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**The prevalence of autoimmune thyroiditis in adolescent girls with polycystic ovary syndrome**

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**ABSTRACT**

**Objectives:** Both polycystic ovary syndrome (PCOS) and autoimmune thyroiditis (AT) are reported to be common endocrinopathies. In recent years the number of publications assessing the coexistence of these two disease entities in adult women has been growing. There are many suggestions regarding pathophysiological mechanisms that can cause the relationship between AT and PCOS. However, there is still a lack of research among adolescent girls.

The aim of the study was to analyze the occurrence of autoimmune thyroiditis in adolescent girls with PCOS.

**Material and methods:** The study group included 80 girls diagnosed with PCOS (chronological age:  $16.54 \pm 1.00$  years, BMI:  $22.80 \pm 3.27$  kg/m<sup>2</sup>), and the control group — 64 regularly menstruating girls (chronological age:  $16.71 \pm 0.63$  years, BMI:  $24.8 \pm 5.2$  kg/m<sup>2</sup>). The thyroid function and morphology were assessed based on the concentration of thyroid stimulating hormone (TSH), free thyroxine (fT4), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG) antibodies and ultrasound scan of the thyroid gland.

**Results:** AT was diagnosed in 18 (22.5%) girls from the study group and nine (14.06%) from the control group ( $p > 0.05$ ). Positive anti-TPO titer was observed more often in the study group [21 patients (26.25%)] than in the control group [9 girls (14.06%)] ( $p = 0.054$ ). Moreover, an abnormal ultrasound scan of the thyroid gland characteristic for AT was found

in 18 girls from the study group (22.50%) and 8 girls from the control group (12.50%) ( $p > 0.05$ ).

**Conclusions:** The results of the analyzed studies do not confirm a significant relationship between PCOS and AT in adolescent girls. However, in the group of girls with PCOS, autoimmune process exponents were more frequent (anti-TPO), reaching the borderline level of statistical significance.

**Key words:** polycystic ovary syndrome; autoimmune thyroiditis; adolescent girls

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**INTRODUCTION**

Polycystic ovary syndrome (PCOS) is considered one of the most common endocrinopathy in women of reproductive age, and depending on the diagnostic criteria adopted, may affect 6–15% of women [1]. In the literature, we can find very divergent data on the epidemiology of PCOS in adolescents most likely due to the frequently modified, non-uniform PCOS criteria in adolescent girls and the large diversity of the group. It is estimated that PCOS may affect 0.56–3.1% of adolescent girls (based on the scarce data) [2, 3]. While the diagnosis of PCOS among adult women is widespread and established, the subject should be approached with some caution among adolescent girls. Diagnosis in this age group is difficult and often requires long-term follow-up because what is considered pathology in adult women may not always be pathology in adolescent girls.

Thyroid dysfunction is also a common endocrinopathy and autoimmune thyroiditis (AT) comes to the fore in terms of its prevalence which may affect 5–20% of women of reproductive age and is the most common cause of hypothyroidism in women [4]. It is estimated that AT occurs in 0.3%–9.6% of children, and it affects girls more often than boys, with a frequency ratio of even 4:1 to 8:1 depending on the ethnic group [5].

To date, several studies evaluating the relationship between AT and PCOS have been published. These studies were conducted on adult women. So far, no clear conclusions have been drawn and research on the search for pathophysiological pathways connecting these disease entities is still ongoing. The mechanisms responsible for the development of

autoimmune thyroid processes are complex and include genetic and environmental factors, such as iodine intake in the diet, drugs, infections [6, 7]. Hormones also influence autoimmune processes. Similarly, among the etiological factors of PCOS, genetic factors are mentioned, as well as hormonal and metabolic factors [8–12]. Recently, the possible autoimmune basis of PCOS has been increasingly emphasized [13], which is confirmed by the published data describing the increased prevalence of AT among women with PCOS [14]. There are no reports analyzing the above relationship in the group of teenagers. For this reason, we undertook a study aimed at assessing the frequency of thyroid disorders, especially autoimmune thyroid disorders, in adolescent girls with PCOS.

## **MATERIAL AND METHODS**

A total of 144 patients were qualified for the research. Eighty girls were included in the study group, while the remaining 64 regularly menstruating girls were included in the control group. The study group was previously described in Skrzynska et al. [15]. It included adolescent girls who, based on the conducted diagnostics, met all the criteria for the diagnosis of PCOS. The presence of the antibodies against thyroid peroxidase (anti-TPO) above 35 IU/mL and/or antibodies against thyroglobulin (anti-Tg) above 40 IU/mL with characteristic for AT thyroid image on USG was required to make a diagnosis of AT [16]. Abnormal thyroid function was not a necessary criterion to diagnose AT.

Both, in the study group and in the control group patients were qualified to participate in the study considering the following exclusion criteria:

- eating disorders of the anorexia nervosa type, bulimia;
- hyperprolactinaemia [concentration of prolactin (PRL)  $\geq 36$   $\mu\text{g/L}$ ];
- adrenal cortex dysfunction;
- decompensated, clinically significant disorders of the thyroid gland (TSH level  $< 0.4$  mIU/L or  $> 10.0$  mIU/L);
- taking drugs within the last 3 months that could interfere with the determination of sex hormone levels.

Patients' data were analyzed: age [years], anthropometric measurements (body weight [kg], height [cm], BMI [ $\text{kg/m}^2$ ]), gynecological age [years], age of menarche [years], hirsutism assessed according to the Ferriman–Gallwey scale [points], parameters of thyroid function (thyrotropic hormone — TSH [mIU/L], free thyroxine — fT4 [pmol/L], anti-TPO [IU/mL], anti-TG [IU/mL]), and the image of the thyroid gland. In the ultrasound examination using the Siemens Medical Solution USA, Inc. apparatus, equipped with the VFX 13-5 linear probe. As an image characteristic of autoimmune thyroiditis, we adopted the description of the

heterogeneous, hypoechoic structure of the thyroid gland.

### ***Statistical analysis***

The obtained results were analyzed statistically using the Statistica 13.3 PL software. The quantitative variables were described with mean (standard deviation) and qualitative variables were defined by frequency (%). Chi-square test for qualitative and Student's t test for quantitative data comparison of variables between the groups were used, as appropriate. A p value less than 0.05 was considered statistically.

The Bioethics Committee of the Medical University of Silesia approved the study (KNW/0022/KB/70/16). Considering the retrospective nature of the work, the Bioethics Committee did not require additional patient consents.

## **RESULTS**

The clinical characteristics of the groups is presented in Table 1. No significant differences were found in chronological age, BMI and age of menarche between the groups ( $p > 0.05$ ). However, it was shown that the gynecological age was significantly older in the control group than in the study group ( $p = 0.01$ ). On the other hand, hirsutism score was significantly higher in the study group than in the control group ( $p = 0.003$ ). Testosterone concentration in the study group was also higher than in the control group ( $p < 0.001$ ).

Elevated anti-TPO titer was found in 30 girls (20.83%) in total. In the study group the increased titer of anti-TPO was reported in 21 patients (26.25%) and in the control group — in 9 patients (14.06%) ( $p = 0.054$ ). Moreover, 9 patients from the study group (11.25%) had an increased titer of anti-TG, while in the control group there were 3 such patients (4.69%) ( $p > 0.05$ ) (Fig. 1).

Eighteen girls from the study group (22.50%) and eight girls from the control group (12.50%) had an abnormal ultrasound scan of the thyroid gland characteristic for AT ( $p > 0.05$ ) (Fig. 2). The difference in thyroid volume between the groups was also not significant ( $p > 0.05$ ) and amounted to  $8.7 \pm 3.4$  mL in the control group and  $9.2 \pm 4.0$  mL in the study group.

A total of 27 patients (18.75%) who participated in the study met the AT criteria. Among them- the major part — 18 girls (22.50%) came from the study group and 9 (14.06%) from the control group. There was no significant difference in the incidence of AT between the groups ( $p > 0.05$ ) (Fig. 3).

In the study group 7 patients (8.75%) and in the control group 9 (14.06%) had

previously started treatment with levothyroxine due to hypothyroidism. Subclinical hypothyroidism (SH) was diagnosed in a total of 6 (4.17%) girls. None of the patients diagnosed with SH had previously been treated with levothyroxine. More patients with SH were recorded in the control group [4 girls (6.25%)] than in the study group, where such a diagnosis was made only in 2 patients (2.50%). What is more, the difference in the incidence of SH was not statistically significant ( $p > 0.05$ ).

## **DISCUSSION**

The aim of the study was to analyze the occurrence of thyroid dysfunction, especially AT, in girls with PCOS. The study group included 80 girls diagnosed with PCOS, and there were 64 girls with regular menses in the control group. AT was diagnosed in 22.5% of girls from the study group and 14.06% from the control group ( $p > 0.05$ ). Positive anti-TPO antibody titer (26.25%) was observed more often in the study group than in the control group (14.06%) ( $p = 0.054$ ). There was no significant difference in the incidence of thyroid dysfunction between the groups.

The incidence of thyroid diseases seems to be increased in women with PCOS what is suggested by published studies. Romitti et al. [17] in their meta-analysis conducted based on 13 studies showed significant relationship between AT and PCOS. It was found that AT is more common in women with PCOS than in the control group, regardless of geographic differences (OR = 3.27; 95% CI 2.32–4.63). The prevalence of AT among women with PCOS in the compared studies ranged between 18.75% and 43.1%, while in the control groups it ranged between 1.25% and 26.2%. Only in 2 out of 13 studies the difference in the incidence of AT between women with PCOS and healthy women was not significant. The differences in the frequency of AT in individual studies are most likely resulted from the variability of the adopted AT diagnostic criteria between studies. What is more, Polish research also showed a relationship between AT and PCOS. The thyroid diseases were diagnosed in 31.3% of young women with PCOS and 70% of all thyroid diagnoses were AT, found in nearly 21% of the patients in the study group [18]. These results are similar to the results obtained in our study. We found AT in 22.5% of girls from the study group and 14.06% from the control group. However, these values did not differ significantly. One of the reasons for the lack of a clear difference between the groups may be characteristics of our study group different from adult women group. The course and the diagnostic criteria of PCOS in adolescent girls are different than in adult women. In addition, studies show that the prevalence of AT in women increases with age, which is not seen in men. AT may affect 5–20% of women of reproductive age and

is the most common cause of hypothyroidism in women [19]. However, it is estimated that AT occurs only in 0.3%–9.6% of children in the pediatric population and is much more common in girls than in boys, with a frequency ratio of even 4:1 to 8:1 depending on the ethnic group [5]. The lack of significant difference between the prevalence of AT in the study group and the control group can arise from the young age of the patients. It cannot be ruled out that with age this difference would gain statistical significance also due to additional risk factors for autoimmune diseases resulting from the hormonal profile of women with PCOS and absent in healthy women. It is emphasized, that sex hormones (estrogens, progesterone and testosterone) have an impact on the functioning of the immune system. In women with PCOS an increased ratio of estradiol to progesterone might be involved in the stimulation of the immune system and consequently in the development of AT. The study involving population of adolescent girls with PCOS showed, that in the group of girls diagnosed with both PCOS and AT, the concentration of E2 was significantly higher than in the group of girls with PCOS but without AT ( $p = 0.04$ ). Additionally, a significant positive correlation between AT and estradiol concentration ( $r_y = 0.27$ ;  $p = 0.04$ ) was found [15]. On the other hand, the lack of a clear difference in AT prevalence between the groups may also be related to the fact that both groups had a similar but high BMI. This seems to be an advantage of the study, because in this way the possible impact of obesity on the incidence of AT in the group of girls with PCOS was eliminated, as the latest research focuses on the relationship between BMI and the occurrence of AT.

The differences in the prevalence of AT among women with PCOS reported by different researchers might result not only from the PCOS diagnostic criteria used, but also from the diagnostic criteria for AT. Arduc et al. [20] obtained similar to ours the prevalence of AT in patients with PCOS, although the prevalence of AT in the control group differed between the work of Arduc et al. and ours [20]. They showed a significantly higher frequency of AT in women with PCOS (22.1%) compared to the control group (5%) ( $p < 0.0004$ ). The similarity of AT prevalence in the study group with the results of our study can be explained by the similar size of the groups, the young age of the patients and the same criteria for the diagnosis of AT, i.e., the presence of a positive titer of anti-TPO and/or anti-TG and an ultrasound image typical of chronic thyroiditis. In the study by Duran et al. [21] AT was diagnosed in as many as 32.5% of women with PCOS and in 23.3% in the control group. In order to diagnose AT, it was enough to meet only 1 of the 3 mentioned criteria, namely the presence of a positive titer of anti-TPO, a positive titer of anti-TG or the description of an abnormal ultrasound image characteristic of chronic thyroiditis.

Furthermore, numerous reports suggest that anti-TPO are claimed to be a more sensitive indicator of the autoimmune process in the thyroid gland than anti-TG. For this reason, some people refrain from determining the titer of anti-TG and use only anti-TPO in the diagnosis of AT. In our study, the frequency of positive anti-TPO titers in the study group was higher than in the control group (26.25% and 14.06%, respectively;  $p = 0.054$ ). The frequency of elevated anti-TG titers was also higher in the study group, but it did not differ significantly between the groups ( $p > 0.05$ ) and amounted to 11.25% in the study group and 4.69% in the control group. Al Saab et al. [22], analyzing 56 patients with PCOS, showed a positive titer of anti-TPO in 19.6% of them compared to 3.3% in the control group ( $p = 0.037$ ) and a positive titer of anti-TG in 21.4% of women with PCOS and only 3.3% without diagnosed PCOS ( $p = 0.026$ ). On the other hand, in a study by Janssen et al. [23], a positive titer of anti-TPO was found in 26.9% of women with PCOS and only 8.3% of women in the control group. Menon et al. [24] also reported significantly more frequent occurrence of a positive titer of anti-TPO in women with PCOS (25%) compared to 5% in the control group. The differences in the percentage distribution of the positive titer of anti-thyroid antibodies in the presented studies may result from the adopted cut-off points defining the positive titer of anti-TPO or anti-TG. It seems that geographical differences do not play a significant role in this case, which is confirmed by the published data [25–29]. Kim et al. [30] came to different conclusions regarding the distribution of anti-thyroid antibodies in women with PCOS. They described a positive titer of anti-TPO in 4.8% of the test group and 7.7% of the control group. Significant differences between the study cited and those described above may result from the analyzed population. In the study by Kim et al. [30], the patients were not hospitalized, but only assessed during follow-up visits to an outpatient health care center. Based on a systematic review of research and meta-analysis, it turns out that the phenotype of PCOS in patients diagnosed in a hospital environment differs compared to random populations [31]. Inpatients meet more PCOS diagnostic criteria and have a higher mean BMI than ambulatory patients. Therefore, it seems that the data of Kim et al. [30] come from an unselected group — difficult to reference and compare.

In our study, we did not find significant differences in the frequency of finding an abnormal image, characteristics of chronic thyroiditis on ultrasound, although in the study group the image typical for AT was found in 22.5% compared to 12.3% of girls from the control group. On the other hand, Janssen et al. [23] described a typical AT picture of the thyroid gland in 42.3% of patients in the PCOS group and in only 6.5% in the control group ( $p < 0.001$ ). Similarly, Sinha et al. [34] showed a significantly higher percentage of the



thyroid image typical for AT in the group of women with PCOS compared to the control group (12.5% vs 2.5%, respectively). In both above-cited studies, no significant differences were found in the volume of the thyroid gland between the groups described. These evident differences in the percentage of patients with abnormal thyroid gland descriptions on ultrasound may be due to differences in BMI in women across studies. It turns out that the mean BMI of patients with PCOS in the work of Janssen et al. was  $30.0 \pm 7.9 \text{ kg/m}^2$ , and in the control group it was  $25.5 \pm 7.1 \text{ kg/m}^2$  [23]. In the study by Sinha et al. [32], the mean BMI of women in the study group was significantly lower and amounted to  $24.68 \pm 3.07 \text{ kg/m}^2$ , and in the control group  $23.55 \pm 3.02 \text{ kg/m}^2$ . Some studies suggest that a significant degree of obesity (so-called morbid obesity,  $\text{BMI} > 40 \text{ kg/m}^2$ ) may affect the morphology of the thyroid gland, i.e., its hypoechoic nature in ultrasound. It is a very good and well-known parameter helpful in the diagnosis of AT but it turns out to be a poor diagnostic parameter in patients with morbid obesity.

## CONCLUSIONS

There was no significant difference in the prevalence of AT between the groups but in the group of girls with PCOS autoimmune process exponents were more frequent (anti-TPO), reaching the borderline level of statistical significance. Considering the young age of the patients and the tendency to increase the incidence of AT with age, it can be assumed that the differences in the incidence of AT may reach the level of statistical significance at a later age.

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**Table 1.** Comparison of the clinical and hormonal characteristics of the study and control groups.

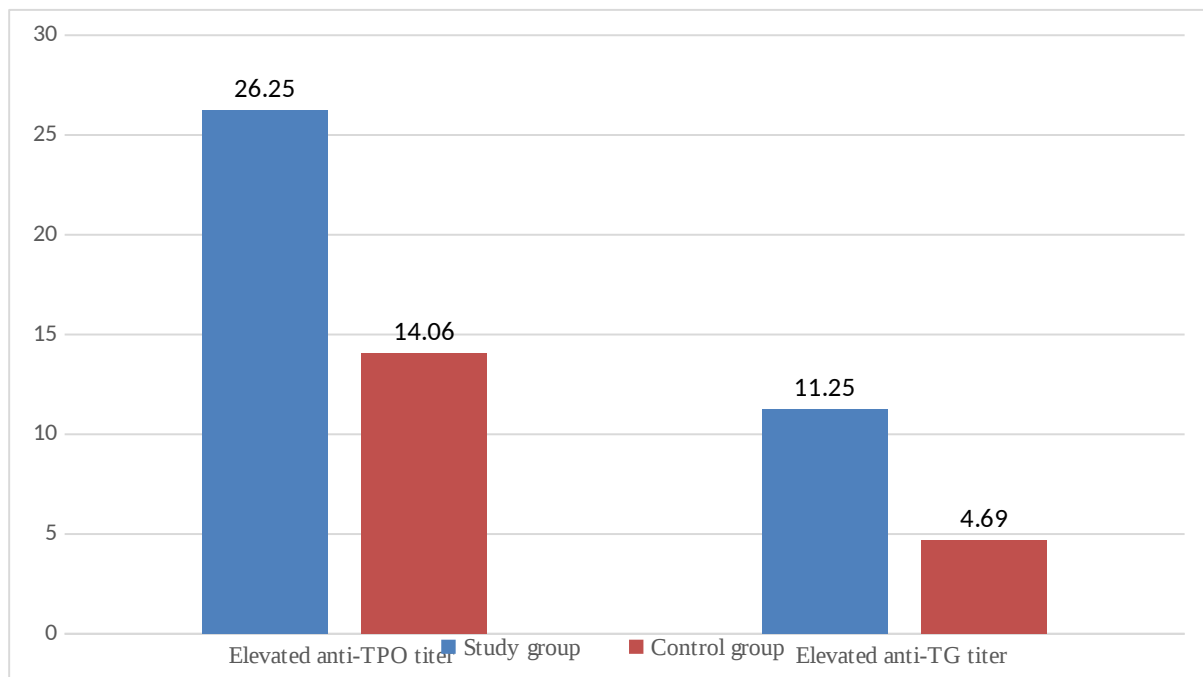
Variable	Study group n = 80	Control group n = 64	p
Age [years]	16.54 ± 1.00	16.71 ± 0.63	> 0.05
BMI [kg/m <sup>2</sup> ]	24.60 ± 4.16	22.80 ± 3.27	> 0.05
Age of menarche [years]	12.00 ± 1.00	12.00 ± 1.00	> 0.05
Gynecological age [years]	3.79 ± 0.94	4.50 ± 0.92	0.01
Hirsutism [points]	6.47 ± 6.00	3.47 ± 4.00	0.003

Testosterone [nmol/L]	2.11 ± 0.70	1.51 ± 0.53	< 0.001
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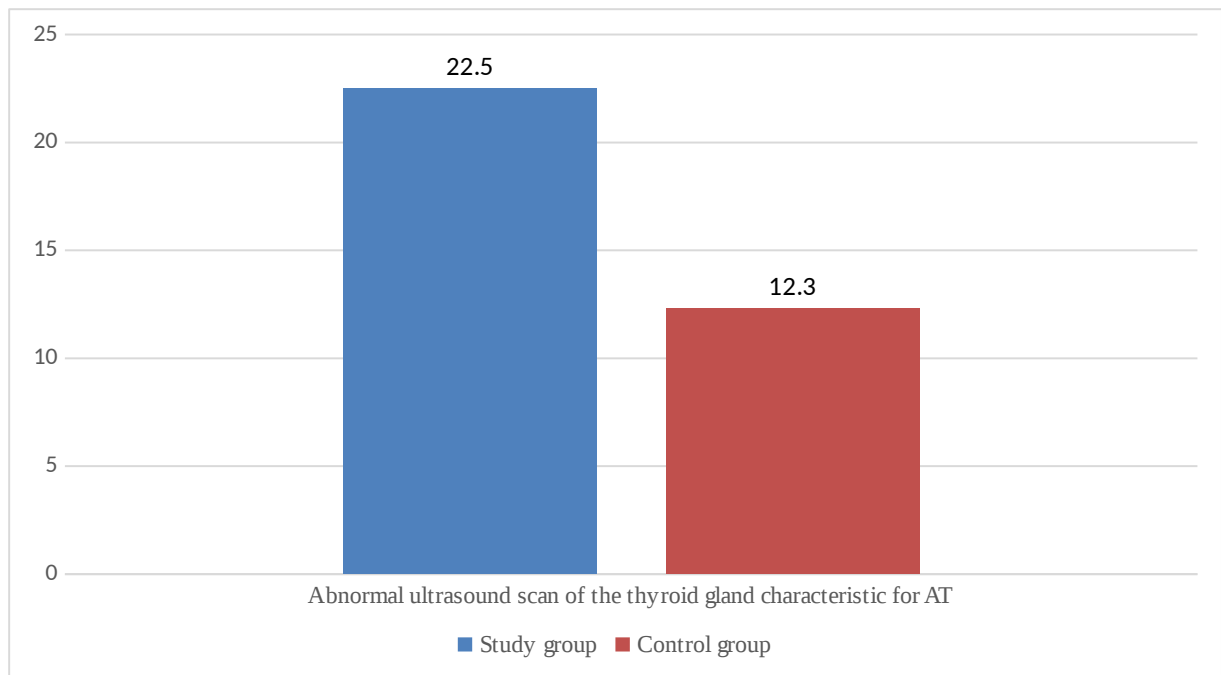
BMI — body mass index

p = 0.054

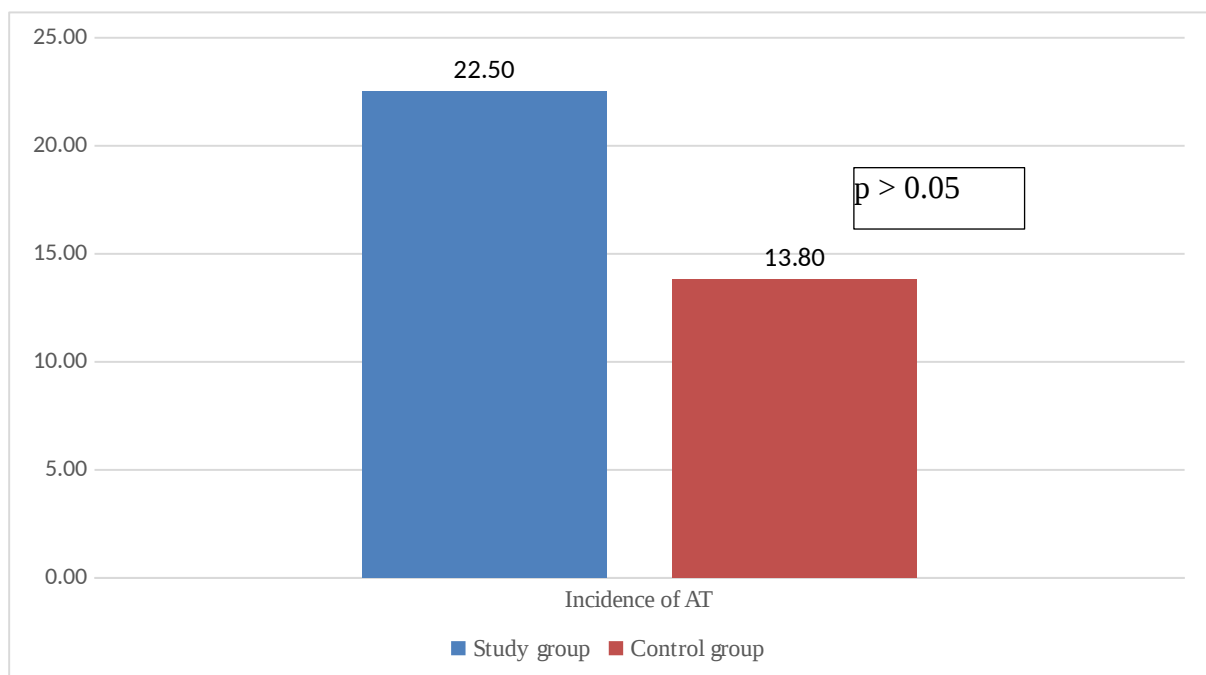
p > 0.05



**Figure 1.** The incidence of positive anti-thyroid antibodies in the study and control groups



**Figure 2.** The frequency of occurrence of the image characteristic of AT in the ultrasound examination in the study and control group



**Figure 3.** The frequency of AT diagnosis in accordance with the diagnostic criteria adopted in the study and control groups