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Thyroid antibodies in euthyroid and subclinical hypothyroidic pregnant women with autoimmune hypothyroidism: effects on hematological parameters and postpartum hemorrhage

Przeciwciała przeciwtarczycowe u ciężarnych z eutyreozą i subkliniczną niedoczynnością tarczycy na tle autoimmunologicznym: wpływ na parametry hematologiczne oraz krwotok poporodowy

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Abstract

Objectives: *The aim of the study was to investigate the relationship between thyroid antibodies and hematological parameters in euthyroid or subclinical hypothyroidic (SH) pregnant women with autoimmune hypothyroidism and to verify whether these pregnant women are affected by a higher rate of postpartum hemorrhage.*

Material and methods: *Thirty-six euthyroid and 21 SH pregnant women with autoimmune thyroid disease and 52 healthy pregnant women were evaluated. The relationship between thyroid hormones, thyroid antibodies level, the dosage of Levotroxin (LT4) and hematological parameters and the amount of postpartum bleeding was investigated.*

Results: *The mean platelet volume (MPV), was significantly higher in the SH group than in the euthyroid group and in the euthyroid group than healthy group (p<0.001). Hemoglobin (Hb) was significantly lower in both the SH group and the euthyroid group than control group (p<0.001). Other hematological parameters and the amount of postpartum bleeding did not differ between the groups. The correlation between Hb and fT3, fT4 was significant and positive, whereas between Hb and TSH was significant and negative (r= 0.3 p<0.01, r=0.2 p=0.01, and r=-0.18 p=0.04, respectively). There was a significant and negative correlation between the PLT count and FT4, PT, and FT3 (r= -0.2 p=0.01, r=-0.3 p<0.01, and r=-0.3 p<0.01 , respectively).*

Conclusion: *It has been described that being thyroid antibody-positive (TAb+) may be a risk factor for anemia and high MPV. However, euthyroid and SH pregnant women with thyroid antibodies do not differ in terms of other coagulation parameters and postpartum hemorrhage from healthy controls.*

Key words: **autoimmune hypothyroidism** / **pregnancy** / **hematological parameters** / / **postpartum bleeding** /

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Streszczenie

Cel pracy: *Celem badania była ocena związku pomiędzy przeciwciałami przeciwtarczycowymi a parametrami hematologicznymi u ciężarnych z eutyreozą lub subkliniczną niedoczynnością tarczycy (SH) na tle autoimmunologicznym oraz zbadanie czy te kobiety są bardziej narażone na krwotok poporodowy.*

Materiał i metoda: *Do analizy włączono 36 ciężarnych z eutyreozą, 21 z SH na tle autoimmunologicznym oraz 52 zdrowe ciężarne. Zbadano związek pomiędzy hormonami tarczycy, poziomem przeciwciał przeciwtarczycowych, dawką lewotyroksyny (LT4) a parametrami hematologicznymi oraz poporodową utratą krwi.*

Wyniki: *Średnia objętość krwinki (MPV) była istotnie wyższa w grupie SH niż w grupie z eutyreozą jak również wyższa była MPV w grupie z eutyreozą niż w grupie zdrowych pacjentek (p<0,001). Hemoglobina (Hb) była istotnie niższa zarówno w grupie SH jak i w grupie z eutyreozą w porównaniu do grupy kontrolnej (p<0,001). Pozostałe parametry hematologiczne oraz poporodowa utrata krwi nie różniła się istotnie pomiędzy grupami. Korelacja pomiędzy Hb a fT3, fT4 była istotna oraz pozytywna, podczas gdy korelacja pomiędzy Hb i TSH była istotna i negatywna (r= 0.3 p<0.01, r=0.2 p=0.01, i r=-0.18 p=0.04, odpowiednio). Znaleziono istotną, negatywną korelację pomiędzy PLT a fT4, PT i fT3 (r= -0.2 p=0.01, r=-0.3 p<0.01, and r=-0.3 p<0.01, odpowiednio).*

Wnioski: *Obecność przeciwciał przeciwtarczycowych (Tab+) może być czynnikiem ryzyka niedokrwistości oraz wysokiego MPV. Jakkkolwiek ciężarne z eutyreozą lub subkliniczną niedoczynnością tarczycy i z obecnymi przeciwciałami przeciwtarczycowymi nie różnią sie pod względem innych parametrów hematologicznych oraz wystąpienia krwotoku poporodowego od zdrowych ciężarnych z grupy kontrolnej.*

Słowa kluczowe: **autoimmunologiczna niedoczynność tarczycy** / **ciąża** / **morfologia** / / **krwawienie poporodowe** /

Introduction

Thyroid dysfunction, mostly hypothyroidism, is a frequent disorder in the general population, especially among women. The worldwide prevalence of hypothyroidism during pregnancy is steadily increasing and is estimated at 0.3–0.5% for overt and 2-3% for subclinical hypothyroidism (SH). Thyroid autoantibodies are found in 5–18% of women in the childbearing age, and chronic autoimmune thyroiditis (Hashimoto disease) is the main cause of hypothyroidism during pregnancy in iodide-sufficient areas [1-4].

Hormone replacement therapy remains the treatment of choice for autoimmune hypothyroidism. It has been suggested that thyroid antibodies may adversely affect the mother or the fetus in women who are positive for thyroid antibodies, despite laboratory euthyroidism or SH with hormone replacement therapy. It has been described that being thyroid antibody-positive (TAb+) constitutes a risk factor for miscarriage, premature delivery, perinatal death, postpartum dysfunction, and low motor and intellectual development (IQ) in the offspring [5-7]. However, the underlying mechanism associated with perinatal morbidity remains to be fully elucidated.

Hypothyroidism is frequently associated with bleeding disorders ranging from menorrhagia to thromboemboembolism [8-12]. Similarly, despite euthyroid state, thyroid autoantibodies are likely to influence the hemapoitic system elements. The relationship between thyroid antibodies and the coagulation system is, however, often ignored. The dual aims of the present study are to assess the relationship between thyroid antibodies and hematological parameters in pregnant women with autoimmune hypothyroidism and euthyroid or SH state and whether euthyroid or SH women positive for thyroid autoantibodies are affected by a higher rate of postpartum hemorrhage.

Material and methods

Our study was approved by the Local Ethics Committee. A written consent to participate was obtained and the procedures were in accordance with the Helsinki Declaration of 1975 (revised in 2008).

Patient selection and study design

This study was conducted between April 2013 and May 2014. During the study period, there were 542 normal vaginal and 787 caesarean section deliveries in our clinic. Pregnant women between 37 and 41 weeks of gestation who were hospitalized to give birth were investigated. Only patients who had undergone planned caesarean section were included in the study to eliminate the impact of blood loss difference between vaginal delivery and cesarean section. Pregnant women with the following conditions were excluded from the study: gestational age <18, maternal age >45, maternal hemoglobin <8 gm%, multiple pregnancy, placental abnormalities such as placenta abruption or placenta previa that can lead to extra bleeding, malpresentation, polyhydramnios, chorioamnionitis, intra uterine fetal death, hypertension, metabolic, rheumatologic or endocrine disorders, history of uterine atony, acquired or congenital thrombophilia, prior pelvic surgery or cesarean section, and patients who underwent cesarean section after failed trial of labor, or emergency cesarean section.

At the time of the study, none of the patients were using any medication, including aspirin or heparin, that might affect the study parameters and none showed symptoms and signs of clinical bleeding. Also, none of the women were current smokers.

The pregnant women who had study criteria were screened for anti-thyroid peroxidase antibody (TPOAb) or anti-tyroglobulin antibody (TGAb) TSH, fT3 and fT4 and LT4 use has been questioned. TPOAb or TGAb (+) women were divided into two groups according to thyroid hormones level: the euthyroid

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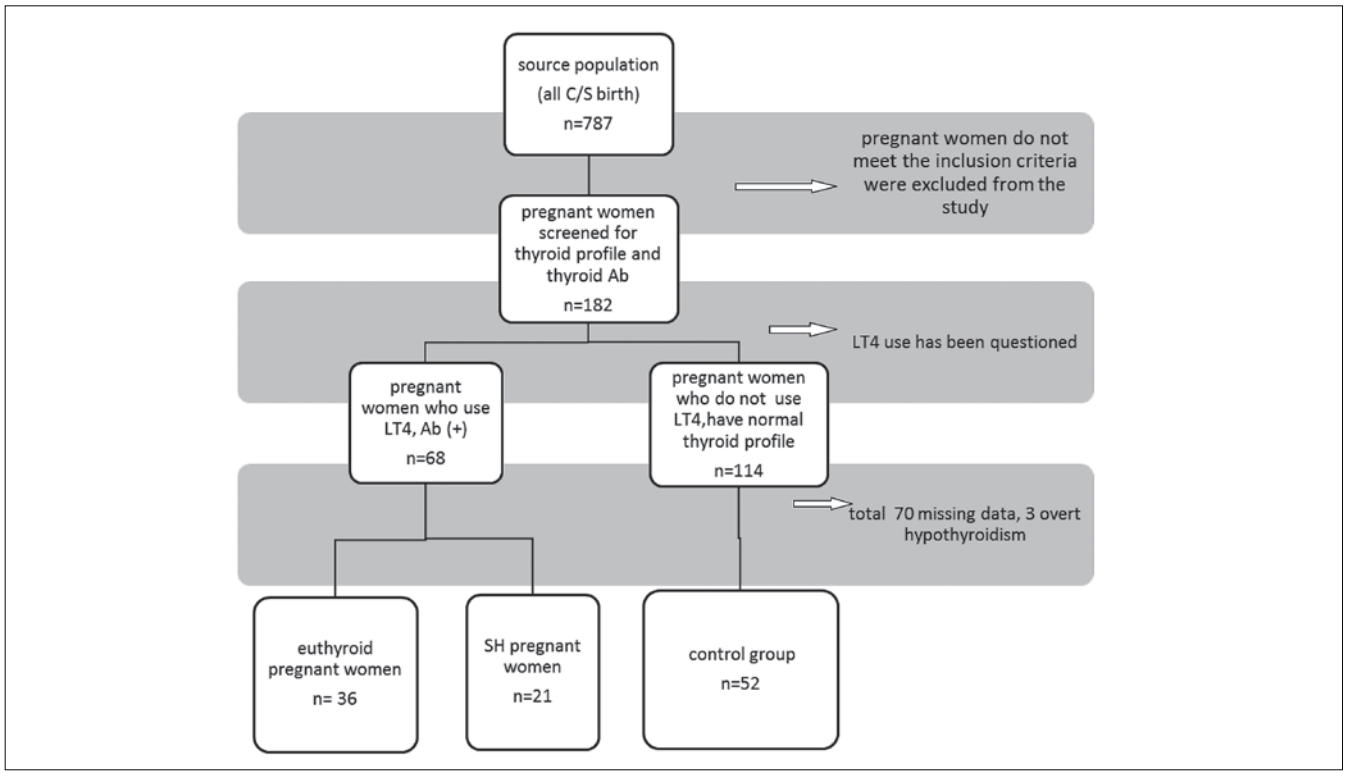

Figure 1. MRI sFlow chart of the study design.

group – normal thyroid hormone profile, treated with LT4, and the SH group – elevated TSH levels (3–10 uIU/ml) with normal serum FT4 and FT3 levels treated with LT4. Pregnant women having overt hypothyroid (elevated TSH levels (≥3 uIU/ml) with abnormal serum FT4 and FT3 levels) were excluded from the study. Volunteers without LT4 treatment and with normal thyroid hormone profile served as the control group. Normal thyroid hormone profile for pregnancy was determined according to the 'Guidelines for diagnosis' developed by the Endocrine Society and endorsed by the 2007 recommendations of the American Thyroid Association (TSH: 0.3-3 uIU/ml, fT3:1.4-4.2 pg/ml, fT4: 0.64-1.92 ng/dL).

Figure I represents a flow chart of the study design.

Methods

Clinical examination included height and body weight measurements, and body mass index (BMI) which was calculated as the weight (kilograms) divided by the square of the height (meters) squared (kg/m^2).

Serum samples were collected just before operation and at 08:00–09:00, at least 8 hours after overnight fasting. TSH, fT3, fT4, TPOAb and TGAb were determined by electrochemiluminescence method (ECLIA) using a Cobas- e 601 analyzer (Roche Diagnostics). Whole blood analysis was made using an autoanalyzer (Coulter LH 500). PT and APTT were measured by coagulation analyzers using kits from Dade Behring Marburg GmbH.

Bleeding time was evaluated by the Duke method: The patients were pricked with a special lancet on the fingertip, after having been swabbed with alcohol. The prick was about 3–4 mm deep. The blood was wiped every 30 seconds with a filter paper until bleeding ceased. The time was recorded in minutes.

The operation time was recorded in minutes.

In order to reduce postpartum hemorrhage and increase uterine contractions, methylergometrine 0.2 mg (Metiler ampoule®) and 5 IU oxytocin (Synpitan forte ampoule®) were intravenously given to all patients soon after delivery.

In order to assess the amount of postpartum hemorrhage, patients sanitary napkins in the first 6 hours of the postpartum period were collected and weighed. Equal number of pads were used to eliminate the effect of pad weight. Pulse rate, temperature and blood pressure were recorded in the first 6 hours of the postpartum period on an hourly basis. None of the patients did not developed uterine atony, or was not needed evacuation of the retained products of conception, or received additional uterotonic in the first 6 hours of the postpartum period.

Statistical analysis

Statistical analysis was performed by using the SPSS (15.0) for Windows (SPSS Inc., Chicago, IL, USA). To examine the differences between groups, one-way analysis of variance was used with the Duncan pairwise comparison of means. The Kruskal-Wallis test, followed by the Mann-Whitney U-test with the Bonferroni correction for multiple comparisons was used for data that did not fulfill the assumptions required for the analysis of variance. Pearson's correlation coefficient was used for evaluating the relationships between thyroid hormones, thyroid antibodies, the dosage of Levotroxine and hematological parameters. *p* value 0.05 was considered to be statistically significant.

Table I. Baseline characteristics, hematological parameters, and the amount of postpartum bleeding among groups. p<0.05 was considered to be statistically significant.

	Ab (+) euthyroid Pregnant women N=36	Ab (+) SH Pregnant women N=21	Control group N=52	P
Age (year)	27,86±0.73[b]	31,62±1,14[a]	29,25±0,69[ab]	**0,02**
Multiparity (n,%)*	52,26	54,64	57,04	0,71
BMI	30,1±0.6	29,6±1,0	29,6±0,5	0,84
TSH (uIU/ml)	2,0±0,1[b]	4,0±0.1[a]	2,0± 0.0[b]	**0,00**
fT3(pg/ml)	2,7±0.1	2,7±0.2	2,5±0.0	0,2
fT4(ng/dl)*	44,50[b]	46,57[b]	65,67[a]	**0,00**
Bleeding time(min)	112.08± 6.5	113.3±8.2	92.6±7.5	0,09
PT	58,11	56,38	52,29	0,67
APTT	27.8±0.3	28.6±0.5	28.1±0.3	0,43
International Normalized Ratio (INR)	0.94± 0.0	1.02±0.0	0.97±0.0	0,37
Platelets (×109/L)	229,6±9,2	251,1±15,3	225,6±9,3	0,30
Hb (g/dL)	10,8±0,2[b]	10,4, ±0,2[b]	11,9±0,1[a]	**0,00**
MPV (fL)	10,8±0,1[ab]	11,2±0,1[a]	10,4, ±0,1[b]	**0,00**
The difference in Htc**	2,678 (,2425)	2,495 (,4135)	2,021 (,3159)	0,28
ped weight in first six-hour time after birth(gr)	252±18	259± 18	218±15	0,21
postpartum blood transfusion(n,%)*	57,54	55,60	53,00	0,12
Operation time (min)	28,7±1,9	30,0±2,0	37,8±5,2	0,26

*:non-parametric values were presented as mean rank,
**: preoperative htc- postoperative htc in 6th hour.

Table II. The correlation between thyroid hormones, thyroid antibodies, the dosage of Levotroxine and hematological parameters.

		TSH	fT3	fT4	Anti-TPO	Anti-TG	The dosage of Levothyroxine
PLT count	r p	0,07 0,4	0,07 0,3	**-0,2** **0,01**	0,03 0,8	0,01 0,9	0,1 0,3
MPV	r p	**0,20** **0,02**	0,1 0,1	-0,6 0,5	-0.05 0,9	0,1 0,4	-0,08 0,6
Hb	r p	**-0,18** **0,04**	**0,3** **<0,01**	**0,2** **0,01**	-0,1 0,5	-0,1 0,5	-0,1 0,4
The difference in Htc	r p	0,13 0,1	0,1 0,1	0,01 0,8	0,09 0,5	0,1 0,2	0,2 0,6
PT	r p	-0,04 0,6	**-0,3** **<0,01**	0,08 0,3	-0,1 0,9	0,03 0,8	-0,1 0,4
APTT	r p	0,19 0,04	0,09 0,3	-0,1 0,2	-0,3 0,06	-0,05 0,7	-0,1 0,3
INR	r p	0,05 0,5	0,1 0,2	-0,01 0,9	-0,5 0,7	-0,06 0,6	0,1 0,4
Bleeding time	r p	0,15 0,1	0,1 0,1	-0,01 0,2	-0,09 0,5	-0,03 0,8	-0,2 0,9
ped weight in first six-hour time after birth	r p	0,08 0,3	0,09 0,3	0,01 0,2	-0,01 0,6	0,03 0,8	-0,2 0,1

r: Pearson correlation coefficient. p<0.05 was considered statistically significant.

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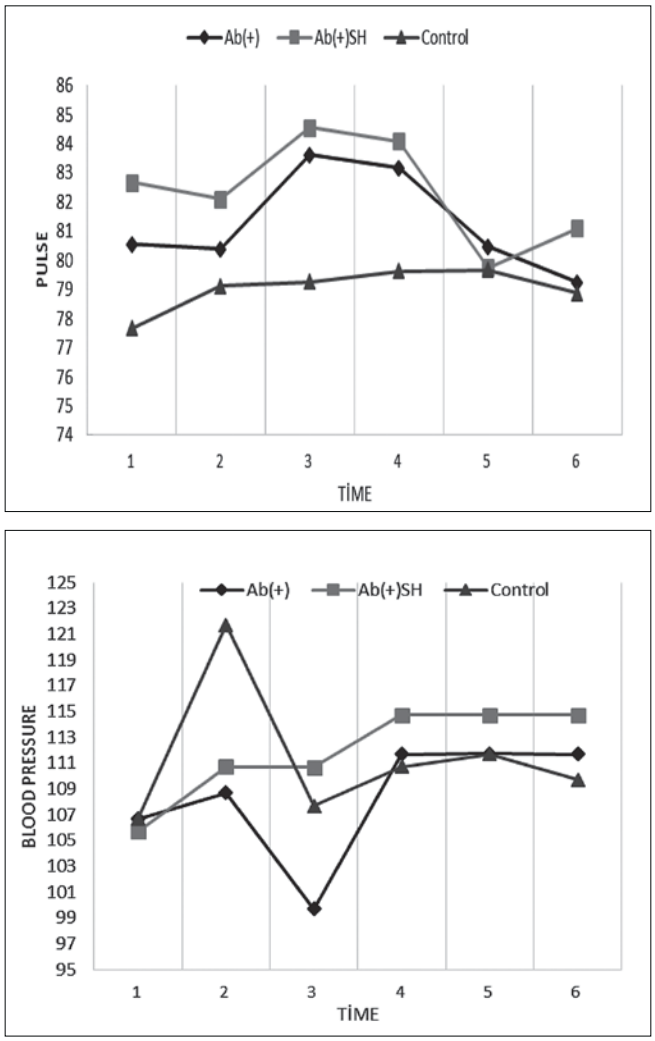

Figure 2. Pulse rate and blood pressure monitoring in postpartum first six hour period.

Results

The main characteristics and laboratory parameters of the study groups are reported in Table I. The level of TSH was significantly higher in the SH group than in the euthyroid and control groups ($p<0.001$), while fT3 was within the normal limits in all subjects, and fT4 was significantly lower in the SH group ($p=0.2$, $p<0.01$). MPV was significantly higher in the SH group vs. the euthyroid group and in the euthyroid group as compared to healthy group ($p<0.001$). Hb was significantly lower in both the SH group and the euthyroid group than control group ($p<0.001$). Other hematological parameters and the amount of postpartum bleeding (pad weight in the first 6 hours after delivery), the difference in hematocrit (Htc) between pre- operative and post-operative 6th hour values, and the need for postpartum blood transfusion did not differ between the groups. Blood pressure and heart rate monitoring in the first 6 hours after delivery were similar among the study groups (Figure II).

We examined the relationship between thyroid hormones levels, LT4 dose, TPOAb or TGAb levels and hematological parameters. We found a statistically significant and positive correlation between MPV and TSH ($r=0.2$, $p=0.02$). The correlation between Hb and FT3, FT4 was statistically significant and positive, whereas between Hb and TSH was statistically significant and negative ($r=0.3$ $p<0.01$, $r=0.2$ $p=0.01$, and $r=-0.18$ $p=0.04$, respectively). There were statistically significant and negative correlations between PLT count and FT4, as well as PT and FT3 ($r=-0.2$ $p=0.01$, and $r=-0.3$ $p<0.01$, respectively). (Table II)

Discussion

In our study, we investigated the hematological parameters and postpartum bleeding level of euthyroid or SH pregnant women with autoimmune thyroiditis and compared them with healthy controls. Analysis of the hematological parameters revealed that Hb, and MPV values were statistically significantly different between the three groups.

Anemia has long been recognized as a complication of overt hypothyroidism, occurring in up to 25% of the affected patients. There appear to be multiple mechanisms by which thyroid hormones stimulate erythropoiesis, including increased erythropoietin production and responsiveness, and effects on iron transport and utilization. In several recent studies, a significant relationship between SH and anemia was found, with anemia of chronic disease as the most frequent type [13]. In a study carried out by Cinemre H. and colleagues, hematological parameters were shown to be related with anemia in women with subclinical hypothyroidism improved after LT4 replacement [14]. Furthermore, in a large cohort study, it was found that small differences in thyroid function are associated with significant differences in erythrocyte indices in euthyroid subjects [15]. In our study, we detected the prevalence of anemia to be significantly higher in both, SH and euthyroid subjects as compared to healthy pregnant women. Furthermore, there was a significant and negative correlation between Hb and TSH levels and a positive correlation between Hb and fT3, as well as fT4 levels. However, we did not observe a correlation between thyroid antibody levels or the dosage of LT4 and Hb level. Independently from the risk of hypothyroidism, it has been described that being TAb+ constitutes a risk factor for anemia in pregnant women.

The results of our study demonstrate a significantly positive association between TSH levels and MPV. MPV, which is used to measure platelet size, can reflect the platelet activity. An increased MPV may lead to a prothrombotic condition with increased thromboxane A2 and B2 and adhesion molecules, such as P-selectin and glycoprotein IIb/IIIa expression, as well as b-thromboglobulin release. Larger and functionally more reactive platelets increase propensity to thrombosis [16]. There are few reports about MPV values in hypothyroidism. Coban et al., and Erikci et al., reported higher MPV values in patients with subclinical hypothyroidism than in healthy controls [17, 18]. In addition, in an other study, it was found that in patients with SH when they became euthyroid after LT4 replacement therapy, the MPV values decreased but still remained higher than in healthy controls [19]. In the obstetric population, increased MPV levels have been described as precursors in the onset of preeclampsia, diabetes mellitus and intrauterine growth restriction [20-22]. It was suggested that there may be a relationship between MPV and adverse perinatal outcomes, which are seen in thyroid antibody-positive pregnant women.

We did not observe statistically significant differences with regard to other hematological parameters between groups. The

influence of thyroid failure on hemostasis has been studied, but there are few studies in the English literature covering patients with SH and their results are often conflicting. Muller et al., reported a hypercoagulable state in patients with SH [23]. Chadarevian et al., observed decreased fibrinolytic activity in patients with SH [24]. In another study, Canturk et al., reported increased fibrinogen, PAI-1 and factor VII and decreased antithrombin III concentrations in a group of patients with SH [25]. In contrast to these studies, Gullu et al., investigated patients with SH who exhibited a hypocoagulable state as shown by decreased factor VIII and vWF activities, and both factors were improved with LT4 treatment [26]. To the best of our knowledge, there have been no studies investigating coagulation state in pregnant women with autoimmune thyroid disease. In our study, we did not examine coagulation factors in detail but PT, APTT and bleeding time, which shows extrinsic and intrinsic pathway and platelet function, did not differ between the groups. Furthermore, the postpartum bleeding level, which was evaluated by pad weight in the first 6 hours after delivery, and the difference in Htc between post- and pre-operative values, were similar. Based on our findings, it may be concluded that LT4 treatment in euthyroid and SH pregnant women with autoimmune thyroid disease improves coagulation parameters and prevents clinically manifested bleeding.

Our study is not without limitations, chief among them a small sample of women. Secondly, we investigated only early postpartum hemorrhage, but there may be some alterations in the late postpartum period. Thirdly, we only evaluated pre-operative hematological parameters and thyroid hormone levels. Observational research such as this should cover the whole pregnancy period in order to identify changes in these parameters, whereby the effect of the LT4 treatment can be better understood.

Conclusions

Our study demonstrated that independently free thyroid hormone levels being thyroid antibody-positive in pregnancy may be a risk factor for anemia and high MPV, which have been described as precursors in the onset of preeclampsia, diabetes mellitus, and intrauterine growth restriction in the obstetric population. However, euthyroid and SH pregnant women with thyroid antibodies do not differ in terms of coagulation parameters and postpartum hemorrhage from healthy controls.

Authors' contribution:

1. Esra B. Gur – concept, analysis, study design, corresponding author.
2. Muammer Karadeniz – revised article.
3. Murat Yalcı– revised article.
4. Hasbiye Inceefe – revised article, article draft.
5. Sumeyra Tatar - analysis of data.
6. Mine Genc – revised article.
7. Serkan Guclu – revised article.

Authors' statement

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- the manuscript has not been published in or submitted to any other journal.
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