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The Effect of Inflammatory Markers in the Hemogram Parameters of Pregnant Women with Thyroid Disease on Obstetric and Neonatal Outcomes

Tiroid Hastalığı olan Gebelerin Hemogram Parametrelerinde İnflamatuar Belirteçlerin Obstetrik ve Neonatal Sonuçlara Etkisi

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ABSTRACT

Aim: This study aimed to determine the differences in hemogram parameters, especially in inflammatory markers and perinatal and neonatal outcomes of pregnant women with thyroid disease, and to examine the effects of these differences on pregnancy outcomes.

Material and Methods: The data of 80 pregnant women diagnosed with thyroid disease according to the American Thyroid Association (ATA) criteria at the first admission between 2016 and 2019 and 100 pregnant women whose thyroid hormone levels were within the normal reference range were retrospectively analyzed. Obstetric outcomes such as type and time of delivery, and the presence of additional disease during pregnancy, and neonatal outcomes such as weight, gender, and Apgar score at birth were compared. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), white blood cell (WBC) count, and hemoglobin (Hb) and mean platelet volume (MPV) values, which are accepted as inflammation markers, were also compared between groups.

Results: There was no significant difference between hypothyroid and hyperthyroid pregnant women in terms of Hb (p=0.319) and PLR (p=0.341) values. Third-trimester WBC (p=0.015) values were higher and MPV (p=0.007) values were lower in the hypothyroid pregnant women compared to the control group. The highest NLR (p=0.005) value was observed in the hypothyroid group. Comorbidities were found to be 27.4% (n=20) in the hypothyroid group, 14.3% (n=1) in the hyperthyroid group, and 1.0% (n=1) in the control group (p<0.001).

Conclusion: Pregnant women with thyroid disease may have differences in hemogram parameters, especially in inflammatory markers, and these differences may affect pregnancy outcomes.

Keywords: Thyroid disease; NLR; PLR; perinatal and neonatal outcomes; pregnancy.

ÖZ

Amaç: Bu çalışmanın amacı, tiroid hastalığı olan gebelerin hemogram parametrelerinde, özellikle inflamatuar belirteçlerde ve perinatal ve neonatal sonuçlardaki farklılıkları belirlemek ve bu farklılıkların gebelik sonuçları üzerindeki etkisini incelemektir.

Gereç ve Yöntemler: 2016 ve 2019 yılları arasında ilk başvurusunda Amerikan Tiroid Derneği (American Thyroid Association, ATA) kriterlerine göre tiroid hastalığı tanısı alan 80 gebe kadın ile tiroid hormon düzeyleri normal referans aralığında olan 100 gebe kadının verileri geriye dönük olarak analiz edildi. Doğum tipi ve zamanı ve gebelikte ek hastalık varlığı gibi obstetrik sonuçlar ile doğumda kilo, cinsiyet ve Apgar skoru gibi neonatal sonuçlar karşılaştırıldı. Yine, nötrofil/lenfosit oranı (neutrophil-to-lymphocyte ratio, NLR), trombosit/lenfosit oranı (platelet-to-lymphocyte ratio, PLR), beyaz kan hücresi (white blood cell, WBC) sayısı ve inflamasyon belirteçleri olarak kabul edilen hemoglobin (Hb) ve ortalama trombosit hacmi (mean platelet volume, MPV) değerleri de gruplar arasında karşılaştırıldı.

Bulgular: Hipotiroidili ve hipertiroidili gebeler arasında Hb (p=0,319) ve PLR (p=0,341) değerleri açısından anlamlı bir farklılık yoktu. Hipotiroidili gebelerde kontrol grubuna göre 3. trimester WBC (p=0,015) değerleri daha yüksek ve MPV (p=0,007) değerleri daha düşüktü. En yüksek NLR (p=0,005) değeri hipotiroid grubunda gözlendi. Ek hastalık hipotiroid grubunda %27,4 (n=20), hipertiroid grubunda %14,3 (n=1) ve kontrol grubunda %1,0 (n=1) olarak saptandı (p<0,001).

Sonuç: Tiroid hastalığı olan gebelerin hemogram parametrelerinde özellikle inflamatuar belirteçlerde farklılıklar olabilir ve bu farklılıklar gebelik sonuçlarını etkileyebilir.

Anahtar kelimeler: Tiroid hastalığı; NLR; PLR; perinatal ve neonatal sonuçlar; gebelik.

INTRODUCTION

After diabetes, thyroid diseases are the second most common endocrine disorder in pregnancy. Thyroid hormone production during pregnancy increases by about 50% with a similar increase in total daily iodine requirement. In addition, following the physiological and hormonal changes caused by pregnancy and human chorionic gonadotropin (HCG), there is an increase of 50% in the daily iodine maternal requirement caused by an increase of up to 50% in thyroxine (T4) and triiodothyronine (T3) production, the thyroid stimulating hormone (TSH) level decreases, especially in the first trimester (1). Thyroid stimulation is started in the first trimester by HCG hormone, which has some structural similarities to TSH. While free T4 and free T3 are at normal or slightly higher elevated levels in the first trimester, they can be lower than normal in the third trimester. The increase in free T3 and free T4 levels in the early stages of pregnancy is associated with the thyrotropic effect of HCG, and related to this effect, TSH is suppressed. Thyroid-stimulating activity causes temporary hyperthyroidism in some women (2,3).

Thyroid hormones have important effects on the fetus. Maternal thyroid hormones play an important role in the development of the fetal brain at 1-20 weeks of gestation (4). Thyroid diseases in pregnancy affect pregnancy outcomes and neurophysiological development of the fetus at a serious rate (5,6). Insufficient thyroid hormone synthesis in the early weeks of pregnancy leads to significant impairments in motor skills and the intelligence of the fetus (7).

Thyroid diseases can be classified as hypothyroidism and hyperthyroidism. In regions where there is insufficient iodine intake, Hashimoto's thyroiditis is the most common cause of hypothyroidism in pregnancy (8). Endemic iodine deficiency is generally associated with hypothyroidism in pregnancy throughout the world. The prevalence of spontaneous hypothyroidism is between 2% and 3%, and of these cases, 3-5% present with evident hypothyroidism, and 2-2.5% with subclinical hypothyroidism (9). The results of untreated hypothyroidism during pregnancy include preterm delivery, preeclampsia, and gestational hypertension in the fetus. There may be postpartum hemorrhage, low birth weight, neurophysiological and cognitive dysfunctions in the fetus, and there can be an increase in perinatal morbidity and mortality (10).

The most common reason for hyperthyroidism seen in pregnancy is Graves' disease (11). Other less common causes are toxic multinodular goiter, toxic adenoma, and thyroiditis. Temporary gestational thyrotoxicosis associated with elevated HCG levels, which affects 1-3% of pregnancies in the first half of pregnancy, is another cause of gestational hyperthyroidism (3). Studies have shown that untreated hyperthyroidism can result in premature birth, spontaneous abortion, retarded intrauterine development, preeclampsia, low birth weight, and fetal malformations (12).

The aim of this study was to investigate the potential relationships between thyroid status measured by serum TSH levels during pregnancy and obstetric and perinatal outcomes, and to compare hemogram parameters and inflammatory markers in hemogram parameters of thyroid patients with those in the control group and to determine their effects on pregnancy outcomes.

MATERIAL AND METHODS

Approval for the study was granted by the Local Ethics Committee (Kocaeli Derince Training and Research Hospital, dated 11.11.2021, and numbered 2021-96). A retrospective review was made of the data of 73 patients diagnosed with hypothyroidism, and 7 diagnosed with hyperthyroidism during pregnancy, who gave birth in the Kocaeli Derince Training and Research Hospital between 2016 and 2019, and healthy pregnant women with no additional diseases.

Serum TSH concentration is the first and most reliable measurement in the evaluation of thyroid function in pregnancy. Physiological changes occur in TSH levels during pregnancy. According to the latest American Thyroid Association (ATA) guidelines, TSH levels were defined using population- and trimester-specific reference ranges (13). Inclusion criteria for the hypothyroid group were TSH above 2.5 mIU/ml in case the patient applied to the hospital in the first trimester, over 3 mIU/ml for the second and third trimesters (Table 1), and high free T4 value, for the hyperthyroid group, it was determined that the TSH level was below 0.45 mIU/ml and the free T4 value was above 1.8 ng/ml. TSH values of the control group were determined as being within normal ranges according to trimester reference intervals (6). The ATA recommends the use of test-specific, trimester-specific reference intervals obtained in women with no known thyroid disease, optimal iodine nutrition, and negative thyroid peroxidase (TPO) antibodies. Currently, such ranges are not widely available. In the absence of such pregnancy-specific reference ranges, the ATA recommends that the TSH lower limit be 0.1 mIU/L, for non-pregnant adults approximately 0.4 mIU/L lower than the lower limit, and the TSH upper limit 4 mIU/L (13).

Pregnant women in all three groups were compared in terms of hemogram parameters. In addition to comparing inflammatory markers during pregnancy, perinatal and neonatal outcomes, gestational age at birth, birth weight, infant sex, and Apgar scores were also compared.

Statistical Analysis

Data were analyzed using SPSS v.23.0 software. Whether the data showed normal distribution was analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the assumption of normality was not met, the Kruskal-Wallis test was applied with the post hoc Bonferroni-Dunn test in the comparisons of continuous variables between groups. In the analysis of the relationship between categorical variables, the chi-square test was used. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study included a total of 180 pregnant women, 73 diagnosed with hypothyroidism, 7 diagnosed with hyperthyroidism, and a control group of 100 healthy pregnant patients. The median age of hypothyroid patients was determined to be statistically significantly older than that of the control group (30 years and 26 years, p=0.001). The rate of premature births (9.6%, n=7) in hypothyroid patients was found to be significantly higher than the rates in the other two groups (p=0.032). Cesarean section delivery rate (56.2%, n=41) was high enough to show a statistically significant difference in the hypothyroid patient group (p=0.018). The birth weights in the three

groups were statistically similar (p=0.108). The 1-minute Apgar score of the infants of hypothyroid patients was significantly higher than the infants in the hyperthyroid group (p=0.042), and the 5-minute Apgar score of the hypothyroid group was significantly higher than the control group (p<0.001). Maternal age, gestational week, infant gender, type of birth, birth weight, and Apgar scores were presented in Table 2.

The results of the analysis of the third-trimester hemogram parameters were reported in Table 3. There was no statistically significant difference between the three groups in terms of hemoglobin (Hb) and platelet-to-lymphocyte ratio (PLR) values (p=0.319, p=0.341, respectively). The white blood cell (WBC) counts of hypothyroid patients were significantly higher than the control group (p=0.015), while the mean platelet volume (MPV) was significantly lower (p=0.007) in the hypothyroid group. The highest neutrophil-to-lymphocyte ratio (NLR) was observed in hypothyroid patients (p=0.005).

Table 1. TSH reference ranges according to weeks of gestation by ATA guidelines (13)

Trimester	Reference Interval
First trimester	0.1-2.5 mIU/ml
Second trimester	0.2-3.0 mIU/ml
Last trimester	0.3-3.0 mIU/ml

TSH: thyroid stimulating hormone, ATA: American Thyroid Association

Comorbidities were determined in the hypothyroid group at the rate of 27.4% (n=20), in the hyperthyroid group at 14.3% (n=1), and in the control group at 1% (n=1). The comorbidity rate in the control group was statistically significantly lower than the other two groups (p<0.001). When the comorbidities were evaluated, there was observed to be a higher rate of gestational diabetes (GDM) in hypothyroid patients (p<0.001) and a higher rate of cholestasis in hyperthyroid patients (p=0.039). Maternal complications were observed in 2 (2.7%) patients in the hypothyroid group and there was no significant difference between the groups (p=0.240). Data related to the comorbidities and maternal complications in groups were presented in Table 4.

DISCUSSION

Thyroid hormones not only play a role in the neurological development of the fetus during pregnancy, but are also necessary for the normal development and differentiation of all cells, metabolic balance, and physiological function of tissues (14). Thyroid hormones regulate human hematopoiesis in bone marrow. Changes in hematological parameters such as Hb, hematocrit (Hct), mean corpuscular volume (MCV), and WBC are associated with thyroid dysfunction (15). There are studies in the literature showing that hyperthyroidism and hypothyroidism are associated with an increased risk of leukocytopenia, neutropenia, and thrombocytopenia (14,16).

In the study, the hemogram parameters of pregnant women with thyroid dysfunction and the differences between these

Table 2. Comparison of patient characteristics

	Normal (n=100)	Hypothyroid (n=73)	Hyperthyroid (n=7)	p
Maternal age (year)	26 (5) [20-40]^{a}	30 (4) [19-52]^{b}	29 (3) [20-38]^{a,b}	**0.001**
Gestational week	39 (1) [36-40]	39 (2) [35-41]	39 (1) [37-40]	0.589
Infant Gender, n (%)				
Male	52 (52.0)	42 (57.5)	4 (57.1)	0.775
Female	48 (48.0)	31 (42.5)	3 (42.9)	
Type of birth, n (%)				
Cesarean	35 (35.0)^{a}	41 (56.2)^{b}	3 (42.9)^{a,b}	**0.018**
Normal delivery	65 (65.0)^{a}	32 (43.8)^{b}	4 (57.1)^{a,b}	
Prematurity, n (%)				
Mature	99 (99.0)	66 (90.4)	7 (100)	**0.032**
Premature	1 (1.0)^{a}	7 (9.6)^{b}	0 (0)^{a}	
Birth weight (g)	3413 (457.5) [2800-4140]	3400 (345.5) [1560-4660]	3200 (423.5) [2900-3750]	0.108
Apgar 1-min	8 (1) [7-9]^{a,b}	9 (1) [5-9]^{a}	8 (1) [8-9]^{b}	**0.042**
Apgar 5-min	10 (1) [9-10]^{a}	10 (2) [7-10]^{b}	10 (1) [9-10]^{a,b}	**<0.001**

Descriptive statistics were presented as median (interquartile range) [minimum-maximum], ^{a,b}: different superscript letters denote significant differences between the groups

Table 3. Last trimester hemogram parameters of the patients

	Normal (n=100)	Hypothyroid (n=73)	Hyperthyroid (n=7)	p
Hb (g/dl)	10.9 (2.1) [8-15.7]	11.1 (1.9) [7.9-14.1]	11.5 (1.8) [10.6-13]	0.319
WBC ($\times 10^9$/L)	12.3 (3.8) [5-26.1]^{a}	13.6 (3.4) [6.7-30.7]^{b}	12.3 (3.9) [8.1-20]^{a,b}	**0.015**
MPV (fL)	8.9 (1.5) [6.1-11.6]^{a}	8.6 (1.3) [5.9-17.9]^{b}	8.7 (1.7) [7.8-13.9]^{a,b}	**0.007**
NLR	5.7 (3.7) [1.5-19.5]^{a}	7.4 (4.1) [2.2-21.4]^{b}	5.8 (2.3) [2.7-7.6]^{a}	**0.005**
PLR	114.8 (70.4) [1.6-481]	127 (46.6) [52.5-296]	108 (41.3) [54-167]	0.341

Hb: hemoglobin, WBC: white blood cell, MPV: mean platelet volume, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, descriptive statistics were presented as median (interquartile range) [minimum-maximum], ^{a,b}: different superscript letters denote significant differences between the groups

Table 4. Comorbidities and maternal complications of the patients

	Normal (n=100)	Hypothyroid (n=73)	Hyperthyroid (n=7)	p
Any comorbidity, n (%)	1 (1.0)[a]	20 (27.4)[b]	1 (14.3)[b]	**<0.001**
Gestational diabetes, n (%)	1 (1.0)[a]	18 (24.7)[b]	0 (0.0)[a]	**<0.001**
Celiac, n (%)	0 (0.0)	1 (1.4)	0 (0.0)	0.444
Asthma, n (%)	0 (0.0)	1 (1.4)	0 (0.0)	0.444
Cholestasis, n (%)	0 (0.0)[a]	0 (0.0)[a]	1 (14.3)[b]	**0.039**
Complication, n (%)	0 (0.0)	2 (2.7)	0 (0.0)	0.240

parameters, especially those accepted as inflammation markers, compared to the health group, and the effect of this difference on pregnancy outcomes was investigated. In the hemogram parameters of pregnant thyroid patients examined in the study, WBC, NLR, and PLR which are considered as especially inflammatory markers, and MPV and Hb values, which are an important focus of thyroid disease studies, were examined. In the third-trimester hemogram parameters of hypothyroid patients, WBC values were higher and MPV values were lower than the healthy control group. The highest NLR was found in the hypothyroid patient group. There was no significant difference between the groups in terms of Hb and PLR values.

It was determined that the rate of preterm birth was higher in the hypothyroid group with high levels of WBC and NLR, which are markers of inflammation, compared to the healthy control group and the hyperthyroid group. Similarly, in a study of 157 pregnant women, including patients with premature rupture of membranes (PPROM), which is one of the causes of preterm birth, the rate of NLR was found to be significantly higher in the PPROM patient group (17).

In another study involving 486 people, including 243 preterm and 243 term delivery patients, NLR, PLR, and MLR scores were found to be significantly higher in the patients who gave premature birth, and NLR had the highest value among the tested scores and had the highest sensitivity (71%) in the study (18).

The MPV value was higher in the patient group with hyperthyroidism in this study. Gestational cholestasis rates were found to be higher in the hyperthyroid patient group compared with the other groups. In a study including 84 pregnant women examining hematological inflammatory markers in mild and severe intrahepatic cholestasis of pregnancy, MPV was found to be significantly increased in severe intrahepatic cholestasis of pregnancy (19).

In another study involving 117 pregnant women with intrahepatic cholestasis, the MPV value was found to be higher in the hemogram parameters of the patient group with intrahepatic cholestasis compared with 100 healthy pregnant women (20).

In the study, the NLR value, which is accepted as an inflammation marker, was determined to be significantly high in the hypothyroid group compared with the values of the healthy control group, and the incidence of GDM was high enough to make a statistically significant difference in this group. In a study including 120 patients with 58 GDM and 62 healthy control groups, the NLR value, which is one of the inflammation markers, was found to be high, which supports our results (21).

Similarly, in the meta-analysis results of 11 studies including 1271 GDM and 1504 healthy control groups, NLR values were found statistically significantly high in the GDM group, compared to the healthy control group (22).

CONCLUSION

In this study, pregnant women with thyroid dysfunction were compared with healthy pregnant women and it was determined that there may be differences in perinatal and neonatal outcomes. The relationship of these differences with inflammatory markers in hemogram parameters was investigated. It was determined that these differences in hemogram parameters, especially in inflammatory markers, can affect pregnancy outcomes in this patient group.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Kocaeli Derince Training and Research Hospital (11.11.2021, 96).

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