

The effect of non-autoimmune thyrotoxicosis to vitamin D status during pregnancy.

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Abstract

Aim: Gestational transient thyrotoxicosis was chosen to identify the effect of a non-immune thyrotoxicosis to vitamin D status during pregnancy. **Material and Methods:** Eighty-three pregnant women with gestational thyrotoxicosis and 28 healthy pregnant women were enrolled to the study. All the patients had thyroid ultrasound and were tested for hCG levels, thyroid function tests, TSH-receptor antibody, anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, calcium, phosphorus, erythrocyte sedimentation rate, C-reactive protein levels. **Results:** There was no statistical significance for age, gestational age, TRAb positivity, Anti-Tg positivity, ESR and CRP levels between the two groups. 25-hydroxyvitamin D levels are below the lower limit in both groups but 1,25-dihydroxyvitamin D levels of both groups were found within the normal range. **Conclusion:** Non-autoimmune thyrotoxicosis does not have any effect to the vitamin D status. The presence of nodules increases the risk of gestational thyrotoxicosis 2.67-fold. The level of 25-hydroxyvitamin D is low during pregnancy. Preserved level of 1,25-dihydroxyvitamin D maintains the balanced levels of calcium and phosphorus which have critical mission in bone metabolism.

Keywords: Non-autoimmune thyrotoxicosis, Vitamin D, Pregnancy.

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Introduction

Gestational transient thyrotoxicosis (GTT) is a condition that is associated with the stimulation of thyroid stimulating hormone (TSH) receptor by human chorionic gonadotropin (hCG) [1]. Human chorionic gonadotropin is a glycoprotein hormone. The similarities between hCG and beta subunit of TSH cause a poor thyroid stimulant activity. The frequency of hCG-mediated hyperthyroidism is 1-3% during pregnancy [2-3]. This transient abnormality arises in the first half of the pregnancy and is associated with suppressed TSH along with increased T3 and T4 levels. Graves' disease can also be diagnosed with a frequency of 0.1-1% during pregnancy, thus Graves' disease should be evaluated in differential diagnosis [4].

It has been reported that serum 25-hydroxyvitamin D level does not change during the pregnancy but the vitamin D binding globulin level increases in consistence with estrogen level. This situation leads to 2-fold increase in 1,25-dihydroxyvitamin D level. The other causes of the elevated levels of 1,25-dihydroxy vitamin D are the increased renal 1-alpha hydroxylase activity and placental 1,25-dihydroxyvitamin D secretion and release [5-6]. Vitamin D also has potential benefits on tissues other than skeletal system. It operates in diabetes mellitus, cardiovascular disease, and cancer as well as in bone mineralization [7,8-10]. instead of Vitamin D deficiency is classically known to cause bone

mineralization defect but recently, another potential benefits of vitamin D have gained the importance except the skeletal ones [7]. Other conditions that come into prominence are the diabetes mellitus, cardiovascular system and cancer [8-10].

Recently, there are some studies that suggest the low vitamin D level in pregnancy may be associated with preeclampsia, preterm delivery and gestational diabetes mellitus [11-12]. There are also some studies that investigate the association between the thyroid autoimmunity with vitamin D levels. It is obvious that there is necessity for further studies on this subject [13]. In our study, we aimed to evaluate thyroid-vitamin D relationship in GTT.

Material and Methods

We enrolled 83 pregnant women with gestational thyrotoxicosis and 28 healthy pregnant women, who were admitted to the Departments of Endocrinology and Obstetrics and Gynecology in Eskişehir State Hospital, from January 2014 to December 2014. All subjects were within their first trimester of pregnancy. The diagnosis of thyrotoxicosis was based on clinical assessment and laboratory findings. All of patients had thyroid ultrasound. TSH levels with normal or high serum free T3; free T4 levels were regarded as gestational thyrotoxicosis. All subjects were tested for TSH-receptor antibody (TRAb), anti-thyroglobulin antibody (Anti-Tg), anti-

thyroid peroxidase antibody (anti-TPO), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, calcium and phosphorus.

The patients who had positive or borderline positive results of TSH receptor antibody were excluded from the study. Twenty-eight age and sex matched healthy pregnant women with normal biochemical and thyroid function tests constituted the control group. Serum thyroid function tests, thyroid autoantibodies, erythrocyte sedimentation rate (ESR), vitamin D, hCG and C-reactive protein (CRP) were measured in all subjects. The patients did not receive any drug that could influence the vitamin D level. 25-hydroxyvitamin D levels below 30 ng/ml were accepted as vitamin D deficiency.

Anti-TPO, anti-Tg, TRAb and 1,25-dihydroxyvitamin D were studied with radioimmunoassay method. 25-hydroxyvitamin D levels were studied with ELISA method. TSH, free T3 and free T4 levels were studied with chemiluminescence method.

Statistical analysis

Continues data were given as mean ± standard deviation while categorical data shown as percentages. Shapiro Wilk test was used to validate the normality. Paired sample mean test was used to compare repeated measurements for normally distributed data; otherwise Wilcoxon Signed Rank test was performed. IBM SPSS Statistics 21 software was used for analysis. $p < 0.05$ was assumed to be statistically significant.

Results

There was no statistical significance for age, gestational age, TRAb positivity, anti-Tg positivity, ESR and CRP levels between the two groups (Table 1). TSH levels were low in patient group. The control group had higher level of anti-TPO positivity but when we checked the number of patients who were positive for anti-TPO, there was no statistical difference.

Additionally there was no statistical difference in vitamin D, calcium and phosphorus between the two groups (Table 2). But if we look at carefully to the results we can see the 25-hydroxyvitamin D levels are below the lower limit in both groups. On the other hand, 1,25-dihydroxyvitamin D levels of both groups were within the normal range.

Table 3 summarizes the ultrasonographic features. The number of subjects with thyroid nodules was found more often in gestational thyrotoxicosis group. The patients with nodules have one or more nodules. The size of thyroid nodules ranged between 2 and 30 mm in diameter. As 25-hydroxyvitamin D levels below 30 ng/ml were accepted as vitamin D deficiency there is only one patient having 25-hydroxyvitamin D level over 30 ng/ml [14].

The sizes of the thyroid nodules were with a diameter of between 2 mm and 30 mm. The presence of nodules was found to be at risk of 2.67-fold increase for developing gestational thyrotoxicosis.

Table 1: The Characteristics of the Study Population. Anti-Tg: thyroglobulin antibody, Anti-TPO: thyroid peroxidase antibody, CRP:

C-reactive protein levels, ESR: Erythrocyte sedimentation rate, TRAb: TSH receptor antibody.

	Patient (n=83)	group	Control (n=28)	p
Age (year)	29.8 ± 4.87		28.6 ± 5.03	>0.05
Gestational age (month)	9.8 ± 2.3		9.9 ± 3.3	>0.05
TRAb (U/L) Positive (>1.5)	0.39 ± 0.24		0.44 ± 0.24	>0.05
Anti-Tg Positive (IU/ml) (>100)	32 ± 58		12.05 ± 11.57	>0.05
Anti-TPO (IU/ml) Positive (>100)	8.7 ± 9.18		12.05 ± 11.57	<0.05
TSH (mIU/ml) (0.35-4.94)	0.19 ± 0.05		0.9 ± 0.5	<0.001
Free- T3 (pg/ml) (1.71-3.71)	3.5 ± 0.85		2.89 ± 0.32	<0.001
Free T4 (ng/dl) (0.7-1.48)	1.39 ± 0.34		1.06 ± 0.12	<0.001
ESR (mm/hour) (0-20)	23.2 ± 13.8		22.3 ± 13.7	>0.05
CRP (mg/dl) (0-0.35)	0.64 ± 0.41		0.57 ± 0.42	>0.05

Table 2: The serum levels of vitamin D, calcium and phosphorus of the study group.

	Patient (n=83)	group	Control (n=28)	group	p
25-hydroxyvitamin D ng/ml (30-150)	15.66 ± 3.41		16.69 ± 7.77		>0.05
1,25-dihydroxyvitamin D pg/ml (19.6-65)	26.7 ± 3.88		27.75 ± 7.4		>0.05
Calcium mg/dl (8.8-10.6)	9.22 ± 0.34		9.17 ± 0.44		>0.05
Corrected Calcium mg/dl	9.13 ± 0.32		9.06 ± 0.44		>0.05
Phosphorus mg/dl (2.5-4.5)	3.3 ± 0.46		3.48 ± 0.54		>0.05

Table 3: The thyroid ultrasonography findings of the study group.

	Patient (n=83)	Group	Control Group (n=28)	p
Nodule (-)	48		22	<0.05
Nodule (+)	35		6	-

Discussion

Gestational transient thyrotoxicosis (GTT) is a condition of non-autoimmune origin. The stimulation of TSH receptors by hCG causes hyperthyroidism. This situation becomes more frequent when the hCG level rises to 70-80000 IU/L levels [15-18]. In our study we found high hCG levels both in thyrotoxic and control groups, but the autoantibody levels were low.

In our study we found the hCG levels of the patient group and the control group were high but the autoantibody levels were low. The patients with positive TRAb (7 patients) and borderline levels (6 patients) were excluded from the study to

distinguish gestational transient thyrotoxicosis from Graves' disease.

Thyroid function tests of the patients with GTT turned to normal range during the follow-up. Thyroid ultrasounds were performed in all participants. One or more nodules were detected in 42.1% of the GTT patient group and 21.4% of the control group. Nodules were more frequent in patients with gestational thyrotoxicosis. The presence of nodules was found to be 2.67-fold increase for developing gestational thyrotoxicosis. There are scarcely few studies showing a relationship between nodules and GTT, but this issue deserves to be investigated. Vitamin D can cross the placenta and it is very important for the fetus. Vitamin D deficiency is detected frequently in pregnancy [19-20]. There are some studies indicating the importance of vitamin D replacement before and during pregnancy and after birth [21-22]. The relationship between Vitamin D and thyroid function has not been not studied sufficiently.

We aimed to evaluate the vitamin D levels in patients with non-autoimmune gestational thyrotoxicosis in our study. The vitamin D levels of patients with gestational thyrotoxicosis and pregnant control group were low and there was no significant difference between the two groups. It was reported that there was no relationship between the vitamin D level and thyroid autoimmunity in one study [13]. Differently, we aimed to search vitamin D levels in patients with non-autoimmune thyrotoxicosis etiology. Similarly, we have reached the result that non autoimmune thyrotoxicosis does not influence the vitamin D status. We detected low levels of 25-hydroxyvitamin D, but the levels of 1,25 dihydroxyvitamin D were within the normal range. This may be due to the following reasons. First, 25- hydroxyvitamin D is transformed to 1,25-dihydroxyvitamin D with an increased renal 1 alpha-hydroxylase activity during pregnancy. Second, the secretion and release of placental 1,25-dihydroxyvitamin D increases during pregnancy (5-6). Calcium and phosphorus levels were also within the normal range in both groups.

Normal levels of calcium and phosphorus which are necessary for the bone metabolism may be due to normal levels of 1,25-dihydroxyvitamin D during pregnancy. Normal 1,25-dihydroxyvitamin D levels in pregnant maintains calcium and phosphorus balance which is critical in bone metabolism.

Conclusion

Non-auto-immune thyrotoxicosis does not have any effect on the vitamin D status. The level of 25- hydroxyvitamin D is low during pregnancy. Preserved level of 1,25-dihydroxyvitamin D maintains the balanced levels of calcium and phosphorus which have critical mission in bone metabolism.

Conflict of Interest

The authors declare that there is no conflict of interest.

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