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Review

Endometriosis and chronic pain syndrome: The role of stress mechanisms

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SUMMARY

Patients with endometriosis report increased levels of perceived stress, which correlates with disease severity and pain intensity, creating feedback loops that perpetuate the cycle of endometriosis inflammation, chronic pain syndrome, and pathological stress response. Stress and chronic pain form an integrated biopsychosocial system in which neuroendocrine dysregulation, central sensitization, neuroinflammation, large-scale network reorganization, and maladaptive threat learning mutually reinforce each other. Sex differences, developmental experiences, and resilience factors modulate this interaction. Chronic pain in endometriosis emerges as the result of a progressive integration of peripheral inflammation and central nervous system plasticity. Thus, mechanism-based therapeutic strategies for endometriosis-associated pain should address both peripheral drivers and central amplification processes. Further research is needed to better understand whether chronic stress is a contributing cause for the onset of endometriosis and whether there is an opportunity to modify this risk factor before endometriosis is fully established.

INTRODUCTION

Endometriosis is a disease caused by the presence of endometrium-like tissue outside the uterus. This condition typically associates with pelvic pain, infertility, and increased risks of autoimmune, chronic inflammatory, and psycho-emotional disorders.[1,2] Its prevalence is not precisely known because the diagnosis is complex and there is no effective screening test, but it is estimated to affect approximately 5%–10% of adult women.[3,4] Because it requires the support of estrogens to maintain cell proliferation and inflammatory activity, endometriosis incidence spans the reproductive years, from menarche to menopause.[5]

Chronic pain, especially visceral pain of diffuse pelvic localization, is a hallmark of endometriosis that accounts for a significant portion of the disease burden. The pain can be either cyclic, worsening in the menstrual period, or acyclic, with a huge impact on personal well-being and professional performance. The most frequent presentations of painful symptoms are dysmenorrhea, deep dyspareunia, acyclic pelvic pain, dysuria, and dyschezia. Treating endometriosis pain with conservative methods such as analgesics and hormonal therapies is the standard of care, but up to one-third of affected individuals have suboptimal response to such treatments[6] and ultimately require surgery. Severe pain not resolving with medical treatment is the main reason for surgical resection of lesions, which is an invasive procedure with risk of complications and still limited resolution.[7–9]

Understanding the mechanisms that induce, maintain, and reinforce endometriosis-related pain is essential to open new therapeutic strategies and overcome failures. Among the factors that can modulate endometriosis pain is chronic stress. Evidence from animal models suggests that a persistent stress response can boost endometriosis lesion growth and inflammation, while human studies have documented that endometriosis increases both subjective symptoms and objective physiological measures of chronic stress. Therefore, unlike genomic, environmental, behavioral, or lifestyle factors that may unidirectionally affect the natural history of endometriosis,[10] chronic stress and endometriosis reinforce each other mutually.[11] Patients with endometriosis report higher levels of perceived stress, anxiety, and depression than healthy women.[1,2] Stress intensity correlates with disease severity, pain intensity, and emotion regulation,[12,13] creating feedback loops that perpetuate the cycle of endometriosis inflammation, chronic pain syndrome, and pathological stress response (Figure 1).

The aim of this narrative review is to assess the available evidence connecting endometriosis with chronic pain and stress, as well as the factors and mechanisms that might contribute to this relationship. To this end, we performed a comprehensive literature search on PubMed and Scopus databases combining

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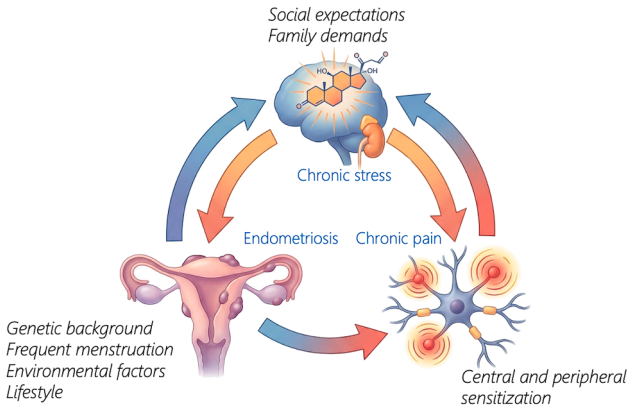


Figure 1. Multidirectional links between endometriosis, chronic pain, and chronic stress

While some biological, environmental, and lifestyle factors may unidirectionally affect the natural history of endometriosis, the persistent painful state may induce pain sensitization and lead to chronic stress, which is worsened by the psychological burden of the disease. Chronic stress reinforces central pain sensitization and may stimulate endometriotic lesions through autonomic imbalance.

the terms "endometriosis," "pain," and "stress," which was complemented by manual search of reference lists.

Endometriosis, chronic pain, and stress

Living with symptomatic endometriosis imposes a daily challenge to endure and adapt to frequent, sometimes debilitating pain. This suffering is often experienced alone, avoiding complains to preserve a normal life as much as possible.[14] Physical pain is already an important stressor, which, combined with the loneliness and hopelessness, may amplify and prolong the stress response.[15] Furthermore, pelvic pain causes sexual dysfunction and work absenteeism,[16] and the disease often associates with female infertility, which provokes family demands and fear of frustrating social expectations.

For women with endometriosis, menstruation can be painful not only because of progesterone withdrawal, increased prostaglandin production in the decidualized endometrium, and uterine hypercontractility, as occurs in primary dysmenorrhea.[17] Menstrual pain is further increased by the inflammatory response and microbleeding of ectopic implants, resulting in dysuria and dyschezia caused by bladder and intestinal lesions, respectively.[18] The frequent association with adenomyosis is another mechanism of severe dysmenorrhea in women with endometriosis. Not surprisingly, endometriosis increases menstrual distress as measured by a 25-item scale, the Menstrual Distress Questionnaire (MEDI-Q), scoring high levels of pain associated with disturbed gastrointestinal function, sleep, sexual activity, cognition, and concentration.[19]

Although the high stress levels that accompany endometriosis are not exclusively triggered by pain, studies using different methodologies showed a clear correlation between pain intensity and stress scales and biomarkers. In two studies of women with deep endometriosis, the perceived stress scales correlated positively with pain scores.[20,21] Stress levels also correlated positively with serum cortisol levels[20] and negatively with the parasympathetic tone, assessed through vagally mediated heart rate variability.[21] The analysis of resting electroencephalogram oscillatory amplitudes showed that women with endometriosis had increased delta and beta frequencies, which may suggest altered cholinergic tone in the brain.[22] A prospective study assessing subjective stress and pain ratings five times daily for 7 consecutive days around menstruation showed a clear correlation between pain and perceived stress.[23]

The multidirectional influence of endometriosis, chronic pain, and chronic stress involves several mechanisms that will be further discussed. These include an inflammatory response elicited by endometriotic implants that becomes systemic and reshapes pain sensitivity, along with disruption of stress response pathways and an autonomic imbalance that amplifies the proinflammatory environment and sustains the vicious cycle (Figure 1).

ENDOMETRIOSIS AND CHRONIC PAIN

Mechanisms

In endometriosis, pain severity does not consistently correlate with lesion size or disease stage.[18] This divergence indicates that symptom intensity is driven not merely by anatomical burden, but by functional and neurobiological alterations underlying pain processing. While surgery can alleviate pain in many cases, symptoms may persist after surgical excision of lesions.[24] Moreover, pain frequently recurs within 12 months postoperatively, even in the absence of detectable lesion regrowth.[25] These findings point to the involvement of persistent peripheral and central sensitization mechanisms. The frequent coexistence of comorbid conditions, such as overactive bladder syndrome and irritable bowel syndrome,[26] further supports a multifactorial pathophysiology in which altered nociceptive processing, rather than ectopic endometrial tissue alone, plays a central role (Figure 2).

At the peripheral level, endometriosis is characterized by a chronic inflammatory microenvironment. Retrograde menstruation, the most widely accepted theory of pathogenesis,[27] results in the backflow of viable endometrial fragments into the peritoneal cavity. In this ectopic environment, impaired immune clearance promotes their survival and implantation, triggering a sustained inflammatory response characterized by enhanced immune activation and pro-inflammatory signaling.[28] Endometriotic lesions and peritoneal fluid contain increased concentrations of pro-inflammatory cytokines and mediators, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, and prostaglandins.[29] These mediators contribute to pain by directly stimulating and sensitizing peripheral nociceptors. IL-1β, in particular, has been shown to aggravate inflammation and pain by increasing brain-derived neurotrophic factor (BDNF) expression in endometrial stromal cells.[30] Elevated IL-6 and IL-8 levels in the peritoneal fluid further promote cellular proliferation, angiogenesis, and maintenance of a pro-inflammatory state.[31]

Macrophages are central to this inflammatory milieu,[32–35] although their contribution to endometriosis cannot be reduced to a uniform pro-inflammatory phenotype. Peritoneal macrophages in women with endometriosis exhibit enhanced activation of nuclear factor kappa-light-chain-enhancer of activated

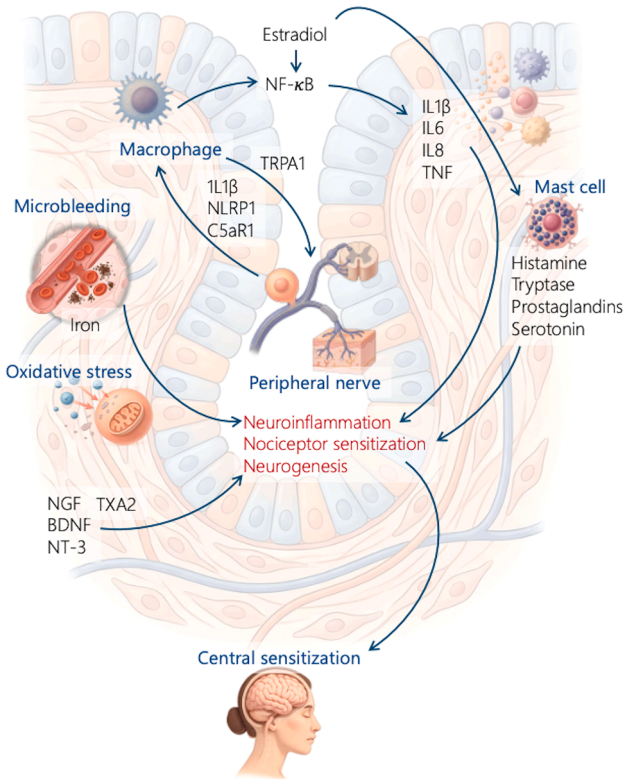


Figure 2. Mechanisms involved in pain generation and chronification by endometriosis

NF-κB, kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor; NLRP1, nucleotide-binding domain and leucine-rich repeat containing protein 1; C5aR1, complement component C5a receptor 1; TRPA1, transient receptor potential ankyrin 1; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin 3; TXA2, thromboxane A2.

B cells (NF-κB) signaling, leading to increased production of TNF-α, IL-1β, IL-6, vascular endothelial growth factor (VEGF), and transforming growth factor β (TGF-β).[36] This sustained release of inflammatory, angiogenic, and profibrotic mediators promotes lesion survival and contributes to the sensitization of adjacent sensory fibers. However, experimental evidence indicates that macrophage activity is strongly determined by cellular origin, localization, and disease-induced transcriptional state. Lesion-resident macrophages may originate from the eutopic endometrium, infiltrating large peritoneal macrophages (LpMs), or recruited circulating monocytes that differentiate within the lesion. Selective depletion experiments showed that embryo-derived macrophages promote lesion growth, whereas monocyte-derived LpMs decrease the number of lesions that develop, suggesting that recently recruited, monocyte-derived LpM may exert an anti-endometriosis or protective function.[37] Endometriosis also progressively remodels the peritoneal macrophage compartment by promoting monocyte recruitment, differentiation through intermediate macrophage states, replenishment of resident LpM, and loss of embryo-derived TIM4-positive LpM. Single-cell transcriptomic analyses identified multiple transitional populations sharing features of small and LpMs, and pharmacological treatment with niclosamide partially normalized these disease-associated dynamics, preserved embryo-derived resident macrophages, and restored disrupted communication between macrophages and B cells.[38] More recent single-cell studies further distinguished two lesion-resident pro-disease phenotypes: a tumor-associated macrophage-like population expressing *Folr2*, *Mrc1*, *Gas6*, and *Ccl8*, with proangiogenic and profibrotic activity, and a scar-associated macrophage-like population characterized by *Mmp12*, *Cd9*, *Spp1*, and *Trem2*, associated with extracellular matrix remodeling and fibrosis. Conversely, a potentially pro-resolving, lipid-associated population of monocyte-derived *LpM* expressing *Apoe*, *Saa3*, and *Pid1* was identified in the peritoneal cavity; accordingly, administration of an ApoE mimetic reduced lesion size and fibrosis in experimental endometriosis.[39] Beyond supporting lesion growth and remodeling, macrophages directly participate in pain generation. Macrophage depletion attenuated spontaneous pain-related behavior and both local and referred mechanical hypersensitivity in mice with endometriosis. Disease-modified macrophages showed increased production of insulin-like growth factor 1 (IGF-1), which was also elevated in the peritoneal fluid of affected women and positively correlated with reported pain intensity. Macrophage-derived IGF-1 promoted dorsal root ganglion (DRG) neurite sprouting and increased neuronal expression of nociceptive mediators, including SCN9A, SCN11A, and TAC1, whereas pharmacological inhibition of IGF-1R reduced endometriosis-associated hyperalgesia.[40] Collectively, these findings indicate that macrophages constitute a highly heterogeneous neuroimmune compartment in which specific populations promote inflammation, angiogenesis, fibrosis, innervation, and nociceptor sensitization, while others may limit lesion establishment or facilitate disease resolution. Therapeutic approaches should therefore aim to selectively eliminate or reprogram disease-promoting macrophages while preserving or enhancing protective and pro-resolving subsets (Figure 2).

Recent experimental evidence further indicates that peripheral neuroimmune interactions extend beyond classical immune cell activation. The close anatomical relationship between immune cells and nerve fibers within lesions establishes a bidirectional neuroimmune interaction that sustains peripheral sensitization. Peripheral glial cells such as Schwann cells have emerged as active regulators of inflammatory nociceptive signaling. In experimental models of endometriosis, increased circulating levels of the complement component C5a activate the C5a receptor 1 (C5aR1) expressed by Schwann cells within peripheral nerves. This activation triggers the nucleotide-binding domain and leucine-rich repeat containing protein 1 (NLRP1) inflammasome pathway, leading to caspase-1-dependent release of IL-1β, which promotes macrophage recruitment to peripheral nerve trunks and amplifies local neuroinflammation. The recruited macrophages generate oxidative stress that activates transient receptor potential ankyrin 1 (TRPA1) channel, establishing a feedforward mechanism that sustains neuroinflammatory signaling and widespread pain hypersensitivity. These findings highlight a previously underappreciated role of Schwann cells as key intermediaries linking immune activation, complement

signaling, and nociceptor sensitization in endometriosis-associated pain.[41]

Mast cells are also increased, particularly in deep infiltrating endometriosis.[42] Beyond their classical role in allergic responses, mast cells release histamine, tryptase, prostaglandins, serotonin, and multiple cytokines that can directly sensitize primary nociceptive neurons.[43] In other tissues, including the carotid body, extracellular acidosis resulting from inflammation or hypoxia has been shown to increase the expression of acid-sensing ion channels (ASICs) in sensory neurons.[44] Although direct evidence in endometriosis remains limited, a cross-tissue extrapolation suggests that the acidic microenvironment generated by inflammation, hypoxia, and altered tissue metabolism within endometriotic lesions may similarly enhance ASIC expression or activity, thereby contributing to chemosensory hypersensitivity in pelvic and visceral nociceptors.

In addition to inflammatory amplification, endometriotic lesions are characterized by enhanced neuroangiogenesis (Figure 2). Considering the chronic and visceral nature of endometriosis-associated pain, most endometrial nerve fibers are described as unmyelinated C fibers, although myelinated Aδ fibers may also contribute. Several neuronal markers, including protein gene product 9.5, substance P, calcitonin gene-related peptide, and tyrosine hydroxylase, have been detected in nerve fibers located within or surrounding different types of endometriotic lesions. Collectively, evidence supports the presence of hyperinnervation in both ectopic and eutopic endometrium of women with endometriosis.[45]

Neurotrophins, including nerve growth factor (NGF), BDNF, neurotrophin 3 (NT-3), and NT-4/5, are key mediators of neural sprouting and hypertrophy. In women with endometriosis, increased levels of NGF have been detected in the peritoneal fluid,[46] whereas endometriotic lesions themselves express BDNF and NT-4/5.[47] Moreover, circulating levels of BDNF, but not NGF or NT-4/5, have been reported to be elevated in the plasma of affected women.[48] These compartment-specific patterns may reflect differences in the sites of neurotrophin production, local tissue retention, release kinetics, and systemic clearance. Thus, NGF and NT-4/5 may predominantly act as local paracrine mediators within the peritoneal and lesion microenvironment, whereas circulating BDNF may additionally have potential as a systemic biomarker of disease-associated neuroinflammation. Importantly, NGF knockdown has been shown to inhibit the growth of endometriotic lesions, reduce nerve fiber density, and alleviate hyperalgesia in experimental models,[49] underscoring its central role in lesion-associated neurogenesis and pain maintenance.

In addition to its role in neuronal growth, NGF directly contributes to nociceptor sensitization. It lowers the activation threshold of specific nociceptors and enhances the release of pro-nociceptive neuropeptides from small-diameter sensory neurons, thereby promoting hyperalgesia.[50] The transient receptor potential vanilloid 1 (TRPV1) channel, an integrator of multiple noxious stimuli, has been reported to be overexpressed in endometriotic and adenomyotic lesions associated with dysmenorrhea and chronic pelvic pain.[51] TRPV1 sensitization may be further amplified by NGF through TrkA receptor activation, which upregulates TRPV1 expression.[52] Estrogen has also been implicated in enhancing TRPV1 expression in sensory neurons,[53] suggesting a convergence of inflammatory and hormonal signaling pathways in pain amplification.

A wide range of lesion-derived molecules can drive neurogenesis and peripheral sensitization. Consistent with the neurotrophic profile of endometriotic tissue, growth-associated protein 43 (GAP43), a marker of neuronal sprouting and neurite outgrowth, has been identified in endometriotic lesions.[54]

Beyond the classical neurotrophic factors, additional mediators may exert neurotrophic activity. Thromboxane A2 (TXA2), for instance, has been shown to promote neurite outgrowth in cortical neurons.[55] This observation is particularly relevant in endometriosis, as endometriotic stromal cells secrete TXA2,[56] and other evidence indicates that TXA2 can function as a neurotrophic factor in dorsal root ganglion-derived neurons.[57] These findings further support the concept that endometriotic lesions actively promote neurogenesis and neural remodeling, providing a structural substrate for persistent nociceptive input.

Hormonal modulation further amplifies inflammatory and nociceptive pathways. Endometriosis is an estrogen-dependent condition, and estradiol can modulate local inflammatory signaling in a context-dependent manner. In particular, estradiol and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), when administered individually, were reported to inhibit chemokine signaling and NF-κB activation. Conversely, their combined exposure enhanced chemokine pathway activation and increased NF-κB signaling, suggesting a synergistic interaction between estrogenic and environmental signals in promoting inflammation.[58] Estrogen may also synergize with TNF-α to increase IL-8 expression, sustaining peritoneal inflammation.[59] Furthermore, estrogen-mediated activation of mast cells via G protein-coupled estrogen receptors contributes to neuroinflammation and lesion progression.[60] This endocrine-immune interaction amplifies peripheral nociceptive signaling and reinforces chronicity.

Oxidative stress represents an additional mechanism linking inflammation and pain. Elevated iron and ferritin levels have been reported in the peritoneal fluid and ectopic lesions of women with endometriosis.[61] Iron overload promotes reactive oxygen species generation and activation of NF-κB pathways, further increasing pro-inflammatory cytokine production.[62] Repeated microbleeding within lesions may contribute to iron accumulation and oxidative damage,[63] thereby perpetuating inflammation and indirectly sustaining nociceptive activation.

Persistent peripheral nociceptive input can, over time, induce maladaptive plastic changes within the central nervous system. Sustained afferent signaling enhances excitability of dorsal horn neurons and disrupts inhibitory pathways.[64] Central sensitization is characterized by hyperalgesia, allodynia, and amplification of pain responses beyond the original site of injury.[65] Clinical data indicate a high prevalence of central sensitization features in women with endometriosis, with approximately half of patients meeting criteria based on validated assessment tools.[66] Central sensitization may explain the persistence of pain after lesion excision and the frequent coexistence of other central sensitivity syndromes, such as irritable bowel syndrome and fibromyalgia.[67,68] Importantly, the transition from inflammatory nociception to centrally mediated nociplastic pain does not exclude ongoing peripheral input; rather, it reflects a shift in the dominant

mechanism sustaining symptoms.[69] In this context, chronic pain in endometriosis emerges as the result of a progressive integration of peripheral inflammation, neuroangiogenesis, immune dysregulation, hormonal amplification, oxidative stress, and central nervous system plasticity. This multilevel model underscores the need for mechanism-based therapeutic strategies that address both peripheral drivers and central amplification processes.

Clinical implications

The growing understanding of endometriosis-associated pain as a complex interaction between peripheral nociceptive drivers, neuroimmune mechanisms, and central nervous system plasticity has important clinical implications. Traditionally, pain in endometriosis was considered a direct consequence of lesion presence and extent. However, accumulating evidence indicates that pain severity frequently diverges from anatomical disease burden, challenging a purely lesion-centered interpretation of symptoms.[18,70] One of the most relevant clinical consequences is the limited correlation between disease stage and pain intensity. Women with minimal lesions may experience severe dysmenorrhea, chronic pelvic pain, dyspareunia, or noncyclical pain, whereas others with extensive disease can remain relatively asymptomatic.[71] This discrepancy suggests that factors such as peripheral sensitization, neuroangiogenesis, and central pain amplification contribute substantially to symptom expression. Consequently, lesion burden alone provides an incomplete assessment of disease impact.

The recognition of chronic pain mechanisms also has implications for diagnostic evaluation. Pain should no longer be considered a simple indicator of lesion activity but rather a multidimensional symptom requiring comprehensive characterization.[19] Clinical assessment should include not only pain intensity, but also pain duration, temporal pattern, distribution, associated symptoms, and the degree of functional impairment. Particular attention should be paid to features suggestive of central sensitization, including widespread pain, hypersensitivity, fatigue, sleep disturbances, and disproportionate symptom severity relative to objective findings.[72]

The recognition of central sensitization and nociplastic mechanisms also provides a framework for understanding why pain may persist or recur despite apparently successful treatment.[73] Pain persistence does not necessarily reflect ongoing lesion progression or treatment failure. Instead, chronic nociceptive input may induce long-lasting neuroplastic changes that maintain pain independently of active disease. This concept may help explain why some patients continue to experience symptoms despite apparently adequate hormonal suppression[74] or complete surgical excision of visible lesions.

The concept of pain phenotyping has therefore emerged as a potentially valuable approach in endometriosis care. Rather than viewing all pain as a homogeneous symptom, patients may be characterized according to the relative contribution of nociceptive, neuropathic, and nociplastic mechanisms. Features suggestive of central sensitization include widespread pain distribution, pain disproportionate to disease extent, hypersensitivity to non-pelvic stimuli, fatigue, sleep disturbances, and the coexistence of other chronic pain conditions.[70] Identifying these characteristics may help clinicians select more individualized treatment strategies and improve expectations regarding treatment outcomes.

Another important implication relates to the high prevalence of pain comorbidities. Women with endometriosis frequently present with overlapping conditions, including irritable bowel syndrome, bladder pain syndrome, vulvodynia, fibromyalgia, migraine, and temporomandibular disorders.[75] These disorders are increasingly recognized as part of a broader spectrum of chronic overlapping pain conditions characterized by shared neurobiological mechanisms.[76] Their presence may contribute substantially to symptom severity and treatment resistance. Consequently, assessment of patients with chronic pelvic pain should extend beyond the reproductive tract and include systematic evaluation of extra-pelvic symptoms and comorbid pain disorders.

Beyond physical symptoms, chronic pain exerts profound effects on quality of life.[77] Women with endometriosis commonly experience limitations in daily activities, reduced work productivity, impaired sexual health,[78,79] and social restrictions. Psychological distress, including anxiety, depressive symptoms, and pain catastrophizing, is also highly prevalent.[80] Neuroimaging shows alterations in brain regions involved in emotion, cognition, and reward, not just nociception.[81] Rather than representing isolated comorbidities, these manifestations are increasingly viewed as integral components of the chronic pain experience,[2] reflecting the bidirectional interactions between biological, psychological, and social determinants of health.

Collectively, these observations support a broader conceptualization of endometriosis as both a chronic inflammatory disease and a chronic pain condition. Such a perspective emphasizes the importance of patient-centered assessment strategies capable of capturing the multidimensional nature of symptoms and their impact on functioning and well-being.

CHRONIC PAIN AND STRESS

Mechanisms

Stress and chronic pain conditions share overlapping biological, psychological, and social mechanisms. Although acute pain and acute stress serve adaptive and protective functions, their persistence produces maladaptive neurobiological and behavioral changes that compromise health and quality of life. Increasing evidence suggests that stress and chronic pain operate within a mutually reinforcing system, conceptualized as a self-perpetuating vicious cycle.[82] Within this framework, stress functions both as a risk factor for pain chronification and a consequence of persistent pain, while shared vulnerability characteristics such as anxiety sensitivity and catastrophizing amplify the interaction[83] (Figure 3). Under physiological conditions, stress and pain responses promote adaptation through allostasis, enabling the organism to maintain stability through change. However, repeated activation of stress systems leads to allostatic load, characterized by cumulative neuroendocrine and neural dysregulation.[84]

Chronic pain persistently activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic system,[84] and prolonged stress exposure disrupts cortisol feedback regulation.[85] In

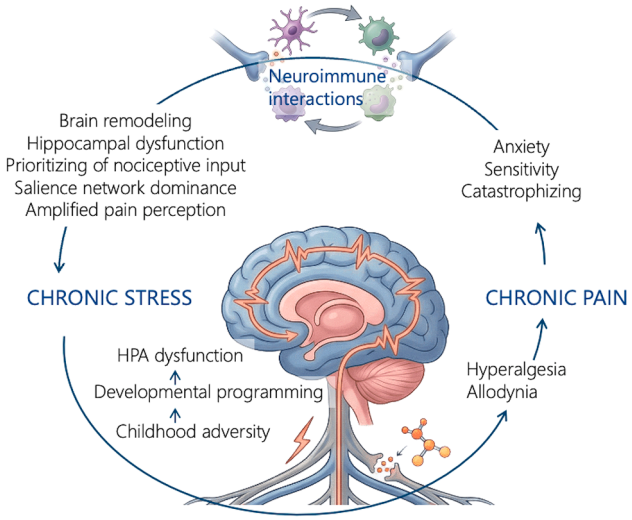


Figure 3. Mechanisms involved in the mutual influence of chronic pain and chronic stress

Chronic pain leads to remodeling of brain areas involved in pain perception and memory, which disrupts the stress response by the hypothalamic-pituitary-adrenal (HPA) axis, while the chronic stress syndrome further amplifies the mechanisms of chronic pain.

patients with chronic pain, dysfunction of the HPA axis is evidenced by altered basal cortisol dynamics and hippocampal structural changes,[86] supporting a stress-based model of pain chronification (Figure 3). However, these mechanisms are largely derived from studies of chronic pain and stress-related conditions other than endometriosis; therefore, their relevance to endometriosis-associated pain should currently be considered an extrapolation, as direct evidence for these specific neurobiological changes remains limited.

Importantly, HPA-axis function is not uniform across individuals. Sex differences significantly modulate stress reactivity, immune signaling, and learning.[87] Estrogens and progesterone modulate amygdala excitability and extinction learning, contributing to sex differences in pain vulnerability and to variability across phases characterized by high versus low estradiol levels in females.[88] These biological differences may partially explain the higher prevalence of chronic pain conditions in women and highlight the need to consider sex as a critical biological variable in stress-pain interactions.

Developmental programming further shapes vulnerability. Early-life adversity recalibrates the HPA axis, sensitizes amygdala circuits, and alters immune setpoints, increasing susceptibility to chronic pain later in life.[89] Longitudinal data indicate that childhood adversity predicts chronic widespread pain in adulthood.[90] Such findings suggest that stress-related neurobiological embedding may create enduring sensitivity to nociceptive and threat-related stimuli (Figure 3).

Emerging evidence also suggests that stress induces epigenetic modifications affecting glucocorticoid receptor expression and inflammatory signaling, potentially creating long-term changes in pain vulnerability.[91] Chronic pain and stress pathways converge on large-scale brain networks, inducing structural and functional alterations in the amygdala, hippocampus, and prefrontal cortex.[92–94] Persistent pain is associated with hippocampal dysfunction and altered connectivity within corticolimbic circuits.[95]

Chronic pain is associated not only with regional brain alterations but also with large-scale network reorganization.[96] Hyperactivity of the salience network increases the prioritization of nociceptive input as biologically relevant or threatening, whereas persistent default mode network engagement promotes self-referential rumination about pain. Concurrent reductions in executive control network function impair cognitive regulation of pain responses. Stress exacerbates this imbalance by further enhancing salience network dominance, thereby biasing attention toward threat and amplifying pain perception.[97]

Central sensitization represents a crucial mechanism linking stress to chronic pain. Heightened excitability of central nociceptive circuits amplifies pain transmission independently of ongoing peripheral input.[65] Clinical evidence identifies central sensitization as a core pathophysiological process underlying chronic widespread pain conditions like fibromyalgia, osteoarthritis, rheumatoid arthritis, spinal pain, migraine, or gastrointestinal disorders.[98] Chronic stress can directly promote hyperalgesia and enhanced tactile sensitivity through spinal neuroinflammatory mechanisms.[99] These observations indicate that stress-induced hyperalgesia and allodynia may substantially contribute to the onset and persistence of chronic pain conditions, underscoring a biological convergence between stress-responsive pathways and central mechanisms of pain amplification. Neuroimmune interactions further sustain this cycle (Figure 3). Psychological stress modulates immune function,[100] and altered cytokine profiles have been observed in chronic pain conditions.[101]

Beyond physiological processes, the experience of pain and stress involves intricate cognitive and behavioral processes, drawing upon various learning mechanisms that shape our responses to these stimuli. Pain, as an emotionally salient threat, engages amygdala-prefrontal circuits underlying fear conditioning.[102] Impaired extinction and reconsolidation processes can maintain maladaptive threat memories.[103] Pain-related fear predicts disability more strongly than pain intensity[104] and meta-analytic data confirm its central role in functional impairment.[105] Stress biases learning toward habitual, threat-driven responses, impairs safety learning,[106] and alters memory dynamics,[107] reinforcing persistent avoidance behaviors. Cognitive-behavioral and exposure-based therapies may restore extinction learning and reduce threat amplification.[108] These protective mechanisms highlight that the stress-pain cycle is modifiable.

Stress and chronic pain form an integrated biopsychosocial system in which neuroendocrine dysregulation, central sensitization, neuroinflammation, large-scale network reorganization, and maladaptive threat learning mutually reinforce each another. Sex differences, developmental experiences, and resilience factors modulate this interaction. Conceptualizing chronic pain through this multidimensional framework advances both mechanistic understanding and translational intervention strategies aimed at interrupting pain chronification.

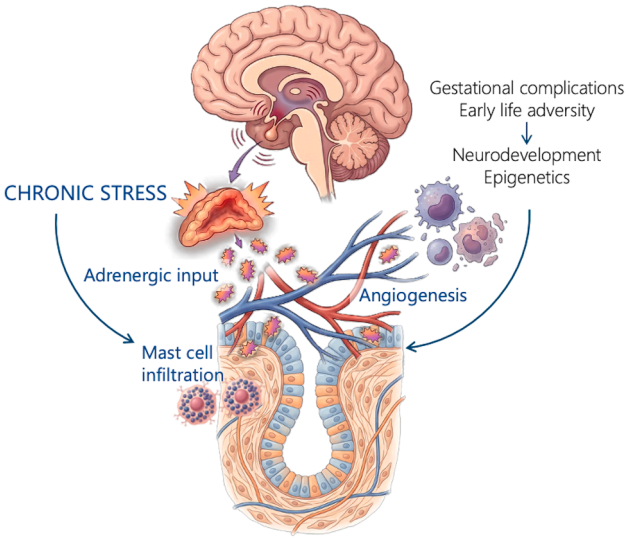


Figure 4. Putative mechanisms by which chronic stress associates with the risk, severity, and symptomatology of endometriosis

Increased adrenergic input, mast cell infiltration, and angiogenesis can be promoted by chronic stress and contribute to endometriosis progression.

Clinical implications

Considering the biological plausibility that chronic stress contributes to reinforce and perpetuate endometriosis-associated pain, several clinical studies were carried out to investigate the effects of stress-reducing therapies on pain severity in women with endometriosis. These interventions include cognitive behavioral therapy,[109] environmental enrichment,[110] music therapy,[111] and mindfulness-based interventions.[112,113] The use of music therapy during endometrioma surgery had no effect on post-operative pain scores.[111] Environmental enrichment plus education for 12 weeks was superior to education only in decreasing anxiety scores and perceived stress but had no benefit on pain scores.[110] Mindfulness-based interventions decreased endometriosis-related pain,[113] increased vagally mediated heart rate variability and improved vitality,[112] while cognitive behavioral therapy led to decreased scores of dysmenorrhea and chronic pelvic pain in women with endometriosis.[109] These heterogeneous outcomes may reflect differences in intervention duration, timing, intensity, and therapeutic targets. In particular, an acute perioperative intervention such as music therapy may be insufficient to modify established pain-processing mechanisms, whereas reductions in psychological stress alone may not necessarily reverse persistent peripheral nociceptive input or central sensitization. More structured and sustained interventions, including cognitive behavioral therapy and mindfulness, may instead influence both stress regulation and pain-related cognitive and emotional processing, thereby producing broader effects on pain severity.

STRESS AND ENDOMETRIOSIS

Epidemiological studies using different methods and covering several populations converge to indicate that chronic stress increases the risk and the severity of endometriosis. A retrospective case-control study found a significant association of endometriosis with a history of childhood abuse including sexual abuse, emotional abuse, and emotional neglect.[114] A population-based cohort study showed an increased risk of endometriosis among women with a history of experiencing intimate partner violence.[115] Another study revealed that exposure to war exacerbates endometriosis symptoms.[116] These epidemiological associations do not prove causality but raise the hypothesis of a pathological process triggered by repeated exposure to severe stressors, which elicits a chronic stress response characterized by altered autonomic and immunological inputs, ultimately aggravating the proliferative and inflammatory milieu of endometriotic lesions (Figure 4).

From bench to bedside

The growing understanding of the biological mechanisms linking endometriosis, chronic pain, and stress has profoundly reshaped the conceptual framework through which this disease is interpreted and managed. Traditionally, pain was considered a direct consequence of lesion burden and anatomical distortion, whereas psychological stress was largely viewed as a secondary consequence of chronic symptoms.[117] However, accumulating experimental and clinical evidence demonstrates that chronic pain and stress are biologically intertwined through complex neuroimmune, endocrine, and central nervous system interactions.[11] Rather than representing parallel phenomena, stress and pain establish a reciprocal feedforward loop in which persistent nociceptive input activates stress-responsive pathways, while chronic stress amplifies peripheral inflammation, central sensitization, and pain perception. This paradigm supports a transition from a lesion-based model toward a systemic, mechanism-oriented approach to endometriosis as a chronic pain syndrome.

One of the most important translational advances emerging from these discoveries is the recognition that women with endometriosis represent biologically heterogeneous pain phenotypes. The relative contribution of peripheral inflammation, neuroimmune activation, central sensitization, and stress-related neuroplasticity varies considerably among individuals and may explain the marked heterogeneity in symptom severity, quality of life impairment, and response to treatment.[70] Consequently, clinical assessment is progressively evolving beyond anatomical characterization of disease to incorporate multidimensional evaluation of pain processing, stress exposure, psychosocial vulnerability, sleep quality, fatigue, and functional impairment. Such an integrated approach acknowledges that the clinical expression of endometriosis reflects not only lesion activity but also the dynamic interaction between biological, psychological, and environmental factors.[118]

The increasing recognition of central sensitization has provided one of the clearest examples of successful translation from basic science to clinical practice. Experimental observations demonstrating long-term plastic changes within pain-processing pathways[81] have been corroborated by clinical studies reporting widespread hyperalgesia, reduced pain thresholds, and high rates of central sensitization among women with persistent endometriosis-associated pain, particularly in those with pain refractory to conventional hormonal treatment.[66] The

incorporation of validated assessment tools, including the Central Sensitization Inventory,[72] together with patient-reported outcome measures and quantitative sensory testing, may facilitate identification of patients at increased risk of pain chronification and persistent disability. Likewise, systematic evaluation of stress-related symptoms may help identify women in whom dysregulation of neuroendocrine and autonomic pathways contributes substantially to symptom persistence.

Advances in translational research have also stimulated the search for objective biomarkers reflecting the biological interactions between stress and pain. Candidate biomarkers include alterations in cortisol dynamics, inflammatory cytokines, neurotrophins such as NGF and BDNF, autonomic nervous system activity,[119,120] and neuroimaging signatures of altered corticolimbic connectivity.[121] Although none of these markers has yet reached routine clinical application, they collectively illustrate the potential for future mechanism-based tools capable of identifying biologically distinct patient subgroups and predicting treatment responsiveness.

Collectively, these advances support a fundamental shift in the clinical management of endometriosis. Rather than targeting pelvic lesions alone, contemporary evidence advocates a comprehensive approach that considers the reciprocal interactions among peripheral inflammation, neuroimmune activation, central nervous system plasticity, and chronic stress. Integrating these biological dimensions into clinical decision-making may facilitate earlier identification of patients at risk for pain chronification, improve patient stratification, and promote personalized therapeutic strategies.[122] Ultimately, translating mechanistic discoveries into clinical practice provides the conceptual foundation for interventions aimed not only at controlling symptoms but also at preventing the progression from recurrent nociceptive pain to chronic pain syndrome.

Strategies to prevent progression of pain and stress in endometriosis

The recognition that endometriosis-associated pain may evolve from predominantly nociceptive mechanisms toward more complex states of central sensitization and nociplastic pain underscores the importance of preventive strategies aimed at limiting pain chronification. Rather than focusing exclusively on the treatment of established chronic pain, contemporary approaches increasingly emphasize early intervention to reduce persistent nociceptive input, mitigate maladaptive neuroplastic changes, and preserve physical and psychological functioning.

One of the most important opportunities for secondary prevention lies in reducing diagnostic delay.[123] Despite increasing awareness of the disease, many women continue to experience symptoms for several years before receiving a definitive diagnosis. During this period, repeated exposure to inflammatory and nociceptive stimuli may facilitate the development of peripheral and central sensitization. Earlier recognition of symptoms and timely initiation of appropriate management may therefore reduce the likelihood of pain chronification and improve long-term outcomes.[122,124]

Effective control of peripheral pain generators represents another key preventive strategy. Hormonal therapies capable of suppressing cyclic lesion activity and reducing inflammation may decrease ongoing nociceptive input and limit sensitization processes. Similarly, when appropriately indicated, surgical treatment may contribute to reducing peripheral sources of pain. Importantly, the objective of these interventions extends beyond symptom relief alone and includes the prevention of long-term alterations in pain processing pathways.[125]

The identification of patients at increased risk of pain persistence may further improve preventive care. Features such as prolonged pain duration, widespread pain distribution, sleep disturbances, psychological distress, and evidence of central sensitization have been associated with poorer outcomes and may signal an increased vulnerability to pain chronification. Early recognition of these factors could facilitate targeted interventions before persistent neuroplastic changes become established.[66]

Stress represents a critical component in the progression of chronic pain. Chronic stress may amplify pain perception, whereas persistent pain itself acts as a significant stressor, creating a bidirectional relationship capable of perpetuating symptom severity and functional impairment. Addressing stress-related factors may therefore represent an important component of preventive strategies aimed at interrupting this self-reinforcing cycle.[11]

In this context, multidisciplinary interventions may offer benefits beyond symptom management alone. Physical activity, pelvic floor rehabilitation, cognitive behavioral interventions, pain neuroscience education, and strategies promoting sleep quality and psychological well-being may help preserve adaptive pain modulation mechanisms and reduce the risk of chronic disability.[126,127] Although evidence regarding their preventive efficacy remains limited, these approaches are increasingly incorporated into comprehensive models of care.

Future efforts should focus on identifying individuals at highest risk for pain chronification through the integration of clinical, molecular, and psychosocial markers. Such risk-stratification strategies may enable the development of personalized preventive approaches targeting both biological and psychosocial determinants of chronic pain. Ultimately, the goal of endometriosis management should extend beyond treating established symptoms to preventing the progression of pain and stress before persistent neuroplastic changes become entrenched.

CONCLUSION AND FUTURE DIRECTIONS

Endometriosis and its associated chronic pain syndrome are fueled by a pathological, chronic stress response that contributes to amplifying pain perception through both peripheral and central neural mechanisms. These mechanisms are multi-vectorial and are modulated by hormonal, neurodevelopmental and epigenetic factors. Evidence suggests that chronic pain in endometriosis is more than a symptom and an unpleasant experience that compromises everyday activities and undermines general well-being. It is also a pathogenic stimulus that induces chronic stress and thereby aggravates the disease course. Therefore, early treatment of endometriosis-associated pain should be the rule for preventing the full vicious circle of pain, stress, and endometriosis progression to unfold.

Despite the remarkable advances reviewed here, further research is still needed to better understand whether chronic

stress is a contributing cause of the onset of endometriosis and whether there is an opportunity to modify this risk factor before endometriosis is fully established. The development of therapeutic strategies, both pharmacologic and behavioral, to interrupt the circle of pain sensitization and chronic stress in women with endometriosis is another research priority for the years to come.

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The authors have no competing interests.

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