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Investigation of the Relationship Between Transient Thyrotoxicosis of Pregnancy and Neutrophil/Lymphocyte Ratio - A Cross-Sectional Study

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Abstract

Background: Gestational transient thyrotoxicosis (GTT) is a type of non-autoimmune hyperthyroidism seen during pregnancy. It occurs due to an increase in hCG levels in the first trimester of pregnancy. The level of hCG decreases as the pregnancy progresses, and it usually resolves spontaneously on its own. It has been found that both neutrophil/lymphocyte ratios (NLR) as well as platelet/lymphocyte ratios (PLR) are pro-inflammatory markers associated with systemic inflammation. Numerous studies have been performed on both of these markers.

Aim: Our aim with this study was to identify factors associated with gestational transient thyrotoxicosis, especially those NLRs and PLRs that are indicative of inflammation, in order to identify potential risk factors.

Study Design: Using the hospital's registry system, 60 pregnant women with transient thyrotoxicosis and 60 healthy pregnant women who applied to the Internal Medicine outpatient clinic between January 2021 and 2023 were retrospectively reviewed. The patients' age, hemoglobin, white blood cell count, neutrophil, lymphocyte, basophil, monocyte, platelet count, NLR, PLR, TSH, fT3, and fT4 values were examined.

Results: In pregnant women with GTT, NLR averages were 3.55±1.37, while in healthy controls, they were 3.48±1.25 (p = 0.96). In pregnant women with GTT, PLR averages were 133597.21±55951.37, while in healthy controls,

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they were 119307.25±40490.29 (p = 0.19). In pregnant women with GTT, platelet count averages were 245766.6±49154.32, while in healthy controls, they were 231383.3±63338.50 (p = 0.04).

Conclusion: It was found that there was no significant relationship between GTT and either NLR or PLR, but there was a significant relationship between platelet count and GTT. Consequently, we can reach a conclusion that GTT is not related to any diseases involving inflammation. We believe that prospective studies with a large number of patients will reveal more information on this matter in the future, due to the limitations of our study.

Keywords: thyrotoxicosis, gestational transient thyrotoxicosis, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

INTRODUCTION

A woman's thyroid gland is directly affected by the physiological, metabolic, and hormonal changes that occur during pregnancy, and thyroid hormones play an essential role in the health and well-being of both mother and child (1). Pregnancy has a reversible effect on thyroid physiology. In pregnancy, particularly during the first trimester, the placenta secretes a hormone known as human chorionic gonadotropin (hCG). hCG and TSH both consist of alpha- and beta-subunits. The alpha subunit of both hormones is the same. Due to this similarity, hCG stimulates the thyroid gland by binding to TSH receptors. In the 10th week of pregnancy, the level of hCG peaks, and there is no significant change thereafter. This increase in hCG causes a slight increase in the free T4 value and a significant decrease in TSH (2). The increase in estrogen during pregnancy causes an increase in thyroglobulin (TBG) levels. The amount of total T4 increases due to the increase in TBG (3). In the second and third trimesters, the peripheral hormonal metabolism of T3 and T4 accelerates (4).

Thyroid hormone is necessary for the growth and development of the fetus as well as for the normal development of the placenta. The disruption of placental development leads to placental abruption, preeclampsia, and premature birth (5). Thyroid hormone is essential for normal development, neuronal proliferation, migration, and structural organization of the fetal brain. It is particularly important for the fetus during the first and second trimesters, as it is dependent on the mother for the proper development of its thyroid hormones during these critical stages (6).

Thyroid dysfunction is the second-most common endocrinological disorder in pregnancy. Approximately 0.2% of pregnant women suffer from hyperthyroidism (7). Pregnancy-related transient thyrotoxicosis is a form of non-autoimmune hyperthyroidism. In pregnancy, 1.7% of women have subclinical hyperthyroidism, while 0.2% have overt hyperthyroidism (8). A hyperthyroid condition occurs when the thyroid gland secretes excess thyroid hormones, resulting in a hypermetabolic state called thyrotoxicosis (9-10). Thyrotoxicosis is a condition characterized by systemic clinical findings caused by excessive thyroid hormone secretion (11).

Due to the fact that the symptoms can also appear in a normal pregnancy, gestational transient thyrotoxicosis is difficult to diagnose on the basis of clinical findings alone (12). Transient thyrotoxicosis in pregnancy should be differentiated from other causes of hyperthyroidism, particularly Grave's disease, so that the patient can receive appropriate treatment, in view of the fact that their follow-up and treatment differs. The diagnosis of gestational transient thyrotoxicosis should be considered if there is no pre-pregnancy hyperthyroidism, nausea, vomiting, goiter, ophthalmopathy, or negative results of anti- tyrosine peroxidase (TPO) tests (13).

As part of this study, pregnant women suffering from gestational transient thyrotoxicosis and healthy pregnant women were compared. Specifically, inflammation-related neutrophil/lymphocyte ratios (NLR) and platelet/lymphocyte ratios (PLR) values were investigated as factors that may influence gestational transient thyrotoxicosis (GTT).

MATERIALS AND METHODS

Sample and patient selection

It is important to note that this study was carried out in a retrospective manner in a single center, where patients and healthy controls were examined.

A study was conducted on 120 pregnant women between January 2021 and January 2023.

Using data obtained from the hospital's registry system, retrospective data analysis was carried out on 60 pregnant women with transient thyrotoxicosis and 60 healthy pregnant women.

The study excluded patients who had a history of taking antithyroid drugs, and who did not attend regular follow-up appointments as well as those who had been diagnosed before pregnancy.

This study included patients over the age of 18 who were diagnosed with gestational thyrotoxicosis during pregnancy and were not taking antithyroid medications at the time of the study.

All patients included in the study were evaluated for their age, TSH, fT4, fT3, WBC, hemoglobin, neutrophil, lymphocyte, platelet, monocyte, basophil, NLR, and PLR.

The clinical research titled " Investigation of the relationship between transient thyrotoxicosis of pregnancy and neutrophil/lymphocyte ratio- A cross-sectional study" was approved by Ethics Committee on 24.10.2023 with the decision number 2023/2-19. The study was conducted in accordance with “Declaration of Helsinki”.

Data analysis

Specifically, we conducted a retrospective, analytical, cross-sectional, single-center study. The IBM SPSS 22 statistical package program was used to analyze the data. In order to determine whether the data consisted of a normal distribution or not, Shapiro-Wilk test was performed. For quantitative data with a normal distribution, mean and standard deviation were used as descriptive statistics, and for variables without a normal distribution, median (minimum-maximum) was used. The Independent Sample T test was used to compare two independent groups with normally distributed continuous data. A Mann-Whitney U test was used to compare two independent groups with non-normally distributed continuous data. Significant differences were indicated by a p value less than 0.05.

RESULTS

A total of 120 pregnant women were enrolled in the study at Adıyaman University Training and Research Hospital between January 2021 and January 2023. Among the pregnant women who

participated in the study, 60 had subclinical hyperthyroidism and 60 had euthyroidism.

TSH and fT4 tests were used as participation criteria (Table 1).

Table 2 shows pregnant women's age statistics. In the GTT group, the mean age was 35,63±24,88, while in healthy pregnant women, it was 30,98±6,08. Pregnant women with GTT had a higher age than healthy controls, but the difference was not statistically significant (p = 0.11).

In Table 3, hemogram parameters are presented according to groups.

Table 1. Each group's description criteria.

Groups	TSH (mU/L)	fT4 (ng/dl)	Description	n/%
Group 1	<0,1	Normal	Gestational Subclinical Hyperthyroidism	60 (%50)
Group 2	0.1-2,5	Normal	Euthyroid	60 (%50)

Table 2. Comparison of the groups' ages

	Group 1 (GTT)	Group 2 (healthy)	P
Age (mean±SD)	35,63±24,88	30,98±6,08	0,118

Table 3. Comparison of the groups' hemogram parameters

Parameters	Group 1 (GTT)	Group 2 (healthy)	P
Hemoglobin (gr/dl)	14,91±16,22	12,32±1,72	0,088
White blood cell count (10^3/UL)	9,41±2,08	9,57±2,14	0,364
Neutrophil (10^3/UL)	6,67±1,78	6,72±1,88	0,578
Lymphocyte (10^3/UL)	2,01±0,58	2,05±0,54	0,609
Monocyte (10^3/UL)	0,56±0,17	0,58±0,20	0,612
Basophil (10^3/UL)	0,04±0,02	0,05±0,03	0,115
Platelet count (10^3/UL)	245766,6±49154,3	231383,3±63338,5	0,042
NLR	3,55±1,37	3,48±1,25	0,967
PLR	133597,2±55951,3	119307,2±40490,2	0,193

Pregnant with GTT had hemoglobin levels of 14.91±16.22, whereas healthy pregnant women had hemoglobin levels of 12.32±1.72. It can be concluded that pregnant women with GTT had higher hemoglobin levels than healthy pregnant women, but it was not statistically significant (p = 0.08).

Pregnant with GTT had WBC levels of 9.41±2.08, whereas healthy pregnant women had WBC levels of 9.5781±2.14732. It can be concluded that healthy control women had higher WBC levels than pregnant women with GTT, but it was not statistically significant (p = 0.36).

Pregnant with GTT had neutrophil levels of 6.67±1.78, whereas healthy pregnant women had neutrophil levels of 6.72±1.88. It can be concluded that healthy control women had higher neutrophil levels than pregnant women with GTT, but it was not statistically significant (p = 0.57).

Pregnant with GTT had lymphocyte levels of 2.01±0.58, whereas healthy pregnant women had lymphocyte levels of 2.05±0.54. It can be concluded that healthy control women had higher lymphocyte levels than pregnant women with GTT, but it was not statistically significant (p = 0.60).

Pregnant with GTT had monocyte levels of 0.56±0.17, whereas healthy pregnant women had monocyte levels of 60.58±0.20. It can be concluded that healthy control women had higher monocyte levels than pregnant women with GTT, but it was not statistically significant (p = 0.61).

Pregnant with GTT had basophil levels of 0.04±0.02, whereas healthy pregnant women had basophil levels of 0.05±0.03. It can be concluded that healthy control women had higher basophil levels than pregnant women with GTT, but it was not statistically significant (p = 0.11).

Pregnant with GTT platelet count of 245766.6±49154.32, whereas healthy pregnant women had platelet count of 231383.3±63338.50. It can be concluded that pregnant women with GTT had a higher platelet count than healthy control women, and this was statistically significant (p = 0.042).

Pregnant with GTT had NLR levels of 3.55±1.37, whereas healthy pregnant women had NLR levels of 3.48±1.25. It can be concluded that pregnant women with GTT had higher NLR than healthy control women, but it was not statistically significant (p = 0.96).

Pregnant with GTT had PLR levels of 133597.21±55951.37, whereas healthy pregnant women had PLR levels of 119307.25±40490.29. It can be concluded that pregnant women with GTT had a higher PLR than healthy control women, but it was not statistically significant (p = 0.19).

Table 4 shows the TSH, fT3, and fT4 parameters.

Table 4. Comparison of the groups' thyroid function tests.

Parameters	Group 1 (GTT)	Group 2 (healthy)	P
TSH (mIU/mL)	0,11±0,11	1,48±0,59	<0,01
fT3 (ng/dL)	3,64±1,42	3,27±0,37	0,010
fT4(ng/dL)	0,92±0,48	0,85±1,07	<0,01

Pregnant with GTT had TSH levels of 0.11±0.11, whereas healthy pregnant women had TSH levels of 1.48±0.59 ($p<0.01$). Pregnant with GTT had fT3 levels of 3.64±1.42, whereas healthy pregnant women had fT3 levels of 3.27±0.37 ($p = 0.01$). Pregnant with GTT had fT4 levels of 0.92±0.48, whereas healthy pregnant women had fT4 levels of 0.85±1.07 ($p<0.01$).

DISCUSSION

The placenta secretes hCG during pregnancy, especially in the first trimester. TSH and hCG both contain beta- and alpha-subunits. Alpha subunits of both hormones are the same. The thyroid gland is stimulated by hCG's binding to TSH receptors because of this similarity. The level of HCG rises at the beginning of pregnancy, peaks at the 10th week, and then does not change significantly. During this period of increased hCG, free T4 increases slightly, and TSH decreases significantly. The effect of pregnancy on thyroid physiology is reversible (12).

In pregnancy, thyroid dysfunction is the second most common endocrinological disorder. If the thyroid gland secretes excessive amounts of thyroid hormones, thyrotoxicosis occurs. Throtoxicosis results from excessive thyroid hormone secretion that affects tissues and causes systemic symptoms. The prevalence of subclinical hyperthyroidism is 1.7% (13).

Gestational transient thyrotoxicosis is a type of non-autoimmune hyperthyroidism that is seen during pregnancy. The peak level of hCG is accompanied by a rise in total serum T4 and T3 levels. T4 and T3 serum levels typically increase slightly within the normal range, while TSH levels decrease accordingly. Therefore, elevated serum hCG levels in the early stages of pregnancy may cause subclinical or slightly overt hyperthyroidism, characterized by low serum TSH and high-normal or slightly high serum free T4 levels (14). In women with thyroid hyperfunction and symptoms, it occurs towards the end of their first trimester, and it declines as their hCG levels decline around the 14th to 18th week of pregnancy.

Due to the fact that the symptoms can also be seen in a normal pregnancy, gestational transient thyrotoxicosis cannot be diagnosed based on clinical findings alone. As their follow-up and treatments differ, transient thyrotoxicosis in pregnancy needs to be distinguished from other

causes of hyperthyroidism, especially Graves' disease. It is important to note that gestational transient thyrotoxicosis is characterized by the absence of prenatal hyperthyroidism, nausea and vomiting, and a lack of goiter and ophthalmopathy (15).

Approximately 2-3% of pregnant women experience gestational transient thyrotoxicosis during their pregnancy, according to a study conducted by Ginoer et al. in 1990. According to Yeo et al., over 11% of 184 pregnant women in Singapore suffered from gestational transient thyrotoxicosis during the first three months of pregnancy (16). It can be concluded from these rates that GTT is approximately 10 times more common than Graves' disease.

In order to differentiate gestational transient thyrotoxicosis from other causes of thyrotoxicosis in pregnancy, it is necessary to examine a patient's ultrasonography, clinical findings, and laboratory results. In accordance with the diagnostic criteria, gestational transient thyrotoxicosis is defined as an increase in thyroid hormone levels during early pregnancy in women with no physical signs of thyroid gland enlargement or exophthalmos, no thyroid autoantibodies, and no history of hyperthyroidism (17). During the course of our study, all pregnant patients met all diagnostic criteria.

It has been shown in previous studies that most patients with gestational transient thyrotoxicosis are asymptomatic, while a few patients may experience severe nausea and vomiting, unexplained weight loss, difficulty gaining weight, palpitations, heat intolerance, tremors, restlessness, and fatigue. Gestational transient thyrotoxicosis and hyperemesis gravidarum (severe nausea and vomiting, weight loss up to 5% of pre-pregnancy weight) are closely related. The relationship between GTT and hyperemesis gravidarum has also been established by prospective studies (18). In our study, most applicants were asymptomatic and diagnosed during routine pregnancy exams.

We analyzed retrospectively the pregnancy outcomes of gestational transient thyrotoxicosis-positive and negative pregnant women. During this study, we examined possible factors that might contribute to gestational transient thyrotoxicosis. It was our primary objective in this study to investigate the relationship between GTT and either NLR or PLR values. The NLR and PLR have been linked to inflammatory processes in clinical studies. As far as we are aware, no research has been performed on the relationship between gestational transient thyrotoxicosis and an inflammatory process. In light of these observations, we sought to determine if there was an association between GTT and inflammation.

Pro-inflammatory markers, such as NLR or PLR, can indicate systemic inflammation and have become a popular subject for research in recent years as a hematological score for inflammatory conditions (19). NLR has the important advantage of being easily calculated from complete blood count parameters in assessing

disease severity, can be found in all hospitals, and can provide results in a short time. The NLR is increasingly used as a marker of systemic inflammation, cancer, and other diseases. Additionally, they are also used as predictors of serious vascular diseases, such as atherosclerosis, as well as for assessing cardiovascular risk and predicting mortality related to cardiovascular diseases (20-21).

The NLR and PLR levels of healthy pregnant women as well as patients with gestational thyrotoxicosis were compared. In the present study, there was not a significant association between gestational transient thyrotoxicosis and either NLR or PLR; however, there was a significant association between platelet count and gestational transient thyrotoxicosis ($p<0.05$). Furthermore, no difference was found between the other parameters investigated.

We also investigated whether there was a connection between gestational age and GTT, which was another aspect of our study. Dieguez et al. conducted a study in Spain in which women living in areas without deficiencies in iodine were studied for thyroid disease during pregnancy. The relationship between maternal age and the risk of developing thyroid dysfunction was also examined in the study. In this study, 2509 women who were pregnant and had a gestational age of less than 13 weeks were included. They found that the frequency of thyroid dysfunction did not increase with gestational age, according to the findings of the study. There were 1.8% of patients with low TSH levels detected at the time of the assessment. Most of these cases were caused by transient thyrotoxicosis of pregnancy, which was found to be the underlying cause of low TSH (22). According to our study findings, we have determined that the frequency of GTT did not exhibit an increase with gestational age.

CONCLUSION

The present study did not find a significant relationship between gestational transient thyrotoxicosis and either NLR or PLR, but a significant relationship was found between platelet count and GTT. Due to these findings, we may conclude that GTT has no relation to any inflammation-related disorders. We believe that prospective studies with a large number of patients will reveal more information on this matter in the future, due to the limitations of our study.

Our study had some limitations. One of them was the retrospective design of the study. An additional limitation was the small number of patients that were included in the research. In order to generalize our results, larger patient sample sizes will be required to conduct potential research in the future.

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Conflict of Interest Statement: The author declares that have no conflict of interest.

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