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DEPRESSION IN ENDOMETRIOSIS: SHARED PATHOPHYSIOLOGICAL MECHANISMS AND CLINICAL IMPLICATIONS – A NARRATIVE REVIEW

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ABSTRACT

Background: Endometriosis is a chronic inflammatory disease associated with substantial physical and psychological morbidity. Depression is common among affected women, and its relationship with endometriosis appears to extend beyond the psychological consequences of chronic pain alone.
Methods: A structured narrative review of peer-reviewed literature was conducted using PubMed/MEDLINE, Scopus, and Google Scholar. Epidemiological, biological, psychosocial, and clinical evidence was synthesized qualitatively.
Findings: Women with endometriosis report greater depressive symptom burden than healthy controls, although chronic pain contributes substantially to this association. Shared genetic susceptibility and inflammatory, neuroendocrine, hormonal, pain-processing, and tryptophan–kynurenine pathways may provide additional biological links, but direct evidence for several mechanisms remains limited. Chronic pelvic pain, infertility, fatigue, sleep disturbances, diagnostic difficulties, and stigma further contribute to psychological distress and impaired quality of life. Evidence for endometriosis-specific pharmacological treatment of depression is scarce, while preliminary studies suggest potential benefits from psychological interventions and multidisciplinary care.
Conclusions: The relationship between endometriosis and depression is multifactorial and best understood within a biopsychosocial framework. Further longitudinal and interventional studies are needed to clarify causal mechanisms and evaluate targeted approaches to treatment.

KEYWORDS

Endometriosis; Depressive Disorder; Chronic Pain; Inflammation; Mental Health; Quality of Life

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1. Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity (Zondervan et al., 2020). Affecting approximately 10% of women of reproductive age worldwide, it is one of the most common gynecological disorders and a major cause of chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, and reduced quality of life (Taylor et al., 2021). Although traditionally regarded as a gynecological condition, endometriosis is increasingly recognized as a systemic disease with substantial physical, psychological, and social consequences (Zondervan et al., 2020).

Among its extra-gynecological manifestations, depression has emerged as one of the most prevalent psychiatric comorbidities. Women with endometriosis consistently report higher rates of depressive symptoms than the general population (van Barneveld et al., 2022). Chronic pain, reproductive concerns, fatigue, and prolonged diagnostic pathways contribute to the broader psychosocial burden of endometriosis and may negatively affect quality of life and emotional well-being (Culley et al., 2013; Nnoaham et al., 2011). However, accumulating evidence suggests that this association cannot be explained solely by the psychological burden of living with a chronic disease. Large population-based studies have demonstrated that the relationship persists even after adjustment for chronic pain and other potential confounders, indicating that shared biological mechanisms may also contribute to the coexistence of endometriosis and depression (Koller et al., 2023).

Potential mechanisms linking endometriosis and depression include chronic inflammation, immune and hormonal dysregulation, altered stress responses, and shared genetic susceptibility, although the strength of evidence varies considerably across these pathways. At the same time, psychological and environmental factors—including chronic pelvic pain, reproductive concerns, fatigue, and stigma—may further amplify emotional distress and reduce quality of life (van Barneveld et al., 2022). Together, these findings support a multifactorial model in which biological and psychosocial processes interact to influence the development and persistence of depressive symptoms in women with endometriosis.

Despite growing interest in this relationship, the available evidence remains fragmented. Epidemiological studies have established a consistent association between endometriosis and depression, while mechanistic research has identified several pathways that may explain their coexistence. However, relatively few reviews have integrated epidemiological, biological, psychological, and clinical evidence into a single comprehensive framework.

The aim of this narrative review is to critically synthesize the current evidence on the relationship between endometriosis and depression. Specifically, this review summarizes the epidemiological association between the two conditions, examines the shared pathophysiological mechanisms that may contribute to their coexistence, discusses key psychological and environmental factors influencing mental health outcomes, and highlights the clinical implications of screening, treatment, and multidisciplinary management. By integrating evidence across these domains, this review aims to offer an overview of the relationship between endometriosis and depression and highlight areas that may benefit from further study.

2. Methodology

A structured narrative review was conducted to critically synthesize the current evidence regarding the relationship between endometriosis and depression. The review integrates epidemiological, biological, psychological, and clinical evidence to provide a comprehensive overview of the mechanisms linking these conditions and their implications for clinical practice. Owing to the heterogeneity of the available literature, no quantitative synthesis or pooled effect estimate was performed.

2.1. Search Strategy

A structured literature search was performed using PubMed/MEDLINE, supplemented by Scopus and Google Scholar, to identify peer-reviewed articles published in English from database inception through July 2026. Earlier landmark studies were included when they remained fundamental to understanding the epidemiological association or proposed biological mechanisms.

Medical Subject Headings (MeSH), where applicable, and free-text terms were combined using Boolean operators (AND, OR). The primary search strategy combined terms related to *endometriosis* ("endometriosis") with terms related to *depression* ("depression," "major depressive disorder," "depressive symptoms," "mental health"). Additional searches included terms describing proposed mechanisms (“inflammation,” “immune dysregulation,” “HPA axis,” “neuroinflammation,” “central sensitization,” “estrogen,” “progesterone resistance,” “tryptophan,” “kynurenine,” “neurotransmitters,” “genetic susceptibility,” “epigenetics,” “DNA methylation”), psychosocial factors (“chronic pelvic pain,” “infertility,” “fatigue,” “sleep disturbances,”

"quality of life"), and clinical management ("screening," "psychological interventions," "pharmacological management," "multidisciplinary care"). Reference lists of relevant systematic reviews and primary studies were also screened to identify additional publications.

Greater emphasis was placed on systematic reviews, meta-analyses, large epidemiological studies, and studies directly investigating the relationship between endometriosis and depression.

2.2. Inclusion and Exclusion Criteria

Studies were selected according to predefined eligibility criteria to ensure both scientific quality and relevance to the objectives of this review.

Inclusion criteria were: (1) peer-reviewed original research articles, systematic reviews, or meta-analyses; (2) studies investigating the association between endometriosis and depression or examining biological, psychological, or clinical mechanisms potentially linking the two conditions; and (3) publications available in English.

Studies focusing on only one of the two disorders were included when they provided important evidence supporting mechanisms that could plausibly contribute to the coexistence of endometriosis and depression. Such publications were considered complementary rather than direct evidence. Authoritative peer-reviewed narrative reviews and professional guidance were used selectively to provide definitions, established background information, and clinical context; these sources were not treated as direct evidence regarding the endometriosis–depression association.

Exclusion criteria comprised conference abstracts, editorials, letters to the editor, case reports, and other non-peer-reviewed publications, as well as non-English articles. Animal studies were excluded unless they were necessary to illustrate fundamental biological processes relevant to mechanisms discussed in this review.

2.3. Study Selection and Data Extraction

Following the literature search, titles and abstracts were reviewed to determine their relevance to the review objectives. Potentially eligible publications subsequently underwent full-text assessment based on the predefined selection criteria. Information extracted from the included studies comprised study design, population characteristics, principal findings, and outcomes related to epidemiological associations, pathophysiological mechanisms, psychosocial determinants, and clinical management.

The evidence was evaluated qualitatively, with greater emphasis placed on studies employing robust methodologies, including systematic reviews, meta-analyses, and large population-based investigations. Mechanistic studies that examined either endometriosis or depression independently were used primarily to support the biological plausibility of shared pathways and were interpreted with appropriate caution.

2.4. Narrative Synthesis and Methodological Considerations

The findings were organized into four thematic areas: epidemiological associations, shared biological mechanisms, psychological and environmental factors, and clinical implications. Owing to substantial variability across study populations, research methodologies, diagnostic criteria, and outcome measures, statistical pooling of results was not considered appropriate.

3. Literature Review

3.1. Epidemiological Association Between Endometriosis and Depression

3.1.1. Depression in Women with Endometriosis

Depression is one of the most common psychiatric comorbidities in women with endometriosis. In a systematic review and meta-analysis of 47 studies, van Barneveld et al. (2022) found significantly higher levels of depressive symptoms in women with endometriosis than in healthy controls. However, no significant difference was observed when women with endometriosis were compared with those experiencing other chronic pelvic pain conditions, highlighting the substantial contribution of persistent pain to psychological distress.

Chronic pain alone, however, may not fully explain this association. In a UK Biobank study involving more than 200,000 women, Koller et al. (2023) found that endometriosis remained strongly associated with depression after adjustment for chronic pain and other potential confounders. The authors also identified a genetic correlation between the two conditions, suggesting that shared biological susceptibility may contribute alongside the psychological effects of chronic illness.

3.1.2. Bidirectional Relationship Between Endometriosis and Depression

Evidence suggests that the relationship between endometriosis and depression may operate bidirectionally. Endometriosis-related pain, fatigue, sleep disturbances, and impaired quality of life are associated with greater depressive symptom burden (van Barneveld et al., 2022). At the same time, maladaptive emotion-regulation strategies, including catastrophizing and rumination, are associated with greater pain burden, depressive symptoms, and poorer quality of life, suggesting that psychological processes may reinforce the overall symptom burden of endometriosis (Carvalho et al., 2025).

Genetically informed evidence also supports a possible influence of depression on endometriosis susceptibility. Koller et al. (2023) identified a significant genetic correlation between the two conditions, while Mendelian randomization suggested that genetic liability to depression may increase the likelihood of endometriosis. However, the reverse direction could not be evaluated reliably because the genetic analysis of endometriosis lacked sufficient statistical power.

3.2. Shared Pathophysiological Mechanisms

3.2.1. Chronic Inflammation and Immune Dysregulation

Chronic inflammation may represent a biological link between endometriosis and depression. In women with endometriosis, Björk et al. (2020) identified increased local and systemic inflammatory cytokine expression alongside regulatory immune responses associated with impaired cytotoxicity, potentially facilitating the persistence of ectopic lesions. Meta-analytic evidence similarly indicates elevated circulating IL-6 and TNF-α in patients with major depression compared with healthy controls (Dowlati et al., 2010).

More directly, Yang et al. (2025) found that women with endometriosis-associated chronic pain and depressive symptoms had higher serum levels of IL-6, IL-1β, TNF-α, and C-reactive protein than those without depression. Pain severity was positively associated with inflammatory-marker levels and with depression and anxiety scores, supporting inflammation as a plausible shared pathway, although the observational design does not establish causality.

3.2.2. Hypothalamic–Pituitary–Adrenal (HPA) Axis Dysfunction

Chronic pain and psychological stress associated with endometriosis may alter hypothalamic–pituitary–adrenal (HPA) axis function. Petrelluzzi et al. (2008) found lower diurnal salivary cortisol levels and a reduced cortisol awakening response in women with endometriosis-related chronic pelvic pain, alongside greater perceived stress and poorer quality of life. However, subsequent findings have been inconsistent: Ortiz et al. (2020) observed no overall difference in ACTH or cortisol responses between women with endometriosis-related pain, pelvic pain without endometriosis, and healthy controls, although greater pain severity was associated with a blunted hormonal response in subgroup analyses.

HPA-axis alterations are also observed in depression, particularly among women, although their direction varies according to the cortisol measure and study design (Wang et al., 2024). HPA-axis dysregulation therefore represents a plausible connection between persistent pain, stress, and depressive symptoms in endometriosis, but direct evidence establishing this pathway remains limited.

3.2.3. Neuroinflammation and Central Sensitization

Direct human evidence that neuroinflammation links endometriosis with depression remains limited. Stronger evidence supports altered central pain processing in endometriosis. In an experimental study, Bajaj et al. (2003) found greater pain responses, larger referred pain areas, and pressure hypersensitivity in women with laparoscopically confirmed endometriosis than in healthy controls, consistent with central sensitization.

More recently, Biasioli et al. (2026) identified central sensitization symptoms in approximately half of a tertiary-care cohort with endometriosis or adenomyosis. These symptoms were associated with longer symptom duration and overlapping pain conditions rather than the anatomical type of endometriosis. Higher baseline sensitization scores have also been associated with worse pelvic pain after endometriosis surgery (Orr et al., 2023). Central amplification may therefore contribute to persistent pain and, indirectly, to depressive symptoms, although direct evidence connecting neuroinflammation, sensitization, and depression in endometriosis remains insufficient.

3.2.4. Hormonal Dysregulation and Estrogen Signaling

Endometriosis involves altered local sex-hormone signaling rather than a uniform increase in circulating estrogen. Hudelist et al. (2007) found aromatase expression in most endometriotic lesions, with higher expression than in paired uterine endometrium, supporting increased local estrogen biosynthesis. Aghajanova et al. (2011) additionally demonstrated a blunted transcriptional response to progesterone in endometrial stromal fibroblasts obtained from women with endometriosis, consistent with progesterone resistance.

The contribution of these alterations to depression is less clearly established. A systematic review and meta-analysis of 14 randomized trials found that estrogen treatment improved depressive mood particularly in perimenopausal women, suggesting that mood may be more sensitive to hormonal fluctuations than to absolute estrogen levels (Zhang et al., 2023). In a small prospective study of women with endometriosis, six months of dienogest reduced menstrual pain but increased depressive symptom scores, with more than one-third of participants reaching a clinically significant threshold (Park et al., 2025). Although this finding requires confirmation in larger controlled studies, it suggests that individual sensitivity to hormonal modulation may influence mood in some women with endometriosis.

3.2.5. Neurotransmitter Imbalance

Evidence for neurotransmitter alterations specifically in endometriosis-associated depression remains indirect. In a prospective metabolomic study, Murgia et al. (2021) found lower serum tryptophan levels in women with severe endometriosis than in controls. Li et al. (2021) additionally identified increased kynurenine concentrations in the peritoneal fluid of women with endometriosis, suggesting altered tryptophan–kynurenine metabolism within the inflammatory disease environment. However, neither study assessed depressive symptoms or central neurotransmission.

In depression, a systematic review and meta-analysis of 22 studies found lower kynurenine and kynurenic acid levels, while increased quinolinic acid was observed specifically in antidepressant-free patients (Ogyu et al., 2018). These findings suggest that altered kynurenine metabolism may provide a plausible connection between inflammation and mood disturbances, but its role in depression among women with endometriosis has not yet been directly established.

3.2.6. Genetic and Epigenetic Factors

Genetic evidence supports partly overlapping susceptibility to endometriosis and depression. A large genome-wide association meta-analysis identified multiple endometriosis risk variants, including loci near ESR1 and FSHB, implicating sex-hormone signaling in disease susceptibility (Sapkota et al., 2017). More directly, Koller et al. (2023) demonstrated a significant genetic correlation between endometriosis and depression and identified a pleiotropic locus associated with both conditions. Their Mendelian randomization analysis also suggested that genetic liability to depression may modestly increase the likelihood of endometriosis.

Epigenetic evidence remains indirect. A systematic review of human endometriosis studies identified altered DNA methylation and histone regulation in genes involved in hormonal, inflammatory, and endometrial pathways (Bedrick et al., 2024). Separately, a meta-analysis linked methylation changes in genes such as BDNF and NR3C1 with depression (Zhu et al., 2023). However, shared epigenetic alterations have not yet been established specifically in women affected by both conditions.

3.3. Psychological and Environmental Factors

3.3.1. Chronic Pelvic Pain and Emotional Distress

Chronic pelvic pain is a major contributor to emotional distress and impaired quality of life in women with endometriosis. In a systematic review of 27 studies involving more than 5,000 women, Kalfas et al. (2022) found that depression, anxiety, and stress were consistently associated with poorer health-related quality of life, while anxiety and pain catastrophizing were the psychosocial factors most consistently related to greater pain. The relationship between pain and depression was further examined by Zarbo et al. (2024), who found that pain severity was independently associated with depressive symptoms in women with endometriosis and that this association was stronger among those reporting higher levels of catastrophizing. These findings indicate that the emotional impact of endometriosis-related pain is influenced not only by pain intensity but also by how patients interpret and cope with their symptoms.

3.3.2. Infertility and Reproductive Concerns

Infertility may add to the psychological burden of endometriosis, particularly when accompanied by chronic pain. In a multicentre study of 229 women with endometriosis, Silva et al. (2024) found the highest depression and anxiety scores among participants experiencing both infertility and pain, whereas pain was the factor most consistently associated with poorer psychological outcomes and quality of life.

Reproductive context may also influence mental health. Among women undergoing IVF or ICSI, Bourdon et al. (2026) reported a higher prevalence of depression in those with endometriosis than in women without the disease, while no comparable difference was observed among women undergoing fertility preservation. These findings suggest that infertility and assisted reproductive treatment may increase emotional vulnerability, although pain-related symptoms remain important contributing factors.

3.3.3. Fatigue, Sleep Disturbances, and Quality of Life

Fatigue and sleep disturbances are common and closely interconnected with depressive symptoms in women with endometriosis. In a multicentre case–control study of 1,120 women, Ramin-Wright et al. (2018) found that frequent fatigue affected approximately half of women with endometriosis, compared with fewer than one-quarter of controls. Fatigue was strongly associated with insomnia and depression, as well as pain and occupational stress.

Similarly, Facchin et al. (2021) found that women with painful endometriosis experienced greater fatigue, poorer sleep quality, increased daytime sleepiness, and more severe insomnia than women without significant pain and matched controls. Within the endometriosis group, poor sleep was associated with worse psychological health and lower quality of life. These findings suggest that pain, fatigue, sleep disruption, and emotional distress form an interrelated symptom burden rather than independent consequences of the disease.

3.3.4. Psychosocial Stress and Stigma

The diagnostic experience itself may contribute to psychosocial stress in women with endometriosis. A qualitative systematic review by Davenport et al. (2023) identified normalization of menstrual pain, menstrual stigma, dismissal of symptoms, and delays in specialist referral as recurring barriers to diagnosis. These experiences may leave patients feeling that their symptoms are not recognized or legitimized.

Mental health burden also appears to be greater among women who experience more difficult diagnostic pathways. In a large cohort of 2,394 women with endometriosis, Breton et al. (2025) found that a greater number of medical consultations before diagnosis was associated with more severe depressive and anxiety symptoms, alongside factors such as pain, poor sleep, and reduced quality of life. These findings suggest that healthcare-related stress and diagnostic difficulties may contribute to the broader psychological burden of endometriosis.

3.4. Clinical Implications

3.4.1. Screening for Depression in Women with Endometriosis

The high prevalence of depressive symptoms among women with endometriosis supports the inclusion of mental health assessment in clinical care. Van Barneveld et al. (2022) found significantly greater depressive symptom burden in women with endometriosis than in healthy controls and identified chronic pain, fatigue, poor sleep, and reduced quality of life as important correlating factors. Similarly, Szypłowska et al. (2023) reported substantial rates of depressive and anxiety symptoms across studies, although prevalence varied considerably depending on the population and assessment method. These findings support particular attention to psychological symptoms in patients with a high symptom burden and functional impairment.

3.4.2. Pharmacological Management

Evidence regarding pharmacological treatment of depression specifically in women with endometriosis remains scarce. In a large Danish registry study, women with endometriosis had higher use of antidepressants and anxiolytics and more psychiatric hospital contacts than women without endometriosis, both before and after diagnosis; however, these findings reflect treatment use rather than effectiveness (Josiasen et al., 2026).

Endometriosis-directed hormonal therapy may itself influence mood. Dietrich et al. (2023) found that women with pre-existing depression or other psychiatric disorders were more likely to discontinue dienogest because of worsening mood. Similarly, Park et al. (2025) reported increased depressive symptom scores after six months of dienogest treatment despite improvement in menstrual pain. These findings highlight the importance of considering psychiatric history and monitoring mood during hormonal treatment.

3.4.3. Psychological and Non-Pharmacological Interventions

Psychological interventions may improve both emotional and physical outcomes in women with endometriosis. In a randomized controlled study of 100 women receiving GnRH agonist therapy, Zhao et al. (2012) found that 12 weeks of progressive muscle relaxation (PMR) training significantly improved depressive and anxiety symptoms and quality of life compared with medical treatment alone. A systematic review by Samami et al. (2023) also identified potential benefits of interventions including CBT, mindfulness, yoga, psychoeducation, and PMR, particularly for endometriosis-related pain. However, the small number and variable quality of available studies limit conclusions regarding their effectiveness specifically for depression.

3.4.4. Multidisciplinary Management

The combination of chronic pain, psychological distress, and impaired quality of life in endometriosis supports a multidisciplinary approach to care. In a systematic review of 19 studies, Fang et al. (2024) identified gynecologists, pain specialists, physiotherapists, psychologists, nurses, and other allied health professionals as common components of multidisciplinary endometriosis care. Patient perspectives particularly emphasized the need for coordinated long-term treatment, symptom validation, reliable information, and emotional support. However, evidence demonstrating that multidisciplinary care directly improves depression or quality of life remains limited, highlighting the need for prospective outcome studies.

4. Conclusions

Current evidence supports a strong association between endometriosis and depression, although the relationship is likely multifactorial. Chronic pain appears to be an important contributor to depressive symptoms, but it does not fully explain the association. Genetic correlation and emerging evidence involving inflammatory, neuroendocrine, hormonal, and pain-processing pathways suggest that shared biological susceptibility may also play a role (van Barneveld et al., 2022; Koller et al., 2023). However, for several proposed mechanisms—including HPA-axis dysfunction, neurotransmitter alterations, and epigenetic changes—direct evidence in women affected by both conditions remains limited.

Psychological and environmental factors further contribute to this relationship. Chronic pelvic pain, infertility, fatigue, sleep disturbances, difficult diagnostic experiences, and stigma are all associated with poorer psychological well-being and quality of life. These factors appear to interact rather than act independently, supporting a biopsychosocial understanding of depression in endometriosis.

From a clinical perspective, greater attention to depressive symptoms is warranted, particularly in women with substantial pain and functional impairment. Evidence for endometriosis-specific pharmacological treatment of depression remains scarce, while preliminary findings suggest potential benefits from psychological interventions such as progressive muscle relaxation and other supportive approaches (Zhao et al., 2012). Multidisciplinary care may help address the overlapping physical and psychological aspects of the disease, although its effect on depression-specific outcomes requires further evaluation (Fang et al., 2024).

Future research should prioritize longitudinal studies capable of clarifying temporal and causal relationships, direct investigation of proposed biological mechanisms in women with both endometriosis and depression, and controlled trials evaluating targeted psychological, pharmacological, and multidisciplinary interventions.

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