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Relationship between gestational transient thyrotoxicosis and vitamin D

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Background/aim: Gestational transient thyrotoxicosis (GTT) is a transient, mild hyperthyroidism that occurs early in pregnancy and is due to human chorionic gonadotropin. There is no clear information about why only some pregnant women develop GTT. Previous papers stated that vitamin D plays a role in thyroid functions. We aimed to evaluate the relationship between vitamin D and GTT.

Materials and methods: Fifty-three patients diagnosed with GTT at the 6th to 10th weeks of gestation were included in the study (GTT group). Thirty-five pregnant women with normal thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) levels served as a control group. Vitamin D, TSH, fT3, and fT4 levels were followed during entire the pregnancy.

Results: TSH levels had been normalized at the 20th week of gestation in all patients with GTT (mean TSH: 0.56 ± 0.2 μIU/mL). Vitamin D levels were significantly lower in the GTT group than the controls (11.1 ± 7.7 and 16.5 ± 0.5 ng/mL, respectively; P = 0.008).

Conclusion: Pregnant women who are diagnosed with GTT should be evaluated for possible vitamin D deficiency.

Key words: Gestational transient thyrotoxicosis, vitamin D, pregnancy

1. Introduction

Thyroid hormone physiology changes during pregnancy. Following conception, levels of human chorionic gonadotropin (hCG), which is structurally homologous to thyroid-stimulating hormone (TSH), increase. hCG has a stimulatory role on thyroid follicular cells by activating TSH receptors, which results in an increase in serum total and free thyroxine concentrations, and this increase causes a slight reciprocal decrease in circulating serum TSH levels. These effects are maximum at the end of the first trimester, at which time hCG levels peak (1,2). This situation is known as gestational transient thyrotoxicosis (GTT), which is diagnosed after excluding other causes of hyperthyroidism, including Graves' disease and toxic nodular goiter. While incidence of developing "true" hyperthyroidism during pregnancy due to any cause is about 0.05% (3), the incidence of GTT is about 2%–11% (4–6).

The classical main function of vitamin D (vit D) is regulation of calcium homeostasis (7). In addition, vit D also plays roles that affect the immune, cardiovascular, and metabolic systems (8–11). Vitamin D deficiency is very common all over the world (12). The relationship between vit D and thyroid hormone biosynthesis is not clear. Previous studies revealed that vit D modulated pituitary TSH secretion by using specific binding sites (13). Low levels of vit D may contribute to autoimmune thyroid diseases, and vit D replacement treatment may suppress autoimmune reaction and reduce serum thyroid autoantibody levels (14).

Maternal thyroid hormones play an important role in fetal development and thyroid disorders are associated with several gestational complications and perinatal outcomes (15).

Although vitamin D deficiency is common in pregnant women in the literature, to our knowledge, there is no publication about the relationship between GTT and vit D. In this study we aimed to investigate the relationship between vit D and GTT during pregnancy.

2. Materials and methods

Fifty-three patients diagnosed with GTT in the 6th to 10th weeks of gestation who had applied to our endocrinology outpatient clinics between April 2014 and June 2014 were included in this study as the GTT group. GTT without thyroid disease was diagnosed when low or undetectable

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serum TSH levels and normal or elevated serum T4 levels were present with normal antithyroid peroxidase antibodies (anti-TPO), antithyroglobulin antibodies (anti-Tg), and TSH receptor antibodies levels (1,2). Thirty-five pregnant women with TSH, free triiodothyronine (fT3), free thyroxine (fT4), and TSH receptor antibody levels within normal limits and normal thyroid findings on ultrasonography served as the control group.

Pregnant women with a history of neck radiotherapy, thyroid disease, thyroid hemiagenesis, hydatidiform moles, choriocarcinoma, or vit D replacement therapy in the last 12 months were excluded. All of the participants in the two groups had similar habits of dressing. All of the patients were followed until the end of the pregnancy on a monthly basis in terms of thyroid functions.

Fasting blood samples were obtained, after an overnight fast, between 0800 and 0900 hours for serum 25-OH vit D, TSH, fT4 and fT3, inorganic phosphorus (P), total calcium (Ca), parathyroid hormone (PTH), anti-TPO, anti-Tg, TSH receptor antibodies, and hCG assays. Vitamin D deficiency or insufficiency was defined as vit D levels of <20 ng/mL or as 20 to 29.9 ng/mL, respectively. Serum Ca and P were assayed photometrically on an AU5800 analyzer (Beckman Coulter, USA). PTH was assayed with the Elecsys 1010 System (Roche, Manheim, Germany). Serum 25-OH vit D levels were quantified by liquid chromatography–mass spectrometry (LC-MS/MS) on Waters analyzers (Acquity UPLC and Quattro Premier XE Micromass Spectrometry, USA). TSH, fT4, fT3, anti-TPO, and anti-Tg levels; TSH receptor antibodies; and hCG were determined by using a chemiluminescent immunoassay (Cobas E6000, Roche Diagnostic, Germany). The patients with low vit D levels (vit D <20 ng/dL) received a daily supplement of 1000 IU cholecalciferol for 3 months and vit D levels were reassayed after replacement.

Patients were also questioned about hyperemesis gravidarum. We used persistent vomiting accompanied by weight loss exceeding 5% of prepregnancy body weight and ketonuria unrelated to other causes as criteria for the diagnosis of hyperemesis (16).

Ultrasonography examinations of the patients were performed in our clinic by an endocrinologist using Aplio 500 (Toshiba Medical Systems Corporation, Otawara, Japan) USG equipment with a 14-MHz linear probe.

This study was approved by the local ethics committee. Informed consent forms in accordance with the Declaration of Helsinki 2013 Brazil version were obtained from all subjects who volunteered to be included in the study.

2.1. Statistical analysis

Statistical analysis was performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). The suitability of the normal distribution of the data was determined with the Shapiro–Wilk test. Two independent samples t-tests and Mann–Whitney U tests were used for comparisons between the groups for quantitative variables. The chi-square test was used for qualitative variables. Data were expressed as frequency and percentage or mean and standard error. Spearman's correlation test was used to investigate the association between two continuous variables. $P < 0.05$ was considered as statistically significant.

3. Results

The characteristics of the pregnant women are presented in Table 1. The two groups were similar with regard to age, body mass index, and gestational week at entry into the study. No patient in either group had a multiple pregnancy. Laboratory findings of the two groups are summarized in Table 2. The mean TSH levels were lower and fT3 and fT4

Table 1. The characteristics of the pregnant women.

Parameter	GTT group (n = 53)	Control group (n = 35)	P
Age (years)	28.7 ± 5.1	26.6 ± 5.1	0.07
Height (cm)	159.8 ± 5.4	159.4 ± 5.2	0.70
Weight (kg)	62.9 ± 9.9	63.0 ± 12.0	0.95
BMI (m^2/kg)	24.5 ± 4.2	25.0 ± 5.3	0.64
Week of pregnancy	9.4 ± 1.1	9.1 ± 2.0	0.60
Thyroid USG			
Normal	28 (53%)	35 (100%)	0.001
Diffuse goiter	4 (7%)	0 (0%)	0.98
Nodular goiter	19 (36%)	0 (0%)	0.79
Thyroiditis	2 (4%)	0 (0%)	0.62

Table 2. Laboratory findings of the groups.

Parameter	6th to 10th gestational weeks			38th to 42nd gestational weeks		
	GTT group (n =53)	Control group (n =35)	P	GTT group (n =53)	Control group (n =35)	P
TSH (0.27–4.2 μIU/mL)	0.01 ± 0.0	1.7 ± 0.7	**<0.001**	1.3 ± 0.3	1.6 ± 0.4	0.08
fT3 (2.1–4.4 pg/mL)	3.4 ± 0.7	2.8 ± 0.4	**<0.001**	2.6 ± 0.6	2.7 ± 0.3	0.69
fT4 (0.8–2.7 ng/dL)	1.4 ± 0.3	1.0 ± 0.1	**<0.001**	1.1 ± 0.2	1.0 ± 0.1	0.37
Vitamin D (19–57.6 ng/mL)	11.1 ± 7.7	16.5 ± 0.5	**0.008**	32.5 ± 4.4	31.8 ± 3.6	0.07
Total calcium (8.4–10.6 mg/dL)	9.2 ± 0.5	9.1 ± 0.4	0.72	9.1 ± 0.2	9.2 ± 0.5	0.68
Phosphorus (2.5–4.6 mg/dL)	2.9 ± 0.2	3.1 ± 0.1	0.86	2.7 ± 0.3	2.9 ± 0.2	0.84
PTH (10–65 pg/mL)	34 ± 4.3	28 ± 3.4	0.67	36 ± 2.1	34 ± 3.3	0.77

Bolded P-values indicate statistical significance (P < 0.05).

levels were significantly higher (P < 0.001 for all) in the GTT group than the controls. All patients in both groups had fT3 and fT4 levels within normal limits. Anti-TPO and anti-Tg were positive in 13.6% and 9.6% of the control group, respectively. Vitamin D levels were significantly lower in the GTT group than the controls (P = 0.008).

TSH levels had normalized at the 20th week of gestation in all patients with GTT and mean TSH level was 0.56 ± 0.2 μIU/mL. Mean week for normalization of TSH was 15 ± 1.3 weeks of gestation (Figure). No one in the control group had abnormal TSH, fT3, or fT4 levels during pregnancy.

When all of women were considered in terms of vit D levels, 84.9% of women in the GTT group population were vit D deficient, 11.3% were vit D insufficient, and 3.7% were vit D sufficient with serum concentrations above 30 ng/mL. In the control group, 57.1% were vit D deficient, 34.2% were vit D insufficient, and 8.5% were vit D sufficient with serum concentrations above 30 ng/mL. After 3 months of vit D supplementation, mean serum vit D levels were increased to 32.5 ng/dL and 31.8 ng/dL in the GTT and control groups, respectively. There were no statistically significant differences among vit D, Ca, P, and PTH between the two groups in the 3rd trimester (P > 0.05).

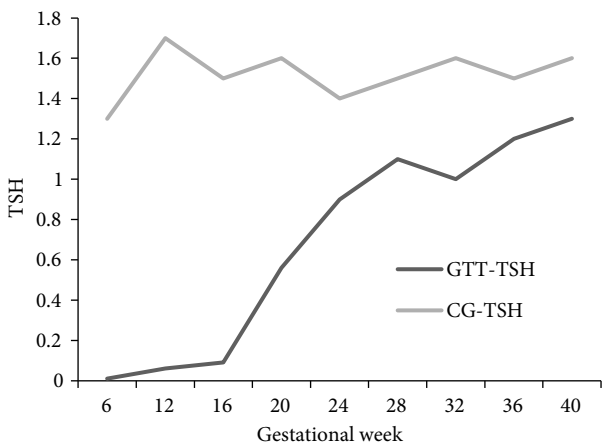

Figure. The mean TSH levels during pregnancy in the GTT group and the control group (CG).

There were no statistically significant differences between groups in terms of TSH, fT3, or fT4 levels when all patients were divided into two groups as those with vit D levels below or above 20 ng/mL (P > 0.05).

We assayed hCG at the 6th to 10th weeks of gestation in both groups. Mean hCG level was significantly higher in the GTT group than the controls (124.254 ± 10.516 vs. 102.865 ± 11.284 mIU/mL, respectively; P < 0.05).

Hyperemesis gravidarum was diagnosed two patients in the GTT group and one woman in the control group.

There was no correlation between vit D and any of the other parameters (TSH, fT3, fT4, and hCG levels) in either the GTT group or the control group (P > 0.05). In the GTT group, there were negative correlations between gestational week and both fT3 and fT4 (r = –48.4, P < 0.001 and r = –40.0, P = 0.004, respectively).

There was no statistically difference between groups with regard to abnormal ultrasonography findings (P > 0.05).

4. Discussion

To the best of our knowledge, this is the first study that showed the pregnant women who had GTT had lower vit D levels than the euthyroid pregnant group. In the literature, research predominantly shows that vit D affects thyroid autoimmunity. However, the relationship between

vit D and TSH levels cannot be explained by autoimmunity as it does not play a role in GTT pathophysiology.

Interaction between thyroid hormones and vit D was not explained completely. Both vit D and thyroid hormone bind to similar steroid hormone receptors. Sar et al. suggested a central effect of vit D on the modulation of thyrotropin secretion in the pituitary gland (13). Administration of vit D has been reported to increase thyrotropin-releasing hormone-induced TSH secretion in rats (17). In another study, vit D level was increased after administration of T3, T4, and TSH in rats (18). In addition, the current literature shows that vit D is deficient in both hypo- and hyperthyroidism. However, these results are contradictory and inconclusive (19–22). Bouillon et al. also revealed that 1,25-dihydroxyvitamin D_3 levels were low in patients with hyperthyroidism, although 1,25-dihydroxyvitamin D_3 levels were high in patients with hypothyroidism (21). Hyperthyroidism may cause low vit D due to the increasing of vit D metabolism. Rosskamp et al. revealed that after thyrotropin-releasing hormone injections, there was no change in serum vitamin D metabolites, calcium, and phosphorus (23). It has been recently demonstrated that vitamin D-receptor gene and vitamin D-binding protein gene polymorphisms are associated with Graves' disease (21,24). Vitamin D levels may effect pituitary cells and/or thyrocytes and VDR gene mutations may affect thyroid function.

Vitamin D deficiency is a widespread disorder seen in approximately 30% to 50% of the adult population (25,26). It is generally due to a lack of adequate sunlight exposure and/or nutritional vit D intake (27). Vitamin D deficiency and insufficiency are present in 74.9% and 13.8% of the Turkish population, respectively (28), and vit D deficiency was revealed in 37%–50% of pregnancies. This ratio may change depending on living conditions and ethnicity (29,30). Pehlivan et al. showed that vit D levels were mostly below 25 ng/mL in pregnant Turkish women (31). We revealed that >90% our study population had vit D deficiency or insufficiency, which could be related to pregnancy due to placental transition (32) and less exposure to direct sunlight due to dressing habits, or less sunny geographical regions.

Limitations of our study were the small sample size and all participants being from the same region with similar dressing habits and the same ethnicity, which can all affect vit D levels. We supplemented vit D for all participants due to ethical reasons. Therefore, we could not evaluate the effects of vit D on thyroid functions.

In conclusion, in this study, we have found lower vit D levels in pregnant patients with GTT than in euthyroid pregnancies. Pregnant women who are diagnosed with GTT should be evaluated for possible vitamin D deficiency. Further studies are needed to assess the role of vitamin D on GTT.

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