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Is there an association between endometriosis and thyroid autoimmunity?

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SUMMARY

OBJECTIVE: It has been suggested that non-uterine endometrial implants can express thyroid-stimulating hormone receptors, thus inducing the formation of thyroid-stimulating immunoglobulin. We aimed to compare the autoantibody positivity in patients with and without endometriosis and to determine whether there is a difference in the incidence of thyroid diseases.

METHODS: This prospective observational study was conducted on 102 women who had been operated on for benign gynecological diseases. Cases enrolling in the study were divided into two groups: the study group with endometriosis (n=51) and the control group without endometriosis (n=51). The blood tests for thyroid-stimulating hormone, free thyroxine (fT4), thyroid-stimulating immunoglobulin, and anti-thyroid peroxidase antibody levels were checked.

RESULTS: The mean thyroid-stimulating immunoglobulin level was found to be higher in the endometriosis group than in the control group. However, this difference was not statistically significant. No significant difference was detected between endometriosis and control groups in terms of anti-thyroid peroxidase antibody and thyroid-stimulating hormone levels. The mean fT4 value (0.97±0.13 ng/dL) of the endometriosis patients was found to be significantly lower than the control group (1.08±0.21 ng/dL) ($p=0.002$; $p<0.05$). The mean anti-thyroid peroxidase antibody value of cases with bilateral endometrioma (82.21±252.29 IU/mL) was significantly higher than cases with unilateral endometrioma (15.81±83.13 IU/mL) ($p=0.028$; $p<0.05$). There is a positive and significant relationship between the size of endometriosis and anti-thyroid peroxidase antibody values ($p=0.011$; $p<0.05$).

CONCLUSION: This study points to an association between endometrioma diameter and anti-thyroid peroxidase antibody values which can be a stepping stone for new studies evaluating this hypothesis further.

KEYWORDS: Endometriosis. Thyroid. Autoantibodies. Autoimmunity. Hypothyroidism.

INTRODUCTION

Endometriosis is a chronic inflammatory disease affecting approximately 10% of women of reproductive age[1,2]. The etiology of endometriosis is still not clear despite some theories and many studies investigating the pathophysiology. In addition to genetic predisposition and structural abnormalities in the endometrial tissue, the impaired immune response also plays an active role in the development of endometriosis[1]. Various types of immune system cells were detected in the peritoneal fluids of women with endometriosis [3]. It is suggested that these cells increase susceptibility to disease rather than prevent disease. Endometrial cells could produce thyroid hormones in response to thyroid-stimulating hormone (TSH). Also, it has been suggested that non-uterine endometrial implants can express TSH receptors, thus inducing the formation of thyroid-stimulating immunoglobulin (TSI)[4]. Additionally, an increased risk of comorbidity of autoimmune diseases including systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, autoimmune thyroid disorder, coeliac disease, multiple sclerosis, inflammatory bowel disease, and Addison's disease was suggested[5,6]. Thyroid autoimmunity is the most common autoimmune disease in women of reproductive age and affects 5–20% of the female population[2]. In a cross-sectional study conducted in the USA, it is reported that hypothyroidism was more common in endometriosis patients[4].

In this study, we aimed to compare the thyroid autoantibody positivity in patients with and without endometriosis and to determine whether there is a difference in the incidence of thyroid diseases.

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METHODS

Patients

This prospective observational study was conducted at Haydarpasa Numune Training and Research Hospital between July 2019 and September 2020. The study was approved by the Local Ethics and Clinical Investigation Committee (Approval Number: HNEAH-KAEK 2019/KK/68). Informed consent was taken from all patients.

A total of 102 women who had been operated on for benign gynecological diseases were included in the study. Cases included in the study were divided into two groups: the study group with endometriosis (n=51) and the control group (n=51). The patients who did not have either endometriosis or adenomyosis were included in the control group. All patients underwent transvaginal ultrasonography by an experienced sonographer, and magnetic resonance imaging was added if needed.

The questionnaire included socio-demographic characteristics (i.e., age, education, weight, and height), medical and obstetric history including infertility and the number of spontaneous abortions, smoking habit, contraceptive methods, and other medications currently in use. It also included menstrual cycle patterns, irregularities, dysmenorrhea, and dyspareunia. Participants were also asked if they had ever been diagnosed or suspected of having hypothyroidism or hyperthyroidism, Hashimoto's thyroiditis, or Graves' disease. Patients who had malignancy and type 1 diabetes mellitus or were pregnant were excluded.

Endometriosis diagnose and stage

The endometriosis and control groups were diagnosed surgically. The diagnosis of endometriosis was approved pathologically. The stage of endometriosis was classified based on the definitions of the American Society for Reproductive Medicine[7]. The endometriotic lesions were categorized according to the number and depth of the lesions as follows: minimal stage 1 (scores 1–5), mild stage 2 (scores 6–15), moderate stage 3 (scores 16–40), and severe stage 4 (scores >40).

Laboratory analysis

The primary outcomes were TSH, free thyroxine (fT4), TSI, and anti-thyroid peroxidase antibody (anti-TPO) levels. A sample of 10 mL of venous blood was taken from each patient on an empty stomach. Blood samples were centrifuged at 4,000 rpm for 10 min and analyzed on the same day. TSH and sT4 levels were considered in the evaluation of the thyroid disease status of participants[8,9]. Serum TSH, sT4, and anti-TPO levels were measured by electrochemiluminescence immunoassay (ECLIA) method (Roche Cobas 8000/ISE). Serum TSI levels were measured by the chemiluminescence immunoassay (CLIA) method. A luminous molecule is used as the label in the immunoassay procedure known as CLIA, which is the real "indicator" of the analytical response. This is a quantitative approach for measuring antigens or antibodies based on the alteration in ECL signal or before and after immunoreaction ECLIA[10,11].

Statistical analysis

Descriptive statistics are presented as mean±standard deviation for normally distributed data and median (minimum–maximum) for non-normally distributed data. Shapiro-Wilk test was used for the assessment of the normality of data. The relationship between the categorical variables was examined using the Pearson chi-square, Fisher's exact test, and continuity Yates test. Mann-Whitney U test was used for data that were not normally distributed. Normally distributed parameters were compared among the two groups using the Student's t-test. Kruskal-Wallis test was used to compare the median of more than two independent groups. The associations between the normally distributed data were tested with Pearson correlation analysis. The results were evaluated against a confidence interval of 95% and a p-value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS v26, Chicago, IL, USA) was used for statistical analyses.

RESULTS

General characteristics

The general characteristics of the groups are shown in Table 1. Among the endometriosis group, 30% (n=30) had stage 3, 26% (n=26) had stage 4, 22% (n=11) had stage 2, and 22% (n=11) had stage 1 diseases. There was no statistically significant difference between the study and control groups in terms of body mass index (BMI) (p=0.095; p>0.05). Also, the mean height values of the endometriosis group (161.54±5.63 cm) were found to be significantly higher than the control group (158.63±6.78 cm) (p=0.022; p<0.05) (Table 1).

Thyroid parameters in endometriosis compared to non-endometriosis patients

Thyroid-stimulating immunoglobulin levels

There was no significant difference between endometriosis and control groups regarding TSI levels (Table 1). Among endometriosis patients, the mean TSI level was found to be

Table 1. Comparison of demographic characteristics and study variables between groups.

	Endometriosis group (n=51)	Control group (n=51)	p-value
	Mean±SD	Mean±SD	
Age (year)	40.34±9.03	45.94±8.8	[a]0.002*
Parity	1.48±1.19	2.22±1.43	[b]0.010*
Height (cm)	161.54±5.63	158.63±6.78	[a]0.022*
Body mass index (kg/m^2)	27.15±6.1	29.5±7.63	[a]0.095
TSI (U/L)	5.34±4.71	4.79±3.55	0.746
Anti-TPO (IU/mL)	37.06±158.49	38.32±112.78	0.982
TSH (μIU/mL)	1.69±0.88	1.66±1.07	[a]0.564
freeT4 (ng/dL)	0.97±0.13	1.09±0.21	0.002*
	n (%)	n (%)	
Educational status			
Primary	20 (42.6%)	40 (80%)	[c]0.001*
High school	12 (25.5%)	6 (12%)	
University	15 (31.9%)	4 (8%)	
Diseases			
Asthma	8 (16%)	6 (11.8%)	[d]0.743
Psychiatric disorders	5 (10%)	5 (9.8%)	[e]0.617
Rheumatological disorders	2 (4%)	2 (3.9%)	[e]0.684
Constipation	7 (14%)	3 (5.9%)	[e]0.151
Thyroid disorders	6 (12%)	3 (5.9%)	[e]0.234
Migraine	11 (22%)	10 (19.6%)	[d]0.959

[a]Student's t-test; [b]Mann-Whitney U test; [c]chi square test; [d]continuity Yates; [e]Fisher's exact test; and *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulant immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

higher in women having bilateral endometriosis (5.41±3.52 μIU/mL) compared to the unilateral group (4.57±3.73 μIU/mL). However, this difference was not statistically significant (p=0.416; p>0.05). There was no significant difference between endometriosis stages regarding TSI levels (Table 2). Also, a significant correlation was not detected between TSI level and endometriosis diameter (Table 3).

Anti-thyroid peroxidase antibody levels

No significant difference was detected between endometriosis and control groups regarding anti-TPO levels (Table 1). However, the mean anti-TPO was significantly higher in women having bilateral endometriosis (82.21±252.29 IU/mL) compared to the unilateral group (15.81±83.13 IU/mL) (p=0.028; p<0.05). The mean anti-TPO level was higher among stage 4 patients, but this difference was not statistically significant (p=0.524; p>0.05). A statistically significant correlation was found between endometrioma diameter and anti-TPO values (p=0.011; p<0.05) (Table 3).

Thyroid-stimulating hormone levels

There was no significant difference between groups regarding TSH levels (Table 2). The mean fT4 value (0.97±0.13 ng/dL) of the endometriosis group was found to be significantly lower than the control group (1.08±0.21 ng/dL) (p=0.002; p<0.05). The coexistence of endometriosis and thyroid dysfunction was detected in 6 cases (6/52). Moreover, there was no significant difference between groups in terms of thyroid dysfunction and hypothyroidism (p>0.05).

DISCUSSION

Endometriosis, a chronic, progressive, inflammatory disease, is very common in women of reproductive age. Although etiopathogenesis is still unclear, it is thought that the immune system may play a role in the pathogenesis as well as genetic and epigenetic factors. The impaired immune system might have a role in the pathophysiology of endometriosis. Alterations in humoral immunity were detected in endometriotic cells.

Table 2. Comparison of thyroid-stimulating immunoglobulin, anti-thyroid peroxidase antibody, thyroid-stimulating hormone, and free T4 levels among endometriosis patients.

	Endometrioma side	n	Mean	Median	Std. deviation	Minimum	Maximum	p-value
TSI	Unilateral	35	4.57	3.66	3.731	0.18	12.80	0.416
	Bilateral	16	5.41	3.85	3.520	0.49	11.00	
Anti-TPO	Unilateral	35	15.81	.49	83.138	0.49	486.00	0.028*
	Bilateral	16	82.21	1.18	252.290	0.49	1,000.00	
TSH	Unilateral	35	1.61	1.48	0.873	0.43	3.26	0.394
	Bilateral	16	1.82	1.69	0.899	0.74	3.99	
fT4	Unilateral	35	0.99	0.97	0.126	0.81	1.34	0.232
	Bilateral	16	0.93	0.90	0.128	0.72	1.15	
	Endometriosis stage		**Mean**	**Median**	**Std. Deviation**	**Minimum**	**Maximum**	**p-value**
TSI	Stage 1	12	5.95	6.15	3.321	0.49	11.02	0.064
	Stage 2	11	5.30	3.85	3.886	0.49	12.00	
	Stage 3	15	2.95	2.33	3.379	0.18	12.80	
	Stage 4	13	5.83	5.12	3.532	0.49	11.00	
Anti-TPO	Stage 1	12	2.01	0.49	4.600	0.49	15.87	0.524
	Stage 2	11	68.83	0.49	156.771	0.49	486.00	
	Stage 3	15	1.64	0.49	2.729	0.49	9.95	
	Stage 4	13	80.68	0.53	276.370	0.49	1,000.00	
TSH	Stage 1	12	1.56	1.74	0.779	0.64	2.88	0.498
	Stage 2	11	1.71	1.67	0.867	0.48	3.26	
	Stage 3	15	1.49	1.17	0.909	0.43	3.16	
	Stage 4	13	1.98	1.72	0.946	0.74	3.99	
fT4	Stage 1	12	0.94	0.94	0.140	0.72	1.28	0.172
	Stage 2	11	0.97	0.99	0.137	0.78	1.24	
	Stage 3	15	1.03	1.00	0.131	0.82	1.34	
	Stage 4	13	0.93	0.90	0.095	0.76	1.15	

Mann-Whitney U test and Kruskall-Wallis test, *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulating immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

Table 3. Correlation analysis between endometrioma diameter and thyroid-stimulating immunoglobulin, anti-thyroid peroxidase antibody, thyroid-stimulating hormone, and free T4 levels.

		Endometrioma diameter (cm)
TSI (U/L)	r	-0.098
	p	0.512
Anti-TPO (IU/mL)	r	0.368
	p	0.011*
TSH (μIU/mL)	r	-0.017
	p	0.908
FreeT4 (ng/dL)	r	-0.009
	p	0.950

Pearson correlation analysis, *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulating immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

The increased incidence of autoantibodies to histones, polynucleotides, and phospholipids was also reported in endometriosis cases[3]. Recently, Vanni et al. reported autoimmunity as a predictor of advanced-stage endometriosis[12]. In their study, Peynaeu et al. detected changes in thyroid hormone metabolism in the endometriotic cells, in a relevant study conducted on mice. In addition, they reported that thyroid hormones aggravated endometriosis focuses[13]. In a case-control study including 172 endometriosis cases and 117 healthy women, a significant association was not detected between anti-TPO levels and endometriosis. They did not find a significant association between hypothyroidism and endometriosis[14]. Similarly, we detected no significant difference between groups regarding hypothyroidism. Besides, we detected a lower mean fT4 value in the endometriosis group. In their study, Petta et al. detected the ratio of thyroid diseases at 20.9% in the control group

and 26.5% in the endometriosis group. Also, they reported that the ratio of anti-TPO positivity was 14.9% in the endometriosis group and 22.2% in the control group. They concluded that there was no increased risk in endometriosis cases in terms of thyroid diseases and they did not suggest routine thyroid disease screening in endometriosis cases[15]. In our study, we detected no significant difference between endometriosis and control groups in terms of anti-TPO levels. However, we found higher anti-TPO levels in women having bilateral endometriomas compared to the unilateral group. Additionally, we detected a statistically significant correlation between endometriosis diameter and anti-TPO values. We proposed that autoimmunity might be triggered after endometrioma is formed.

Graves' disease is an autoimmune thyroid disease characterized by binding IgG antibodies to the TSH receptor. TSI is considered pathognomonic for Graves' disease and is positive in approximately 98% of patients[16]. There are conflicting results about the association between Graves' disease and endometriosis. While a higher incidence of Graves' disease was reported in some studies, no significant association was proposed by several studies[15,17,18]. Ek et al. detected 93% TSI positivity in endometriosis cases and only 7.9% positivity in the control group. They found a significant association between TSI levels and endometriosis[14]. It was reported that endometrial tissue could be a focus for extrathyroidal hormone production in response to TSH. Also, it was suggested that non-uterine endometrial implants could express TSH receptors and induce TSI formation[4]. In our study, the mean TSI level was found to be higher in the endometriosis group. However, the difference was not significant. Studies with larger sample size are required to determine the association between endometriosis and autoimmune diseases such as Graves having a low incidence in the population (4.6/1,000)[19].

It was reported that autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, hypothyroidism, systemic lupus, and Sjogren's disease were more common in endometriosis patients[20,21]. Recently, Porpora et al. reported a high prevalence of autoimmune diseases in endometriosis patients[6].

There may be a potential link between autoimmune disease and endometriosis. Research has been done on this subject in the past 20 years, but the available data are contradictory. Some of the studies on this subject have only a questionnaire or retrospective design, and the heterogeneity of the study populations makes it difficult to establish a cause-effect relationship.

Some potential limitations of this study should be noted. Age, parity, height, and education status show significant differences between endometriosis and control groups. In accordance with the literature, we detected higher mean height and lower mean parity values in the endometriosis group. By considering the differences in these results, multivariate analyses were performed, and corrections were made by adding factors to the model as covariates and factors. The sample size of the study is also another limitation. By increasing the sample size, the association between endometriosis and autoimmune diseases can be revealed more clearly. The time between blood samples taken and the date of surgery may make a difference in evaluating the association between active endometriosis and autoantibody positivity.

In conclusion, we detected no significant difference between endometriosis and control groups in terms of mean TSI and anti-TPO levels. There was no statistically significant difference between the patients with and without dysmenorrhea and dyspareunia in terms of mean TSI, anti-TPO, TSH, and fT4 values. The mean anti-TPO was significantly higher in women having bilateral endometrioma. A statistically significant correlation was found between endometrioma diameter and anti-TPO values. We hypothesize that autoantibody positivity can be triggered after the formation of endometrioma. This study points to an association between endometrioma diameter and anti-TPO level which can be a stepping stone for new studies evaluating this hypothesis further. Exploring alternative etiologic hypotheses can be assessed to identify alternative immunomodulator therapy and development of new diagnostic tools. If the effect of autoimmunity is evident in the etiopathogenesis of endometriosis, the coexistence of autoimmune diseases could be considered in the follow-up of endometriosis patients. In addition, we detected lower free T4 levels in endometriosis cases. This difference can be considered in endometriosis cases who receive thyroid hormone replacement therapy.

AUTHORS' CONTRIBUTIONS

HS: Data curation, Writing – original draft. **OP:** Formal Analysis. **FV:** Writing – review & editing. **SAA:** Formal Analysis, Methodology, Supervision, Writing – review & editing.

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