Endometriosis and autoimmunity

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Abstract

Endometriosis is an inflammatory oestrogen-dependent chronic disease and is mainly expressed by pain and increased infertility. Several studies showed an increased prevalence of autoimmune systemic diseases and various autoantibodies in endometriosis. The association of these autoimmune markers and diseases could raise the fact that endometriosis is an authentic autoimmune or inflammatory disease and thus could argue for the use of immunomodulatory therapies. Usually, it is considered that the autoantibodies did not directly act in endometrium implants growth, and could be rather implicated in endometriosis-related infertility. The use of immunomodulatory strategies could be an important alternative or additional strategy to the use of hormones and surgery but need prospective well-designed trials.

Keywords

Endometriosis, autoimmune diseases, immunomodulation

Introduction

Endometriosis is an inflammatory oestrogen-dependent disease characterized by extra-uterine infiltration of endometrial glands and stroma [1]. Endometriosis prevalence is from 5–10% in women with pelvic pain, dyspareunia, and dysmenorrhea. About 30% of patients with endometriosis also suffer from infertility [2]. Many women remain asymptomatic, but some of them complain with a variety of symptoms and pain with severe impact on the quality of life and fertility [3]. Endometriosis is a particularly original multifaceted disease, with physiopathological aspects including not only hormonal but also immunological and inflammatory aspects. Different causes could reduce the fertility in endometriosis women, such as adhesions, chronic peritoneal inflammation, disturbed folliculogenesis, and hormonal disturbance. Various immunological
factors, such as increased inflammatory factors and immune antibodies mediated disturbances could be also involved in the fertility of endometriosis women. The management actually includes the hormonal therapies (oral contraceptives, progestins, and gonadotropin-releasing hormone agonists), and surgery could be proposed in some refractory cases. These therapies are not sufficient in most cases of endometriosis-related infertility and complementary strategies should be developed.

The frequency of associated autoimmune diseases, of autoantibodies, and the increase of various pro-inflammatory markers should consider the endometriosis as an autoimmune or inflammatory disease. These statements argue for the use of immunomodulatory therapies in the management of endometriosis-related infertility. Despite these arguments, the use of immunomodulation is actually limited in the routine management of endometriosis. Usually, it is considered that autoantibodies do not directly act in endometrium implants growth, which could be rather implicated in endometriosis-related infertility, and represents markers of immune mechanisms. This review aims to describe the prevalence of autoimmune diseases associated with endometriosis, the prevalence of various autoantibodies, and the perspectives of immunomodulatory therapies.

Endometriosis and autoimmune diseases

The prevalence of several autoimmune diseases is increased in women with endometriosis. Among them, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), celiac disease, inflammatory bowel disease, Sjogren’s syndrome (SS), and autoimmune thyroiditis are particularly involved. A case-control study of 150 women with endometriosis, SLE, celiac disease, inflammatory bowel disease, and autoimmune thyroiditis was more frequent in those with endometriosis [4]. Another case-control study demonstrated an increasing number of immune-mediated conditions and co-occurring endometriosis [5]. A nationwide population-based study showed an increased risk of RA in patients with endometriosis during more than 10-year follow-up [6]. A population-based, retrospective cohort study from Taiwan including endometriosis (n = 16,758) and non-endometriosis (n = 16,758) women showed a significantly higher incidence rate in women with endometriosis (0.3 vs. 0.1 per 1,000 person-years) and hazard ratio (HR) for SLE [adjusted HR (aHR), 2.37; 95% confidence interval (CI) 1.35–4.14] as compared to the non-endometriosis group [7]. Another retrospective study from Taiwan with a total of 17,779 patients with endometriosis and 17,779 controls without endometriosis showed an increased risk of SLE in those with endometriosis (0.85 vs. 0.57 per 1,000 person-years, HR = 1.86; 95% CI 1.36–2.53) as compared to those without endometriosis [8].

In a Swedish study of women with endometriosis from 1964 to 2011, including 2,834 cases of SLE and 14,164 controls, a significant association between endometriosis and subsequent SLE was noted with an odds ratio of 1.39 (95% CI 1.09–1.78) [9]. Among 114,453 women from the Nurses’ Health Study II study followed since 22 years, 103 incident cases of SLE and 390 cases of RA were confirmed and endometriosis was significantly associated with SLE (HR = 2.03; CI 1.17–3.51) and RA diagnosis (HR = 1.41; 95% CI 1.05–1.89) [10]. In a case-control study of 58 primary SS (pSS)-patients and 157 controls, endometriosis was reported in 8.5% of pSS patients vs. 2.1% of those without pSS [11]. Celiac disease was diagnosed in 5 of 223 (2.2%) women with endometriosis and in 2 of 246 (0.8%) controls (P = 0.265) [12]. Among 11,097 women with celiac disease, 118 patients with celiac disease developed endometriosis in comparison with 399 controls without celiac disease among 54,992 age-matched control women [13]. Among 37,661 women with endometriosis from Danish Hospital Discharge Register (1977 to 2007), 13,054 and 86 cases of multiple sclerosis (MS), SLE and SS were noted, respectively, with standardized incidence ratios (SIR) at an odds ratio of 1.2 (95% CI 1.05–1.5) for MS, odds ratio 1.6 (95% CI 1.2–2.1) for SLE and odds ratio 1.6 (95% CI 1.3–2.0) for pSS [14]. When the analysis was restricted to 9,191 women with laparoscopy or laparotomy confirmed endometriosis, associations were significant for MS (SIR = 1.4; 95% CI 1.04–1.9), but not for SLE (SIR = 1.1; 95% CI 0.6–2.1) and pSS (SIR = 1.4; 95% CI 0.9–2.3). Thus, endometriosis could be associated with various autoimmune diseases, even if the force of this demonstration of these associations remains low due to the study biases.
Autoantibodies in endometriosis

Various autoantibodies in blood and peritoneal fluids have been studied in endometriosis women, and their prevalence could be increased even in the absence of any autoimmune disease [15, 16]. The list of autoantibodies that have been detected in endometriosis is very large, and includes antinuclear antibodies (ANAs), antiphospholipids (aPLs), antithyroid, anti-endometrial, anti-α-enolase, anti-PDIK1L, anti-survivin, anti-laminin-1, anti-carbonic anhydrase, anti-granulocyte macrophage-colony stimulating factor (anti-GM-CSF) autoantibodies, etc.

For instance, studies showed that anti-endometrial antibodies are more frequent in sera of women with endometriosis and that they are directed against the cytoplasm of glandular and surface epithelium [17]. In women with endometriosis, ANAs, anti-Sjogren’s-syndrome-related antigen A (anti-SSA/Ro), and aPL autoantibodies were also more commonly detected usually in the absence of any clinical autoimmune disease [18]. In 323 various stage endometriosis women, anti-cardiolipin antibodies and anti-sperm antibodies were both found to be more frequent in sera and peritoneal fluids [19]. Both levels and prevalence of anti-laminin-1 autoantibodies were increased in endometriosis-associated infertility, but these autoantibodies failed to predict in vitro fertilization (IVF) failure [20, 21]. Other rare autoantibodies, such as anti-ovary, anti-theca, anti-granulosa cells, and anti-endometrium autoantibodies have been more frequent in infertile endometriosis women [22]. Among 23 women with endometriosis-associated infertility, aPL except for lupus anticoagulant (LAC), and ANAs were significantly more frequent in women with endometrioses than controls with tubal infertility [23]. Anti-GM-CSF antibodies levels in 106 sera of endometriosis women were increased in patients with endometriosis and with the levels correlated to the severity of the disease [24]. The clinical value and the predictive impact of these various autoantibodies, the correlation of the endometriosis stage, and the value in patients with endometriosis-related infertility remain unclear. Among 35 IVF cycles with at least one aPL or ANA, 8 (23%) women became pregnant, vs. 16 (46%) in autoantibodies-negative ones ($P = 0.04$) [25]. The levels of anti-alpha enolase antibodies have been found to be increased from stages I to III, but not in stage IV [26]. Anti-PDIK1L and anti-survivin antibodies have not been found to be correlated with the stage of endometriosis [27, 28]. The relevance of these factors thus seems to be limited in clinical practice, and probably reflects more an immunological overall disturbance (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Immune factors associated with endometriosis-related infertility</th>
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<td><strong>Auto-immune diseases, in particular</strong></td>
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<td>SLE</td>
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<td>Celiac disease</td>
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<td>Inflammatory bowel disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<td>Autoimmune thyroiditis</td>
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<td><strong>Various autoantibodies, in particular</strong></td>
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<td>ANAs</td>
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<td>Anti-α-enolase</td>
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<td>Anti-PDIK1L</td>
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<td>Anti-carbonic anhydrase</td>
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<td>Anti-GM-CSF antibodies</td>
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<td>Anti-syntaxin 5</td>
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<td>Anti-PEP</td>
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<td><strong>Proinflammatory factors (blood, peritoneum)</strong></td>
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<td>anti-PEP: anti-peptide</td>
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Immunomodulatory therapies

This probable immunological origin of endometriosis, the increased prevalence of various autoimmune biomarkers and autoimmune systemic disorders could raise the interest in immunomodulatory strategies. In particular, in patients with chronic pain resistant to hormonal therapies and surgery, and women with endometriosis-related infertility, alternative strategies are urgently needed. Despite this evidence, the available data about these strategies are extremely scarce.

In an amurine embryo assay, the addition of dexamethasone with endometriotic peritoneal fluid significantly improved the rates of blastocyst expansion [29]. Steroids used in 21 patients with endometriosis before IVF, at 10 mg/day from the third day of the cycle until the day of oocyte retrieval [30] allowed an increase of clinical pregnancies rates at 42.6% in the steroid-treated women vs. 22.8% without steroids ($P < 0.05$). The clinical pregnancy rates were higher in the steroid-treated group with positive autoantibodies as compared to the non-treated group (40.9% vs. 14.8%; $P < 0.05$). In 84 infertile women with endometriosis which received steroids during the IVF cycle or 5 days before embryo transfer, steroid use during the IVF cycle in 35 autoantibodies-positives patients was associated with clinical pregnancy in 8/10 cases vs. 0/25 in those without steroid treatment (80% vs. 0%; $P < 0.05$) [25].

Several studies demonstrated increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-6 (IL-6), transforming growth factor-$\beta$ (TGF-$\beta$) and IL-1$\beta$, both in sera and peritoneal fluids of women with endometriosis [31]. In a rat/baboon model of endometriosis, the neutralization of TNF-$\alpha$ activity with recombinant TNF binding protein 1 decreased the endometriotic lesions [15, 16, 32–34]. TNF-$\alpha$ induced peritoneal endometriosis was significantly reduced under anti-TNF-$\alpha$ in endometriosis baboons [35]. Female rats were randomized to receive either etanercept (0.4 mg/kg body weight) subcutaneously or placebo once weekly during 4 weeks in a randomized placebo-controlled study using rat endometriosis model [36]. The volume and extension of endometrial implants were significantly reduced in female rats under etanercept. Infliximab is a monoclonal antibody targeting soluble TNF-$\alpha$ and is usually used in several autoimmune and inflammatory diseases, such as RA, Crohn’s disease, etc. In a randomized trial of women with endometriosis-related pain, the pain severity decreased in 30% of infliximab-treated women and was not significantly different from women who received a placebo [37]. Nineteen women with endometrioma received etanercept 50 mg on the second day of the menstrual cycle preceding IVF cycle with higher clinical pregnancy rate in patients who received etanercept: odds ratio 4.17 (95% CI 1.23–14.14) [38]. In the rat model of endometriosis, a humanized monoclonal antibody against IL-6 receptor, tocilizumab significantly suppressed the volume of endometriotic lesions and the ectopic endometrial-like epithelium: in 42.8% of treated rats vs. 0% in the control group [39, 40].

Conclusions

Endometriosis is associated with an increased prevalence of various autoimmune markers and autoimmune diseases. The use of immunomodulatory strategies could be an important alternative or additional strategy to the use of hormones and surgery but need prospective well-designed trials.

Abbreviations

ANAs: antinuclear antibodies
anti-GM-CSF: anti-granulocyte macrophage-colony stimulating factor
aPLs: antiphospholipids
CI: confidence interval
HR: hazard ratio
IL-6: interleukin-6
IVF: in vitro fertilization
MS: multiple sclerosis
Declarations

Author contributions
NA, GK and AM contributed conception and design of the study; NA and AM wrote the first draft of the manuscript; KK, MC, LS, EA, GK wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Conflicts of interest
AM is an investigator of CELGENE, ROCHE, CHUGAI founded trials with APHP and Hospital 15–20 promotion; AM received several fees for congress travels and experts’ use from LFB, SANOFI, SHIRE, and CELGENE.

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Not applicable.

Consent to publication
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References


