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THE NEUROBIOLOGICAL AND IMMUNOLOGICAL BASIS OF THE CO-OCCURRENCE OF ENDOMETRIOSIS WITH DEPRESSION AND ANXIETY: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Endometriosis is a chronic, oestrogen-dependent inflammatory condition affecting approximately 10% of women of reproductive age worldwide. In addition to its well-documented gynaecological symptoms, endometriosis is increasingly associated with psychiatric disorders, particularly depression and anxiety disorders. The neurobiological and immunological mechanisms underpinning this comorbidity remain poorly understood.
Objective: This systematic review aims to synthesise current data on the neurobiological, neuroendocrine and immunological mechanisms linking endometriosis to depression and anxiety disorders, taking into account additional psychiatric symptoms such as sleep disorders, post-traumatic stress disorder (PTSD) and sexual dysfunction.
Methods: A systematic search of the PubMed/MEDLINE database was conducted to identify articles published between January 2008 and March 2026, using predefined search terms relating to endometriosis, mental health, neuroinflammation and immune dysregulation. Study selection was carried out in accordance with the PRISMA 2020 guidelines. Studies analysing the association between endometriosis and psychiatric outcomes, or investigating the underlying biological mechanisms, were included.
Results: Thirty studies met the inclusion criteria. The data consistently indicate elevated rates of depression (prevalence 9.8-98.5 per cent) and anxiety (11.5-87.5 per cent) in women with endometriosis compared with the general population. Key mechanisms identified include: dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis; systemic and central neuroinflammation mediated by pro-inflammatory cytokines (IL-1beta, IL-6, TNF-alpha), oestrogen-induced neurotransmitter imbalances, central sensitisation, oxidative stress and gut-brain axis dysfunction.
Conclusions: The relationship between endometriosis and psychiatric disorders is bidirectional and mediated by combined neuroendocrine-immunological pathways. These findings highlight the need for integrated, multidisciplinary management strategies that take into account both the somatic and psychological dimensions of endometriosis.

KEYWORDS

Endometriosis, Depression, Medication, Neuroinflammation, Hypothalamic-Pituitary-Adrenal Axis, Cytokines

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1. Introduction

Endometriosis is a chronic, estrogen-dependent gynaecological condition characterised by the presence of endometrium-like tissue outside the uterine cavity, most commonly on the ovaries, fallopian tubes, peritoneum and other structures of the lesser pelvis [1]. Affecting an estimated 10 per cent of women of reproductive age and 2–5 per cent of postmenopausal women worldwide, endometriosis represents a significant burden on public health, with prevalence estimates ranging from 2-10% in the general population to 50% among women presenting with infertility, and from 15 to 75% in women undergoing laparoscopy for chronic pelvic pain (Moradi et al., 2021). Core symptoms include chronic lower pelvic pain, painful periods (dysmenorrhoea), painful sexual intercourse (dyspareunia), dysuria, dyschezia and infertility, which significantly impair patients' daily lives[1] [2].

In addition to the established gynaecological consequences, a growing body of evidence identifies endometriosis as a systemic disease with far-reaching implications for mental health. Numerous systematic reviews and meta-analyses have shown that women with endometriosis experience significantly higher rates of depressive and anxiety symptoms compared with the general population. The ELEMI (Endometriosis and Mental-Health Sequelae) project, a large-scale meta-analysis, confirmed that patients with endometriosis exhibit a significantly greater burden of symptoms of both depression and anxiety. The prevalence of anxiety disorders among women with endometriosis was 31.8% (95% CI 26.5%–37.1%), and that of depression was 28.9% (95% CI 8.6%–49.2%) [4]. Van Barneveld also confirmed in his study a correlation between

endometriosis and psychological symptoms: depression ([SMD] = 0.71; 95% CI 0.36–1.06) and anxiety (SMD = 0.60; 95% CI 0.35–0.84) compared with healthy control groups [3]. Similarly, Gambadauro et al. reported higher levels of depression among women with endometriosis (SMD = 0.22; 95% CI 0.13–0.32) in a meta-analysis of 24 studies involving 99,614 women [5].

Endometriosis increases the risk of depression and anxiety, but this is not solely due to the difficulties of living with pain and anxiety; it is also because the condition can directly influence the onset and development of mental health disorders. New evidence points to shared biological mechanisms involving the neuroendocrine and immune systems. The hypothalamic-pituitary-adrenal (HPA) axis, the centre of the stress response, shows significant dysregulation in women with endometriosis and chronic pelvic pain, manifesting as altered patterns of ACTH and cortisol secretion and suppressed stress reactivity[6];[7]. Shewarani et al. note in their study that the chronic inflammatory environment characteristic of endometriosis (marked by elevated levels of pro-inflammatory cytokines, including interleukin-1 beta (IL-1beta), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha)), constitutes a direct link to depression, in which increased secretion and production of the same pro-inflammatory molecules are observed.[8] [9].

In their review, Chang et al.[10] examined the relationship between endometriosis and the bidirectional neuroendocrine-immune axis and demonstrated its significant influence on the release of neurotransmitters and pro-inflammatory cytokines, which may represent a key link to the occurrence of mental health disorders in this patient group. According to this model, endometriosis causes chronic inflammation, which leads to increased secretion of pro-inflammatory cytokines; these enter the central nervous system and may promote the onset of symptoms of depression and anxiety. At the same time, chronic psychological stress - via activation of the HPA axis -exacerbates the inflammatory and endocrine disturbances that sustain the growth of endometriotic lesions [11]. This creates a vicious circle in which somatic and psychological pathology reinforce one another.

Despite the clinical significance of this association, the underlying mechanisms have not yet been comprehensively synthesised in a single systematic review. Existing reviews have typically focused on the epidemiological association between endometriosis and mental health outcomes, or on the analysis of individual mechanisms. This systematic review aims to analyse the neurobiological, neuroendocrine and immunological mechanisms linking endometriosis to depression and anxiety disorders.

2. Materials and Methods

This systematic review was conducted in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al., 2021). The review protocol was not registered with PROSPERO.

A comprehensive search of the PubMed/MEDLINE electronic database was carried out to identify articles published between January 2008 and March 2026. The search strategy included combinations of the following MeSH (Medical Subject Headings) terms and keywords:

- **Population:** “endometriosis” OR “endometriotic”
- **Exposure/Mechanism:** “neuroinflammation” OR “HPA axis” OR “hypothalamic-pituitary-adrenal” OR “cortisol” OR “cytokines” OR “interleukin” OR “TNF-alpha” OR “immune dysregulation” OR “neuroendocrine” OR “neuroimmune” OR “oxidative stress” OR “central sensitisation” OR “microbiome” OR “gut-brain axis” OR “oestrogen” OR “serotonin” OR “dopamine”
- **Result:** “depression” OR “anxiety” OR “mental health” OR “psychiatric” OR “psychological distress” OR “quality of life” OR “PTSD” OR “sleep disorders” OR “sexual dysfunction”

Logical operators (AND, OR) were used to combine search terms. The reference lists of the included studies were manually reviewed to identify additional relevant publications.

Inclusion criteria: 1. Original research articles (cross-sectional, cohort and case-control studies), systematic reviews, meta-analyses and narrative reviews published in peer-reviewed journals 2. Studies analysing the association between endometriosis and depression, anxiety or other psychiatric outcomes 3. Studies addressing neurobiological, neuroendocrine or immunological mechanisms relevant to the endometriosis–mental health relationship 4. Studies published in English 5. Studies involving humans or animal models.

Exclusion criteria: 1. Case reports and conference abstracts 2. Studies not available in English 3. Studies without a direct link to the issue of comorbidity between endometriosis and psychiatric disorders 4. Editorial articles, commentaries and letters to the editor.

The study selection process comprised two phases. In the initial assessment phase, the titles and abstracts of all retrieved records were reviewed for relevance. In the full-text assessment phase, potentially eligible articles were read in full to determine final inclusion. The following data were extracted from each included study: authors, year of publication, study design, sample size, population characteristics, outcome measures, main results and indicators of methodological quality.

The methodological quality of the included studies was assessed using appropriate tools depending on the study design. Systematic reviews and meta-analyses were assessed using the AMSTAR 2 checklist (A Measurement Tool to Assess Systematic Reviews). Observational studies were assessed using the Newcastle-Ottawa Scale (NOS). The quality assessment influenced the interpretation of the results but was not used as an exclusion criterion.

Due to the heterogeneity of study designs, populations and outcome measures, a narrative synthesis approach was adopted. The results were organised thematically according to the following domains: (1) epidemiological evidence of psychiatric comorbidity; (2) HPA axis dysregulation; (3) inflammatory and immunological mechanisms; (4) neuroinflammation and central nervous system pathways; (5) oestrogen–neurotransmitter interactions; (6) additional mechanisms (oxidative stress, the gut-brain axis, central sensitisation); and (7) secondary psychiatric symptoms (PTSD, sleep disorders, sexual dysfunction).

3. Results

An initial search of PubMed yielded 487 records. After removing 62 duplicates, 425 unique records were screened for titles and abstracts, of which 89 were shortlisted for full-text assessment. Following full-text review, 30 studies met the final inclusion criteria and were included in the qualitative synthesis. The included studies comprised 8 systematic reviews and/or meta-analyses, 6 narrative reviews, 10 cross-sectional or case-control studies, 4 cohort or longitudinal studies, and 2 animal model studies with translational relevance.

The reviewed data consistently point to a strong association between endometriosis and psychiatric disorders, in particular depression and anxiety. In 2023, Szypłowska conducted a systematic review showing that the prevalence of depressive symptoms among patients with endometriosis ranged from 9.8% to as high as 98.5%, whilst the prevalence of anxiety symptoms ranged from 11.5% to 87.5%, (depending on the diagnostic tools used). It was also noted that the prevalence of depression was higher in women under 35 years of age.[12] This wide variation reflects differences in study methodologies, with studies using validated clinical diagnostic criteria reporting lower prevalence rates than those based on self-assessment screening tools.

In a comprehensive meta-analysis of 24 studies (99,614 women), Gambadauro demonstrated that women with endometriosis had significantly higher levels of depressive symptoms compared with control groups (SMD = 0.22; 95% [CI] 0.13–0.32).[5] The ELEMI project's meta-analysis provided even clearer estimates, noting that anxiety disorders occur in 31.8% of patients (95% CI 26.5%–37.1%), and depressive disorders in 28.9% (95% CI 8.6%–49.2%) [3].

In his meta-analysis of 44 articles from 4 continents and 13 countries, Wang confirmed that endometriosis impairs both mental health and health-related quality of life, with effects observed in both the physical and mental health domains (HRQoL). Van Barneveld et al. (2022) further identified that the severity of depressive and anxiety symptoms in patients with endometriosis correlates with the severity of chronic lower pelvic pain, suggesting that pain may act as a mediating variable. In their systematic review, Brasil et al. reported elevated levels of psychological stress in women with endometriosis at 68% (95% CI: 57%–79%) and a correlation between increased stress and disease severity. [14]

Davenport et al. conducted a meta-analytic review examining the role of neuroticism and cognitive factors in the depression–endometriosis relationship, finding that neuroticism and maladaptive cognitive patterns (pain catastrophising, rumination and a perception of the illness as having low controllability) are significantly associated with the severity of depression and anxiety in this population [15].

The HPA axis, the central coordinator of the neuroendocrine stress response, has been shown to be a key component of the mechanism linking endometriosis to psychiatric comorbidity. Under physiological conditions, the HPA axis operates via a tightly regulated negative feedback loop: hypothalamic corticotropin-releasing hormone (CRH) stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn stimulates the secretion of cortisol by the adrenal glands. Cortisol, via a feedback mechanism mediated by the glucocorticoid receptor, inhibits further production of CRH and ACTH. In endometriosis, this regulatory mechanism appears to be significantly impaired.

Ortiz et al. provided direct evidence of HPA axis dysfunction in women with chronic pelvic pain, both endometriosis-related and non-endometriosis-related. Their study revealed altered circadian cortisol profiles, characterised by a suppressed morning cortisol peak during the follicular phase and elevated concentrations in the evening. Hypoadrenocorticism may cause immune dysfunction and thereby exacerbate inflammation in endometriosis. [6] Importantly, this pattern mirrors the HPA axis abnormalities consistently reported in severe depression, suggesting a common neuroendocrine substrate.

Petrelluzzi et al. similarly reported hypocortisolism in women with endometriosis and chronic lower pelvic pain, manifested by reduced salivary cortisol concentrations throughout the day and a blunted cortisol response upon waking. The authors proposed that chronic pain-driven activation of the HPA axis may lead to a final downregulation of glucocorticoid receptors and cortisol resistance - a phenomenon analogous to the glucocorticoid resistance hypothesis in depression. [7]

Quinones et al. investigated the interaction between anxiety and HPA axis function in women with endometriosis, finding that increased anxiety was associated with maladaptive cortisol responses. These findings suggest that psychological vulnerability may be bidirectional: chronic pain and stress drive HPA axis dysregulation, whilst such dysregulation may in turn cause immunological changes and exacerbate symptoms.[16]

Appleyard et al. provided a comprehensive translational perspective in their review linking stress and endometriosis in animal models and clinical studies. They demonstrated that chronic psychological stress continuously activates the HPA axis and the sympathetic nervous system, increasing the release of CRH and uro cortin. In animal models of endometriosis, exposure to stress accelerated the growth of lesions and exacerbated pain symptoms, establishing a clear biological pathway through which psychological stress can exacerbate the disease. These findings open up new therapeutic possibilities focusing on the modification of brain–body–brain pathways. [11]

Endometriosis is a chronic pro-inflammatory disease, and the immune environment it creates has a profound impact on mental health. The peritoneal microenvironment in endometriosis is characterised by elevated concentrations of pro-inflammatory cytokines, activated macrophages and dysregulated immune cell populations [17].

Bjork et al. demonstrated increased local and systemic expression of inflammatory cytokine mRNAs in women with endometriosis, primarily IL-6, IL-8, IL-1β and TNF-α, accompanied by a compensatory adaptive regulatory response which, paradoxically, impairs cytotoxicity and facilitates the survival of inflammatory foci. This immune dysregulation results in a state of chronic, low-grade systemic inflammation that extends beyond the peritoneal cavity and may be associated with other chronic inflammatory diseases. Similar inflammatory responses are also observed in conditions such as rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease. [18]

Siedentopf et al. directly investigated the intersection of immune status, psychosocial stress and quality of life in infertile patients with endometriosis. Their findings revealed that patients with endometriosis exhibited both immune activation (elevated inflammatory markers) and heightened psychological stress, with significant correlations between immune parameters and scores on depression scales. This demonstrates once again that methods of stress reduction and coping can assist in the treatment of depression, but also help to break the vicious cycle of inflammation, disease symptoms and psychological dysfunction. [19]

The significance of these immunological findings for depression is well documented in the wider neuropsychiatric literature. In 2009, Miller et al. presented a landmark review demonstrating that pro-inflammatory cytokines, in particular IL-6 and TNF-alpha, play a causal role in the pathophysiology of major depression through a number of mechanisms: (a) activation of the enzyme indoleamine 2,3-dioxygenase (IDO), which redirects tryptophan metabolism from serotonin synthesis to the kynurenine pathway, thereby depleting the main substrate for serotonin production; (b) stimulation of the HPA axis leading to hypercortisolaemia; (c) inhibition of the expression of brain-derived neurotrophic factor (BDNF), thereby impairing neuroplasticity; and (d) effects on the reuptake of monoamines. [9]

Felger and Lotrich elaborated on these mechanisms, demonstrating that peripheral cytokines gain access to the CNS via multiple routes - including active transport across the blood–brain barrier (BBB), activation of vagal afferent fibres, and direct damage to the BBB - where microglia are activated and a neuroinflammatory cascade is initiated. In the context of endometriosis, chronically elevated systemic cytokine concentrations provide a persistent peripheral inflammatory signal that may drive persistent CNS inflammation and mood disorders. [20]

Sherwani et al. described a vicious cycle between chronic endometriosis and depression, mediated by immunological and physiological pathways. Depression is associated with the production of highly pro-inflammatory molecules (IL-6, IFN-γ, TNF-α, IL-1B), exacerbates oxidative stress and increases ROS, whilst endometriosis, through inflammation and associated immunological disturbances, may increase the risk of developing depression; conversely, depression, by exacerbating inflammatory processes, may influence the further course of the disease. [8]

The concept of neuroinflammation as a bridge between peripheral immune dysregulation and central mood disorders has gained particular significance in the context of endometriosis. Mokhtari et al. (2024) demonstrated that endometriosis is associated with elevated levels of pro-inflammatory cytokines, whilst there is also dysregulation of the HPA axis, leading to a reduction in the production of inflammatory mediators in the circulatory system and the brain. Cytokines cause the breakdown of the blood-brain barrier, activate microglia and lead to neuroinflammation. The overproduction of cytokines affects signalling pathways, disrupts neuronal plasticity and leads to neuronal death, which in the long term may contribute to the development of mental health disorders such as depression or anxiety. [24]

In 2022, Maulitz et al. published a paper in which they highlighted the impact of endometriosis on the brain and introduced the concept of the ‘endometrial brain’. Within endometrial lesions, the density of nerve fibres is higher; furthermore, these fibres are constantly stimulated by inflammatory mediators and nerve-sensitising proteins. Pain signals are transmitted to the thalamus, brainstem and cerebral cortex. This triggers a reorganisation of peripheral synapses and accelerated conduction along nerve fibres. Persistent stimuli may increase the activity of dorsal horn neurons, lower the pain threshold and exaggerate pain perception. As the inflammatory process persists, inter-organ sensitisation and difficulties with pain relief may occur, even following the excision of endometriosis lesions.[25]

Chang et al. [10] highlighted several important aspects in their study, paying particular attention to the role of the neuroendocrine-immune axis in endometriosis. Oestrogen mediates the interaction between macrophages and nerve fibres and may exacerbate the inflammatory response and increase the sensitivity of nerve endings to pain stimuli. Furthermore, by enhancing neuroimmune signalling (stimulation of the secretion of IL-6, TNF-α and NGF), it may contribute to the development of neuroinflammation and, in the longer term, to the remodelling of the central and peripheral nervous systems. All these processes increase the risk of central sensitisation and mental health disorders, such as depression or anxiety. [10]

As an oestrogen-dependent condition, endometriosis creates a hormonal environment that directly influences the neurotransmitter systems of the CNS relevant to mood regulation. Bendis et al. (2024) provided a comprehensive analysis of the effect of oestradiol on the serotonergic, glutamatergic and dopaminergic systems, demonstrating that fluctuations in oestrogen concentrations profoundly modulate these neurotransmitter pathways.

Oestradiol enhances serotonergic neurotransmission through the overexpression of tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis), an increase in serotonin receptor density, and the inhibition of monoamine oxidase activity. In endometriosis, the state of hyperoestrogenism characteristic of the active phases of the disease may, paradoxically, disrupt these regulatory mechanisms through downregulation of receptors and desensitisation, whilst relative states of hypoestrogenism induced by hormonal treatment (GnRH agonists, progestogens) may further impair serotonergic function [26]

Similarly, oestradiol modulates dopaminergic neurotransmission in the mesolimbic and mesocortical pathways, affecting the reward system. Fluctuations in oestrogen levels associated with endometriosis and its treatment may contribute to dopaminergic dysregulation, manifesting clinically as anhedonia, fatigue and cognitive difficulties - symptoms that largely overlap with those of depression

Chang et al. [10] further documented that the neuroendocrine-immune axis exerts cross-regulation through interactions between neurotransmitters, hormone-like substances, cytokines and their receptors. This complex interaction means that the hormonal disturbances inherent in endometriosis may amplify both inflammatory and neurotransmitter pathways leading to depression and anxiety.

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and the capacity for antioxidant defence, has been identified as an additional mechanism contributing to both the progression and development of endometriosis, as well as the accompanying psychiatric symptoms. Scutiero et al. (2017) conducted a systematic review demonstrating that oxidative stress is involved in the pathophysiology of endometriosis, with elevated markers of oxidative damage documented in peritoneal fluid, serum, follicular fluid, ovarian cortex and endometrial tissue of women affected by the disease. [22]

In the CNS, oxidative stress contributes to depression via mitochondrial dysfunction, peroxidation of neuronal membrane lipids and direct damage to monoaminergic neurons. [23]

Systemically elevated ROS concentrations in endometriosis may therefore represent a common pathophysiological mechanism linking the disease to depression, acting in concert with inflammatory and neuroendocrine pathways.

The microbiota-gut-brain axis is emerging as a new pathway that may link endometriosis with psychiatric symptoms. Hearn-Yeates et al. (2024) reviewed the impact of this axis on endometriosis-related symptoms, documenting that women with endometriosis often exhibit gut microbiome dysbiosis, altered intestinal permeability and gastrointestinal symptoms overlapping with those of irritable bowel syndrome (IBS).

The gut microbiome influences brain function via multiple pathways: the production and utilisation of neuroactive metabolites (short-chain fatty acids, tryptophan derivatives), modulation of vagal afferent signalling, regulation of systemic inflammation, and influence on the HPA axis. Dysbiosis in endometriosis may therefore contribute to psychiatric symptoms by disrupting communication between the brain and the gastrointestinal tract. [21]

Patients with endometriosis show a significantly higher prevalence of PTSD (10–20%) compared with the general population (5–7%). Dipankar et al. (2025) indicate that this risk increases in women with severe forms of the disease and a long duration of pain. The main traumatic factors are: chronic pain, a 7–10-year delay in diagnosis, multiple operations, and the psychosocial effects of infertility. [27]

Sumbodo et al. [33] demonstrated a strong association between endometriosis and insomnia and sleep quality. Insomnia and fatigue were twice as common in patients with the painful form of endometriosis. The bidirectional relationship between mood and sleep is well documented: pain and depression disrupt sleep architecture, whilst sleep deprivation lowers the pain threshold and increases the severity of mood disorders.

Sexual dysfunction associated with dyspareunia is often an under-recognised factor contributing to psychological distress in endometriosis. Privitera et al. demonstrated that symptoms of endometriosis, dyspareunia and sexual distress are significantly associated with avoidance of sexual activity and a negative impact on sexual relations, with each unit increase in the severity of dyspareunia being associated with a significant increase in the likelihood of avoiding intercourse. Psychological consequences, such as a distorted body image and a loss of intimacy, as well as a deterioration in relationships, further exacerbate depressive and anxiety symptoms [32]

4. Discussion

This systematic review provides an integrated analysis of the neurobiological, neuroendocrine and immunological mechanisms underpinning the comorbidity of endometriosis with mental health disorders, with a particular focus on depression and anxiety. The synthesised data support a model of bidirectional causality, in which endometriosis and mental health disorders overlap through a network of biological links.

The relationship between endometriosis and mental health disorders is mediated by a complex, bidirectional neuroendocrine-immunological axis. In the proactive direction, endometriosis triggers chronic peripheral inflammation (elevated IL-1β, IL-6, TNF-α), which in turn triggers a cascade of neuroinflammation. Consequently, this leads to impaired neurotransmission in the serotonergic, dopaminergic and glutamatergic systems, directly promoting depressive and anxiety symptoms [10]

Conversely, psychological distress induces chronic activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, increasing the secretion of glucocorticoids and catecholamines. These hormones suppress cellular immunity, exacerbate the production of inflammatory cytokines and promote angiogenesis and the growth of lesions in the peritoneal environment, thereby increasing the severity of endometriosis [11]. This bidirectional model has been termed the ‘vicious circle’ of endometriosis and depression by Sherwani et al. (2024) [8] and explains why treating just one component of the disease in isolation often yields suboptimal results.

The mechanisms identified in this review demonstrate strong synergism. Dysfunction of the HPA axis amplifies inflammatory signalling, which in turn promotes neuroinflammation. Gut microbiota dysbiosis in patients with endometriosis affects immune regulation, tryptophan metabolism (a precursor of serotonin) and vagal signalling, which further destabilises neurotransmitter systems already subject to fluctuations under the influence of oestradiol.[21]

Concurrently, a process of central sensitisation occurs, in which persistent pain signals lead to structural and chemical changes in the CNS. The intensification of pain involves affective circuits, transforming

nociceptive pain into chronic centralised pain with a strong emotional component. The overall clinical picture is complemented by post-traumatic stress disorder and sleep disorders, along with sexual dysfunction [3]

The convergence of these pathways explains the considerable heterogeneity in the prevalence of psychiatric symptoms reported in individual studies, suggesting the need for personalised treatment based on the immunological and microbiological profiling of patients [12]

The findings summarised in this review have significant implications for clinical practice. Firstly, they highlight the need for routine screening for psychiatric disorders as part of the care of patients with endometriosis. Given the high prevalence of depression and anxiety and their bidirectional relationship with disease progression, validated screening tools (such as the Patient Health Questionnaire-9 [PHQ-9] and the Generalised Anxiety Disorder-7 [GAD-7]) should be incorporated into standard gynaecological assessments of patients with endometriosis. Furthermore, given the strong correlation between pain and insomnia and fatigue, routine assessment of sleep quality is essential for improving treatment outcomes

Secondly, the identification of common neuroendocrine-immunological pathways suggests potential new therapeutic targets that could simultaneously address both the somatic and psychiatric dimensions of the disease. Anti-inflammatory interventions, stress-reduction techniques (including cognitive-behavioural therapy and mindfulness-based approaches) and therapies targeting the gut microbiome represent promising avenues requiring further research (Donatti et al., 2022). [28]

Thirdly, the evidence supports a multidisciplinary management model integrating gynaecological, psychological and psychiatric care. Donatti et al. (2022) demonstrated that cognitive behavioural therapy (CBT) significantly reduces pain perception, improves mood parameters and enhances patients' quality of life, making it a key component of a comprehensive treatment plan [28]

The strengths of this review include its comprehensive scope, integrating data ranging from the molecular level (oestradiol modulation) to clinical aspects (PTSD, sexual dysfunction), and compliance with the PRISMA 2020 guidelines. However, several limitations must be acknowledged, such as the heterogeneity of the included studies; the varied study designs, populations and measurement tools made it impossible to conduct a quantitative meta-analysis. Measurement errors - some studies relied on unvalidated questionnaires or diagnoses based solely on patients' subjective complaints. Causal inference - the predominance of cross-sectional studies limits the ability to unequivocally establish causal relationships in a bidirectional model.

In order to fill the gaps in the current evidence base, the following research activities are necessary. Longitudinal studies will help to elucidate the temporal dynamics of the relationship between biological markers (cytokine panels, cortisol profiles, the microbiome) and the mental state of patients. The use of advanced neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), enables a detailed analysis of structural and functional changes in the brains of patients with endometriosis. Comparative studies of individuals with and without psychiatric comorbidity may help to identify the central neural correlates of peripheral inflammation and elucidate the mechanisms underlying central sensitisation. Standardisation of methods - future studies should aim to standardise diagnostic sleep assessment tools and incorporate objective measurement methods, such as polysomnography. Randomised controlled trials evaluating integrated therapeutic approaches combining surgical or hormonal treatment with psychological and anti-inflammatory interventions are essential to determine whether addressing multiple pathways simultaneously improves outcomes compared with single-pathway treatment. Finally, genetic and epigenetic studies analysing shared susceptibility loci for endometriosis and depression may reveal new biomarkers, thereby facilitating early diagnosis and personalised therapy

This systematic review demonstrates that the comorbidity of endometriosis with psychiatric disorders - in particular depression and anxiety - is mediated by a complex, bidirectional neuroendocrine-immunological axis.The pathogenesis of these disorders involves HPA axis dysfunction, systemic inflammation inducing neuroinflammation, molecular modulation of neurotransmitter systems by oestradiol, oxidative stress, and dysbiosis of the microbiota–gut–brain axis. These mechanisms, together with the process of central sensitisation, form a self-perpetuating 'vicious circle' in which disease progression and psychological distress mutually exacerbate one another. The conclusion to be drawn from this review is that endometriosis should be recognised not merely as a gynaecological disorder, but as a systemic disease with a neuropsychiatric dimension requiring an integrated, multidisciplinary approach. Routine psychiatric screening, psychological interventions and research into anti-inflammatory and microbiome-targeted therapies represent critical next steps in improving outcomes for the estimated 190 million women affected by endometriosis worldwide. Future research directions should prioritise longitudinal studies with serial collection of biomarkers, the use of advanced neuroimaging to identify neuronal correlates of pain and inflammation, and genetic studies. Only a holistic and personalised approach to the patient will maximise therapeutic success and minimise the long-term effects of this chronic condition.

Authors' contributions:

- Development of the study concept: Julia Wawerska, Martyna Grzywacz
- Literature review: Rafał Ejsner, Weronika Wrzosek
- Data analysis and interpretation:Balbina Tybulczuk, Bartłomiej Markowski
- Preparation of the first draft of the manuscript: Mateusz Zugaj, Marta Rząsa
- Proofreading and editing of the manuscript: Maciej Kisielewski, Bartosz Okliński
- Supervision of the work: Julia Wawerska, Martyna Grzywacz

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REFERENCES

1. As-Sanie, S., Mackenzie, S. C., Morrison, L., Schrepf, A., Zondervan, K. T., Horne, A. W., & Missmer, S. A. (2025). Endometriosis: A review. *JAMA, 334*(1), 64–78. https://doi.org/10.1001/jama.2025.2975
2. Masciullo, L., Viscardi, M. F., Piacenti, I., Scaramuzzino, S., Cavalli, A., Piccioni, M. G., & Porpora, M. G. (2021). A deep insight into pelvic pain and endometriosis: A review of the literature from pathophysiology to clinical manifestations. *Minerva Obstetrics and Gynaecology, 73*(5), 511–522. https://doi.org/10.23736/S2724-606X.21.04779-1
3. van Barneveld, E., Manders, J., van Osch, F. H. M., van Poll, M., Visser, L., van Hanegem, N., Lim, A. C., Bongers, M. Y., & Leue, C. (2022). Depression, anxiety, and correlating factors in endometriosis: A systematic review and meta-analysis. *Journal of Women's Health, 31*(2), 219–230. https://doi.org/10.1089/jwh.2021.0021
4. Delanerolle, G., Ramakrishnan, R., Hapangama, D., Zeng, Y., Shetty, A., Elneil, S., Chong, S., Hirsch, M., Oyewole, M., Phiri, P., Elliot, K., Kothari, T., Rogers, B., Sandle, N., Haque, N., Pluchino, N., Silem, M., O'Hara, R., Hull, M. L., … Raymont, V. (2021). A systematic review and meta-analysis of the endometriosis and mental-health sequelae: The ELEMI project. *Women's Health, 17*, 17455065211019717. https://doi.org/10.1177/17455065211019717
5. Gambadauro, P., Carli, V., & Hadlaczky, G. (2019). Depressive symptoms among women with endometriosis: A systematic review and meta-analysis. *American Journal of Obstetrics and Gynaecology, 220*(3), 230–241. https://doi.org/10.1016/j.ajog.2018.11.123
6. Ortiz, R., Gemmill, J. A. L., Sinaii, N., Stegmann, B., Khachikyan, I., Chrousos, G., Segars, J., & Stratton, P. (2020). Hypothalamic-pituitary-adrenal axis responses in women with endometriosis-related chronic pelvic pain. *Reproductive Sciences, 27*(10), 1839–1847. https://doi.org/10.1007/s43032-020-00201-x
7. Petrelluzzi, K. F. S., Garcia, M. C., Petta, C. A., Grassi-Kassisse, D. M., & Spadari-Bratfisch, R. C. (2008). Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. *Stress, 11*(5), 390–397. https://doi.org/10.1080/10253890701840610
8. Sherwani, S., Khan, M. W. A., Rajendrasozhan, S., Al-Motair, K., Husain, Q., & Khan, W. A. (2024). The vicious cycle of chronic endometriosis and depression—An immunological and physiological perspective. *Frontiers in Medicine, 11*, 1425691. https://doi.org/10.3389/fmed.2024.1425691
9. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029
10. Chang, L., Shan, J., Li, D., & Wang, X. (2025). The neuroendocrine-immune axis in endometriosis: A review on how the nervous system goes beyond pain perception. *Biomolecules, 15*(11), 1536. https://doi.org/10.3390/biom15111536
11. Appleyard, C. B., Flores, I., & Torres-Reveron, A. (2020). The link between stress and endometriosis: From animal models to the clinical scenario. *Reproductive Sciences, 27*(9), 1675–1686. https://doi.org/10.1007/s43032-020-00205-7
12. Szyplowska, M., Tarkowski, R., & Kulak, K. (2023). The impact of endometriosis on depressive and anxiety symptoms and quality of life: A systematic review. *Frontiers in Public Health, 11*, 1230303. https://doi.org/10.3389/fpubh.2023.1230303
13. Wang, Y., Li, B., Zhou, Y., Wang, Y., Han, X., Zhang, S., He, Z., & Ouyang, L. (2021). Does endometriosis affect mental health and quality of life? A systematic review and meta-analysis. *Gynecological and Obstetrical Investigation, 86*(4), 315–335. https://doi.org/10.1159/000516517

14. Brasil, D. L., Montagna, E., Trevisan, C. M., La Rosa, V. L., Lagana, A. S., Barbosa, C. P., Bianco, B., & Zaia, V. (2020). Psychological stress levels in women with endometriosis: Systematic review and meta-analysis of observational studies. *Minerva Medica, 111*(1), 90–102. https://doi.org/10.23736/S0026-4806.19.06350-X
15. Davenport, R. A., Krug, I., Dang, P. L., Rickerby, N., & Kiropoulos, L. (2024). Neuroticism and cognitive correlates of depression and anxiety in endometriosis: A meta-analytic review, evidence appraisal, and future recommendations. *Journal of Psychosomatic Research, 187*, 111906. https://doi.org/10.1016/j.jpsychores.2024.111906
16. Quinones, M., Urrutia, R., Torres-Reveron, A., Vincent, K., & Flores, I. (2015). Anxiety, coping skills and the hypothalamic-pituitary-adrenal (HPA) axis in patients with endometriosis. *Journal of Reproductive Biology and Health, 3*, 2. https://doi.org/10.7243/2054-0841-3-2
17. Ahn, S. H., Monsanto, S. P., Miller, C., Singh, S. S., Thomas, R., & Tayade, C. (2015). Pathophysiology and immune dysfunction in endometriosis. *BioMed Research International, 2015*, 795976. https://doi.org/10.1155/2015/795976
18. Bjork, E., Vinnars, M.-T., Nagaev, I., Nagaeva, O., Lundin, E., Ottander, U., & Mincheva-Nilsson, L. (2020). Enhanced local and systemic inflammatory cytokine mRNA expression in women with endometriosis evokes a compensatory adaptive regulatory mRNA response that mediates immune suppression and impairs cytotoxicity. *American Journal of Reproductive Immunology, 84*(4), e13298. https://doi.org/10.1111/aji.13298
19. Siedentopf, F., Tariverdian, N., Rucke, M., Kentenich, H., & Arck, P. C. (2008). Immune status, psychosocial distress and reduced quality of life in infertile patients with endometriosis. *American Journal of Reproductive Immunology, 60*(5), 449–461. https://doi.org/10.1111/j.1600-0897.2008.00644.x
20. Felger, J. C., & Lotrich, F. E. (2013). Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. *Neuroscience, 246*, 199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060
21. Hearn-Yeates, F., Horne, A. W., O'Mahony, S., & Saunders, P. T. K. (2024). The impact of the microbiota-gut-brain axis on endometriosis-associated symptoms: Mechanisms and opportunities for personalised management strategies. *Reproduction and Fertility, 5*(2), e230085. https://doi.org/10.1530/RAF-23-0085
22. Scutiero, G., Iannone, P., Bernardi, G., Bonaccorsi, G., Spadaro, S., Volta, C. A., Greco, P., & Nappi, L. (2017). Oxidative stress and endometriosis: A systematic review of the literature. *Oxidative Medicine and Cellular Longevity, 2017*, 7265238. https://doi.org/10.1155/2017/7265238
23. Allen, J., Romay-Tallon, R., Brymer, K. J., Caruncho, H. J., & Kalynchuk, L. E. (2018). Mitochondria and mood: Mitochondrial dysfunction as a key player in the manifestation of depression. *Frontiers in Neuroscience, 12*, 386. https://pmc.ncbi.nlm.nih.gov/articles/PMC5997778/
24. Mokhtari, T., Irandoost, E., & Sheikhbahaei, F. (2024). Stress, pain, anxiety, and depression in endometriosis—Targeting glial activation and inflammation. *International Immunopharmacology, 132*, 111942. https://doi.org/10.1016/j.intimp.2024.111942
25. Maulitz, L., Stickeler, E., Stickel, S., Habel, U., Tchaikovski, S. N., & Chechko, N. (2022). Endometriosis, psychiatric comorbidities and neuroimaging: Estimating the odds of an endometriosis brain. *Frontiers in Neuroendocrinology, 65*, 100988. https://pubmed.ncbi.nlm.nih.gov/35202605/
26. Bendis, P. C., Zimmerman, S., Onisiforou, A., Zanos, P., & Georgiou, P. (2024). The impact of oestradiol on serotonin, glutamate, and dopamine systems. *Frontiers in Neuroscience, 18*, 1348551. https://doi.org/10.3389/fnins.2024.1348551
27. Dipankar, S. P., Kushram, B., Unnikrishnan, P., Gowda, J. R., Shrivastava, R., Daitkar, A. R., & Jaiswal, V. (2025). Psychological distress and quality of life in women with endometriosis: A narrative review of therapeutic approaches and challenges. *Cureus, 17*(3), e80180. https://doi.org/10.7759/cureus.80180
28. Donatti, L., Malvezzi, H., Azevedo, B. C., Baracat, E. C., & Podgaec, S. (2022). Cognitive behavioural therapy in endometriosis: A psychological-based intervention. *Revista Brasileira de Ginecologia e Obstetricia, 44*(3), 295–303. https://doi.org/10.1055/s-0042-1742406
29. Facchin, F., Buggio, L., Roncella, E., Somigliana, E., Ottolini, F., Dridi, D., Roberto, A., & Vercellini, P. (2021). Sleep disturbances, fatigue and psychological health in women with endometriosis: A matched pair case-control study. *Reproductive Biomedicine Online, 43*(6), 1027–1034. https://doi.org/10.1016/j.rbmo.2021.08.011
30. Moradi, Y., Shams-Beyranvand, M., Khateri, S., Gharahjeh, S., Tehrani, S., Varse, F., Tiyuri, A., & Najmi, Z. (2021). A systematic review on the prevalence of endometriosis in women. *Indian Journal of Medical Research, 154*(3), 446–454. https://doi.org/10.4103/ijmr.IJMR_817_18
31. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hrobjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery, 88*, 105906. https://doi.org/10.1016/j.ijsu.2021.105906
32. Privitera, G., O'Brien, K., Misajon, R., & Lin, C.-Y. (2023). Endometriosis symptomatology, dyspareunia, and sexual distress are related to avoidance of sex and negative impacts on the sex lives of women with endometriosis. *International Journal of Environmental Research and Public Health, 20*(4), 3362. https://doi.org/10.3390/ijerph20043362
33. Sumbodo, C. D., Tyson, K., Mooney, S., Lamont, J., McMahon, M., & Holdsworth-Carson, S. J. (2024). The relationship between sleep disturbances and endometriosis: A systematic review. *European Journal of Obstetrics & Gynaecology and Reproductive Biology, 293*, 1–8. https://doi.org/10.1016/j.ejogrb.2023.12.010