Pro-Inflammatory and Anti-Inflammatory Cytokines in Pathophysiology

Subjects: Obstetrics & Gynaecology

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Endometriosis is a chronic inflammatory disease, which explains the pain that such patients report. Currently, we are faced with ineffective, non-invasive diagnostic methods and treatments that come with multiple side effects and high recurrence rates for both the disease and pain. These are the reasons why researchers are exploring the possibility of the involvement of pro-inflammatory and anti-inflammatory molecules in the process of the appearance of endometriosis.

Keywords: endometriosis ; ectopic endometrial tissue ; pro-inflammatory cytokines ; anti-inflammatory cytokines

1. Introduction

Endometriosis is a pathology characterized by ectopic endometrial tissue implanted and developed on host tissues [1]. It is characterized by pain, dysmenorrhea, dyspareunia, infertility, and pelvic organ dysfunction [2][3]. Endometriosis affects fertility, and the involvement of endometriosis in embryo transfer during in vitro fertilization (IVF) is being investigated. It appears that inflammation plays a key role in the failure of embryo transfer, but we currently lack clear data on how it affects pregnancy outcomes [4].

Currently, we are faced with ineffective, non-invasive diagnostic methods and treatments that come with multiple side effects and high recurrence rates of both the disease and pain [2]. Moreover, the disease is characterized by an impaired quality of life, a negative impact on social and family life, mental health issues, and high healthcare costs [2]. Hence, there is great attention and importance given to this pathology, and there is an inclination towards understanding its etiopathogenesis as the main starting point for finding new diagnostic and treatment methods.

Similar to cancer, ectopic endometrial tissue can lead to tissue spread, invasion, organ damage, and neoangiogenesis. It has been established that a history of endometriosis is more common in women with invasive clear cell tumors and endometrioid neoplasms compared to healthy women. Some cytokines show increased levels in both pathologies, indicating a link between cytokine levels and the pathophysiology of endometriosis. Cytokines play an important role in the progression of endometriosis, influencing cell proliferation and differentiation. Endometriosis may serve as a precursor for ovarian cancer [5].

The pathophysiology of endometriosis is not fully understood. There is a combination of causes, including hormonal, immunological, genetic (gene polymorphism), and environmental factors [2][3]. Theories on the histogenesis of endometriosis include retrograde menstruation, celomic metaplasia, embryogenic cell rests, induction, and lymphatic and vascular dissemination. Genetic alterations, elevated gonadotropins, elevated estrogens, progesterone deficiency, and chronic inflammation are all implicated in the development of endometriosis [6].

The most widely accepted explanation of the etiopathogenic mechanism is retrograde menstruation, with endometrial epithelial and stromal cells implanting in the peritoneal cavity. The lesions are classified based on the following colors: white, red, brown, and black, with the latter being due to the presence of glandular content and adjacent stromal reactions rather than the severity of the disease, an important detail for the histopathologist [1]. Genetic and epigenetic factors, as well as environmental factors, are essential because 90% of women experience retrograde menstruation, but only a few develop endometriosis. Additionally, hormonal factors play a role, as elevated estrogen levels lead to bleeding in ectopic lesions, with the secondary release of pro-inflammatory cytokines that contribute to iron overload. This results in the infiltration of monocytes and macrophages, which stimulate lipid peroxidation and the accumulation of malondialdehyde (MDA) in the stroma [1]. Thus, there is a link between reactive oxygen species (ROS) and pro-inflammatory factors that contribute to pain and the failure to detoxify lipid peroxidase products under oxidative stress. IL-1 beta, IL-6, IL-10, IL-17,

and VEGF are involved in this process, leading to the increased activity of superoxide dismutase (SOD). Oxidative stress has proven to be a hallmark of the disease [1][7][8][9].

2. Pro-Inflammatory Cytokines

Cytokines, both proinflammatory and anti-inflammatory, were discovered in endometriosis biopsy specimens, and it was already postulated that they are involved in the etiopathogenesis of this disease, which is more studied in cancers. A study evaluated, alongside IL-1, another pro-inflammatory cytokine observed in endometriosis, the macrophage migration inhibitory factor (MIF). MIF plays a regulatory role in the immune response, angiogenesis, and excessive estrogen production [10].

Cytokines have various mechanisms of action with various effects in endometriosis, related to their involvement in pain, embryonic implantation, and angiogenesis, all related to oxidative stress and implicated in IL-8 and IL-12, but they need to be validated for significance, specificity, and sensitivity [11].

A non-invasive diagnostic test for endometriosis using the antibody array approach was conducted, and IL-31 showed potential as a possible biomarker for endometriosis. The lack of non-invasive diagnostic tests contributes to a diagnostic delay of 8–11 years. In order to reduce this delay, a non-invasive diagnostic using biomarkers is needed. Until now, the most frequent marker was CA-125, but there is a lack of sensibility and specificity [12]. This is because various proinflammatory cytokines, such as IL-17 and IL-33, are also found in both endometriosis and cardio-vascular diseases [13].

Studies have investigated the relationship between endometriosis and ovarian cancer. Cytokines such as IL-2, IL-5, IL-6, IL-8, and IL-10, both pro-inflammatory and anti-inflammatory, have been measured in serum, intracystic fluid, and peritoneal fluid in endometriomas and ovarian cancers. The aim has been to determine the optimal cut-off point for serum cytokines to differentiate between patterns of ovarian malignancy and endometriosis. It has been demonstrated that significantly elevated levels of IL-6, IL-8, and IL-10 are exhibited in cancers. But the cut-off values for these cytokines in serum were 5.3 pg/mL (IL-6), 56.2 pg/mL (IL-8), and 12.56 pg/mL (IL-10) [5].

Oxidative stress has been suggested as a potential factor associated with the progression of the disease. One study assessed the diagnostic performance of high mobility group box-1 (HMGB1) and toll-like receptor 4 (TLR4), which seem to be associated with this process of damage-associated molecular patterns (DAMPs) and induce endometriosis. Immunohistochemistry has revealed their presence in biopsy specimens, both in epithelial and stromal cells. It appears that NF-kB inhibitors and TLR4 agonists lead to the suppression of HMGB1 and decreases in IL-6 levels, demonstrating their involvement in endometriosis and the clinical relevance of this new finding. Additionally, HMGB1 plays a physiological role in the nucleus, but when secreted extracellularly, it acts as a damage-associated molecular pattern, triggering an inflammatory response and progesterone resistance [14]. It is associated with increased levels of IL-6, TNF-alpha, and IL-1 beta, representing another pathogenic mechanism associated with the development of endometriosis. It shows potential clinical applications by targeting HMGB1 in endometriotic cells. HMGB1 levels increase under hypoxic conditions, thus involving ROS [15].

A study evaluated the accuracy of immunohistochemical and immunofluorescence analyses, which showed the presence of interleukin-1 receptor type 1 (IL-1RI) in endometriotic tissue, especially in the glands, and also in endothelial cells, macrophages, and T-cells in typical black-blue endometriotic tissue. It is also found in red endometriotic implants, which are highly vascularized, showing a relationship with the activity of the disease and an involvement in endometriotic tissue growth, development, and oxidative modifications [1].

Cytokines are found in intrafollicular fluid. They have an impact on telomeres and mRNA expression in endometriosis. In patients with endometriosis, there is a significantly reduced number of antral follicles and a decreased number of oocytes retrieved through punctures. Among these retrieved oocytes, only a few have been mature and of optimal quality. It appears that increased levels of NF-kB and TNF-alpha in follicular fluid have a negative influence on the quantity and quality of oocytes [16]. Some studies have evaluated the follicular fluids of patients with endometriosis undergoing IVF, assessing the levels of IL-5, IL-6, and IL-3. It has been observed that there is a failure in the immunological defense system in endometriosis, but these cytokines do not have relevance as biomarkers [17].

Regarding infertility, the role of vitamin D has been studied, including its concentration in follicular fluid. An inverse proportion between vitamin D and IL-6 has been found. Additionally, there appears to be a correlation between vitamin D and other inflammatory factors such as TNF-alpha, IL-1 beta, IL-6, IL-8, and IL-10, as well as its involvement in autoimmune diseases and cancers. However, the association with endometriosis and clinical pregnancy rates has yielded

inconclusive results [18]. Nevertheless, it clearly influences maternal–fetal communication and fetal development without being able to demonstrate their relevance as biomarkers [19].

Macrophages remain the most prominent immune cells observed in endometriotic cysts, as they are responsible for the production of IL-6 and TNF-alpha, according to another study [20]. These cytokines function as factors involved in the carcinogenesis of ectopic endometria, particularly clear cell carcinoma [20].

IL-6, IL-10, and TNF-alpha are implicated in the growth of endometriotic stromal cells. An additional study specifically addressed ovarian endometriosis and the involvement of these cytokines, and researchers present its findings [20].

They are pro-inflammatory cytokines and are part of the inflammatory status associated with the carcinogenesis of endometriosis. Local hypoxia, the production of reactive oxygen species, and iron overload are involved. The chocolate fluid in endometriotic cysts contains blood and cytokines that are implicated in both the carcinogenesis process and infertility. Macrophages infiltrate the cyst wall and are the main component of inflammatory cells. Infiltration is more pronounced during episodes of fresh hemorrhage, as only fresh hemoglobin stimulates increases in IL-6, which is essential in cancer [20].

The stromal cells of an endometriotic cyst, upon exposure to the cyst's fluid, undergo ferroptosis, which, surprisingly, triggers the release of angiogenic growth cytokines, such as VEGF-A and IL-8, in endometriotic cells. Iron overload, along with genetic and epigenetic factors, is implicated in this process. Small, dysmorphic mitochondria are closely associated with iron accumulation. Ferroptosis is modulated by the intracellular iron overload resulting from repeated episodes of bleeding [21]. These findings could be the basis for future targeted treatments.

Another mechanism implicated in infertility is the compromise of embryo implantation, a well-known factor in pelvic inflammatory disease, polycystic ovary syndrome, and endometriosis [22][23]. Dysbiosis of the endometrial microbiota and pro-inflammatory cytokines such as IL-6, IL-8, and IL-17 are implicated in infertility and in cancer. And a study evaluated the accuracy of these findings [22].

The effect of cytokines, angiogenesis, and extracellular matrix degradation augmented by oxidative stress on the pathogenesis of endometriosis remains unclear. Amalesh Nanda et al. (2020) demonstrated in his study that VEGF, MMP2, MMP9, and cyclooxygenase COX 2 were higher in endometriosis, but IL-10 was the most significant variable capable of discriminating endometriosis samples from controls, being considered a potential biomarker [24].

According to another study, extracellular vesicle (EV)-associated VEGF-C secreted by proinflammatory cytokine-stimulated endometriotic stromal cells is a critical modulator of endometriosis by promoting lymphangiogenesis. Invaded lymphatic vessels may serve as a canal for the infiltration of immune cells, which enhances the inflammatory status of endometriosis. VEGF-C can be a non-invasive diagnostic biomarker and a potential therapeutic target for endometriosis. VEGF-C is upregulated by IL-1 beta, and TNF-alpha extracellular vesicles may serve as cargos that carry and deliver VEGF molecules to the remote lymphatic vessels. Researchers used a nanoparticle tracking assay [25].

There is a genome-wide association study of endometriosis that identified independent loci SNPs (single nucleotide polymorphism) at the IL-1A gene locus, which is associated with endometriosis risk. IL-1A is implicated in the pathogenesis of endometriosis [26].

Common genetic alterations, such as PTEN, p53, bcl gene mutations, and ARID1A mutations, have been established for both endometriosis and cancers. A chronic inflammatory state leads to cytokine release, followed by the unregulated mitotic division, growth, differentiation, migration, and apoptosis, similar to malignant mechanisms [6]. Tripartit-motif-containing 24 (TRIM24) appears in inflammation associated with cancers, while the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome are implicated in endometriosis. The relationship between them is mediated by IL-1 beta. TRIM24 is inversely proportional to the progression of endometriosis [27].

Repeated tissue injury, repair, and fibrosis play a pivotal role in endometriosis. Fibrotic tissue consists of extracellular matrix proteins, regulated by transcriptional factors. Periostin is a key extracellular matrix protein. Periostin and transcription factor 21 TCF21 is not detected in the stromal cells of women without endometriosis, but it is strongly detected in deep endometriosis. One study evaluated how IL-4 and IL-13 increase the expression of periostin and TCF21, which are involved in the regulation of fibrosis in endometriosis. TCF21 may be a promising therapeutic target and biomarker in endometriosis [28].

On the other hand, there are studies like that led by Tamara Knific (2019) that have shown no differences in the concentration of the measured 40 cytokines between patients and controls, demonstrating that the panel of cytokines used in their study were not relevant biomarkers [29].

3. Anti-Inflammatory Cytokines

Furthermore, the reciprocal influence between anti-inflammatory and pro-inflammatory cytokines and their role in the pathogenesis of endometriosis has been assessed. One study showed that IL-37, an anti-inflammatory factor primarily produced by T-helper cells, acts as a trigger for pro-inflammatory factors such as IL-6, IL-8, and VEGF, thereby participating in the pathogenesis of endometriosis and enhancing angiogenesis. Further studies are needed to provide evidence for this mechanism [2]. IL-37 is produced by numerous cells, including stromal cells, fibroblasts, and endothelial cells. The heterogeneity of endometriotic lesions makes it challenging to identify the specific cells involved in this mechanism. However, it has been observed that the level of IL-37 decreases by simply removing endometriotic lesions, so it can probably be used as a biomarker [2].

A study revealed there are potential differences in the immune profiles between women with and without endometriosis. IL-13 is lower in the endometriosis group, according to the study by H. Jorgensen et al. (2017), but future analyses of the pathophysiological mechanisms of endometriosis, including dysregulated Th1/Th2 responses, are needed [30].

Anti-inflammatory cytokines produced by T-helper 2 cells, such as IL-4, IL-10, and IL-13, have been investigated in endometriotic lesions to understand their roles. Other innate cytokines produced by thymic stromal lymphocytes, such as IL-25 and IL-37, have been found in peritoneal fluid in cases of endometriotic lesions. It has been observed that while pro-inflammatory cytokines increase during the progression of the disease, anti-inflammatory cytokines increase in the advanced stages. Researchers are trying to determine their value in the diagnosis of the pathology. These cytokines originate from immune cells, endometrial epithelial cells, endometriotic mesenchymal stem cells, peritoneal mesothelial cells, and platelets. Their established roles include the regulation of immunity, inflammation, cell proliferation, apoptosis, adhesion, and migration, and they have crucial roles in epithelial–mesenchymal transition (EMT), fibroblast-to-myofibroblast differentiation, smooth muscle metaplasia, fibrogenesis, and angiogenesis. All these phenomena have been observed in biopsies and cell cultures [2].

One study revealed that prostaglandin E2 is also involved in endometriosis, stimulating P450 aromatase and increasing estrogen production in endometriotic tissue, as well as enhancing the Th2 immune response. It also increases local estrogen production [2].

IL-37 is an anti-inflammatory cytokine found in the serum and peritoneal fluid of patients with endometriosis. At the same time, TNF-alpha in the peritoneal fluid has been evaluated, and it increases and shifts helper T cells towards Th2, leading to increased levels of IL-37 and IL-33. NF-kB is also activated, and ICAM-1 expression in endometriosis confirms the inflammatory pattern, according to Kaabachi's study (2017). IL-33 and IL-37 belong to the IL-1 family, though with an unclear role [31]. IL-37 is a relatively recently discovered cytokine, with its most biologically active isoform being IL-37b, and it has been studied in cancers where it appears to have a protective role. However, it has also been found in endometriosis and adenomyosis, with a suppressor role in the control of cell proliferation, inhibiting migration, and invasion and decreasing the expression of matrix metalloproteinase 2 (MMP2) via the Rac1/NF-kB signaling pathway. It does not, however, influence the epithelial–mesenchymal transition. It attenuates the occurrence of tumor metastases and can be used as a novel target for the diagnosis and treatment of malignant transformations in endometriosis [32].

Disturbed T-cell interactions have been observed in endometriosis. The defective expression of ICAM-1 (CD54) on secretory endometrial cells indicates the interaction between pro-inflammatory and anti-inflammatory mediators in the development of endometriosis [31].

IL-4 inhibits the expression of IL-37. IL-37 has been studied in chronic autoimmune diseases and cancers. It appears to affect gene transcription through its binding to smad 3. Recently, it has also been investigated in endometriosis biopsy specimens [31].

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