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Comparison of thyroid volumes in patients with and without endometrioma

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Ethics Committee Approval
The study was approved by the Ethical Committee of Adana City Training and Research Hospital, Adana, Turkey (Decree No: 1557/2021). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Endometriosis is a condition characterized by endometrial tissue outside the uterus; it can lead to pelvic pain, although most cases remain asymptomatic. Abnormalities in the immune system have been hypothesized to contribute to development of ectopic endometrial tissues. Endometriosis is a chronic local inflammatory disorder associated with autoimmunity and thyroid disorders. This study aims to compare thyroid gland volumes between patients diagnosed with pathological endometrioma and those undergoing the removal of ovarian cysts for other gynecological reasons. Additionally, the study seeks to identify the coexistence of thyroid disease and determine the threshold value for thyroid volume in cases of endometriosis.

Methods: This prospective cohort study included 64 patients who met the defined inclusion criteria. Thyroid volumes were measured in women aged 18–45 with ovarian cysts before surgery. Group 1 comprised individuals with surgically planned endometrioma diagnoses later histologically confirmed after surgery. The control group (Group 2) consisted of women with similar anthropometric characteristics undergoing gynecological surgery for non-endometrioma ovarian cysts. Thyroid volume, functional thyroid hormone levels, tumor markers, and demographic data were compared between the groups.

Results: The endometrioma group exhibited a significantly higher thyroid volume. The thyroid volume variable demonstrated a diagnostic performance of 0.863 (0.771–0.956) regarding ROC-AUC in the presence of endometrioma, with a determined cutoff of 7.40. Although patients with endometrioma displayed a notably larger thyroid volume, cases of goiter were not observed. While there was no significant difference in thyroid hormones (serum TSH, T3 levels) between the groups, serum T4 was elevated in the endometrioma group, albeit within the normal laboratory range. All thyroid levels were within the normal range (euthyroid). As anticipated, serum CA-125 and CA19-9 levels were notably higher in the endometrioma group. Pathological reports did not indicate the presence of malignant cysts.

Conclusions: Patients with endometriosis experience increased thyroid volume, even without clinical signs of thyroid disease. The potential clinical interplay between thyroid diseases, thyroid volume, and endometriosis warrants consideration during patient follow-ups.

Keywords: endometriosis, thyroid disease, thyroid volume, ultrasonography

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Introduction

Endometriosis is a condition characterized by the presence of tissues resembling the endometrium outside the uterine cavity. This estrogen-dependent chronic inflammatory process affects 5–10% of women of reproductive age [1]. Despite extensive research, the definitive etiology of this condition remains elusive. The prevailing hypothesis suggests that recurrent retrograde menstruation, followed by the implantation of ectopic endometrial tissue within the pelvic or abdominal cavities, is the most widely accepted cause [1,2]. Moreover, it is noteworthy that immunological factors can contribute to the persistence of endometriotic tissues beyond the uterus. These factors may also induce alterations in progesterone receptor levels and the production of crucial transcription factors [1-3]. The realm of endometriosis holds much yet to be unveiled.

The clinical manifestations of this condition, which encompass pelvic pain, gastric reflux, inflammatory bowel disease, and infertility, exhibit a spectrum of variation due to its distinct molecular pathogenesis [2-4]. Surgical detection and pathological confirmation yields designations such as endometriomas (ovarian endometriosis), peritoneal endometriotic implants, and rectovaginal nodules, all representing forms of pelvic endometriosis [5].

Recent studies have illuminated the relationship between autoimmune and endocrine disorders in individuals with endometriosis [6,7]. Aghajanova et al. [8] conducted a study elucidating the expression and cellular localization of thyroid receptors and thyroid-stimulating hormone receptors (TSHR) within the endometrium of women devoid of prior medical history. Additionally, they unveiled that thyrotropin could bind to TSHR in endometrial cells independently of the hypothalamic-pituitary system. Thyroid disorders are often intertwined with conditions such as miscarriage, preterm delivery, or infertility, and thyroid hormones have already been linked to the physiology of the endometrium and ovaries [9].

This study aimed to perform a comparative analysis of thyroid gland volume and investigate the coexistence of concurrent thyroid disease in patients diagnosed with endometrioma via pathological examination who had undergone surgery for diverse gynecological indications involving the ovaries. As far as we know, there is a lack of research concerning thyroid volume in individuals with endometriosis. Thyroid volume measurements have been undertaken in patients with diabetes mellitus and pregnant women [10-12]. Should a substantial association between thyroid volume and endometriosis emerge, our study could potentially provide insights into the monitoring and management of patients.

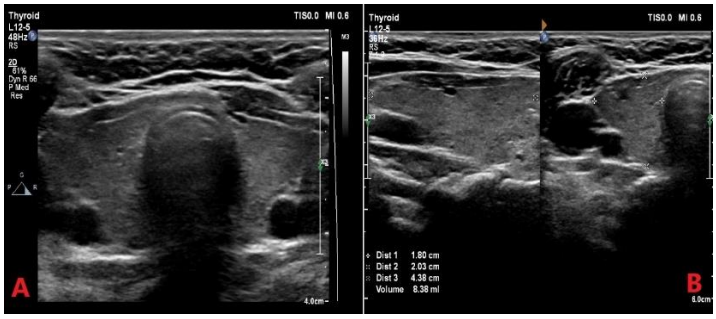
Materials and methods

This study was conducted at a tertiary Training and Research Hospital from September 2021 to May 2022. Written informed consent was acquired from all participants. The Ethical Committee of Adana City Training and Research Hospital approved the study under Decree No: 1557/2021. The clinical trial number assigned was NCT05323539.

The study included 18–45-year-old women who presented at our clinic with a pre-diagnosis of surgically planned endometrioma (Group 1). The control group (Group 2) consisted of women undergoing gynecological surgery for reasons other than endometriosis, specifically non-endometrioma ovarian cysts. Prior to surgery, gynecological ultrasounds and assessments were conducted for all patients. Following surgery, all cysts underwent pathological examination to confirm the histology of endometriosis.

During preoperative hospitalization, ultrasonography was employed to measure the thyroid volume of all participants. Longitudinal and transverse scans were conducted while participants were supine, encompassing depth, width, and length measurements for each lobe. The ellipsoid formula was applied to estimate thyroid volume, calculated as the sum of both lobes with the exclusion of the isthmus [12]. These measurements were consistently acquired by a single experienced radiologist (BP) using the same equipment – an advanced high-resolution ultrasound system (Philips EPIQ 7) equipped with a high-resolution linear transducer (12-5 MHz) manufactured by Philips Healthcare, Bothell, WA, USA (Figure 1).

Figure 1: Thyroid volume measurement A: Thyroid gland, B: Measurement of thyroid volume.



Confirmation of the patients' pathological diagnoses was undertaken, and those with divergent results (e.g., malignancy or pelvic abscess) were excluded from the study. Patients with diabetes goiter, individuals with historical or current autoimmune thyroid dysfunction, those undergoing thyroid hormone or iodine-containing medication treatments, patients with chronic autoimmune conditions, and pregnant participants were also excluded.

Body mass index (BMI, kg/m²) and demographic characteristics of the patients, including gravidity (G), parity (P), and comprehensive gynecological history, were meticulously documented. Moreover, serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (T3), total thyroxine (T4), and ovarian cyst-related serum tumor markers such as carbohydrate-associated antigen 19-9 (CA19-9) and cancer antigen 125 (CA125) were meticulously analyzed and recorded for all enrolled patients. The reference ranges for normal serum TSH, T4, and T3 levels are 0.34–5.6 mU/L, 0.61–1.38 ng/dL, and 2.6–4.37 ng/dL, respectively.

The sample size was determined based on a power analysis utilizing the study by Gomez et al., which investigated thyroid volume in patients with type 1 diabetes mellitus [13]. The calculated number of participants needed for the study was 60, with 30 allocated to the study group and an additional 30 for the endometrioma-negative group.

Statistical analysis

All analyses were executed utilizing the SPSS 22.0 statistical software package. Normally distributed continuous variables in the group data were presented as mean (standard

deviation). Calculations were performed using the G*power 3.1.9.7 software, with an effect size of 1.019, a study power of 95%, and a type I error of 5%. For non-normally distributed variables in the study, descriptive statistics were provided in the form of the median and the range of values (from minimum to maximum). Categorical variables were represented using numerical values along with corresponding percentages. The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. The continuous variables between the two groups were compared by employing either Student's t-test or the Mann-Whitney U test, based on the fulfillment of statistical assumptions. A receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point for thyroid volume. A significance threshold of 0.05 was applied to all statistical tests.

Results

The mean age of women in the endometrioma-positive group was 41 (8.2), while 46 (7.5) was in the endometrioma-negative group. Gravida and parity were significantly higher in the endometrioma-negative group (P=0.003 and P=0.006, respectively). No statistical differences were observed in mean BMI and abortion history. The comparison of variables between the groups with and without endometrioma is presented in Table 1. There was no significant difference in thyroid hormones (serum TSH and T3 levels) between the groups, although serum T4 was found to be higher in the endometrioma group (P=0.016). Notably, the T4 levels fell within the normal laboratory range, indicating euthyroid status. Serum CA-125 and CA19-9 levels were significantly higher in the endometrioma group, as anticipated. Pathological reports did not indicate the presence of any malignant cysts.

Table 1: Comparison of variables between groups with and without endometrioma.

Variables	Endometrioma		*P*-value
	Negative Mean (SD)	Positive Mean (SD)	
Age (year)	48.750 (7.556)	41.000 (8.219)	<0.001
BMI (kg/m²)	25.090 (3.052)	24.380 (3280)	0.368
Gravidity*	2.50 (0.0–6.0)	2.00 (0.0–7.0)	0.003
Parity*	2.00 (0.0–5.0)	1.00 (0.0–6.0)	0.009
Abortion*	0.00 (0.0–2.0)	0,.0 (0.0–2.0)	>0.999
CA125*	28.50 (8.0–56.0)	46.50 (29.0–108.0)	<0.001
CA19-9*	14.00 (6.0–32.0)	29.00 (21.0–49.0)	<0.001
Thyroid volume (mL)	5.972 (1.981)	8.859 (1,936)	<0.001
T3 (mg/dL) (2.6–4.37)*	3.700 (2.10–4.60)	3.555 (2.50–4.60)	0.984
T4 (mg/dL) (0.61–1.38)*	0.975 (0.60–1.40)	1.280 (0.76–165)	0.016
TSH (MUI/L) (0.34–5.6)	2.869 (1.342)	3.462 (1.184)	0.065

BMI: body mass index, TSH: thyroid-stimulating hormone, * Median (min-max) was used as descriptive statistics.

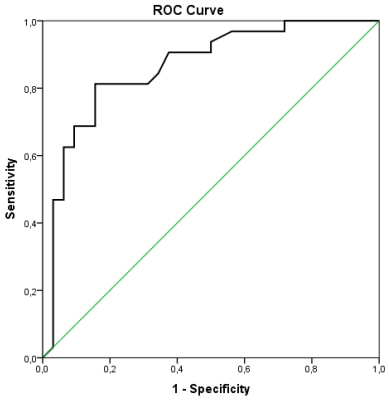
Thyroid volume exhibited a noteworthy increase in the endometrioma group. When considering the presence of endometrioma, the diagnostic performance of the thyroid volume variable yielded a value of 0.863 (0.771–0.956) in terms of ROC-AUC, and an optimal cutoff value of 7.40 was identified. Refer to Table 2 and Figure 2 for the ROC curve representation.

Table 2: ROC curve characteristics of the thyroid volume.

	ROC-AUC	*P*-value	Cutoff	Sensitivity	Specificity
Thyroid volume	0.863 (0.771-0.956)	<0.001	7.40	0.813	0.844

ROC: receiver operating characteristic, AUC: area under the curve

Figure 2: The thyroid volume and cutoff value in the ROC curve.



Discussion

This study discovered a greater thyroid volume in women with endometrioma. In the context of endometrioma, the diagnostic accuracy of thyroid volume was calculated to be 7.40 for the optimal cutoff level. Among the patients, there were no thyroid dysfunction, diabetes, or other chronic diseases. As a result, our findings demonstrated no notable elevation in thyroid function hormones.

Petta et al. [14] assessed the risk of autoimmune thyroid disease or dysfunction in women with endometriosis. They collected data through self-administered questionnaires and compared serum values of thyroid function hormones, thyroid peroxidase antibody (TPO-Ab), and thyroglobulin antibody (TG-Ab) between groups with endometriosis (n=148) and control subjects (n=158). According to their findings, women with endometriosis do not face an elevated risk of developing thyroid disease. It is important to note that these results pertain specifically to the Brazilian female population of reproductive age.

On a different note, Sinaii et al. [6] concluded that women with endometriosis exhibited increased rates of hypothyroidism in a comprehensive survey analysis of the female population in the US. However, it is worth mentioning that they did not substantiate these diagnoses with laboratory tests.

A recent study compared the prevalence of thyroid diseases between women with and without endometriosis. The study participants were drawn from Korean health insurance reviews, resulting in two distinct groups (5615 with endometriosis and 22,460 controls). Their findings indicated an association between Graves' disease and endometriosis, whereas hypothyroidism, including autoimmune hypothyroidism, did not display a similar correlation [15]. The potential link between Graves' disease and endometriosis could be explained by autoimmunity. While the cause of endometriosis remains unknown, the disease shares common pathways with autoimmune disorders, encompassing factors like polyclonal B cell activation, imbalanced T and B cell ratios, and inflammation [16].

Furthermore, estrogen is pivotal in the pathogenesis of endometriosis and Graves' disease [15]. This is primarily due to antibodies binding to the TSH receptor, which leads to hyperplasia and hypertrophy within the thyroid gland. However, it is noteworthy that Yuk et al. [15] did not delve into the

assessment of thyroid volume or the histology of endometriosis within their study group.

In contrast, our study undertook a comprehensive approach. We not only compared the thyroid gland volume but also scrutinized the presence of concurrent thyroid diseases among patients diagnosed with endometrioma and those with ovarian cysts who underwent surgical procedures for other gynecological indications. It is crucial to mention that individuals with diabetes, goiter, prior or ongoing autoimmune thyroid dysfunction, and those utilizing thyroid hormones or medications containing iodine were deliberately excluded from our study. Consequently, we did not investigate serum TPO-Ab or TG-Ab levels.

Remarkably, our investigation yielded a noteworthy cutoff value of 7.4 concerning thyroid volume measurement. It is important to acknowledge that thyroid gland volume can exhibit variability across different nations and is influenced by factors such as age, gender, and BMI. In our country, a total thyroid volume exceeding 10.94 ml indicates goiter [17]. Despite observing a significantly larger thyroid volume in patients with endometrioma, no instances of goiter were detected among them. This outcome implies an inflammation-linked condition in patients with endometrioma who exhibit neither thyroid-related complaints nor abnormal hormone levels.

Within our study, patients with endometrioma displayed elevated tumor marker levels, aligning with existing literature. Notably, the average age of patients lacking endometrioma was significantly greater. This disparity can be attributed to endometrioma predominantly precipitating infertility, pelvic discomfort, and mass-related complications during the reproductive years. Consequently, the mean age of patients within the endometrioma-negative group skewed higher. Moreover, this divergence in age also translated into distinct patterns concerning gravidity and parity, with both parameters being notably lower among individuals in the endometrioma-positive group.

Gomez et al. [13] conducted a study involving individuals with type 1 diabetes mellitus (DM1) who lacked thyroid dysfunction. Their findings suggested that DM1 patients exhibited a greater thyroid volume than healthy controls within similar anthropometric populations. It is worth noting that factors like autoimmunity and inflammation could potentially contribute to alterations in thyroid volume among these patients. However, it is important to highlight that a consensus has yet to be reached, as discrepancies in thyroid volume have not been consistently observed in analogous studies conducted in diverse nations [18].

A notable strength of the present study lies in the histological confirmation of endometriosis diagnosis and the absence of any chronic conditions that might impact the thyroid gland.

Limitations

The primary limitation of the study was its small sample size. Conducting larger-scale investigations across diverse nations could potentially influence the outcomes.

Conclusion and recommendations

In summary, endometriosis presents a challenging scenario with many symptoms and no definitive treatment options. Given its multifaceted pathophysiology, exploring its connections and interactions with other organ systems is imperative. Specifically, diligent monitoring of patients for potential thyroid diseases and assessing potential goiter development should be undertaken. Additionally, prospective longitudinal studies are warranted to unravel the clinical interplay between thyroid health and endometriosis, providing valuable insights for patient follow-up protocols.

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