)	
	4	7 (21.2%)	3 (11.1%)	
Live	0	8 (24.2%)	11 (40.7%)	0.638
	1	14 (42.4%)	9 (33.3%)	
	2	9 (27.3%)	6 (22.2%)	
	3	2 (6.1%)	1 (3.7%)	
TSH		1.08±1.24	1.31±1.17	0.281
sT4		1.13±0.48	0.97±0.21	0.209
sT3		3.26±0.86	3.28±0.61	0.634

Data are presented as mean T standard deviation, median (interquartile range), and n(%), where indicated, based on two-tailed Students' t-test, Mann–Whitney U test. A P value of <0.05 was considered as statistically significant.

Discussion

Nausea and vomiting in pregnancy usually begin at 5 weeks from the the last menstrual period and peaks during the 8th-12th weeks (1). Nausea and vomiting during pregnancy is a condition that causes a serious decrease in the life quality in women and hospital admissions with this complaint constitute a significant percentage of the reasons for first trimester admission. It has a very important place in the practice of obstetrics with its diagnosis and treatment process (2). This situation which occurs in the first weeks of pregnancy, causes loss of labor force, need for inpatient treatment and high costs in health economy.

Vitamin D deficiency and severe deficiency are seen in high prevalence in both general population and pregnant women in Turkey and worldwide. Vitamin D deficiency is observed in different prevalences in the studies. Long-term results of vitamin D deficiency have not been elucidated yet. There are a lot of studies performed in our country and worldwide. While some of these studies showed a significant relationship between vitamin D deficiency and pregnancy complications and fetal development, some of them showed no significant relationship. Maternal vitamin D deficiency has been associated with adverse pregnancy outcomes such as gestational diabetes mellitus, preeclampsia, premature membrane rupture, preterm labor and postpartum endometritis (10). However, further studies are needed on these subjects.

Vitamin D deficiency is common in both general population and pregnant women in Turkey and worldwide. Risk factors for vitamin D deficiency are not clearly known. Studies on its etiology are ongoing. Maternal and fetal complications that may occur as a result of vitamin D deficiency are still being investigated. It is recommended that vitamin D supplementation should be started at 1200 IU/day for all pregnant women who have passed the 12th gestational week and it should be continued for 6 months during the lactation period after delivery. Another issue that needs to be discussed in this context is the initiation of vitamin support regardless of serum 25 (OH) D levels. The evaluation of hypercalcemia symptoms (loss of appetite, nausea, constipation, polyuria, polydipsia) of the mother after the initial use of vitamins are recommended and it is also recommended that in the patients with hypercalcemia symptoms, measurement of serum calcium, serum 25 (OH) D and urinary calcium levels should be taken; in patients without these kinds of symptoms the vitamin supplementation should be continued for 6 months postpartum. However, HG, which complicates especially the first trimester of pregnancy, is seen more prominently before the 12th week of pregnancy. When a significant relationship between vitamin D deficiency and hyperemesis gravidarum is shown, vitamin D supplementation is expected to be started before the 12th gestational week.

In our study, we have guided our work considering it is necessary to investigate vitamin D deficiency which may cause increased gastric inflammation in HG, which is a common disease seen in the first weeks of pregnancy and causing loss of labor force, need for hospitalization, high costs in health economy and severely impaired quality of life.

Hyperemesis gravidarum is a disease with severe nausea, vomiting and dehydration leading to weight loss (5% of body weight), ketosis, electrolyte and acid-base imbalance. In our study, the mean BMI levels were significantly lower in the hyperemesis gravidarum group than the control group as expected.

In a study by Lacasse et al. (11), it was stated that the incidence of HG increased in primigravids and young patients. In our study, no statistically significant difference was found between two groups when the number of gravida, parity and living children were evaluated. This was thought to be due to cultural differences.

Nausea and vomiting may start at 5-6th week and peak at 9th week. The studies carried out on HG observed that it frequently occurs during 8-12th weeks (12). In our study, the mean gestational week was 8.85 in the HG group and 8.46 in the control group. There was no statistically significant difference between these two groups.

In our study, vitamin D deficiency was found as 40% (n=48) and severe deficiency was found as 59% (n=71) in all pregnant women. Normal vitamin D

levels were found in only 0.08% (n=1) of pregnant women. Although Turkey is a sunny country, vitamin D deficiency and insufficiency are seen at higher rates. Different factors such as life and clothing style have an effect on this. We believe that limited sunlight exposure and reduced vitamin D intake may be the causes of this. In a study conducted in Turkey in 2013, vitamin D level was significantly lower in pregnant women who wore more clothing that covered most of the body (13).

In a study by Cantorna et al. (14), the relationship between gastric inflammation and vitamin D levels was demonstrated. It has been shown that T cells carry the vitamin D receptor (VDR) and these cells are direct and indirect targets of vitamin D. In addition, 1,25-Hydroxyvitamin D (1,25 (OH) 2D), which is the active form of vitamin D, has been shown to suppress the development of T-cell mediated diseases. In another study, T cells with VDR defect were shown to secrete more IL-17 and IFN-gamma, proliferate more rapidly and produce a more severe form of gastric inflammation (15). In our study, it was thought that the symptoms of nausea and vomiting seen in pregnancy will increase due to the fact that gastric inflammation will increase in experimentally generated VDR defect and Vitamin D deficiency.

When the vitamin D levels of the patients with HG and the control group were examined, the mean vitamin D level of the patients was detected as 9.92±3.67 in the case group and 13.88±5.38 in the control group. Vitamin D levels were significantly lower in the case group ($p<0.001$). When vitamin D levels were compared according to age groups, no significant difference was found between the two groups ($p>0.05$). There is no study in the literature on this subject.

When the vitamin D levels of patients with HG were examined according to the groups of severe deficiency and deficiency, it was found statistically significantly higher that the vitamin D levels were severely deficient (<10 ng/ml) in pregnant women diagnosed with HG. This condition may be explained by the increase in the severity of vitamin D deficiency and therefore the increase in the severity of the symptoms.

There is a strong association between HG and abnormal thyroid function tests. In normal pregnancy, in addition to physiological changes in thyroid activity (changes in iodine metabolism, serum thyroid binding proteins and maternal goiter development), physiological stimulation of the thyroid gland is common in early pregnancy. The most common hormonal disorder commonly seen together with nausea and vomiting during pregnancy is transient hyperthyroidism. This is caused by the similarity of β-hCG to the TSH. In a cohort study of 67 patients diagnosed with HG, it was detected that 66% of them had biochemical hyperthyroidism (increased free thyroxine, suppressed TSH) (16).

Similarly, in our study, fT3 and fT4 values were found to be significantly higher in the patients with HG than the control group. TSH levels were significantly lower than the control group. These results correlate with the results of previous studies.

Vitamin D affects Th3 cells (regulatory cells) and prevents overstimulation of Th2 cells, thereby maintains the Th2/Th1 balance and prevents the development of allergies and autoimmune diseases. On the contrary, if the Th2/Th1 balance increases in favor of Th2, the immune tolerance deteriorates. When vitamin D is given in animals with vitamin D deficiency, it is observed that thyroid functions are greatly improved (17).

In our study, no significant difference was found between the groups as a result of comparing the mean values of thyroid function values according to vitamin D levels (severe deficiency-deficiency) in the patients diagnosed with HG. This may be explained by the absence of patients with normal vitamin D levels in this group.

Conclusion

In our study, there was a significant relationship between patients with HG and vitamin D deficiency. We think that in addition to routine vitamin D supplementation program in our country that is currently recommended after the first 12 weeks of pregnancy, with further studies supporting these data,

it is needed to measure the vitamin D levels in earlier weeks of pregnancy and if a deficiency of vitamin D is detected in patients with HG which is seen commonly seen in the first trimester of pregnancy, the replacement should be recommended in earlier periods.

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