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High prevalence of autoimmune diseases in women with endometriosis: a case-control study

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ABSTRACT

The immune system seems to be involved in the pathogenesis of endometriosis. Peritoneal chronic inflammation is present and natural killer cells and macrophages abnormalities have been reported in women with the disease. Moreover, a higher production of serum autoantibodies has been found, which could be related to various factors; some still need to be clarified. The correlation between endometriosis and autoimmune diseases is still unclear with few and conflicting available data. The aim of this study was to evaluate the prevalence of autoimmune diseases, as conditions with a possible common pathogenetic factor, in women affected by endometriosis, in order to address future research on its pathogenesis. This retrospective case-control study includes one hundred and forty-eight women with endometriosis and 150 controls. All women were aged between 18 and 45. Informed consent was obtained from all participants of the study. Considered autoimmune diseases include systemic lupus erythematosus (SLE), celiac disease (CD), inflammatory bowel disease (IBD), and autoimmune thyroiditis. Statistical comparison of patients and control group was performed by means of chi-square test or Fisher's exact test as appropriate. Statistical comparison of parametric variable (age) among the groups was performed by *t*-test for unpaired data. Age was expressed as mean. A value of .05 or less was considered as significant. In the case group, five patients were affected by IBD, while the disease was not observed in the control group ($p = .07$). SLE was found in eight patients in the case group, while only one was found in the control group ($p = .01$). Fifteen women in the case group were affected by CD, while the disease was present only in one woman in the control group ($p < .0001$). A significant correlation was also found between endometriosis and autoimmune thyroiditis: 80 patients with endometriosis had thyroid diseases versus 14 patients in the control group ($p < .0001$). Our study reports an association between endometriosis and autoimmune disorders, showing a higher prevalence of autoimmune diseases in women affected by endometriosis. These results support a possible autoimmune pathogenesis of endometriosis.

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Background

Endometriosis is a common disease affecting 10% of women during their reproductive years [1]. Endometriosis is an inflammatory disease characterized by the presence of endometrium-like tissue in sites outside the uterine cavity, primarily on the pelvic organs, ovaries, fallopian tubes, bladder, recto-sigmoid colon, utero-sacral ligaments, and uterine myometrium. The main clinical symptoms are chronic pelvic pain, dyspareunia, and infertility [2,3].

The pathogenesis of endometriosis is not completely clear. The immune system participates in the homeostasis of the peritoneal cavity, and modifications in its functioning have been proposed to explain endometriosis occurrence (Figure 1). Endometriosis is characterized by the presence of abnormal lymphocyte activation, particularly, antigen-presenting cells (APCs) that contribute to pathogenesis by presenting autoantigen to autoreactive T cells in the context of the major histocompatibility complex. The reduced natural killer (NK) cells activity during endometriosis could in part explain the increased autoimmune reactivity associated with the disease in the peritoneal cavity; NK cells might be less effective in killing autologous DCs loaded with endometrial self-antigens, facilitating their presentation to autoreactive T cells and the production of autoantibodies [4,5]. An impaired immune response leads to the failure in removing endometrial debris in the pelvic cavity, and indeed increases their implantation, neoangiogenesis, and proliferation [6]. Some inhibitory cytokines seem to be involved in this altered immunosurveillance: anti-inflammatory cytokine IL-10 is increased in the peritoneal fluid (PF) and/or peripheral blood in women with endometriosis [6].

Exposure to some pollutants (polychlorobiphenyls – PCBs) increases the risk of endometriosis probably also through the negative effect on the immunological status [7]. PCBs could promote endometriosis via chronic stimulation of the expression of the pro-inflammatory cytokines and via the induction of inappropriate estrogen production in the endometrium [8]. In women exposed to these contaminants, a significant down regulation of the NK cell activity associated with a significant decrease in the production of IL-1 beta and IL-12 was found by Quaranta et al. [8,9].

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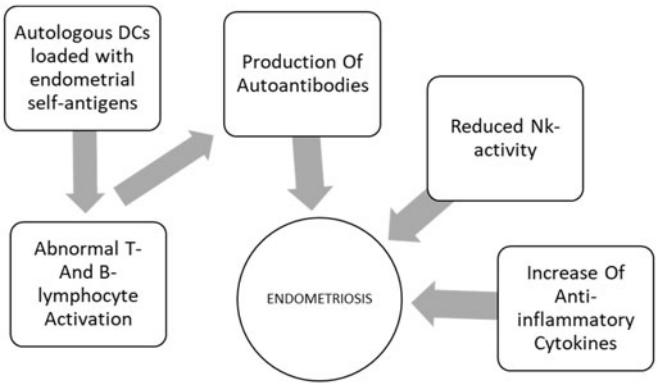

Figure 1. Immunological mechanisms underlying endometriosis.

It is well known that women have more susceptibility to develop autoimmune diseases than men. This could be related to hormonal factors, as androgens show a protective role in developing these diseases [10]. Furthermore, the XX sex chromosome complement seems to be implicated in promoting antibody mediated diseases, even if the precise gene involved has still to be determined [11,12]. Furthermore, a large number of studies have shown that the prevalence of autoimmune diseases was higher among patients with endometriosis than in general female population.

Women with endometriosis share some common autoimmune disorders, such as a chronic local inflammatory process and the presence of autoantibodies [4,5]. The potential link between autoimmune disease and endometriosis has been investigated over the last 20 years but the available data are conflicting.

In 2002, Sinaii et al. [13] published the results of a 1998 survey of 3680 members of the Endometriosis Association. The study reported that members of the Endometriosis Association in the United States had higher rates of hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and multiple sclerosis. Results of a recent survey of the U.S. Endometriosis Association suggested that women affected by endometriosis had a higher prevalence of autoimmune diseases compared to the general U.S. female population [14].

Recently, some studies have hypothesized a potential link between endometriosis and celiac disease (CD), since these conditions share some similarities in the pathogenesis [15].

To provide a new insight into the possible link between endometriosis and the autoimmune diseases, we performed a case-control study to investigate the prevalence of some of the most frequent autoimmune diseases, such as SLE, CD, autoimmune thyroid diseases, and inflammatory bowel disease (IBD) among Italian women with endometriosis compared to a control group not affected by endometriosis.

Methods

From January 1 2014 to December 31 2017, 148 women in reproductive age affected by endometriosis were enrolled in the study. Informed consent was obtained from all participants to the study. Inclusion criteria for the case group were a diagnosis of endometriosis confirmed by laparoscopy and histology. A control group of 150 patients with no clinical or ultrasound (US) signs of endometriosis was enrolled. Both patients in case and in control groups referred to endometriosis and chronic pelvic pain outpatient clinic of Policlinico Umberto I of Rome. All women were 18–45 years old. Considered autoimmune diseases were: SLE, CD, IBD (Crohn's disease and ulcerative colitis), autoimmune thyroiditis. Patients with CD were previously diagnosed by endomysial IgA (EMA), tissue transglutaminase (t-TGA) antibodies measurement, and serum total IgA dosage, and in case of antibody positivity, upper digestive endoscopy with intestinal biopsy. Autoimmune thyroiditis had been diagnosed by US, thyroid peroxidase antibodies (TPOAbs), thyroglobulin antibodies (TgAbs), and TSH-Ab serum measurement. The other autoimmune diseases had been previously diagnosed on the basis of specific autoantibodies for each disease: antinuclear antibodies (ANAs), extractable nuclear antigen (ENA), anti-cardiolipin antibodies, antiphospholipid antibodies, and lupus anticoagulant (LAC) for SLE. Inflammatory bowel disease was confirmed by colonoscopy and intestinal biopsy.

Exclusion criteria were: menopause, lack of data of the autoimmune diseases and absence of laparoscopic diagnosis in patients with endometriosis. Due to the reduced sample number, SS and rheumatoid arthritis were decided to exclude from the evaluation of the study.

Table 1. Presence of autoimmune diseases in the case and in the control.

Autoimmune diseases	Case group *n* (%)	Control group *n* (%)	OR	95% CI	*p*
Autoimmune thyroiditis	80 (54.4%)	14 (9.3%)	11.37	6–21.5	<.001
IBD	5 (3.4%)	0			.07
SLE	8 (5.4%)	1 (0.7%)	8.63	1.07–69.91	.01
Celiac disease	15 (10.2%)	1 (0.7%)	12.04	2.22–130.79	<.001

Statistical analysis

Statistical comparison of patients and control group was performed by means of chi-square test or Fisher's exact test as appropriate. OR and 95% CI was analyzed. Statistical comparison of parametric variable (age) among the groups was performed by *t*-test for unpaired data. All values were expressed as total count and percentage. Age was expressed as mean. A value of .05 or less was considered as significant.

Results

No significant difference was found in the mean age of cases (31.6 years) and controls (28.3 years), familiar history of autoimmune diseases (26% in case and 23% in controls) and BMI (24 for case patients and 24.9 in control group).

In the study group, nine (6.1%) patients were classified as minimal endometriosis, 20 (13.6%) as mild endometriosis, 46 (31.3%) as moderate endometriosis, and 72 (49%) as severe endometriosis according to the revised American Society for Reproductive Medicine classification of endometriosis [16].

SLE was found in eight patients of the case group (5.4%) and in one patient of the control group (0.7%) ($p = .01$). CD was found in 15 (10.2%) women with endometriosis while only one case (0.7%) was found in the control group ($p < .0001$). IBD was found in five case-patients (3.4%) whereas no controls had the disease ($p = .07$). Endometriosis and autoimmune thyroiditis were found in 80 case-patients (54.4%) versus 14 controls (9.3%) ($p < .0001$). Overall, patients with endometriosis had higher prevalence of autoimmune diseases than controls except for IBD ($p = .07$). The results are reported in Table 1.

Discussion

Despite decades of extensive research, the pathogenesis of endometriosis is not completely clarified. Endometriosis is considered a multifactorial disorder and the leading hypothesis is the retrograde menstruation theory, being the menstrual blood flowing into the abdominal cavity responsible of the growth of endometrial cells promoting oxidative stress and consequent inflammation [17,18]. The immune system participates in the homeostasis of the peritoneal cavity; it plays an important role in the pathogenesis of endometriosis due to the action of antibodies, and cell-mediated immunity. The chronic inflammation and the associated increased oxidative stress present in endometriosis, are also found in patients with other chronic inflammatory diseases [19]. In addition, a genetic predisposition has been hypothesized for development of endometriosis, such as HLA DQ7 haplotype being reported as the first allele significantly associated with endometriosis [20]. Moreover, Owen et al. found several genetic polymorphisms both in endometriosis and autoimmune diseases as well as some genetic alleles involved in the release of autoantibodies [21]. This hypothesis is supported also by familial occurrence, female preponderance, and increased likelihood of other autoimmune diseases [5,13,22].

The present retrospective case-control study reports a higher prevalence of some autoimmune diseases in Italian women with endometriosis than women of general population.

This study shows a higher incidence of CD in the case group, in agreement with some studies. Conversely, others report no significant association between CD and endometriosis [23,24]. We also found a significant association between SLE and endometriosis, in agreement with the study of Harris et al. [25]. In contrast, a Spanish case-control study despite a higher prevalence of SLE in women with endometriosis, did not find a significant difference, maybe due to the low number of patients recruited in the study [26]. In the present study, a statistically significant correlation between autoimmune thyroid diseases and endometriosis was also found. Similarly, Yuk et al. found a correlation between these two diseases, in particular with Graves' disease [27].

No significant correlation was found between IBD and endometriosis. It is important to underline that the quite small sample's size is probably the reason of the large fork of 95% CI. Due to the small number of patients affected by IBD, we did not calculate OR and CI for this correlation.

The presence of numerous similarities in the pathogenesis of autoimmune diseases and endometriosis may explain their association. Inflammation is a key feature of endometriosis with an overproduction of metalloproteinases, prostaglandins, and cytokines, such as interlukein-6 and tumor necrosis factor (TNF) that promote the adhesion of endometrial tissue on ectopic surfaces [28]. Women with endometriosis exhibit altered immune surveillance with depressed cell-mediated immunity and higher humoral immune response [12].

Altered cell-mediated immunity is also involved in the development of the CD. As shown by Salvati et al., CD is linked to a critical role of interleukin-18 (IL-18) and interferon-γ (IFN-γ) in inducing and maintaining Th1 responses after gluten exposure has been suggested [29,30]. Similarly, a Th1 imbalance with involvement of IL-18 and IFN-γ has been reported in endometriosis and it has been shown that IL-18 is a key cytokine in developing the pathogenesis of endometriosis [31]. Higher levels of IL-18 have been found in patients with endometriosis than non-endometriotic controls [24,32].

A potential shared pathogenesis between SLE and endometriosis has been hypothesized. Indeed, ANAs, common in women with SLE, have been observed in women with endometriosis [25].

Humoral immunity can explain the correlation with autoimmune thyroid diseases. A higher reactivity of some autoantibodies (e.g. TPOAb) in patients with endometriosis has been found. Moreover, it seems that the incidence of positive ANAs is higher in patients with endometriosis as in patients with Graves' disease. A further possible link between Graves' disease and endometriosis is the estrogen effect: Graves' disease is fivefold more prevalent among women than men. Estrogens are important modulators of the immune system as regulators of cytokine expression, antigen presentation, and B-cell lymphopoiesis. The exact effect of the estrogen receptor β on the function of the immune system is not clear but available data suggest that signaling through estrogen receptor beta gene (ESR2) may have a suppressive effect. Differential expression of the ESR2 was confirmed recently in patients with endometriosis. In addition, polymorphism of the ESR2 is associated with susceptibility to Graves' disease. Thus, changes in ESR2 function might be a common link between Graves' disease and endometriosis [27,33].

The underlying mechanisms of the association between endometriosis and autoimmune diseases are still unclear and deserve further investigations; it is possible that common genetic polymorphisms and/or common pathogenetic factors may be involved. The main limitation of the study is the small sample size; therefore, further studies provided with a good accuracy in diagnosis, are required to confirm our data.

Conclusions

Our study reports a significant higher prevalence of autoimmune diseases in women affected by endometriosis than in controls. This association seems to confirm the hypothesis of a possible autoimmune pathogenesis of endometriosis even though common genetic factors cannot be ruled out.

In addition, the awareness of these correlations is helpful to address the physician to consider the coexistence of other comorbid conditions in women affected by endometriosis.

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Ethical approval

The authors declare that all data were collected meeting ethical guidelines.

Authors' contributions

MGP and PBP designed the study. MGP performed the original clinical study. CS, VB , MGP and RO collected the new data for this study and IP, CS, LM analyzed the data. MGP and SS wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript and have read and approved the final version of this manuscript.

Disclosure statement

The authors declare that they have no competing interests. The manuscript was not previously submitted.

Availability of data and material

The dataset is available from the corresponding author on reasonable request.

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