ABSTRACT

Endometriosis is a chronic condition that affects women of reproductive age worldwide. Although the etiology is still uncertain, it has been characterized as endometrial stroma and glands outside the uterus cavity. Evidence suggests that women with this condition have implications like immunological alterations, the frequent presence of comorbidities, and chronic inflammation, which has been described to cause pain and contribute to the disease's aggravation. Besides that, patients with endometriosis have not been considered a higher-risk group to severe cases of COVID-19. However, the real implications of the infection in patients with endometriosis are still unknown. Since hyper inflammation in endometriosis is related to severe disease cases and exacerbated inflammatory response in COVID-19 may worsen clinical symptoms. Even to patient's death, the purpose of this review is to correlate inflammation in both conditions, drawing to a possible risk factor related to an exacerbation of inflammatory response in patients with endometriosis followed by COVID-19 infection.

Keywords: COVID-19; Endometriosis; IL-6; Inflammation; Inflammatory response; SARS-CoV-2.

Endometriosis is a chronic condition that affects almost 200 million women worldwide. The World Health Organization (WHO) recently declared endometriosis an essential concern for health and the economy. However, due to inconsistent results of available studies and because of the difficulty in diagnosis endometriosis, prevalence and incidence of the condition are still not well established.

The disease has been characterized by endometrial stroma and glands outside the uterus cavity. The most common anatomical distribution of endometriotic lesions in the bladder, uterosacral ligament, vagina, ureter, and intestines. More rarely, it can be found in scars of laparotomy operations and cesarean section scars, in thoracic structures such as lung, diaphragm, and pericardium.

The etiology is still uncertain, but there are some accepted hypotheses to explain its pathogenesis. While the coelomic metaplasia theory proposes that the endometriotic tissue develops from the metaplasia of peritoneum cells, the metastatic or embolic endometriosis theory postulates that the implantation of the endometriotic lesions near veins promotes the dissemination of these cells into circulation vessels, arriving in distant sites which microenvironment allows its implantation. However, the most convincing theory is the "Retrograde Menstruation Theory," which considers that during menses, endometrial cells disseminate to the peritoneum cavity in a retrograde flow, followed by receptivity intrinsic to survival, adhesion, and implantation of the cells, leading to the endometriotic lesions, which are similar to the eutopic endometrium that proliferates, flakes off and bleed when stimulated by the ovarian estrogens. It is also known that surgical dissemination may happen in operations in the uterine cavity since ectopic endometrial cells were observed in scars of previous surgical interventions such as laparoscopy and cesarean.
It is important to note that endometriosis has an important social and economic impact due to the delay in diagnosis, added to the reduction in life quality and work performance of young women related to the symptoms and disease complications. In symptomatic cases, patients usually reported painful menses (dysmenorrhea), dyschezia (painful defecation), dysuria (painful urination), acyclic pelvic pain, and dyspareunia (painful intercourse), and have also been associated with infertility.

Approximately 20% to 30% of women with infertility have endometriosis, and conversely, the disease is also associated with 20 times more chances of infertility. One of the correlations between endometriosis and infertility indicates that inflammation plays a significant role in this process since infertile patients with endometriosis demonstrate high levels of cytokines like Interleukin-6 (IL-6), IL-8, IL-10, Tumour Necrosis Factor-alpha (TNF-a), and Vascular Endothelial Growth Factor (VEGF) when compared to non-infertile patients with endometriosis, and with fertile controls without endometriosis.

In addition to influencing infertility in endometriosis, inflammation has been described to cause symptoms such as pain and contribute to the aggravation of the disease. The rash can be attributed to the ectopic endometrial tissue, which produces inflammatory mediators, and promotes a local inflammatory response with systemic repercussion.

Studies point out that women with endometriosis have an endometriotic immune microenvironment that presents a higher expression of the type M1 macrophages, associated with the impaired presentation of angiogenesis-supportive M2 macrophages in endometriotic tissue and increased levels of macrophage-derived cytokines. In the peritoneal fluid of these patients, an increase of TNF-a, IL-6, IL-8, and IL-10 cytokines is observed. The high levels of TNF-a stimulate macrophages to produce IL-6, which is associated with impaired activity of Natural Killer cells caused by a hyperexpression of killer cell inhibitory receptors (KIRs) and could explain why endometriotic cells can evade the immune system. Increased levels of IL-10, a regulatory cytokine, may suppress the immune response contributing to impaired clearance and removal of endometriotic cells.

Considering the importance of inflammatory phenomena in endometriosis, it is suggested that women with this condition have a higher risk of developing chronic diseases, autoimmune conditions, thyroid and gastrointestinal disorders, celiac disease, asthma, and chronic fatigue syndrome, atopic diseases, among others. Even with evidence of chronic inflammation, a possible implication of immunological alterations, and the frequent presence of comorbidities, patients with endometriosis have not been considered a higher-risk group for severe cases of Coronavirus disease 19 (COVID-19). However, studies pointed out that patients with endometriosis had worse outcomes after COVID-19 infection, developing more severe symptoms and complications in various gastrointestinal, dermatologic, hematologic, and neuronal systems.

COVID-19 is attributed to the coronavirus-associated acute respiratory disease caused by the infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) declared a pandemic by WHO in March 2020. Clinical presentation of the condition includes symptoms such as fever, cough, fatigue, myalgia, sputum production, headache, hemoptysis, diarrhea, and dyspnea. The disease is characterized by an acute respiratory infection followed by severe pneumonia, leading to acute respiratory distress syndrome that often causes death.

The histopathological finds in the lung of a patient who died from COVID-19 indicate diffuse alveolar damage in the organizing phase, with denuded alveolar lining cells, reactive type II pneumocyte hyperplasia, loose interstitial fibrosis, and chronic inflammatory infiltrate. In addition, it was also observed intra-alveolar fibrinous exude, with loose fibrous plugs of organizing pneumonia and organizing fibrin. In the immunostaining with antibodies to the Rp3 nucleocapsid protein (NP) of SARS-CoV-2, they found prominent expression on alveolar epithelial cells and damaged desquamated cells within alveolar space.

As in endometriosis, the exacerbated inflammatory response in COVID-19 may be related to a worsening of the disease and even to the patient's death. When the immune response becomes dysregulated, it can cause damage to organs and tissues, which may happen in COVID-19 exacerbated inflammatory reaction due to “cytokine storm” described in recent studies, affecting patients' prognosis due to the severity of the disease.

The “cytokine storm” results from excessive activation of immune cells caused by an external agent, such as SARS-Cov-2 infection. The virus infection activates immune system cells, such as macrophages and lymphocytes, which release excessive inflammatory cytokines, causing tissue injury and systemic inflammation. Interleukin-6 (IL-6) is a cytokine produced by many cells in the immune system, having an essential role in the cytokine storm. It can be considered the main cytokine in inflammation progress since the severity of clinical presentation is associated with IL-6 levels in the plasma.

Studies conducted to determine the cytokines and clinical features related to COVID-19 found higher levels of C-reactive protein, procalcitonin, B lymphocyte proportion, IL-2, IL-6, IL-7, IL-8, IL-10, TNF-a, Granulocyte colony-stimulating factor (G-CSF), Interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP 1), and macrophage inflammatory protein-1 alpha (MIP-1A). It was also observed differences between the levels of some of these cytokines in patients with endometriosis compared to non-infertile patients with endometriosis, and with fertile controls without endometriosis.
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Biomarkers in mild and severe patients that commonly developed pneumonia or needed intensive care unit (ICU) treatment and, in some cases, progressed to death. The main results suggested IL-6 as a possible biomarker that could be used as a predictor of risk for the development of disease severity and the need for invasive mechanical ventilation.\textsuperscript{31,39,40}

After the SARS-CoV-2 infection, immune cells are activated due to the presence of the virus and start producing IL-6 and other cytokines to enhance the body's defense. After releasing IL-6, it creates two signal transduction pathways, one with classical signal through a membrane receptor (mIL-6R), which has anti-inflammatory effects, and a trans-signaling pathway with a soluble form (sIL-6R), this one with inflammatory outcomes. The classical signal pathway is limited because not all cells express mIL-6R, while most of these cells respond to trans-signaling pathways resulting in the transduction of the signal. This signal transduction activates the Janus kinase-signal transducer and activator of transcription (JAK/STAT) and Mitogen-activated protein kinase/ nuclear factor-κB to interleukin-6 (MAPK/NF-κB-IL-6) pathways, which both will synthesize acute reactive protein and consequently lead to cytokine storm.\textsuperscript{36-38,41,42}

IL-6 was identified to be up-regulated in patients with endometriosis and the evolution of COVID-19 infection. This cytokine is produced when diseases and damaged tissue occurs, and its function involves stimulating the immune response in the acute phase, being necessary for the patient's defense. However, when IL-6 production is dysregulated and is found at high levels, it contributes to pathological inflammation, causing more tissue damage than recovery.\textsuperscript{31}

In endometriosis, the augmentation of macrophages global and in local ectopic tissue, the dysregulated production of cytokine leads to systemic inflammation, maintenance, and worsening of the disease, which similarly happens in COVID-19, when exacerbated inflammatory response, induced by cytokine storm, contributes to complications as organ failure, sepsis, or acute respiratory distress syndrome (Figure 1).

\textbf{FIGURE 1. RELATIONSHIP BETWEEN THE IMMUNOPATHOLOGY OF ENDOMETRIOSIS AND COVID-19.} Endometriosis is an inflammatory and chronic disease. The endometriotic lesions induce inflammatory TNF-a mediators' release, followed by IL-6 synthesis and release by activated macrophages. High levels of IL-6 are associated with impaired activity of Natural Killer Cells and could explain why endometriotic cells evade the immune system and survive out of the uterus, leading to the progression of the disease. In SARS-CoV-2 infection, macrophages and other immune cells are activated due to the presence of the virus, starting the synthesis and release of IL-6 to improve body defense. The up release of IL-6 and its signal transduction activates the JAK/STAT and MAPK/NF-κB-IL-6 pathways, which synthesize acute reactive protein, leading to cytokine storm and an exacerbated inflammatory response. Finally, the high levels of IL-6 lead to tissue injury and organ failure, affecting patients' prognosis and resulting in the progression of endometriosis and severe symptoms cases of COVID-19.
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Given the correlation between the high levels of these cytokines, especially IL-6, in the progression of both conditions, attention should be drawn to a possible risk factor related to an exacerbation of inflammatory response in patients with endometriosis followed by COVID-19 infection. This may contribute to the evolution of severe cases, leading to a cytokine storm and hyper inflammation that can favor pneumonia and acute respiratory distress syndrome. Considering such scientific evidence and better protection, prospective observational and clinical cohort studies are needed to determine the real outcomes of infection in patients with endometriosis. They need better medical counseling and appropriate attention and treatment of critical cases.

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