

# Endometriosis allergic or autoimmune disease: pathogenetic aspects - a case control study

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## Summary

**Purpose of investigation:** The aim of this study was to evaluate the correlation between endometriosis and pathologies on an immune basis for the possible involvement of the immune system in the pathogenesis of endometriosis. **Materials and Methods:** In this retrospective study, data of 304 patients with endometriosis and 318 without endometriosis were collected in a uniform manner for both groups and inserted into two databases, respectively, for patients with and without endometriosis. The authors calculated the percentages of patients with allergies, autoimmune diseases, asthma in both groups, and later statistical analysis were performed with two different chi-square tests. **Results:** The results obtained have shown that patients with endometriosis have a higher prevalence of allergies ( $p = 0.0003$ ) and coexistence of both allergies and autoimmune diseases ( $p = 0.0274$ ), compared to those without. **Conclusions:** The present study seems to support the possible association between endometriosis and allergic diseases.

**Key words:** Endometriosis; Immune system diseases; Allergies; Autoimmune diseases; Asthma.

## Introduction

Endometriosis is a benign gynecologic pathology, characterized by the presence of ectopic endometrial tissue. The prevalence of endometriosis is about 3-10% in women in fertile age, and about 2-5% in women after menopause [1].

There are two types of endometriosis: 1) adenomyosis or internal endometriosis, whose centers of lesion are inside the myometrial thickness and 2) simple or external endometriosis: ovary, tube, intestine, bladder, ureter, Douglas's cavity, urorectal septum, and many others sites which are distant, like lungs [2].

The most frequent symptoms are chronic pelvic pain which may include: dysmenorrhea, painful menstruation which may be primary, when lacking either anatomic anomalies or pathologies, secondary, if caused either by anatomic anomalies or pathologies such as endometriosis [3], periovulatory pain, menorrhagia, dyspareunia, pain with penetration more or less deep, with sexual intercourse, associated with pressure on the endometriotic nodules and on deep lesions infiltrating the uterus-sacral and cardinal ligaments, the Douglas, the posterior fornix of the vagina, and the anterior rectal wall or to fix some pelvic structures because of the fibrotic processes [4]; dysuria: difficult emission of urine with or without pain, dyschezia: painful defecation; changes in bowel function, there might be alternating periods of constipation and diarrhea; the other frequent symptom is infertility due to difficult sexual intercourse, destruction of the ovarian parenchyma because of the endometrioma itself and to the fibrotic processes that may involve the tubes, ob-

structing them or causing a changed motility of the cilia. Besides all this, there are other more or less specific symptoms. Halis and Arici, in their work in 2004, noticed that among their suffering patients, about 2-20% were asymptomatic, 10-70% suffered from chronic pelvic pains, and 50% reported to suffer from infertility [1].

Etiopathogenesis is not well known yet there are different theories in this respect and among them, the "retrograde menstruation" theory is the most popular. According to this theory, during menstruation, endometrial cells from the uterine cavity, moving towards the tubes, may come out from them and adhere outside the uterine cavity. This event may be found in some women who do not suffer from this pathology, hence the present authors believe that other possible mechanisms may be involved, such as a defect of the immune surveillance and hormonal causes linked to the environment which allow adhesion and the growth of such cells to other structures. According to the aforementioned, many studies have been performed which stress different alterations of the immune components of the suffering women, such as a function anomaly of the T and B lymphocytes and the attendant high serum levels of IgG, IgA and IgM, but contemporary reduction of the activity of the natural killer (NK) cells [5-10]. Another accomplice of this proliferation is enhanced inflammatory response with the overproduction of prostaglandins, metalloproteinases, cytokines, and chemokines that create a favoring environment for the survival and proliferation of endometriotic cells outside from the uterine cavity [11].

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The possible involvement of the immune system in the pathogenesis of endometriosis and coexistence of diseases that involve the immune system such as allergies, asthma, and autoimmune diseases, seem to be related. In fact, women with endometriosis seem to have an increased risk of developing autoimmune diseases and allergies [12, 13].

The aim of this study was to evaluate the correlation between endometriosis and pathologies on an immune basis, while making a comparison between a group lacking the endometriotic pathology and a group suffering from such pathology, and calculating the respective percentages of patients with allergies, autoimmune illnesses, and asthma.

## Materials and Methods

The authors performed a retrospective study in the Department of Gynecologic-Obstetrical Sciences and Urological Sciences, University of Rome Sapienza, S. Andrea Hospital, in Rome (Italy). The data was collected in the outpatient clinics of the present unit from 2009 to 2013, where about 600 patients were recruited; 304 of them with endometriosis (case group) and 318 without endometriosis (control group), with an age range between 19 and 53 years, with an average age 50.1 years for case group and 53 years for control group.

In the case group, the diagnosis of endometriosis in 192 patients was made surgically, with laparoscopic or laparotomic evidence, and a subsequent histologic confirmation; in the remaining 112 patients, it was not possible to make surgical diagnosis because the patients refused to undergo any surgery and chose the medical therapy only, therefore the diagnosis for such patients was clinical-radiological with the symptomatology reported by the patients themselves as Engemise S., Gordon C., Konje J. C., describe, "endometriosis should be taken into consideration in young women with chronic pelvic pain non responsive to conventional therapy", and in patients with symptoms such as dysmenorrhea, bleeding, sleepiness, chronic pelvic pain, constipation, backache, deep dyspareunia, dyschezia, infertility, clinical rectal bleeding, menorrhagia, diarrhea, and hematuria. The strong diagnostic suspect in these patients was motivated both by the remission or the great reduction of the symptoms after a three-month therapy either with gonadotropin-agonist or with the combined pill.

On the contrary, the control group included patients who did not have the above described symptoms of endometriosis, who did not show, in the imaging techniques, any pathological lesions, and did not suffer from any illnesses that might interfere with the immune system such as infections, cancer, fibromas, and myomas.

For both groups the authors took into consideration the following elements: age, nationality, smoke, parity, characteristics of the menstrual cycle, and other pathologies, including those on an immune basis adding, in patients with endometriosis, of the place of the lesion, identified with ultrasound scan (US) or magnetic resonance (MRI), symptomatology, dosage of the markers CA125, CA19.9, CA15.3, type of surgery, and medical therapy.

With regards to the illnesses on an immune basis, the authors included allergies, autoimmunity, and asthma, for which the patients had to resort to therapies or for which they had to avoid taking dangerous substances or be in contact with them.

Data of 304 patients with endometriosis and 318 without endometriosis were collected in a uniform manner for both groups and inserted into two databases, respectively, for patients with and without endometriosis. Initially, the authors calculated the percentages of patients with allergies, autoimmune diseases, and asthma in both groups and later statistical analysis were performed with two different chi-square tests ( $\chi^2$ ):  $\chi^2$  and  $\chi^2$  Yates.

## Results

Out of a total of 622 patients, 304 were suffering from endometriosis and 318 are not affected by it. Allergic women were 75 (24.67%) among the patients with endometriosis vs. 42 (13.21%) without endometriosis ( $p = 0.0003$ ;  $p = 0.0004$ , Yates), nine (2.96%) of the case group were affected by allergies and at the same time by autoimmune diseases vs. two (0.63%) in the control group ( $p = 0.0274$ ;  $p = 0.0573$ , Yates), then the total number of patients suffering from autoimmune diseases was 108 (35.53%) in patients with endometriosis and 72 (22.64%) in patients without endometriosis ( $p = 0.004$ ,  $p = 0.006$ , Yates). Instead, the comparison of other immune pathologies between the two groups was not statistically significant. Nineteen (6.25%) of 304 patients with endometriosis had autoimmune diseases and four (1.32%) were asthmatic; only one (of 0.33%) patient was affected by allergy and at the same time by asthma and no patients had both autoimmune diseases and asthma at the same time. Twenty-two (6.92%) of 318 patients without endometriosis had autoimmune diseases and four (1.26%) were asthmatic; only two (0.63%) patients were affected by allergy and at the same time by asthma and no patients have both autoimmune diseases and asthma at the same time (Table 1).

From the evidence of the results obtained and comparing these two categories of patients, allergies and coexistence

Table 1. — Percentages of immune diseases in case and control groups.

	Endometriosis n	Tot. 304 %	Control group n	Tot. 318 %	$\chi^2$	$\chi^2$ Yates
Allergies	75	24.67%	42	13.21%	0.0003	0.0004
Autoimmune diseases	19	6.25%	22	6.92%	ns	ns
Asthma	4	1.32%	4	1.26%	ns	ns
Allergies + autoimmune diseases	9	2.96%	2	0.63%	0.0274	0.0573
Autoimmune diseases + asthma	0		0		ns	ns
Allergies + asthma	1	0.33%	2	0.63%	ns	ns
Total immune diseases	108	35.53%	72	22.64%	0.004	0.006

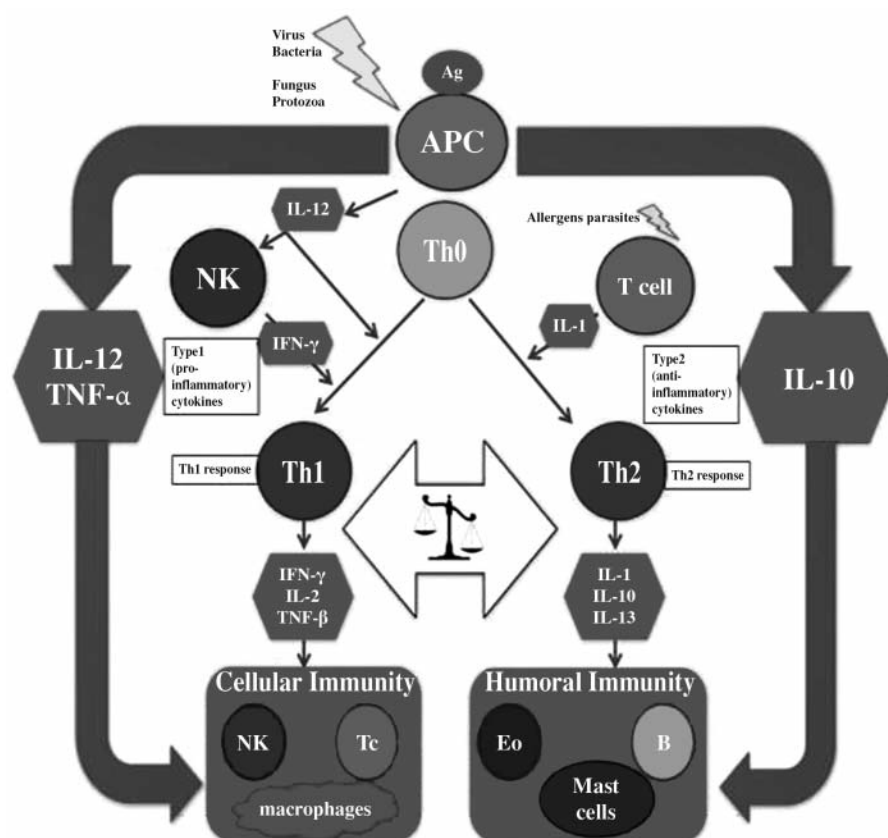


Figure 1. — Role of APCs, Th1, and Th2 cells, and proinflammatory and anti-inflammatory cytokines in the regulation of cellular and humoral immunity. *Abbreviations:* Ag, antigen; APC, antigen presenting cell; NK, natural killer cell; B, B cell; Th, T helper cell; Tc, T cytotoxic cell; Eo, eosinophil; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

of both allergies and autoimmune diseases were more prevalent in patients with endometriosis compared to those without. Consequently, such a difference resulted in a total of 108 (35.53%) patients ( $p = 0.004$ ), with diseases involving the immune system increase.

## Discussion

According to the present authors' experience, it seems that patients with endometriosis were more prone to allergies, but neither to asthma nor to autoimmune diseases. Already in 2005, Ferrero *et al.* did not confirm an increased prevalence of asthma in patients with endometriosis [14].

Several teams have performed studies to understand the relationship between endometriosis and the immune system. At first in 2000, Blumenthal *et al.* demonstrated that the products of eosinophil degranulation, such as cytokines and chemotactic activators, and the interleukin-5 and eotaxin, regulated T cells which participate in the immunity response, shared by endometriosis, allergies, and asthma [15]. In 2003, Oikawa *et al.* demonstrated an increased expression of IgE, from which histamine releasing factor (HRF), depended on endometriotic implants [16]. Finally Sugamata *et al.* in 2005 found that activated and degranulated mast cells were found in peritoneal en-

dometrios; this is noteworthy as activation of mast cells in response to the binding of IgE with a certain antigen, plays a pivotal role in hypersensitivity reaction [17].

In patients with endometriosis, endometrial cells in ectopic sites cause an inflammatory process that leads to the production of proinflammatory cytokines, and then to all the aforementioned consequences. This phenomenon may explain why patients with endometriosis are also subject to frequent allergies of various kinds and therefore would also explain the results obtained in the present study.

The present study aimed to assess the relationship between endometriosis and immune-based diseases by comparing a group with endometriosis and a group without, and to calculate the respective percentages of patients with allergies, asthma, and autoimmune diseases in patients with and without endometriosis. The results obtained indicated a high prevalence of allergies and the coexistence of both allergies and autoimmune diseases, in patients with endometriosis compared to those without. Consequently, this difference affects also the total value of autoimmune diseases.

Oikawa *et al.*, which obtained an increased expression of IgE in endometriotic implants, have already demonstrated the correlation between IgE and endometriosis and the HRF, which is implicated in allergic mechanism, depending on IgE [16]. Furthermore, high CD-23, a protein that is expressed

on the surface of cell membrane, commonly identified as the low affinity IgE receptor on B cells, eosinophils, monocytes, dendritic cells, epithelial Langerhans cells, and platelet concentrations, have been observed in peritoneal fluid of women with endometriosis, suggesting the activation of B cells and a possible alteration of humoral immune system in endometriosis [18]. The action of cells that mediate inflammatory response seems to play a fundamental role in the genesis and/or maintenance of endometriosis.

Immune responses are regulated firstly by antigen-presenting cells (APCs), such as the macrophages and dendritic cells (innate immunity), and by the T helper (Th) lymphocyte subclasses Th1 and Th2, which are components of acquired (adaptive) immunity (Figure 1).

IL-12, produced by activated macrophages or other APCs, is the major inducer of Th1 differentiation and, hence, cellular immunity; this cytokine acts in concert with natural killer (NK)-cell-derived IFN- $\gamma$  promote Th1 response. APC-products, IL-12 and TNF- $\alpha$ , in concert with NK- and Th1-cell-derived IFN- $\gamma$  stimulate the functional activity of T cytotoxic (Tc) cells, NK cells, and activated macrophages, which constitute the major components of cellular immunity.

Th1-lymphocytes are primarily involved in response to microbes that infect or activate macrophages and NK cells, and in response to viruses. Th2-lymphocytes are primarily involved in response to helminths, allergens, and extracellular microbes and toxins. The Th2-type cytokines include interleukins 4, 5, and 13, which are associated with the promotion of IgE (severe allergies) and eosinophils response.

It is important to consider the Th1/Th2 challenge, where Th2 responses counteract the Th1 action: when the activity of one subset increases, it represses the activity of the other (Figure 1). Therefore, the high incidence of allergies in the endometriosis group could be explained by the inhibitory effect on Th1. The inhibition of Th1 would reduce NK cells, which would lead to an impaired clearing of endometrial cells, playing a fundamental role in endometriosis [19].

## Conclusion

The present study aimed to assess the relationship between endometriosis and immune based diseases by comparing a group with endometriosis and a group without, and to calculate the respective percentages of patients with allergies, asthma and autoimmune diseases in patients with and without endometriosis.

The results obtained indicated a high prevalence of allergies in patients with endometriosis compared to those without. The high incidence of allergies in the endometriosis group could be explained by the inhibitory effect on Th1. A more detailed understanding of the molecular mechanisms involved, would undoubtedly lead to the future development of adjuvant medical therapies for a better clinical management of endometriosis.

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