ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2022;6(3): 345-351
DOI: 10.29058/mjwbs.1141211

Investigation on Demographic Characteristics of Pregnant Patients with Thyroid Dysfunction- Ege University Sample

Tiroid Disfonksiyonu Olan Gebelerin Demografik Özelliklerinin Araştırılması- Ege Üniversitesi Örneklemi

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Cite this article as: Erdogan M et al. Investigation on demographic characteristics of pregnant patients with thyroid dysfunction- Ege University sample. Med J West Black Sea. 2022;6(3):345-351.

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Received
06.07.2022

Revision
18.08.2022

Accepted
21.08.2022

ABSTRACT

Aim: Thyroid diseases can cause maternal and fetal adversities, and proper diagnosis, follow-up and treatment during pregnancy requires special attention. In the evaluation of thyroid functions during pregnancy, free thyroxine (FT4) is used primarily with thyroid-stimulating hormone (TSH). Our aim is to investigate the prevalence and the effects of thyroid dysfunction during pregnancy.

Material and Methods: Our study is a prospective study including 960 pregnant women and spanning from November 2017 to May 2019 in Ege University Endocrinology outpatient clinic.100 pregnant women with thyroid dysfunction out of 960 pregnant women were included in the study. Maternal age, gestational trimester, family history of the thyroid disorder, TSH, FT4, free triiodothyronine (FT3), anti-thyroid peroxidase antibody (Anti-TPO), anti-thyroglobulin antibody (Anti-TG), thyrotropin (TSH) receptor antibody (TRAb) were collected. The correlations between TSH, FT3 and FT4 were examined.

Results: In the study, the mean age of pregnant patients was 29.33 ± 5.97. Anti-TPO was positive %18 and Anti-TG was positive (5%). 24 of 100 (24%) patients had nodules. 1 (8.3%) patient with hyperthyroidism was positive for TRAb. Age differences in patients with or without nodule were not statistically significant. 1 (1%) of the patient had Graves disease, 81 (81%) had subclinical hypothyroidism, 7 (7%) had clinical hypothyroidism, 11 (11%) had gestational thyrotoxicosis. The frequency of prematurity was determined in 7 patients (15.6%) by the data of 45 pregnant women who gave birth.

Conclusion: TSH levels in pregnant patients with positivity for anti-TPO and anti-TG were significantly higher than pregnant patients with negativity for anti-TPO and anti-TG. In addition, the relationship between thyroid diseases and nodule frequency, autoimmunity, premature birth in pregnant women were not detected. More comprehensive study series are needed.

Keywords: Pregnancy, Thyroid autoimmunity, Premature birth, Hypothyroidism

ÖZ

Amaç: Tiroid hastalıkları maternal ve fetal olumsuzluklara neden olabilir ve gebelikte doğru tanı, takip ve tedavi özel dikkat gerektirir. Gebelikte tiroid fonksiyonlarının değerlendirilmesinde öncelikle Tiroid Stimulan Hormon (TSH), ile birlikte serbest tiroksin (FT4) kullanılır. Çalışmamızda, gebelikte tiroid disfonksiyonunun prevalansını ve etkilerini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamız Ege Üniversitesi Endokrinoloji polikliniğinde Kasım 2017-Mayıs 2019 tarihleri arasında 960 gebeyi kapsayan prospektif bir çalışmadır. 960 gebe kadından tiroid disfonksiyonu olan 100 gebe çalışmaya alındı. Anne yaşı, gestasyonel trimester, ailede tiroid hastalığı öyküsü, TSH,

FT4, serbest triiyodotironin (FT3), anti-tiroid peroksidaz antikoru (Anti-TPO), anti-tiroglobulin antikoru (Anti-TG), TSH reseptör antikoru (TRAb) ile ilgili bilgiler kaydedildi. TSH, FT4 ve FT3 arasındaki korelasyonlar incelendi.

Bulgular: Çalışmada gebelerin yaş ortalaması 29.33 ± 5.97 idi. Tüm gebelerin %18'inde anti-TPO antikor pozitifti ve %5'inde Anti-TG antikor pozitifti. 100 hastanın 24'ünde (%24) nodül vardı. Hipertiroidili 1 (%8.3) hasta da TRAb pozitifti. Nodülü olan ve olmayan hastalardaki yaş farklılıkları istatistiksel olarak anlamlı değildi. Hastaların 1'inde (%1) Graves hastalığı, 81'inde (%81) subklinik hipotiroidi, 7'sinde (%7) klinik hipotiroidi, 11'inde (%11) gestasyonel tirotoksikoz vardı. Doğum yapan 45 gebenin verilerine göre 7 hastada (%15.6) prematürite saptandı.

Sonuç: Anti-TPO ve anti-TG pozitif olan gebelerde TSH düzeyleri, anti-TPO ve anti-TG negatif olan gebelere göre anlamlı derecede yüksekti. Ayrıca gebelerde tiroid hastalıkları ile nodül sıklığı, otoimmünite, erken doğum arasında ilişki saptanmadı. Daha kapsamlı çalışma serilerine ihtiyaç vardır.

Anahtar Sözcükler: Gebelik, Tiroid otoimmunitesi, Prematür doğum, Hipotiroidi

INTRODUCTION

Thyroid gland dysfunctions are frequently observed during pregnancy. During pregnancy, changes occur in thyroid physiology and thyroid function tests. These changes include an increase in thyroxine (T4), thyroid binding globulin (TBG) and resulting in higher total T4 and triiodothyronine (T3) concentrations than in non-pregnant women. In addition, high serum human chorionic gonadotropin (hCG) levels cause a decrease in thyroid stimulating hormone (TSH) concentrations during the first trimester, especially during early pregnancy. In the guidelines of the American Thyroid Association (ATA) 2017, it is recommended that TSH levels are 0.1-2.5 mIU/ml in the first trimester; it should be between 0.2-3.0 mIU/ml in the second trimester and 0.3-3.0 mIU/ml in the third trimester. During pregnancy hypothyroidism, hyperthyroidism and thyroid autoimmunity can be detected at rates of 2% -3%, 0.1%-0.4% and 17%, respectively (1).

The prevalence of hypothyroidism during pregnancy is 0.3-0.5% and 2-3% for subclinical hypothyroidism. Hypothyroidism is a type of thyroid hormone deficiency associated with low free thyroxine (FT4) and high TSH levels. Subclinical hypothyroidism is a kind of thyroid hormone deficiency with normal FT4 and high TSH levels**.** Hyperthyroidism in pregnancy is rarely seen and its prevalence is approximately 0.2%**.** Hyperthyroidism during pregnancy can result from Graves' disease (GD) and there are stimulating antibodies against TSH receptors. In cases of hyperemesis gravidarum and gestational transient thyrotoxicosis (GTT), transient hyperthyroidism may be seen due to the stimulating effect of hCG on the thyroid. In GD, symptoms are exaggerated in the first trimester with the stimulating effect of hCG initially. Symptoms partially improve in the second trimester (2).

The prevalence of the thyroid nodules during pregnancy is between 3-21%. Studies have shown that age and high TSH increase the frequency of nodules (3, 4).

2-17% of all pregnant women are positive for anti-thyroid peroxidase antibody (Anti-TPO) or anti thyroglobulin antibody (Anti-TG). It has been evaluated in studies that anti-TPO positivity adversely affects maternal thyroid status, pregnancy and developing fetus (1).

In the present study, we aimed to investigate the prevalence and the effects of thyroid dysfunction during pregnancy.

MATERIAL and METHODS

This study was a prospective study in Ege University Faculty of Medicine Endocrinology outpatient clinic. Among 960 pregnant women, we obtained the medical records of 100 (10.41 %) pregnant women with thyroid dysfunction for the study and admitted to our outpatient clinics in the period of November 2017- May 2019.

The inclusion criteria were pregnant patients with age of >18, thyroid dysfunction during pregnancy and history of normal thyroid function before gestation. Exclusion criteria were pre-existing thyroid dysfunction, having diabetes before gestation (types 1 and 2) and having gestational diabetes mellitus.

Clinical data related to the gestational trimester when the patients were admitted to our outpatient clinics, maternal age, gestational trimester, family history of the thyroid disorder were obtained. In addition, TSH, FT4, free triiodothyronine (FT3), Anti-TPO, Anti-TG, TSH receptor antibody (TRAb) were collected. Thyroid ultrasonography was made in our outpatient clinic for each subject and detected nodules. After delivery, files of 45 patients could be accessed about their preterm delivery.

Ultrasonic device was Aloka-ARIETTA V60 model from Hitachi Company. In addition, ultrasonographies were performed by the same user.

The study protocol was approved by the Ethics Committee of Ege University Faculty of Medicine (18-5/44). Informed consents were obtained from all subjects.

Thyroid Function

TSH, FT4, FT3, anti-TPO, anti-TG were measured by chemiluminescence immunoassay. The laboratory references were selected as TSH (0.27-4.2 mU/L), FT4 (0.89-

1.76 ng/dL), FT3 2-4.4 pg/mL. Anti-TPO was elevated if the level was equal or more than 34 IU/mL (5). In addition, Anti-TG was elevated if the level was equal or more than 115 IU/mL, TRAb was elevated if the level was equal or more than 1 mU/L. The guidelines of Endocrine Society, American Thyroid Association [ATA], European Thyroid Association [ETA] were considered (6) during thyroid status evaluation. Trimester-specific reference range of ATA for TSH, pregnant patients were classified into groups as euthyroid (TSH < 2.5 mIU/L) (these patients were excluded); subclinical hypothyroidism (SCH) (TSH 2.5–10 mIU/L); hypothyroidism (TSH > 10 mIU/L) (1). Gestational transient thyrotoxicosis (GTT) is limited to the first half of pregnancy. GTT is characterized by suppressed serum TSH and elevated FT4, which is due to elevated hCG levels (7). In early pregnancy, the differential diagnosis for hyperthyroidism is between GD and gestational transient thyrotoxicosis. The detection of no prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), a self-limited mild disorder, and symptoms of emesis indicates the diagnosis of GTT (1). According to ATA 2011 guideline pregnant women who were positive for TPOAb and had TSH>2.5 mU/L or who were negative for TPOAb and had TSH> 4.2 mU/L initiated to be treated with L-thyroxine (8).

Statistical Analysis

We conducted a priori and a post hoc power analysis with the program G*Power 3.1.9.4. The post hoc analyses revealed the statistical power calculated for this study for by using one-way ANOVA for detecting a large effect size of 0.70 with a power of 0.99 for the sample size of 100 assuming a significance level 5%. Categorical variables were examined with frequency tables for each patient group and descriptive statistics for continuous variables were calculated. Shapiro-Wilk normality test was used to examine whether the continuous variables were normally distributed. While continuous variables were presented as mean ± standard deviation (SD) or median and inter quantile range (IQR), categorical variables were presented as frequencies and percentages. Since data were not distributed normally, the Spearman's correlation coefficient was used to examine the correlation between TSH, FT3 and FT4. While the Mann-Whitney U test was used to compare two independent groups, the Kruskal-Wallis test was performed to compare more than two independent groups. Categorical variables were evaluated by the Chi square test. A p value of less than 0.05 was accepted as statistically significant. All statistical analyses were performed by using IBM SPSS Version 25.0 statistical package.

RESULTS

The demographics and clinical characteristics of all patients were demonstrated in Table 1,2. The overall mean age was 29.33± 5.97 years in patients. The vast of patients were in first trimester among overall group. We found that TSH, FT4, FT3 and anti TPO were statistically different between groups (p=0.005, p<0.001, p=0.003 and p=0.040, respectively).

In the total patients' data set, the correlation between FT4 and FT3 were statistically significant (p<0.001; r=0.391) (Figure 1). However, the correlation between TSH and FT4, TSH and FT3 were not statistically significant (p=0.541, r=0.066; p=0.924, r=-0.010, respectively). In addition, TSH levels in patients with positivity of anti-TPO and anti-TG were significantly higher than patients with negativity of anti-TPO and anti-TG (Median, IQR; anti TPO (+): 5.24 IU/mL, 3.83; anti TPO (-): 3.83 IU/mL, 1.37; p=0.001; anti TG (+): 6.64 U/mL, 3.78; anti TG (-): 3.95 U/mL, 1.42; p=0.031).

All patients with TSH below 0.1 were evaluated for GD. TRAb value of pregnant patients with hyperthyroidism was evaluated, and it was positive in one case (8.3%) and negative in 11 (91.7%) patients. Anti-TPO was positive in 15 (17%) of 88 patients with hypothyroidism, and a case (6.6%) of these patients had clinical hypothyroidism and 14 (93.3%) had subclinical hypothyroidism. Thyroid ultrasonography was performed in all patients to determine

Table 1: The demographics and clinical characteristics of all patients.

Variables*		All patients (n=100)
Age (years)		29.33±5.97 (29.00, 9.00)
Gestational trimester	1. Trimester	56 (56%)
	2. Trimester	17 (17%)
	3. Trimester	27 (27%)
Family History of Thyroid Dysfunction	Absent	89 (89%)
	Present	11 (11%)
TSH (mU/L) (n=88)		4.5±1.99 (3.98, 1.64)
FT4 (ng/dL)		1.12±0.44 (1.04, 0.23)
FT3 (pg/mL)		3.27±1.29 (3.15, 0.78)
Anti TPO (IU/mL)	<34 (negative)	82 (82%)
	≥34 (positive)	18 (18%)
Anti TG (U/mL)	< 115 (negative)	95 (95%)
	≥ 115 (positive)	5 (5%)

*Mean ±Standard Deviation (Median, Interquartile range (IQR)) for continuous variables, n (%) for categorical variables

TSH thyroid-stimulating hormone (0.27-4.2), FT4 free thyroxine (0.89-1.76), FT3 free tri-iodothyronin (2-4.4), Anti TPO anti-thyroid peroxidase antibody (<34), Anti TG anti- thyroglobulin antibody (<115)

Note: There was only one patient with Graves' disease, because of this reason the mean and standard deviation values were not included in the table. Since TSH value of patients with Gestational Transient Hyperthyroidism was <0.1 mU/L, the mean TSH value was not given.

Table 2: The demographics and clinical characteristics of all patients

Variables*		Subclinical hypothyroidism (n=81)	Hypothyroidism (n=7)	Graves Disease (n=1)	Gestational Transient Hyperthyroidism (n=11)	p
Age (years)		29.86±6.12 (29.00, 10.00)	29.86±4.88 (27.00, 8.00)	23	32±5.11 (30.00, 6.00)	0.283
Gestational trimester	1. Trimester	44 (78.6%)	4 (7.1%)	-	8 (14.3%)	0.314
	2. Trimester	13 (76.5%)	1 (5.9%)	1 (5.9%)	2 (11.8%)	
	3. Trimester	24 (88.9%)	2 (7.4%)	-	1 (3.7%)	
Family History of Thyroid Dysfunction	Absent	72 (80.9%)	6 (6.7%)	1 (1.1%)	10 (11.2%)	0.970
	Present	9 (81.8%)	1 (9.1%)	-	1 (9.1%)	
TSH (mU/L) (n=88)		4.18±1.32 (3.9, 1.40)	8.15±4.17 (6.64, 8.74)	-	-	**0.005**
FT4 (ng/dL)		1.03±0.17 (1.03, 0.18)	0.87±0.16 (0.83, 0.22)	-	1.87±0.93 (1.43,1.71)	**<0.001**
FT3 (pg/mL)		2.98±0.57 (3.13, 0.69)	3.31±0.62 (3.10, 1.11)	-	4.79±2.35 (3.79,2.56)	**0.003**
Anti TPO (IU/mL)	<34 (negative)	68 (82.9%)	4 (4.9%)			**0.040**
	≥34 (positive)	13 (72.2%)	3 (16.7%)	1 (5.6%)	1 (5.6%)	
Anti TG (U/mL)	< 115 (negative)	77 (81.1%)	6 (6.3%)	1 (1.1%)	11 (11.6%)	0.593
	≥ 115 (positive)	4 (80%)	1 (20%)	-	-	

*Mean ±Standard Deviation (Median, Interquartile range (IQR)) for continuous variables, n (%) for categorical variables, p<0.05 was significant.

TSH thyroid-stimulating hormone (0.27-4.2), FT4 free thyroxine (0.89-1.76), FT3 free tri-iodothyronin (2-4.4), Anti TPO anti-thyroid peroxidase antibody (<34), Anti TG anti- thyroglobulin antibody (<115)

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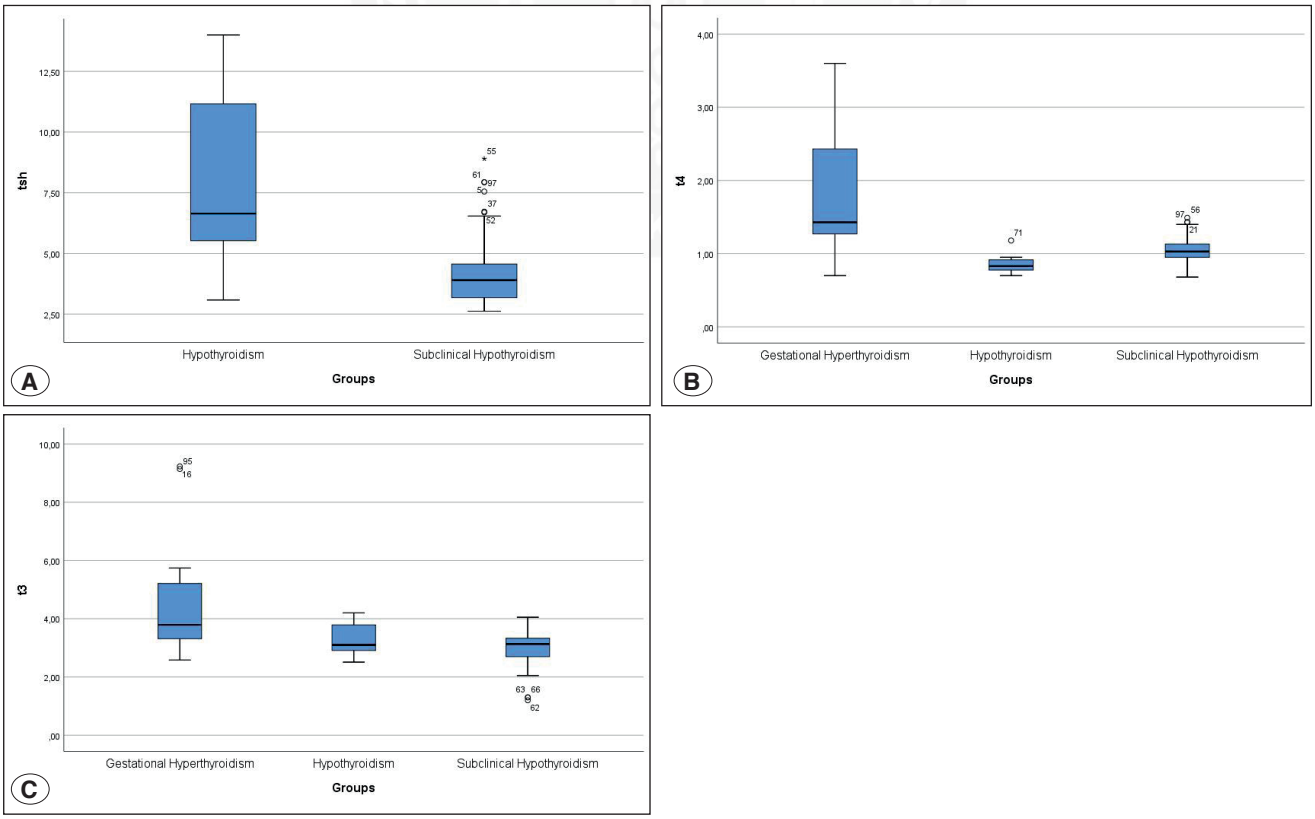

Figure 1: TSH, FT4, FT3 levels in subgroups that were found to be statistically significant in boxplots.

the presence of nodules and parenchyma structure. While there was not any nodule in 76% (n=76) of 100 patients included in our study, nodules were detected in 24% (n=24). While the parenchyma structure was homogeneous in 70% (n=70) of our patients, it was evaluated as heterogeneous in 30% (n=30).

Age differences in patients with and without nodule were not statistically significant (p=0.472). In addition, 88 patients with TSH >2.5 were evaluated. While 68 of these patients did not have nodules, 20 patients had nodules. The relationship between TSH increase and nodule frequency was evaluated but no significant relationship was found (p=0.089). When it comes to the size of the nodules, there were 23 patients (95.8%) with one cm or less in size, and a patient (4.2%) ≥1 cm. There was only one patient (4.2%) with biopsy indication, and the biopsy result of this patient was reported as atypia of undetermined significance.

Out of 100 patients, 45 gave birth in our hospital, thus their delivery week could be accessed. The others gave birth in the external hospitals and their data could not be accessed. The relationship between anti-TPO positivity and premature birth were examined. While anti-TPO was negative in 6 (85.7%) of 7 patients with a gestational age of birth 36 weeks and below, anti-TPO was positive in one (14.5%) patient with gestational age of birth 36 weeks and below. Moreover, anti-TPO was negative in 30 (78.9%) of 38 patients in 37 weeks and over, and eight (21.1%) were positive with gestational age of birth**.** The relationship between premature birth and Anti-TPO positivity was evaluated, but no significant relationship was found (p>0.05).

DISCUSSION

In our study, TSH levels in pregnant patients with positivity for anti-TPO and anti-TG were significantly higher than pregnant patients with negativity for anti TPO and anti TG. Anti-TPO was positive in 15 (17%) of 88 patients with hypothyroidism, and one (6.6%) of these patients had clinical hypothyroidism and 14 (93.3%) had subclinical hypothyroidism. We did not found a relationship between premature birth and Anti-TPO positivity.

The alpha subunits of TSH and hCG are the same, but the beta subunits are different. In the first trimester, increasing hCG binds to the TSH receptor and stimulates thyroid ligand like TSH. In addition, hCG can cause subclinical hyperthyroidism and sometimes a mild clinical hyperthyroidism. TSH levels are suppressed in most of the pregnant women in the first trimester, and there may be an increase in FT3 and FT4 levels slightly exceeding the upper normals (9).

The rate of gestational transient thyrotoxicosis (GTT) showed geographical differences. As a result of studies, the frequency of GTT was detected at a rate of 2-3% at the 8th and 14th weeks of gestation in Europe, this rate was found to be much higher in Asian pregnant women, at 11% (10, 11). Cooper et al. revealed GTT was at a rate of 0.1-0.2% and usually detected in the first trimester (12). Wen et al. reported that, the incidence of GTT of pregnancy in the first trimester was observed as 7.86% in China (13). In our study, GTT was detected in 11 of 100 patients (11%) with thyroid dysfunction. Moreover, GTT was mostly seen in the first and the second trimesters. It was detected in 10 patients (83.2%) in the first and second trimesters and in one patient (8.3%) in the third trimester**.**

While the incidence of GD in the pre-pregnancy period is 0.4%-1%, its incidence in pregnancy is 0.2% (13). GD is most prevalent in the second and the third trimesters. In the differential diagnosis of GD and GTT, positivity of anti-TPO together with TRAb will also be very significant. In addition, FT3/FT4 ratio may be useful in differential diagnosis (14-16). Krassas et al. revealed GD was detected at a rate of 0.1-1%, GTT was detected 1-3% (17). In our study, GD (1%) was found in 1/12 patients with hyperthyroidism. TRAb positivity and FT3/FT4 ratio were observed to be high. Propylthiouracil treatment was initiated at a low dose to the patient diagnosed with GD in the second trimester, and the pregnancy was concluded at normal delivery week without any complications.

The most common cause of hypothyroidism during pregnancy is Hashimoto's disease. Hashimoto's disease is the most common cause of hypothyroidism, especially in iodine-sufficient areas, and it is seen in 4-7% of pregnant women. While the incidence of subclinical hypothyroidism during pregnancy is around 2.5%, the incidence of hypothyroidism is between 0.3-0.9% (18). Thyroid antibodies are detected in 30-60% of pregnant women with elevated TSH (19, 20). Thyroid antibodies are found in 2% to 17% of pregnant women and vary according to ethnicity (1). Moreno-Reyes et al. reported that the anti-TPO level was found to be 13.8% among women in European iodine deficient cities. The ratio of these women who had low TSH was 4.1%. In addition, 3.6% had subclinical hypothyroidism, 0.5% had overt hypothyroidism (21).

In our study, 81% of 100 pregnant patients with thyroid dysfunction had subclinical hypothyroidism, while 7% had hypothyroidism. We found high prevalence of subclinical hypothyroidism during pregnancy. This result might be due to the lack of determination of pregnancy-specific reference values. Moreover, the patients were evaluated in terms of the trimester and upper limits of TSH. Of the anti-TPO positive hypothyroid patients, 13 (72.2%) were evaluated as subclinical hypothyroidism and 3 (16.7%) patients were detected as hypothyroidism. Furthermore, anti-TG was positive in 5 (5%) and anti-TPO was positive in 18 (18%) of a total of 100 pregnant patients. Of the patients positive for anti-TPO, 2 (5.6%) had hyperthyroidism and 16 (93.7%) had hypothyroidism.

The majority of studies have shown that anti-TPO positivity increases the risk of preterm birth (1). Negro et al. revealed the risk of preterm birth increased in women with anti-TPO positivity and levothyroxine treatment reduced this risk (22). In our study, prematurity was observed in 7 patients (15.6%). According to the results of our study, no significant correlation was found between anti-TPO positivity and preterm birth ($p>0.05$)

The prevalence of thyroid nodules in pregnancy ranges from 3% to 21% (4). Similarly, in our study nodules were detected in 24% of the patients. Struve et al. (3) reported that there was a relationship between age and the frequency of nodules in pregnant women. In contrast, age differences in patients with and without nodule were not statistically different in the current study.

Nevertheless, our study also has limitations. First, we did not consider nutritional status, iodine use, and lack of urine iodine in our study population. Secondly, our study consisted of the small number of patients and did not conduct sequential follow-up of thyroid function in pregnant women.

In conclusion, TSH measurement should be performed initially in all pregnant women and those who have pregnancy plans. Pregnancy complications should be prevented by initiating treatment, and malignancy should be ruled out by performing fine needle aspiration biopsy on suspicious nodules during pregnancy. More comprehensive study series are needed.

Acknowledgment

We are grateful to Ahmet Topaçoğlu for his grammar support.

Author Contributions

Concept: **Mehmet Erdoğan, Günel Bayramova,** Design: **Hatice Özışık,** Data collection or processing: **Günel Bayramova,** Analysis or Interpretation: **Aslı Suner,** Literature search: **Hatice Özışık, Günel Bayramova,** Writing: **Hatice Özışık,** Approval: **Mehmet Erdoğan, Günel Bayramova, Aslı Suner, Hatice Özışık.**

Conflicts of Interest

All authors declared that no conflict of interest.

Financial Support

No financial support

Ethical Approval

The study protocol was approved by the Ethics Committee of Ege University Faculty of Medicine (18-5/44).

Review Process

Extremely peer-reviewed and accepted.

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