Ann Med Res 2020;27(5):1492-7

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.853

Original Article

Association of altered thyroid hormone levels with insulin resistance and vitamin D levels in pregnancy

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Abstract

Aim: Thyroid disorders have a crucial impact on maternal and fetal health During pregnancy, there are different results regarding the relationship between thyroid disorders, insulin resistance (IR) and vitamin D levels in different studies.We aimed to investigate the association between thyroid hormone levels and IR and vitamin D levels in pregnant women.

Material and Methods: In this study, a total of 187 pregnant women between 5-39 gestational weeks consisting of 101 patients with altered TSH and free T4 (FT4) levels, and 86 patients with normal TSH and FT4 levels, were enrolled in four months period. Their TSH, FT4, Anti TG, Anti TPO,25-hydroxy vitamin D, insulin, glucose,creatinine,hemoglobin levels and age, gravidea, gestational week and insulin resistance (IR) were defined. Statistical methods were used for analyses.

Results: In the group with thyroid hormone alterations, FT4 (p=0.010), creatinine (p=0.001) and glucose (p=0.044) levels were significantly higher.Pregnancy week was significantly earlier in the hyperthyroidism group (p=0.001). Vitamin D levels were not associated with BMI, TSH, FT4, anti TG and anti TPO. Although not significant TSH, anti TPO and vitamin D mean levels were higher in patients who had IR .Those with positive anti-TG and anti-TPO and presence of IR were higher in the study group.

Conclusion: In our study, levels of vitamin D and thyroid hormones were not associated; anti TG and anti TPO levels and higher IR presence were observed in pregnant women with altered thyroid hormone levels. During the early gestational weeks, patients should closely be monitored for hyperthyroidism and hypothyroidism as well as insulin resistance for detecting DM throughout the trimesters of gestational period.

Keywords: Insulin resistance; pregnancy; thyroid hormone; vitamin D

INTRODUCTION

Diabetes Mellitus (DM) and thyroid disorders are the two most common endocrine disorders which affect women in their reproductive period. It is crucial to screen, diagnose and manage thyroid disorders detected during pregnancy at the earliest period in order to ensure maternal and fetal health.Overt hyperthyroidism, which is present in approximately 0.2% of pregnancies, is defined as serum TSH level below the trimester-specific reference interval with high levels of free T3, free T4, or both. Subclinical hyperthyroidism is reported to be 2.5% of pregnancies with serum TSH levels below trimester-specific reference interval and normal levels of free T3 and T4 (1). On the other hand, it was observed that overt hypothyroidism which is defined as high TSH level with low free T4 level, affects approximately 0.4% of pregnant women, whereas subclinical hypothyrodism with normal free T4 level and high TSH level affects about 3% of pregnancies (1). Thyroid autoantibodies have also been investigated in pregnant women and spontaneous abortion and increased risk of pregnancy loss have been reported in women with thyroid autoantibody positivity (2-5).

Gestational diabetes mellitus (GDM) is seen in 2-5% of normal pregnancies (6). In the majority of gestational diabetic pregnancies, the β-cell dysfunction and increased insulin resistance are present. In particular, the increase in pregnancy-related circulating hormones, reduces the insulin sensitivity of tissues. As a result, the increase of insulin secretion as a compensator from pancreatic β-cells leads to hyperinsulinemia and after a while pancreatic β-cells become insensitive to insulin response and fasting hyperglycemia occurs. Increased glucose is

Received: 18.12.2019 **Accepted:** 20.02.2020 **Available online:** 26.05.2020
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transmitted to the fetus by placental transport and leads to fetal hyperinsulinemia, which leads to the development of macrosomia (7,8). Increased risk of macrosomia in GDM is also due to increased maternal insulin resistance (8). It has been reported that in women who are diabetic before pregnancy or who have gestational diabetes, the risk of congenital malformations in infants increases 3 to 4 times (7).

Impaired thyroid function has been found to be associated with gestational hypertension (9). Vitamin D deficiency in pregnancy has been reported to be associated with preeclampsia (10), gestational diabetes (11) and impaired neurodevelopment in infants (12). There are different reports on the association of thyroid dysfunction, insulin resistance and vitamin D levels in pregnant women.

In this study, we aimed to compare and explore the relationship between the insulin resistance, thyroid hormones and vitamin D levels in pregnant women with and without altered thyroid hormone levels.

MATERIAL and METHODS

Study group

This study was conducted in the four-month period, with pregnant women who applied to the outpatient clinics of Obstetrics and Gynecology and Internal Medicine Departments of our tertiary training and research hospital. Pregnant women who had altered TSH and free T4 levels and were between the 5 th and 39 th weeks of pregnancy were included to the study group. The control group consisted of healthy pregnant women with no present symptoms or biochemical alterations in the same gestational weeks.

Individuals who had undergone thyroidectomy, had a history of thyroid hormone replacement therapy, had medications that interfered with thyroid hormone levels, individuals with pre-gestational or gestational diabetes mellitus, who had a history of pre-pregnancy vitamin D replacement, patients who received infertility treatment and patients with hyperprolactinemia were excluded from the study.

Body mass index (BMI) was calculated as body weight / square of height (kg/m²) formula by measuring height and body weight. The BMI, age, number of pregnancies and gestational week of all the participants were recorded.

This study was approved by the ethics committee of the hospital with the reference number 2014/282. It was supported by the hospital Education Planning Board. Patients who volunteered to participate were informed about the study and informed consent forms were obtained. The study was planned and conducted in line with the Helsinki Declaration.

Biochemical measurements

After 12 hours of fasting, blood samples for blood glucose, creatinine, hemogram, insulin, TSH, FT4, anti-TG and anti-TPO, 25-hydroxy D vitamins were obtained from all the participating patients into dry flat tubes. After coagulation, the samples were centrifuged at 3000 rpm and the separated serum samples were stored -20ºC until analysis time. All biochemical evaluations were performed in our hospital biochemistry laboratory. Anti-TG, anti-TPO, insulin and 25-hydroxy vitamin D (25-OH vitamin D) were detected by the "ECLIA" (electrochemiluminescence immunoassay) competition principle in the cobas 6000 device by enzymatic reference method. Hypothyroidism, hyperthyroidism and normothyroidism were classified according to reference ranges for pregnancy which are 0.3<TSH <3 (mIU/L) and 0.88 <free T4<2 (ng/dL). In these subgroups according to thyroid hormone levels, autoimmune factors were considered positive if anti-TG>25mIU / L and anti-TPO> 34mIU / L.

HOMA-IR indices were calculated for each case based on fasting blood glucose and insulin levels according to the Formula (HOMA-IR = fasting insulin (mU/L) x fasting glucose (mg/dL)/405). The insulin resistance (IR) was considered if HOMA-IR > 2.5 (13).

Levels of 25-hydroxy vitamin D between 30-100 ng/mL were considered in the normal reference range, and levels <20 ng/mL and 21-29 ng/mL were defined as deficiency and insufficiency; respectively (14).

Statistical analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. The Kolmogorov-Smirnov Test was used to determine if the quantitative variables were normally distributed. Descriptive statistical methods (mean, standard deviation) were used. Independent t test, Mann-Whitney U test, chi-square test and Spearman and Pearson test for correlation analysis were used where necessary. Correlation coefficients were defined as 0-0.24 weak, 0.25-0.49 medium, 0.50-0.74 strong and 0.75-1.00 very strong. The results were evaluated according to p <0.05 and 95% CI for descriptive data.

RESULTS

A total of 187 patients, 101 pregnant women with altered thyroid hormone levels as the study group and 86 healthy pregnant women as the control group were included to this prospective study. Gestational weeks varied from 5 to 39.

Table 1. Comparison of the mean values between study and control groups

	Control Group N=86	Study Group N=101	P
Age	28.05±5.54	29.27±5.67	0.141
Gravidity	2.64±1.35	2.54±1.37	0.619
Gestational week	18.35±9.39	15.79±9.04	0.060
TSH	2.16±2.76	1.7±3.24	0.311
Free T4	1.16±0.37	1.36±0.62	**0.010**
Hemoglobin	11.86±1.19	11.77±1.13	0.596
Glucose	86.06±12.24	90.86±18.53	**0.044**
Creatinin	0.49±0.07	0.54±0.11	**0.001**

Table 2. Presence of insulin resistance and thyroid antibodies in both groups						
		Control Group N=86		Study Group N=101		p
Insulin Resistance	Negative	59	68.6%	68	67.33%	0.852
	Positive	27	31.4%	33	32.67%	
Anti TG*	Negative	70	81.4%	74	73.27%	0.188
	Positive	16	18.6%	27	26.73%	
Anti TPO*	Negative	76	88.37%	81	80.2%	0.129
	Positive	10	11.63%	20	19.8%	
*Thyroid antibodies						

Thyroid hormone alterations during pregnancy in the study group (n=101) are shown in Figure 1. Pregnant patients with hyperthyroidism were more frequent (44.55%).

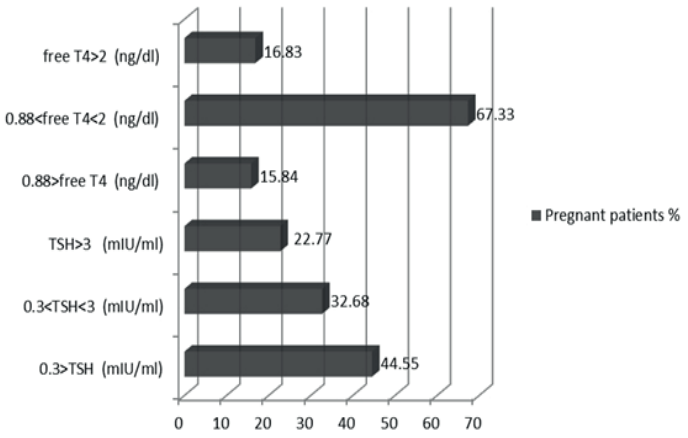

Figure 1. Pregnant patients with altered thyroid hormone levels (n=101; alterations of both TSH and Free T4 may be present in the same patient)

There was no significant difference between the mean values of the study group and the control group in terms of age, gravidity, gestational week,TSH, and hemoglobin mean values. Glucose; creatinine; FT4 mean values were significantly higher in the study group (Table 1).

Insulin resistance was present in 60 (32%) of pregnant patients. In Table 2, the groups were compared in terms of presence of insulin resistance and thyroid antibodies. Although not significant, it was observed that those who had IR and those with positive anti-TG and anti-TPO were higher in the study group consisting of pregnant women with altered thyroid hormone levels (Table 2).

Patients who had subclinic or overt hyperthyroidism had earlier mean gestational week (12.94±6.77) than patients who had subclinic or overt hypothyroidism (16.32±9.4) (p=0.001). There was no significant difference between the groups in terms of age, gravidity, glucose, creatinine, hemoglobin and vitamin D mean levels. As expected, mean levels of TSH was higher (5.83±4.85), FT4 was lower (1.05±0.4), anti-TG (103.97±193.17) and anti-TPO (116.33±199.37) were higher significantly in hypothyroidism group than mean levels of TSH (0.11±0.09), FT4 (1.58±0.67), anti-TG (72.84±133.50) and anti-TPO (36.82±75.66) in hyperthyroidism group (p=0.001; p=0.001; p=0.011; p=0.021; respectively).

A correlation analysis was performed between thyroid hormone levels and BMI, glucose, creatinine, anti TG, anti TPO, 25-hydroxy Vitamin D levels. There was a significant positive correlation between TSH and anti TPO values as expected (R = 0.593, p = 0.001) (Table 3). In another analysis, there was no correlation between levels of vitamin D and levels of TSH, FT4, glucose, creatinine, anti TG, anti TPO and BMI (p>0.05).

There was no association between the presence of insulin resistance and mean values of TSH, FT4, Vitamin D, anti TG, anti TPO (p>0.05) . However, TSH , anti-TPO and vitamin D mean levels were higher in patients with IR (Table 4).

Table 3. Correlation of TSH ve FT4 values with BMI and other laboratory levels			
		TSH	Free T4
BMI*	R	-0.04	0.088
	p	0.594	0.236
Glucose	R	-0.026	-0.07
	p	0.731	0.344
Creatinin	R	0.064	-0.013
	p	0.388	0.857
Anti TG**	R	0.134	-0.084
	p	0.084	0.277
Anti TPO**	R	0.593	-0.084
	p	**0.001**	0.274
25-OH Vitamin D	R	0.005	0.028
	p	0.951	0.715
*BMI: Body mass index; **Thyroid antibodies			

Table 4. Mean levels of Vitamin D and thyroid parameters according to the presence of insulin resistance

	Insulin Resistance(-) N=127	Insulin Resistance(+) N=60	p
TSH	1.56±1.76	2.65±4.64	0.182
Free T4	1.3±0.55	1.21±0.47	0.155
Anti TG*	56.35±117.7	53.53±132.16	0.886
Anti TPO*	38.57±83.03	59.54±148.58	0.190
25-OH Vitamin D	7.75±5.62	8.33±5.79	0.481

*Thyroid antibodies

DISCUSSION

In this study, we investigated the association of thyroid hormone levels and insulin resistance and 25-hydroxy vitamin D levels. Thyroid autoantibody levels were found similar between individuals with or without thyroid hormone alterations. The effect of insulin resistance on thyroid hormone levels and vitamin D levels was not significant either. In our study, pregnant patients with hyperthyroidism and those with hypothyroidism had earlier mean gestational week than those with normal thyroid hormones. The mean fasting glucose and creatinin levels were higher in patients with altered thyroid hormones.

Insulin resistance and thyroid hormone and autoantibody levels

Although fasting hyperglycemia was significant in patients with thyroid dysfunction, we did not find a significant effect of altered thyroid hormones on presence of insulin resistance and thyroid antibodies during gestational period.

In literature, there are different reports about the relationship between thyroid autoantibody positivity and insulin resistance. In a retrospective analysis by Pascual Corrales et al, in pregnant women who have TSH level≥2.5 mIU/L, the risk of developing GDM and the presence of antithyroid antibodies were investigated and in 37.5% of pregnancies autoantibodies were high but there was no association between this group and the development of GDM (15). In a meta-analysis by Yang et al; studies involving pregnant women with positive thyroid antibodies were examined and was found that thyroid antibody positivity in the first trimester was not associated with GDM development. It has been reported that GDM risk may not increase in euthyroid pregnant women with positive thyroid antibodies (16).

However, in a randomized controlled study of 181 pregnant women, Olivier et al. examined thyroid autoantibody levels and glucose tolerance tests of pregnant women at risk of GDM, and high thyroid autoantibody levels were found in 29 cases. Those who were at risk of GDM, also carried a risk for thyroid autoantibody positivity during pregnancy. They have indicated that this patient subgroup should routinely be monitored for the risk of subclinical hypothyroidism (17). In another review by Bitterman et al, the prevalence of thyroid autoimmunity was high in GDM patients compared to the control group and it was reported that scanning for thyroid diseases should be prolonged in this group of patients (18).

Aqarwal et al, investigated the frequency of abnormal thyroid function and antithyroid antibodies in early pregnancy in a population at high-risk of GDM, there was no significant difference in thyroid function tests between GDM and non-GDM women. In patients with anti TPO positivity, the mean TSH levels were found to be higher (19). Similarly, there was a strong correlation between TSH and anti TPO values as expected in our study.

In the study by Velkoska Nakova et al, 83 pregnant women -40 with GDM, 30 healthy and 13 with Type-1 DM were included in the study group to investigate the prevalence of abnormal thyroid functions and autoimmunity in women with GDM and Type-1 diabetes. In women who developed GDM, mean FT4 values were found to be lower than the other groups. In 25% of women with GDM despite normal TSH values, FT4 values were below the cut-off values and in diabetics, prevalence of anti TPO was higher than healthy women (20).

In a study by Shahbazian et al. thyroid function tests and thyroid autoantibodies were examined in 61 diabetic and 35 control pregnant women. Thyroid dysfunction was more frequent in the pregestational DM group. Prevalence of thyroid dysfunction in the control group was similar in the GDM group, and there was no statistically significant correlation with thyroid autoimmunity (21). In another retrospective study in which Stohl and colleagues aimed to investigate the incidence of GDM in pregnant women with hypothyroidism and hyperthyroidism, 14.3% of women with hypothyroidism, and 5.8% of those with hyperthyroidism developed GDM (22). In a recent Chinese study, in pregnant women with GDM and subclinical hypothyroidism (SCH), TSH levels were higher than healthy pregnant women; FT4 levels were not different (23). In our study, fasting glucose mean levels were higher in pregnant patients with altered thyroid hormones relevant to a recent study that reported thyroid hormone levels were associated with maternal glucose and with C-peptide (24).

In our study, thyroid hormone and thyroid autoantibody levels were not found different between individuals with or without IR. However, TSH and anti-TPO mean levels were higher in patients with IR than in the group without insulin resistance which needs further investigation according to the trimesters of pregnancy.

Insulin resistance and vitamin D levels

We have found no significant difference between vitamin D levels when we compared pregnant women with and without IR. A relationship was found between vitamin D, GDM and insulin resistance in pregnant women and researchers concluded that maternal low vitamin D levels were associated with GDM development and adverse

perinatal results in a recent study in Turkey (25).

Takiishi et al. reported in their review that besides certain genetic and environmental factors, vitamin D has a role in the pathogenesis of both Type-1 and Type-2 DM and that the incidence of vitamin D deficiency is high in DM, which may be explained by possible immunomodulator role and direct effects of vitamin D. It has also been reported that the administration of vitamin D improves insulin sensitivity and reduces inflammation (26).

In another review it was reported that in Type-2 DM, vitamin D directly influences beta-cell function and through plasma calcium regulation regulates secretion and synthesis of insulin in experimental models (27). Also vitamin D deficiency leads to impaired glucose tolerance have been reported in another review (27). In pregnant women with GDM and SCH, 25-OH vitamin D levels were found lower than pregnant women without GDM and SCH (23).

Thyroid function and vitamin D levels

We have found no significant relationship between thyroid hormones and vitamin D levels. In a study conducted by Zhao et al in China, the relationship between vitamin D levels and thyroid parameters in pregnancies was investigated and 25 (OH) vitamin D, TSH, FT4, anti TPO, anti TG levels were examined and no significant difference was found between vitamin D levels and thyroid parameters in patients during pregnancy (28).

The association of low vitamin D levels with autoimmune thyroid disease has been suggested by Choi et al, although the exact mechanism is not clear (29). In a meta-analysis; low vitamin D levels have been reported to be associated with increased risk of Graves' disease and Hashimoto thyroiditis, and that vitamin D replacement may suppress autoimmunity (30). However, in some studies, no relationship was found between vitamin D deficiency and autoimmune thyroid diseases (31).

Our patients with thyroid dysfunction had significantly higher mean levels of creatinin. Pathogenesis of thyroid dysfunction and kidney disease interaction may be bi-directional and further studies are needed (32).

Screening the abnormalities associated with thyroid diseases, GDM and vitamin D status is recommended during prepregnancy and pregnancy (33,34). Participation of family medicine doctors in pregnancy related educational activities to raise awareness and to increase the level of knowledge in pregnant women is necessary for early diagnosis (33).

Strengths and limitations of the study

The most remarkable strength of this study is that though there were strict exclusion criteria, the number of patients included is relatively high when compared to similar studies. It was conducted in a special group consisting of pregnant women with altered thyroid hormone levels, in whom the presence of insulin resistance, thyroid autoantibodies and vitamin D were investigated at the same time. The exclusion of patients with previous endocrine pathologies such as thyroid, prolactinoma and adrenal diseases or those who had anamnesis of hormonal replacements and the formation of the study group as pregnant women who have only thyroid hormone alterations were also remarkable in our study.

There are some limitations in this study. Pregnant women are prescribed vitamins which include vitamin d and iodine also and this may affect the measurements but this is an entity in all of the patients. The measurements were made only once. We investigated the association between the hormones at that time of the measurement. Levels of thyroid hormones and the other hormone levels which have effects on glucose regulation such as insulin are variable in gestational periods and that multifactorial effects may be present.

CONCLUSION

In conclusion, we could not find any significant relationship between thyroid hormone levels and vitamin D and insulin resistance in pregnant women in this study. Nevertheless, the significance of the results may be increased by performing follow-ups and multiple measurements during pregnancy in future studies.

This study was presented at the 7th International Trakya Family Medicine Congress in 2018.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: This study was supported by the Hospital Education Planning Board (hospital resources).

Ethical approval: This study was approved by the ethics committee of the hospital with the reference number 2014/282.

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