

INVESTIGATING THE PREVALENCE OF AUTOIMMUNE DISEASES IN ENDOMETRIOSIS PATIENTS

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ABSTRACT

Aims: This study aims to determine the prevalence of autoimmune diseases in women with endometriosis who were admitted to the Department of Gynecology and Obstetrics, Trakya University Hospital.

Methods: The comorbid autoimmune diseases of 231 women older than 18 years diagnosed with endometriosis by surgery and pathology were examined. Considered autoimmune diseases were: Systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), autoimmune thyroiditis, Addison's disease, rheumatoid arthritis, multiple sclerosis, celiac disease, and Sjögren's syndrome.

Results: The mean age of women was 41.94±0.5. The association rate of endometriosis with at least one autoimmune disease was 11.69%. There were 18 patients with autoimmune thyroiditis (7.8%), 9 patients with rheumatoid arthritis (3.9%), 4 patients with ulcerative colitis (1.7%), 2 patients with systemic lupus erythematosus (0.9%), 2 patients with Crohn's disease (0.9%), 1 patient with Addison's disease (0.4%), 1 patient with celiac disease (0.4%), 1 patient with multiple sclerosis (0.4%) and no patients with Sjögren's syndrome. No statistically significant differences were found between the stages of endometriosis in patients with or without autoimmune diseases.

Conclusion: To our knowledge, this is the only Türkiye-based study investigating the prevalence of autoimmune diseases in endometriosis patients. We examined the relationship between endometriosis and autoimmune disease depending on the endometriosis stage and patient age, but we could not reach a statistically significant conclusion. However, our data must be analyzed with caution due to the retrospective single-center study design and the small sample size.

Keywords: Endometriosis, autoimmune diseases, epidemiology

INTRODUCTION

Endometriosis is a chronic inflammatory disease that is distinguished by the existence of endometrial tissue outside the uterine cavity, most commonly on the pelvic peritoneum, ovaries, and fallopian tubes (1). The cardinal symptoms include severe pelvic pain, dysmenorrhea, dyspareunia, adnexal mass, and infertility (2, 3). According to studies conducted in the United States of America, the prevalence of endometriosis in women of reproductive age was found to be 5-10% (3). However, since surgical methods make the definitive diagnosis, the true

incidence may not be determined clearly (3). The pathogenesis of endometriosis has not been fully elucidated yet, but it is known to be an estrogen-dependent chronic disease (1). Many theories have been put forward about the etiology of endometriosis, such as Sampson's theory of retrograde menstruation, coelomic metaplasia, and lymphovascular invasion theory (2). Among them, Sampson's retrograde menstruation theory is the most accepted, and it explains the formation of endometriosis due to the backward flow of blood in the normal menstrual cycle (4). However, a study demonstrated that although



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up to 90% of women experience retrograde menstruation, only 6-10% of them develop endometriosis (5). Although retrograde menstruation is seen in the majority of women, it has been assumed that endometriosis develops in women with congenital dysregulated immune mechanisms whose immune systems cannot respond to refluxed endometrial debris (6). This deficiency recalls the idea that the immune system cannot sufficiently remove the ectopic endometrium tissue. As demonstrated in earlier studies, menstrual debris is naturally removed by innate and adaptive immune system components followed by tissue restoration (1, 3, 6, 7). However, menstrual debris may cause "immune system overload" and "immune malfunction" over time. It is unclear whether this immunological deficiency is the consequence or the cause of endometriosis (6). Both cellular immunity and antibody-dependent immunity are impaired in endometriosis (8). Disruption of cellular immunity helps the implantation process of endometriotic cells in the peritoneum (7, 9). At the same time, the inability of peritoneal immune cells to eliminate the misplaced endometrium also leads to the ectopic development of endometrial tissue (7, 9). In addition, it is observed that the cytotoxic activity of natural killer cells is decreased in patients with endometriosis (10). Consequently, the endometrial cells in the peritoneal cavity can remain present for an extended period, increasing the probability of their adherence (10). In a study comparing the serum of 71 laparoscopically staged endometriosis patients and 109 healthy individuals, antibodies to nuclear, phospholipid, smooth muscle, and sperm antigens were investigated, and at least one type of the abovementioned antibodies was found in 58% of endometriosis patients (11). In addition, antinuclear antibodies, smooth muscle antibodies, anticardiolipin antibodies, and lupus anticoagulant levels were found to be significantly higher in endometriosis patients compared to the control group (11). Based on this connection between endometriosis and the immune system, we believe autoimmune factors might be more prominent than currently thought in the pathophysiology of the disease. Therefore, autoimmune diseases are seen more often in women with endometriosis. In this retrospective study, 231 women with endometriosis were admitted to the Department of Gynecology and Obstetrics, Trakya University Hospital, were included and examined in terms of other autoimmune diseases, and we aimed to determine the prevalence of autoimmune diseases in women with endometriosis.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (protocol code: TÜTF-BAEK 2021/235, date: 17.05.2021). Data for this retrospective epidemiological study was collected through the database of Trakya University School of Medicine between January 2014 to 31 December 2021. Two hundred thirty one women older than 18 years old that were identified with endometriosis were included in the study. The inclusion criterion was a diagnosis of endometriosis confirmed by surgery

and pathology. The staging was performed by the location, size, and type of lesions and the extent of adhesions present by using the revised scoring system of the American Society for Reproductive Medicine (rASRM) (12). Scoring system of the American Society for Reproductive Medicine Stages for endometriosis is first defined in 1979 and revised in 1997. rASRM is the most widely used staging method for endometriosis. With this way, score is determined by the location, infiltration and posterior culdesac obliterations of the endometriotic lesions. It has 4 different stages: I (1-5 points, minimal), II (6-15 points, mild), III (16-40 points, severe), and IV (>40 points, extensive). Data for staging, patient age, and the presence of any comorbid autoimmune disease, regardless of the time of diagnosis, were recorded. Included diagnoses of autoimmune diseases did fulfill the diagnosis requirements of International Classification of Diseases-10 (13). Considered autoimmune diseases were systemic lupus erythematosus (SLE) (M32.1), inflammatory bowel disease (Crohn's disease and ulcerative colitis) (K50 and K51), autoimmune thyroiditis, Addison's disease (E27.1), rheumatoid arthritis (RA) (M06.9), multiple sclerosis (MS) (G35), celiac disease (K90.0), and Sjögren's syndrome (M35.00) (13). Patients with negative clinical signs or autoimmunity markers were considered as patients without autoimmune diseases.

Statistical Analysis

The data were analyzed with IBM SPSS version 23.0. Nominal variables were expressed as total count and percentage. Age was expressed as mean (\pm standard deviation). Normality of the data was determined via Shapiro-Wilk test and statistical comparison of groups was performed by chi-square test or Fisher's exact test as appropriate. Statistical comparison of parametric variables among the groups was performed by Independent sample t-test. For all analyses, a p-value threshold of <0.05 was set for statistical significance.

RESULTS

Among 231 patients in this study, 204 did not have an autoimmune disease, 27 had one or more autoimmune diseases, and the distribution of these 27 patients was as follows: 20 patients had only one autoimmune disease, 4 had two autoimmune diseases, 2 had three autoimmune diseases and 1 had four autoimmune diseases. The association rate with at least one autoimmune disease was 11.69%. The number of diagnoses of co-existing autoimmune diseases is as follows, regardless of whether patients have one or more diagnoses: 18 patients with autoimmune thyroiditis (7.79%), 9 patients with RA (3.90%), 4 patients with ulcerative colitis (1.73%), 2 patients with SLE (0.87%), 2 patients with Crohn's disease (0.87%), 1 patient with Addison's disease (0.43%), 1 patient with celiac disease (0.43%), 1 patient with MS (0.43%) and no patients with Sjögren's syndrome. The mean age of patients with endometriosis was 41.94 ± 0.5 . No statistically significant difference was found in the mean age of patients with autoimmune diseases (40.6 ± 7.4 years) and without autoimmune diseases (42.1 ± 8.9 years) ($p=0.364$) (Figure 1).

There were 20 patients with stage I (8.7%), 2 patients with stage II (0.9%), 171 patients with stage III (74%), and 38 patients with stage IV (16.5%) endometriosis. Among patients who did not have autoimmune diseases 17 (8.3%), 2 (1%), 151 (74%), and 34 (16.7%) patients had stage I, II, III, and IV endometriosis, respectively. Whereas among patients with autoimmune diseases 3 (11.1%), 20 (74.1%), and 4 (14.8%) patients had stage I, III, and IV endometriosis, respectively. Patients who had autoimmune diseases with stage II endometriosis were not found. No statistically significant difference was found between the stages of endometriosis in patients with or without autoimmune diseases ($p=0.913$) (Figure 2).

DISCUSSION

Current studies strengthen the theory that endometriosis may be an autoimmune disease (7-10). The fact that endometriosis does not occur in every woman with retrograde menstruation

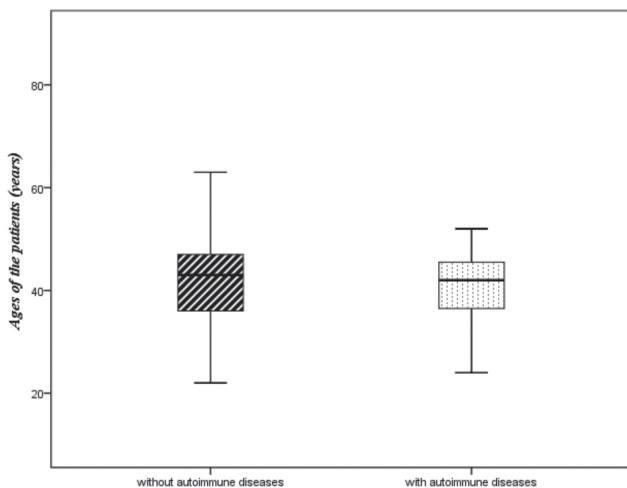


Figure 1: Boxplots of the distribution of patients' ages in endometriosis without and with autoimmune diseases.

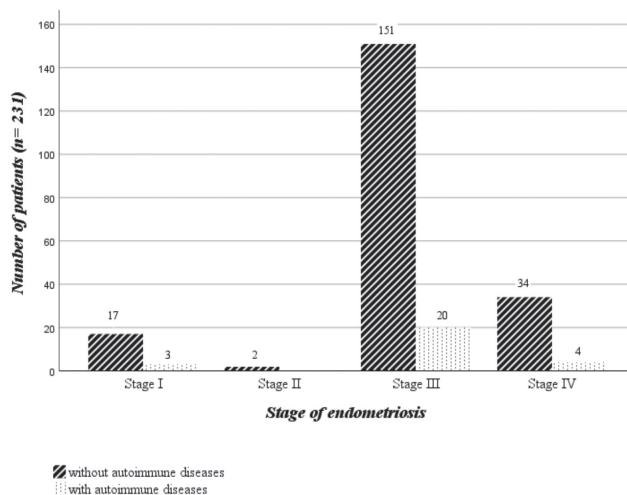


Figure 2: Comparison of the number of patients with and without autoimmune diseases in different stages of endometriosis.

suggests that while this debris can be easily cleaned in women with a healthy immune system, the disease occurs due to the debris that cannot be cleaned well in individuals with immune defects (6). However, it is still unclear whether immune disorders can cause endometriosis or whether these diseases occur secondary to events resulting in endometriosis (7). In our study, 231 patients were examined, and the association rate with at least one autoimmune disease was 11.69%. The study by Caserta et al. (14) showed that patients with endometriosis have a higher rate of coexistence of autoimmune diseases than those without. Another study examined 3680 female patients surgically diagnosed with endometriosis and found that patients with endometriosis had higher rates of hypothyroidism, RA, SLE, Sjögren's syndrome, and MS, but not hyperthyroidism or autoimmune diabetes, compared to the general population (15). Further, a study in Denmark with data from 37661 patients showed an association between endometriosis and MS, SLE, and Sjögren's syndrome (16). We found that autoimmune thyroiditis was the most frequently associated with endometriosis among autoimmune diseases, with a rate of 7.79%. A cross-sectional study by Petta et al. (17) detected 38 autoimmune thyroiditis patients among 148 endometriosis patients and calculated this rate as 25.67%. In the study of Ek et al. (18), elevated Immunoglobulin G titers of thyroid stimulating hormone receptor antibody were found to be associated with endometriosis, which supports the link between endometriosis, autoimmunity, and thyroid pathophysiology. However, a more recent study showed an increased risk of Graves' disease but did not find an increased risk of hypothyroidism or autoimmune hypothyroid disease (19). The coexistence of RA and endometriosis was found to be 3.9%. In addition, patients with endometriosis were associated with an increased risk of RA in the retrospective cohort study of Xue et al. (20). However, Ek et al. (18) examined the relationship between endometriosis and RA, and no association was found. In a case-control study of 223 patients, in which the coexistence of celiac disease and endometriosis was investigated, 7 patients (3.1%) had celiac disease (21). In our study, which included 231 patients, this rate was 0.4%. Although the sample sizes are close, the coexistence of endometriosis and celiac disease detected in our study was 1 in 8 compared to the result obtained by the other study (21). In our study, the coexistence of Crohn's disease or ulcerative colitis with endometriosis was 0.87% and 1.73%, respectively. The study by Jess et al. (22) reported an increased incidence of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) in women with a history of endometriosis compared to women without known endometriosis. Our study found the association between SLE and endometriosis to be 0.87%. In a cohort study, 37661 women diagnosed with endometriosis were examined, and a statistically significant 1.6-fold increase in the risk of SLE was observed (16). Another nationwide population-based cohort study revealed that patients with endometriosis are at increased risk of SLE and that adequate hormonal therapy can reduce the risk of SLE (23).

We found that 1 patient had Addison's disease (0.43%) in our study. Gemmill et al. (24) reported that the prevalence of Addison's disease in women with endometriosis was higher compared to all women (2.31 per 1000 population versus 0.09 per 1000 population). While the association of MS was detected in 0.43% of our study, we could not find concomitant Sjögren's disease in 231 endometriosis patients. In a cross-sectional study conducted by Sinaii et al. (15), it was found that the incidence of Sjögren's syndrome was higher in women with endometriosis. MS was the least associated disease, with a rate of 0.43%. In a study with 16 patients with relapsing-remitting MS, assisted reproductive technology using gonadotropin-releasing hormone agonists and recombinant follicle-stimulating hormone for the treatment of infertility was found to be associated with a 7-fold increase in the risk of MS exacerbation (25). This has shown that hormonal factors also play an essential role in increasing the activity or severity of autoimmune diseases. We also examined the relationship between endometriosis and autoimmune disease depending on the endometriosis stage and patient age, but we could not reach a statistically significant conclusion. In light of all this information, there are many studies trying to explain the relationship between autoimmune diseases and endometriosis, but they were either conducted in a single center or focused on a single disease. If there is a pathophysiological correlation, the only way to elucidate it is to conduct more comprehensive studies. We looked up a possible relationship between endometriosis and several autoimmune diseases, that could be reached on our hospital database. As a result, we did not find any remarkable associations with a high percentage. The strength of our study is the first and only Türkiye-based study investigating the prevalence of autoimmune diseases in endometriosis patients. However, since our sample size was small (n=231), slight differences in the number of patient groups were reflected as relatively remarkable differences in percentages. Since the definitive diagnosis of endometriosis in the current literature can only be made with the pathological examination of a surgical sample, many patients can be overlooked. In addition, retrospective analysis of the hospital database brought some limitations to the study. There were missing data because some patient data were incompletely processed into the database. In addition, since the data were analyzed retrospectively, the patient's data (e.g., biochemical results, CA-125 values) that were not examined at the time of diagnosis could not be examined later, and these data could not be compared. The pathophysiology of endometriosis can be clarified by further studies investigating the association between various autoimmune diseases and endometriosis, and thus treatment methods for endometriosis can be improved. Furthermore, multicenter studies with a large sample size are required to deepen our understanding of endometriosis in Turkey.

CONCLUSION

In this retrospective single-center study with a small sample size, the prevalence of at least one autoimmune disease in patients with endometriosis is 11.69%. Clinicians should keep in mind that patients with endometriosis may also have additional autoimmune diseases and possible endometriosis in autoimmune patients. Further research may help understand the association between endometriosis and the immune system.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (protocol code: TÜTF-BAEK 2021/235, date: 17.05.2021).

Informed Consent: Retrospective study.

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