REVIEW ARTICLE
Iran J Allergy Asthma Immunol
In press.

Effects of Post-COVID-19 Conditions on Endometriosis

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Received: 3 February 2026; Received in revised form: 3 May 2026; Accepted: 21 May 2026

ABSTRACT

Evidence indicates that Long COVID is associated with menstrual cycle disruptions, hormonal changes, immune dysfunction, and persistent inflammation. Owing to these overlapping inflammatory mechanisms, Long COVID may aggravate endometriosis, potentially worsening pelvic pain and increasing the risk of developing the disease. We searched Scopus, PubMed, Google Scholar, and Science Direct for English-language articles from 2000 to 2024. After screening titles and abstracts, the authors assessed the full texts of potentially relevant studies. Studies were included if they provided robust, impactful data pertinent to the topic. Direct clinical evidence indicates that women with endometriosis report worsening of pelvic pain, dysmenorrhea, and fatigue after COVID-19, and that Long COVID causes menstrual cycle irregularities and chronic inflammation. Extrapolation of separate studies in Long COVID and endometriosis, several hypothesized mechanisms may contribute to symptom exacerbation: elevated C-X-C motif chemokine ligand 5 (CXCL5) and vascular endothelial growth factor (VEGF) may promote ectopic endometrial tissue growth and angiogenesis; neutrophil extracellular trap (NET) formation and extracellular matrix (ECM) alterations could further endometriosis progression; stress-related hormonal fluctuations may enlarge lesions; and altered pain perception and fatigue may limit beneficial physical activity. The long-term effects of COVID-19 could exacerbate the severity of endometriosis through several mechanisms.

Keywords: Endometriosis; Inflammation; Post-acute COVID-19 syndrome; SARS-CoV-2

INTRODUCTION

Long COVID, or the post-acute sequelae of SARS-CoV-2 infection, is a consequence of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] This condition can persist for weeks or even months after the initial recovery from coronavirus disease 2019 (COVID-19). It is characterized by a range of symptoms that cannot be explained by an alternative diagnosis.[2] Fatigue and cognitive impairment (often referred to as "brain fog") are the most common symptoms of Long COVID.[3] Approximately 10% of patients who contract SARS-CoV-2 do not fully recover and develop Long COVID.[4] The underlying

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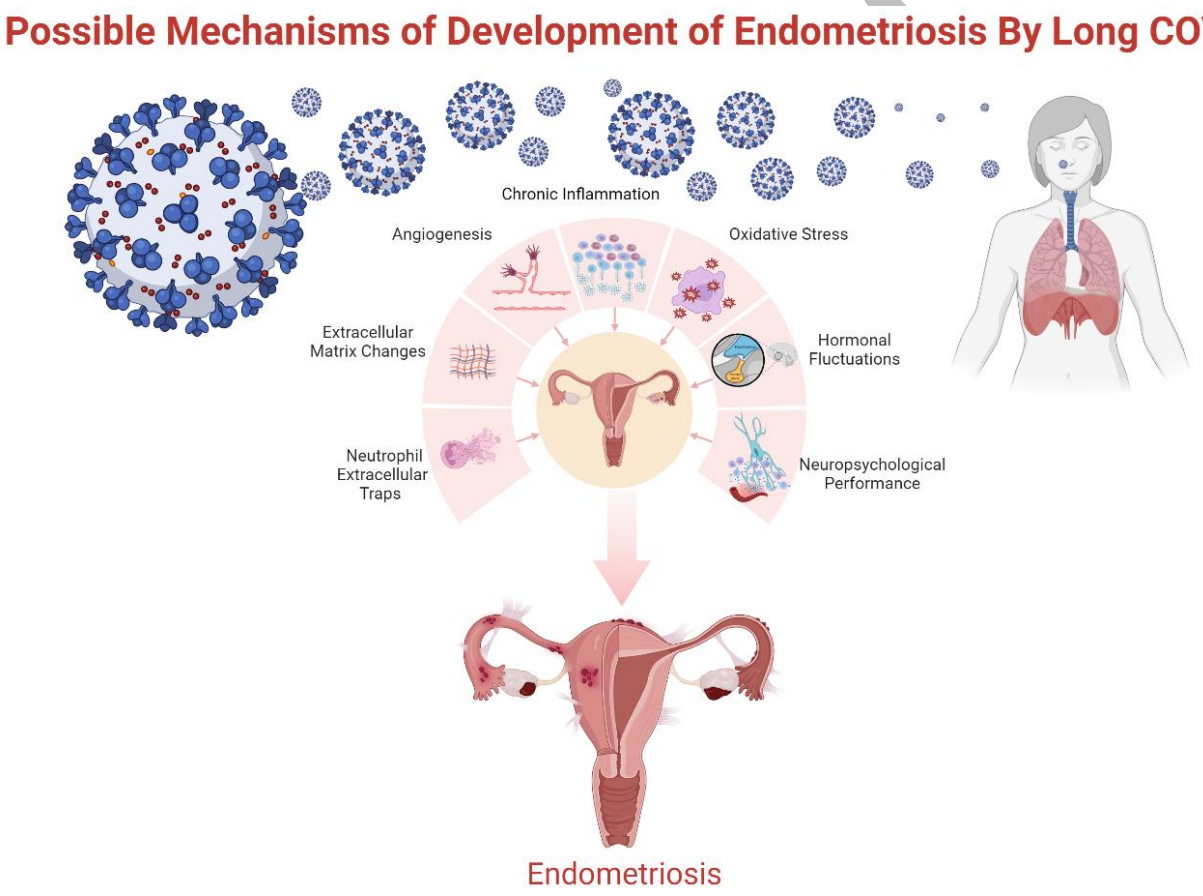
pathophysiology of Long COVID is not yet fully understood. However, it likely includes a combination of factors, including impaired immune regulation, autoimmunity, endothelial dysfunction, continuous viral presence, and coagulation activation.[5] Also, there is accumulating evidence of significant post-infection complications. These long-term effects, which garnered attention early in the pandemic, encompass various autoimmune disorders—such as multisystem inflammatory syndrome and autoimmune hemolytic anemia—and related coagulopathies.[6] Interestingly, the development of Long COVID in people after SARS-CoV-2 infection is not linked to the severity of the primary COVID-19 disease.[7] Premenopausal women are more likely to develop Long COVID.[7] Women under the age of 50 are 5 times less likely to return to full health before COVID-19 after contracting the virus.[8] Furthermore, neurological, cardiological, cardiopulmonary, gastrointestinal, and rheumatological complications among people with Long COVID are more common in women than in men.[9]



Graphical Abstract. Long COVID can cause endometriosis or exacerbate symptoms of the disease through chronic inflammation, angiogenesis, oxidative stress, neutrophil extracellular traps, extracellular matrix changes, hormonal fluctuations, and neuropsychological effects. (created in Biorender.com)

The presence of endometrial tissue outside the uterus is referred to as endometriosis.[10] The prevalence of endometriosis in women of childbearing age is 10%.[10] Dysmenorrhea (painful menstruation), heavy menstrual bleeding, dyspareunia (pain during intercourse), and infertility are common symptoms of endometriosis.[11,12] The etiology of this disease has not been well understood, although hormonal, neurological, and immune factors are implicated.[13] Many studies have focused on retrograde menstruation and lesions in the pathogenesis of endometriosis. Inflammation and pain are important features of this chronic disorder.[14] While endometriosis itself is not usually life-threatening, its symptoms can significantly reduce a person's quality of

life. The severity of pain varies among different individuals, ranging from very severe in some cases, in which it incapacitates them, to no pain in others. The diagnosis of endometriosis, even in patients with severe pain, can be delayed for years, and most symptoms are not taken seriously by health professionals.[15] Because the causes and mechanisms of pain in endometriosis are unknown, treatment options have limited effectiveness. Some chronic pain mechanisms in endometriosis include inflammation, neurogenic inflammation, neuroangiogenesis, peripheral sensitization, and central sensitization.[14]

The increased risk of COVID-19 in people with endometriosis has been investigated in various studies. Some studies have reported that endometriosis increases the risk of contracting COVID-19,[16] whereas others have found no such association.[17] However, it is important to note that the severity of COVID-19 symptoms may differ between patients with and without endometriosis. Among individuals infected with SARS-CoV-2, the severity of fever, myalgia or arthralgia, and rare symptoms is greater in women with endometriosis than in healthy women.[16,17] In contrast, COVID-19 in patients with endometriosis affects symptoms and aggravates them. COVID-19 may exacerbate symptoms of endometriosis, including chronic pelvic pain, dysmenorrhea, dyspareunia, gastrointestinal symptoms, fatigue, stress, anxiety, and depression.[18]

Recent studies have reported that endometriosis symptoms worsen after COVID-19.[18,19] Given the high prevalence of endometriosis among women of reproductive age and the increased likelihood of these individuals developing Long COVID, the impact of post-COVID-19 condition on individuals with endometriosis is a matter of considerable importance for research. To our knowledge, this is the first dedicated review specifically examining the effects of Long COVID on endometriosis. Unlike previous general discussions of COVID-19 and endometriosis, we systematically dissect mechanistic pathways (inflammation, angiogenesis, oxidative stress, neutrophil extracellular trap formation [NETosis], extracellular matrix [ECM] changes, hormonal and neuropsychological factors) and propose an integrated model. This review advances the field by identifying testable hypotheses for future research and highlighting clinical management strategies tailored to women with both conditions. The purpose of this study was to explore the effects of Long COVID on endometriosis.

MATERIALS AND METHODS

A comprehensive literature search was conducted in Scopus, PubMed, Google Scholar, and Science Direct for English-language articles published from January 2000 to March 2024. The following keyword combinations were used: (“Long COVID” OR “post-COVID-19” OR “PASC”) AND (“endometriosis”) AND (“inflammation” OR “cytokine” OR “chemokine” OR “angiogenesis” OR “oxidative stress” OR “NETosis” OR “extracellular matrix” OR “pain” OR “fatigue”). We included original research, case series, animal studies, and in vitro studies that presented data on Long COVID or endometriosis mechanisms. Editorials, opinion pieces, conference abstracts, and articles not directly addressing Long COVID or endometriosis were excluded. Titles and abstracts were screened, then full texts of potentially relevant articles were assessed. The final selection was based on robustness and relevance to the topic. The article selection process is summarized in a PRISMA-style flow diagram (Figure 1).

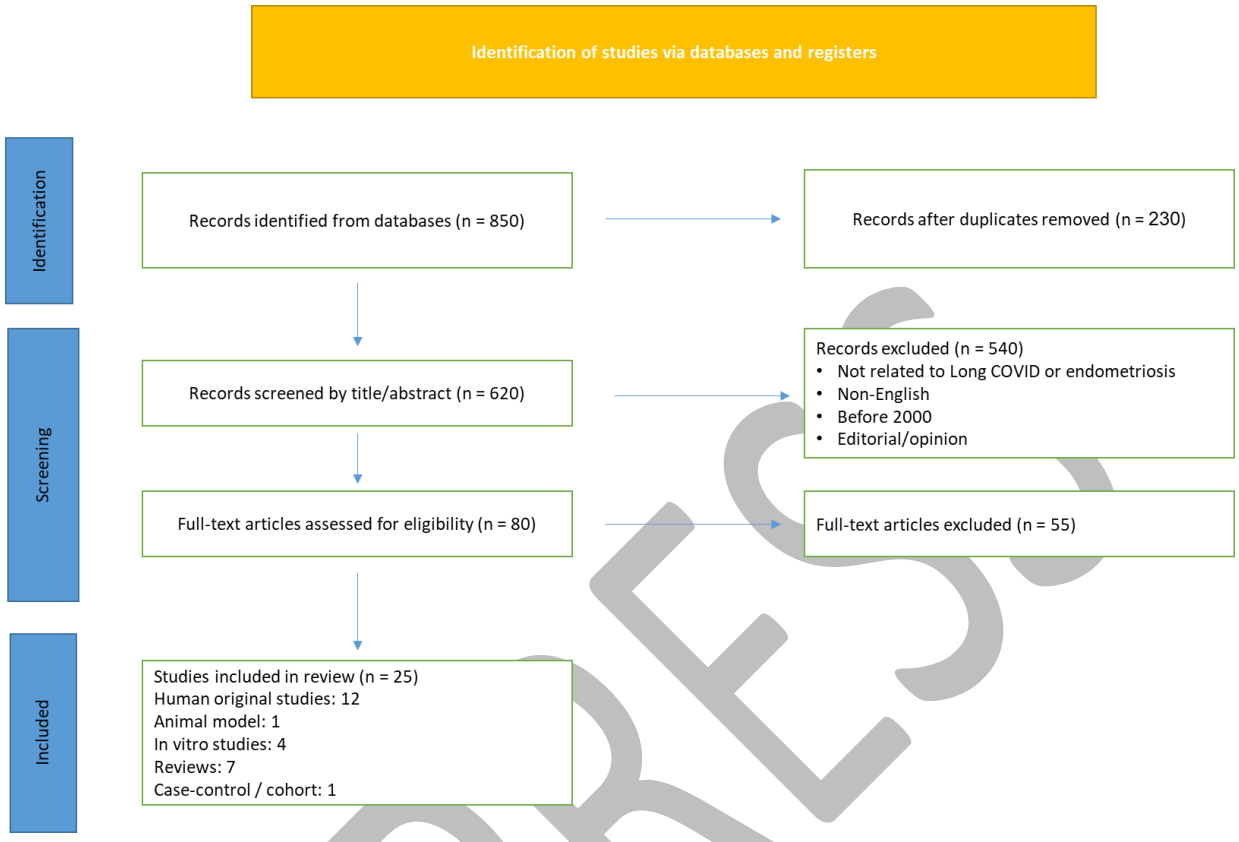


Figure 1. PRISMA flow diagram of study selection.

RESULTS

Long COVID and Menstrual Cycle

Long COVID has been implicated in disrupting the menstrual cycle.[7] Post-COVID-19 recovery periods revealed notable alterations in sex hormone profiles among female individuals who had experienced the disease.[20] These hormonal fluctuations have been linked to potential disruptions, such as a shortened menstrual cycle duration, extended periods of bleeding, and a heightened risk of infertility stemming from ovarian insufficiency.[20] Furthermore, the manifestation of irregular menstrual cycles and increased severity of menstrual bleeding represent additional complexities associated with the enduring effects of Long COVID.[21] However, a study reported that Long COVID could result in abnormal uterine bleeding without impairing ovarian function.[22]

Long COVID and the Development of Endometriosis

Endometriosis research has shown that immune dysfunction plays a significant role in the development and progression of the condition.[13] Immune system dysfunction is also observed in Long COVID.[23,24] Based on this mechanistic overlap, it is hypothesized that the presence of Long COVID could exacerbate the condition of a person with endometriosis. Long COVID may worsen the symptoms of endometriosis, especially those related to inflammation, such as pelvic pain. Additionally, the long-term inflammatory state caused by Long COVID might potentially lead to endometriosis in susceptible individuals.

Long COVID can lead to the development of endometriosis or exacerbate the symptoms of this disease through various mechanisms, as described below.

Chronic Inflammation

Long COVID is characterized by a sustained inflammatory response. It is suggested that Long COVID has a genetic basis, predisposing certain individuals to this condition. In these susceptible individuals, the immune system cannot completely clear the virus, leading to an overproduction of inflammatory

cytokines and persistent inflammation.[24] Inflammatory mediators such as cytokines and chemokines have been identified in the blood of patients with Long COVID.[23] These patients exhibited elevated levels of inflammatory mediators, including interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-17, and C-C motif chemokine ligand 3. IL-6, CRP, and TNF-α are recommended for use as biomarkers for Long COVID.[23]

Among the important inflammatory cells that increase in chronic inflammatory diseases are platelets. Platelets are so important in inflammation that the systemic immune-inflammation index (SII)—a marker of the systemic immune inflammatory response in the human body—is calculated using the counts of platelets, neutrophils, and lymphocytes. Research has shown that the SII can be used as a prognostic indicator in various clinical conditions, including cancer, cardiovascular disease, and sepsis.[25] A worse prognosis and higher mortality have been observed in patients with increased SII values. The SII is directly related to an increasing number of neutrophils and platelets and inversely related to the lymphocyte count.[25] The number of platelets and white blood cells is greater in patients with Long COVID.[26] As expected, the SII is also higher in people with Long COVID.[27] The platelet count and its indices in advanced endometriosis differ from those in primary endometriosis. The platelet count and mean platelet volume are greater in patients with advanced endometriosis, but the platelet distribution width is greater in patients with primary endometriosis. These findings suggest that evaluating the number of platelets and platelet markers can help determine the stage at which endometriosis progresses.[28] Another index that may be helpful in Long COVID is the neutrophil-to-lymphocyte ratio (NLR). The importance of this index in the acute phase of the disease has previously been investigated. NLR may be a reliable marker to evaluate the severity of COVID-19. NLR had a high diagnostic value for differentiating COVID-19 patients from healthy subjects, and it could predict the severity and outcome of the disease.[29,30]

Inflammation in the acute phase of the disease is characterized by increased inflammatory cytokines and decreased complement.[31] Inflammation promotes the growth and expansion of endometrial tissue cells circulating in women's blood and can increase pain, heavy menstrual bleeding, and severe pelvic pain. Systemic inflammation, triggered by the immune system's response to the virus, could exacerbate the inflammatory response in endometriosis. Symptoms of endometriosis may worsen due to persistent inflammation caused by Long COVID, or the likelihood of developing endometriosis may increase as a result. Endometriosis is a chronic, inflammatory disease; therefore, in addition to genetic and hormonal factors, inflammatory factors should be considered for controlling and treating the disease.[32]

Cytokines

One of the most important mediators in chronic diseases is cytokines. Cytokines are glycoproteins secreted mainly by immune cells that regulate immune responses and inflammation. Cytokine profiling in patients with COVID-19 has shown an overall increase in some cytokines such as interleukin-1β (IL-1β), interleukin-1 receptor antagonist, TNF-α, IL-6, interleukin-2, interleukin-8, and interleukin-18, and impaired production of others such as interferon-α and interferon-β.[33] Excessive production of inflammatory cytokines such as IL-6, IL-1β, and TNF-α has been observed in Long COVID.[23] Increased levels of inflammatory cytokines have also been observed in patients with endometriosis. Research has shown that serum levels of IL-1β, IL-6, and TNF-α are significantly higher in women with endometriosis compared with healthy women.[34] These cytokines play essential roles in inflammatory processes that contribute to the development and progression of endometriosis. Additionally, the peritoneal fluid of patients with endometriosis contains a distinct pattern of cytokines that promote angiogenesis and cell proliferation.[35] The increase in levels of these cytokines as a result of Long COVID provides the basis for the growth and expansion of endometrial tissue outside the uterus, thereby increasing the severity of endometriosis symptoms.

Chemokines

Chemokines are a family of small glycoproteins that attract immune cells to the site of infection or injury.[36] Some chemokines are increased in Long COVID. One of these chemokines, which is increased in Long COVID, is C-X-C motif chemokine ligand 5 (CXCL5).[37] CXCL5 is a potent chemotactic protein that, in addition to recruiting neutrophil cells, also plays a role in activating them. In the tumor microenvironment, CXCL5 plays an important role in tumor growth and metastasis by recruiting immune cells and promoting

angiogenesis. CXCL5 levels are increased in various samples, including endometrium, peritoneal fluid, follicular fluid, and menstrual blood, of women with endometriosis compared with healthy women. Therefore, these data suggest that changes in CXCL5 expression play important roles in the pathogenesis of endometriosis.[38] Several studies have substantiated the presence of endometrial cells circulating within the peripheral blood of individuals diagnosed with endometriosis. This pathological condition, characterized by the ectopic growth of endometrial-like tissue outside the uterine cavity, has been consistently associated with the detection of these displaced endometrial cells in the systemic blood circulation of affected women. The identification of these extrauterine endometrial cell populations in the peripheral blood represents a significant diagnostic marker, providing valuable insight into the underlying pathophysiology of endometriosis and its systemic manifestations.[39] Due to the role of CXCL5 in metastasis and angiogenesis, the increase in this chemokine associated with Long COVID may enhance the ability of circulating endometrial cells to induce endometriosis. Additionally, after contracting Long COVID, an increase in this chemokine is likely to increase lesions and symptoms of endometriosis.

Angiogenesis

The growth, division, and differentiation of cells are regulated by proteins called growth factors.[40] The levels of growth factors, including vascular endothelial growth factor (VEGF), may increase during post-COVID-19.[23] The serum concentration of VEGF is elevated in individuals with endometriosis. Furthermore, studies have demonstrated a positive correlation between the expression of VEGF in both serum and endometrial tissue and the severity of dysmenorrhea in affected women.[41] Research has shown that VEGF facilitates the growth of endometrial tissue outside the uterus. VEGF is an important factor in angiogenesis and plays a role in both the development and progression of endometriosis.[42] In addition to the role of VEGF in endometriosis, the function of its receptor has also been investigated. The importance of vascular endothelial growth factor receptor 1 signaling in promoting the growth and angiogenesis of host-derived cells, which contributes to the development of endometriosis, has been established. Knockout of this receptor strongly reduces endometrial growth in a mouse model.[43] Therefore, the increase in VEGF due to Long COVID may lead to an increase in the incidence of endometriosis. Additionally, this growth factor can be one of the most important factors influencing the severity of endometriosis symptoms, especially dysmenorrhea, in people who developed Long COVID after contracting COVID-19.

Oxidative Stress

Reactive oxygen species (ROS) are highly reactive molecules that can cause damage to cellular components and contribute to the pathogenesis of various diseases.[44] When oxidative stress exceeds cellular antioxidant defenses, it leads to significant oxidative damage to cell molecules, so overproduction of ROS causes or exacerbates cell damage in diseases.[45] Long COVID increases oxidative stress and inflammation.[46] In fact, it is the increased production of ROS in Long COVID that contributes to oxidative stress and inflammation. By increasing cell proliferation and extracellular signal-regulated kinase 1/2 activation, cells in endometriosis exhibit increased levels of ROS, which are involved in the progression of endometriosis.[47] An increase in ROS production by macrophages and changes in the expression of pro-oxidant and antioxidant enzymes have been observed in patients with endometriosis. These findings highlight the role of oxidative stress in the pathogenesis of endometriosis.[48] Antioxidant therapies are recommended to treat and reduce the symptoms of endometriosis.[49] Long COVID may increase cell proliferation by increasing ROS production. Increased cell proliferation in ectopic endometrial tissue leads to the development of lesions and the progression of endometriosis.

Neutrophil Extracellular Traps

Neutrophil extracellular traps (NETs) are important innate immune mechanisms that, in addition to defending against bacteria and fungi, play a role in antiviral defense.[50] The structural composition of NETs comprises extracellular chromatin that is associated with a variety of proteins, including histones, neutrophil elastase, defensin, and myeloperoxidase.[51] Neutrophils capture and kill microorganisms via this mechanism and prevent their spread.[50] Despite the importance of forming NETs in the innate immune response against microbial infections, including viruses, NETs can have harmful effects on the body when released excessively.[50] The excessive formation of NETs has been investigated in many diseases. It has been found to play a role in the

pathogenesis of various diseases, including myocardial infarction, acute kidney damage, pneumonia, autoimmune diseases such as rheumatoid arthritis and lupus, diabetes, thrombosis, and cancer.[52]

Furthermore, following SARS-CoV-2 infection, NET formation has been identified as a key mediator of the pathophysiological sequelae associated with this disease.[53] Research examining the induction of NETosis in neutrophils has shown that the plasma of individuals with Long COVID has a greater ability to induce NETosis.[54] In addition, research has shown that both the frequency of positive NETosis and the mean amount of NETosis detected in women with endometriosis are significantly greater than those detected in healthy women.[55] Considering that in the tumor environment, NETs accelerate the proliferation of cells and inhibit apoptosis,[56] it is likely that in the case of endometriosis, NETosis inhibits the apoptosis of ectopic endometrial cells and promotes their proliferation.

Extracellular Matrix Changes

The extracellular matrix (ECM) is a complex network of proteins and carbohydrates that both protect cell structure and regulate cellular behavior.[57] The migration, proliferation, survival, and metabolism of cells are also affected by the ECM.[58] Changes in the ECM in patients with endometriosis may increase the invasive potential of retrograde endometrial fragments.[59] An altered ECM leads to increased inflammation and cell proliferation, thus contributing to pathogenesis and disease progression. Matrix metalloproteinases (MMPs) are a group of enzymes involved in the degradation of the ECM and are important regulators of the regeneration of the ECM.[60] Matrix metalloproteinase 1 (MMP-1) and matrix metalloproteinase 9 (MMP-9) are increased in patients with Long COVID and have been suggested to be used as diagnostic markers.[23] The expression level of MMP-1 in patients with endometriosis is higher in epithelial and stromal cells in endometriosis lesions than in those in the uterine endometrium.[61,62] Research has shown that inhibiting MMP activity prevents endometriosis in a chicken chorioallantoic membrane model.[63] *MMP-9* mRNA expression in ectopic and eutopic endometria[64] and menstrual blood[65] was greater in patients with endometriosis than in healthy women. Even in plasma samples, there was a significant difference in MMP-9 levels between patients with endometriosis and controls.[66] Hence, the data suggest that the upregulation of MMP-1 and MMP-9 enzymes in individuals affected by Long COVID contributes to alterations in the ECM, potentially predisposing susceptible patients to endometriosis development and exacerbating disease severity and symptoms in those already afflicted.

Hormonal Fluctuations

Endometriosis is a hormonally influenced condition, whereby factors inducing hormonal fluctuations within the body can exert a substantial effect on the disease. Stress, as one of these factors, has the potential to disrupt hormonal equilibrium and exacerbate the symptoms associated with endometriosis.[67] Stress is considered one of the most common symptoms of Long COVID.[68] Stress increases the size and severity of endometriosis lesions in animal models.[69] Stress has the capacity to modulate the severity of endometriosis through its disruptive influence on the hypothalamic-pituitary-adrenal (HPA) axis, as well as its ability to induce alterations within the inflammatory response system.[70] Stress also affects vitamin D receptor expression and macrophage penetration in endometriosis.[71] Serum concentrations of various hormones, for example, glucocorticoids, catecholamines, growth hormones, and prolactin, may undergo alterations in response to stress.[72] Studies have demonstrated that elevated levels of cortisol, a stress hormone, have the potential to perturb the intricate hormonal equilibrium of endometrial function, thereby exacerbating symptoms associated with endometriosis.[73] This disruption of hormones can increase inflammation, and inflammation is a key factor in the development and progression of endometriosis.[74] The catalysis of cortisol by the enzyme 11β-hydroxysteroid dehydrogenase-2 may increase endometrial angiogenesis, thereby contributing to the disease.[75] The stress experienced by individuals affected by Long COVID has been shown to induce hormonal alterations. The complications arising from these hormonal fluctuations include the exacerbation of symptoms associated with endometriosis.

Neuropsychological Performance

Altered Pain Perception

Behavioral tests performed on mouse models of endometriosis revealed that mice with endometriosis were more depressed, anxious, and more sensitive to pain than control mice.[76] Long COVID can alter perceptions of pain by affecting the nervous system. One of the mediators that increases pain sensation in people

with Long COVID is likely to be substance P (SP). The expression of the SP mRNA in people with Long COVID is 4 times greater than that in normal individuals.[77] SP is a neurotransmitter, and its receptor is the neurokinin 1 receptor (NK1R).[78] Pain leads to the release of this neuromodulatory agent from the trigeminal nerve of the brainstem. SP and its receptors are expressed by the enteric, central, and peripheral nervous systems; the cardiovascular system; and immune cells such as lymphocytes, monocytes, and macrophages. The effects of SP are extensive. In addition to autocrine and paracrine functions, it can affect distant cells via endocrine functions. The immune system plays a role in both the migration of immune cells and the secretion of cytokines[78] and induces the proliferation of T lymphocytes, B lymphocytes, and natural killer cells.[79] Dilating vessels, increasing their permeability, and activating immune cells are other ways in which this substance increases inflammation.[80] In contrast, SP significantly augments transforming growth factor-β production.[81] SP has been directly linked to respiratory illnesses such as COVID-19 infection and increases inflammation and symptoms associated with the disease.[78] SP increases the proliferation, migration, and invasion of endometriosis epithelial cells. The severity of dysmenorrhea is positively related to fibrosis in endometrial lesions and the level of NK1R.[82] Therefore, Long COVID can increase pain sensitivity and exacerbate pain caused by endometriosis. Additionally, symptoms of Long COVID, including pain in different parts of the body reported by people with Long COVID, can overlap with the pain experienced in endometriosis and increase pain in people with endometriosis after contracting Long COVID.

Fatigue

More than 70% of Long COVID patients suffer from chronic fatigue.[83] This type of fatigue can be severe and affect daily activities and quality of life.[84] Physical activity and exercise affect endometriosis and are suggested as alternative treatments for endometriosis-related symptoms.[85] Symptoms of endometriosis can be managed by exercise.[86] An animal model study of endometriosis has shown that physical activity may protect against the onset of endometriosis and reduce related inflammation by modulating the HPA axis and immune responses.[87] However, the majority of individuals affected by Long COVID exhibit a diminished capacity for physical activity engagement compared with their pre-infection ability, thereby precluding them from deriving the beneficial effects of exercise.[83,84] In addition, persistent fatigue and weakness experienced by those with Long COVID may diminish their ability to cope with chronic pain and other symptoms of endometriosis, consequently exacerbating the overall impact of the disease.

Stress, Anxiety, and Depression

Research has shown that Long COVID patients are at risk for mood changes, including depression and anxiety, and these symptoms may persist for several months after the onset of COVID-19 symptoms.[88] Among people with Long COVID, anxiety is reported more often in women than in men.[89] Stress and anxiety can have a significant impact on endometriosis symptoms. The stress and anxiety induced by Long COVID may increase systemic inflammation,[90] resulting in pain and other symptoms associated with endometriosis exacerbated by increased systemic inflammation. There is also a significant relationship between endometriosis and depression.[91] Patients with endometriosis experience greater levels of depressive symptoms than healthy people do.[92] Furthermore, patients with endometriosis who have pelvic pain symptoms have significantly greater levels of depression than do those without pain.[93] Due to the prevalence of depression in patients with Long COVID,[68] Long COVID may exacerbate depression associated with endometriosis and potentially lead to a worsening pain sensation. Research has shown that high levels of anxiety and depression can exacerbate the severity of pain.[91]

Sleep Disorders

Sleep disorders such as insomnia and poor quality of sleep are common among patients with Long COVID.[94] Compared with healthy women, women with endometriosis have significantly poorer sleep quality.[95] Ensuring sufficient sleep is crucial for managing endometriosis symptoms, as adequate rest plays a vital role in strengthening the immune system and promoting overall physical well-being. Consequently, Long COVID can significantly impact the quality of life of individuals with endometriosis by diminishing the quality of their sleep.

The mechanisms by which Long COVID may affect endometriosis, along with the current strength of evidence for each pathway, are summarized in Table 1 and Table 2.

Table 1. Summary of key mechanisms by which Long COVID may affect endometriosis

Mechanism	Key mediators	Evidence in Long COVID	Evidence in Endometriosis	Proposed effect
Chronic inflammation	Cytokines, chemokines	Increased IL-6, CRP, TNF-α, IL-1β, IL-17, CXCL5, and CCL3	Increased IL-1β, IL-6, TNF-α, and CXCL5 in serum and peritoneal fluid	Worsening of pelvic pain, heavy bleeding
Angiogenesis	VEGF	Elevated VEGF in post-COVID	VEGF correlates with dysmenorrhea severity	Growth of ectopic endometrial tissue
Oxidative stress	ROS, ERK1/2	Increased ROS production	ROS promotes cell proliferation in endometriosis	Lesion development and progression
NETosis	NETs, chromatin, elastase	Higher NETosis induction in Long COVID plasma	Increased NETosis in endometriosis	Inhibition of apoptosis, cell proliferation
ECM changes	MMP-1, MMP-9	Upregulated MMP-1, MMP-9	Higher MMP-1/9 in lesions, menstrual blood, plasma	Increased invasiveness of endometrial fragments
Hormonal fluctuations	Cortisol, catecholamines, prolactin	Stress-induced HPA axis disruption	Stress worsens lesion size in animal models	Exacerbation of endometriosis symptoms
Neuropsychological effects	SP, NK1R	SP mRNA ↑ 4-fold in Long COVID	SP increases proliferation, migration, and invasion of endometrial cells	Altered pain perception

CCL3: C-C motif chemokine ligand 3; CRP: C-reactive protein; CXCL5: C-X-C motif chemokine ligand 5; ECM: extracellular matrix; ERK1/2: extracellular signal-regulated kinase 1/2; HPA: hypothalamic-pituitary-adrenal; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-17: interleukin-17; MMP-1: matrix metalloproteinase 1; MMP-9: matrix metalloproteinase 9; mRNA: messenger RNA; NETs: neutrophil extracellular traps; NETosis: neutrophil extracellular trap formation; NK1R: neurokinin 1 receptor; ROS: reactive oxygen species; SP: substance P; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor.

Table 2. Evidence strength for each mechanism in the Long COVID–endometriosis interaction

Mechanism	Strength of evidence	Justification
Chronic inflammation	Strong	Multiple overlapping cytokines (IL-6, TNF-α, IL-1β) are well documented in both conditions; clinical studies show symptom worsening.
Angiogenesis	Strong	VEGF is elevated in both; a direct link to dysmenorrhea severity
Oxidative stress	Moderate	ROS increased in both, but no direct human studies linking Long COVID to endometriosis via ROS
NETosis	Moderate	Clear evidence in both separately; no direct study on NETosis as mediator between Long COVID and endometriosis yet
ECM changes (MMPs)	Moderate	MMP-1 and MMP-9 were upregulated in both; strong mechanistic plausibility
Hormonal fluctuations	Moderate	Animal models show stress worsens endometriosis; human data on Long COVID stress are indirect.
Neuropsychological effects	Moderate to strong	SP and pain pathways are well-defined; fatigue and anxiety are common in both, but direct causal studies are lacking.

ECM: extracellular matrix; IL-1β: interleukin-1β; IL-6: interleukin-6; MMPs: matrix metalloproteinases; MMP-1: matrix metalloproteinase 1; MMP-9: matrix metalloproteinase 9; NETosis: neutrophil extracellular trap formation; ROS: reactive oxygen species; SP: substance P; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor.

DISCUSSION

Interplay Between Mechanisms

Based on the separate lines of evidence presented in the sections above, we propose the following potential interactions between mechanisms, which are supported by the cited studies but have not yet been directly tested in the context of Long COVID and endometriosis. For instance, stress-induced hormonal fluctuations can directly increase inflammation, as shown by the link between stress hormones and pro-inflammatory cytokines.[68,70,74] In turn, inflammatory cytokines and chemokines can promote angiogenesis and cell proliferation.[35,38] Additionally, oxidative stress and NETosis may influence each other: reactive oxygen species (ROS) are known to play a role in endometriosis progression,[47] while NETs can affect cell proliferation and apoptosis.[55,56] However, direct evidence for a bidirectional ROS-NET loop in Long COVID-endometriosis interaction is currently lacking. Finally, extracellular matrix remodeling by MMPs and VEGF-driven angiogenesis may synergistically facilitate lesion growth and invasion, as both are upregulated in both conditions.[23,41,42,61,62,66] Recognizing these interconnections is crucial for developing holistic therapeutic strategies targeting multiple pathways simultaneously.

It is important to note that while direct clinical evidence supports symptom worsening and menstrual irregularities after COVID-19, most of the mechanistic pathways discussed below are hypothesized based on overlapping biology between Long COVID and endometriosis. A clear distinction between direct evidence and hypothesized mechanisms is provided in Table 3.

Table 3. Direct clinical evidence vs. hypothesized mechanisms

Statement	Type of evidence	Supporting references
Women with endometriosis report worsening of symptoms (pelvic pain, dysmenorrhea, fatigue) after COVID-19	Direct clinical	Kabani et al 2022[18], Nicolás et al 2022[19]
Long COVID causes menstrual cycle irregularities	Direct clinical	Pollack et al 2023[7], Madaan et al 2022[20], Davis et al 2021[21]
Long COVID induces chronic inflammation (elevated IL-6, CRP, TNF-α)	Direct clinical	Lai et al 2023[24]
Endometriosis is an inflammatory disease with elevated cytokines	Direct clinical	Malutan et al 2015[34], Rakhila et al 2016[35]
Long COVID may aggravate endometriosis via shared inflammation	Hypothesized	Lai et al 2023[24], Malutan et al 2015[34], Rakhila et al 2016[35]
VEGF increase in Long COVID may promote endometriosis lesion growth	Hypothesized	VEGF in Long COVID: Lai et al 2023[24]; VEGF in endometriosis: Zhang F et al 2018, Zhishun et al 2009[41,42]
Long COVID-induced NETosis may inhibit apoptosis of ectopic endometrial cells	Hypothesized	NETosis in Long COVID: Krinsky et al 2023[54]; NETosis in endometriosis: Berkes et al 2014[55]; tumor NETosis: Islam et al 2023[56]
Stress from Long COVID alters hormones and worsens endometriosis	Hypothesized	Stress in Long COVID: Bautista-Rodriguez et al 2023[68]; stress exacerbates endometriosis in animal models: Cuevas et al 2012, Appleyard et al 2020[69,70]
Long COVID increases pain sensitivity via substance P, adding to endometriosis pain	Hypothesized	Substance P in Long COVID: Schirinzi et al 2023[77]; SP in endometriosis: Yan et al 2019[82]

CRP: C-reactive protein; IL-6: interleukin-6; NETosis: neutrophil extracellular trap formation; SP: substance P; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor.

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The COVID-19 pandemic appears to have had a significant effect on patients with endometriosis. Understanding how Long COVID may worsen endometriosis symptoms is key to mitigating its effects. Direct clinical evidence confirms symptom worsening and menstrual irregularities. At the same time, most mechanistic pathways (inflammation, angiogenesis, oxidative stress, NETosis, ECM changes, hormonal fluctuations, and neuropsychological effects) remain hypothesized based on overlapping biology. Future research should prioritize the elucidation of the biological mechanisms underlying the potential exacerbation of endometriosis symptoms in individuals afflicted with Long COVID. A comprehensive investigation into the roles of inflammation, the immune response, and hormonal changes in these individuals is warranted. In addition, research should strive to develop efficacious strategies for managing endometriosis symptoms in individuals with Long COVID, encompassing a multidisciplinary approach that integrates medical treatment, psychological support, and lifestyle modification as a critical component of endometriosis management, and strategies for managing stress, improving sleep quality, optimizing nutrition, and incorporating proper physical activity or relaxation techniques should be considered. Improved understanding in this field willaid in the management of endometriosis.

STATEMENT OF ETHICS

Not applicable

FUNDING

IR.SBMU.MSP.REC.1403.663

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable

DATA AVAILABILITY

Not applicable

AI ASSISTANCE DISCLOSURE

Not applicable

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