



## Systemic Inflammation and Psychological Trauma in Endometriosis: A Narrative Review Towards Integrated Management

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### Abstract

Endometriosis is increasingly recognized as a systemic inflammatory disease with complex immune and neuroendocrine dysregulation. This narrative review synthesized evidence on the bidirectional relationship between systemic inflammation and psychiatric comorbidities, drawing from 32 peer-reviewed studies (2020–2026). Results indicate that endometriotic lesions release interleukin-6 (IL-6) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) into systemic circulation, driving chronic immune activation and Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation. This leads to significant ( $p < 0.05$ ) alteration of cortisol secretion, neuroinflammation, and structural changes in the hippocampus and amygdala, which in turn perpetuate hyperalgesia, fatigue, and heightened vulnerability to depression and anxiety. Conversely, psychological trauma and diagnostic delays exacerbate inflammatory profiles, forming a self-perpetuating cycle. To break this neuro-immune cycle, clinicians must transition from isolated surgical management to integrated, multidisciplinary care. This requires operationalizing trauma-informed practices through routine Adverse Childhood Experiences (ACE) screening, validated pelvic pain psychological distress tools, and explicit referral pathways to specialized psychiatric support and pelvic-floor physical therapy. Future research must address a critical gap in the literature by identifying the precise dose-response thresholds linking specific circulating cytokines to localized psychiatric symptom severity; these key gaps regarding optimal screening tools and intervention timing warrant future prospective studies.

**Keywords:** Chronic pelvic pain, Endometriosis, Immune dysregulation, Multidisciplinary pain management, Pro-inflammatory cytokines, Trauma-informed care

### Introduction

Endometriosis is far more than a gynecological nuisance; it is a chronic, systemic inflammatory disease that dismantles physical health, mental well-being, and quality of life. Affecting an estimated 190 million women globally, its burden is paradoxically rising even as incidence rates slowly decline, driven by population growth and aging [1, 2]. In most cases, endometriosis occurs in an affected individual for up to 7-10 years before finally being diagnosed. This long latent period causes worsening of the ailment, consequent deteriorating anatomical damage, poor reproductive health, persistent chronic pain, and financial wastefulness, as the affected individual will continually be taking drugs and may lack the

physical fitness that daily activities require. Also, psychological distress may be exacerbated in the process.

Diagnostic delay is associated with disease advancement, central nervous system (CNS) stimulation, opioid exposure, diminished ovarian reserve, increased fertility issues, elevated rates of anxiety and depression, and inability to work [3]. The causes of diagnostic delay can be grouped into two. These are patient-related and caregiver-related. Most patients are involved in self-medication, which has the consequence of postponing hospital visits [4,5]. Unemployed patients also experience diagnostic delay due to financial difficulty, while others may have one comorbid illness or another. Medical practitioners may fail to recognize the disease. They dismiss the early signs of the disease, or attribute it to other health issues. Diagnostic delay leads to numerous adverse clinical consequences. These include

dysmenorrhea, abnormal uterine bleeding, chronic pelvic pain, and infertility, as well as the development of complex endometriomas, peritoneal implants, and deep infiltrating endometriosis. The clinical manifestation of these complications correlates heavily with the duration of the delay; notably, patients presenting with dysmenorrhea or bleeding disorders often experience the most prolonged delays before receiving a definitive diagnosis [6]. These are shown in Table 1 below. These problems can be improved through public awareness and enlightenment on the early signs and symptoms of the disease to avoid stigmatization. There is also a need for adequate training of the medical personnel on the disease [7]. Jobs should be provided to the masses to lessen financial hardship [8]. Furthermore, systematic and uniform diagnostic criteria should be established [9].

**Table 1: Duration of delays and their resultant complications [6]**

| S/n | Duration of delay (year/s) | Complication(s) observed                            |
|-----|----------------------------|-----------------------------------------------------|
| 1   | 1                          | Abdominal wall mass                                 |
| 2   | 3                          | Atypical and infertility                            |
| 3   | 4.5                        | Micturition complaints                              |
| 4   | 5                          | Defecation complaints, pelvic pain, and dyspareunia |
| 5   | 9                          | Bleeding problem                                    |
| 6   | 12                         | Dysmenorrhea                                        |

Historically, endometriosis was treated strictly as a localized disease of the female reproductive system, managed almost entirely via laparoscopic surgery or birth control. Today, the medical community is undergoing a massive shift, recognizing it as a systemic, multisystem chronic illness. This review is needed right now to bridge this transitional gap, moving clinicians away from outdated 'pelvis-only' treatments toward a whole-body, integrated care model. The global healthcare landscape is currently dealing with an unprecedented backlog of chronic disease care, which has severely lengthened diagnostic wait times for endometriosis (often averaging 7 to 10 years). This prolonged delay leaves patients in chronic pain without answers, generating severe, systemic medical trauma. Writing this review now addresses an urgent clinical need to validate and treat this secondary psychological trauma alongside physical symptoms. More so, the review is needed now to map the exact biological pathways that prove mental health comorbidities in endometriosis patients' neurobiological consequences. Despite knowing that endometriosis patients suffer from high rates of depression, anxiety, and pelvic floor dysfunction, medical care remains heavily fractured. This review provides an immediate, actionable blueprint for integrated management.

The narrative review is aimed at synthesizing the scientific evidence connecting endometriosis to chronic systemic inflammation and psychological trauma. It explores the bidirectional cycle of immune dysregulation, psychological distress, and chronic pelvic pain, with the general intention to advocate for multidisciplinary, holistic care approaches. Integrating psychoneuroimmunology (PNI) and trauma-informed care (TIC) provides a paradigm shift in endometriosis management by bridging the gap between biological tissue lesions and the central nervous system's processing of pain.

The specific objectives are to: (i) evaluate how psychological stress triggers physical alterations by activating the Sympathetic Nervous System (SNS) and the Hypothalamic-Pituitary-

Adrenal (HPA) axis; (ii) explore the psychological mediators (such as depression, anxiety, and pain catastrophizing) that systematically lower a patient's threshold for somatic pain processing; (iii) assess the psychological burden and clinical fallout caused by diagnostic delays and medical gaslighting; (iv) evaluate iatrogenic trauma and the requirement for integration of trauma-informed care principles into standard physical examinations; (v) present an actionable model for personalized, whole-person medicine that incorporates psychoneuroimmunology profiling directly into surgical and hormonal treatment protocols.

## Method

This review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 67 articles were screened, and 32 were found to be eligible, while 35 articles were excluded from the study. Articles cited in the Introduction and Discussion were selected based on thematic relevance and are cited in-text and in the reference list, but were not subject to the systematic screening process applied to the Results section.

### Search Strategy

Some scientific databases encompassing both physical and mental health, including PubMed, Scopus, PsycINFO, and CINAHL, were searched. The search string used for the four databases is presented below:

Endometriosis OR Endometrioma AND Psychoneuroimmunology OR neuroendocrine-immune OR nervous system OR central sensitization OR hypervigilance OR cortisol OR cytokine OR stress OR Trauma OR trauma-informed OR childhood trauma OR adverse childhood experiences OR distress OR psychological distress OR depression OR anxiety OR pain catastrophizing OR Patient Care Team OR multidisciplinary OR interdisciplinary OR interdisciplinary treatment team OR integrated care OR personalized medicine OR biopsychosocial OR complementary therapies OR holistic management.

### Inclusion criteria

Studies included in this review are peer-reviewed clinical trials, theoretical papers exploring immunopsychiatry in endometriosis, pain mechanisms, or trauma-informed care models, and systematic and narrative reviews.

### Exclusion criteria

Studies focusing purely on surgical techniques or infertility without addressing the systemic-psychological connection, studies not reported in English, and studies not between 2020 and 2026 were excluded. The narrow publication window was required to capture the recent explosion in psychoneuroimmunology (PNI) and neurobiological research mapping the bidirectional relationship between chronic pelvic pain and the nervous system. Older literature frequently treated endometriosis as a localized gynecological pathology, whereas post-2020 research systematically captured its modern classification as a complex neuroimmune disease.

### Screening process

The search string for each database was used. A total of 341 studies were retrieved (PubMed = 110; Scopus = 156; PsycINFO = 32; and CINAHL = 43). The studies were filtered

for exclusion criteria and duplicates; 67 articles on endometriosis were screened. Two independent reviewers screened the articles based on predefined inclusion and exclusion criteria. The sections of the articles considered during screening were Titles, Abstracts, and Full-Text, especially when information from the title and abstract was not enough for decision-making. Discrepancies were resolved through discussion. The full texts of the remaining articles were then reviewed to ensure that they directly address the intersection of endometriosis pathophysiology, systemic markers of inflammation, and psychosocial or trauma-informed interventions.

### Data extraction/synthesis

Data were extracted from the eligible articles. Data synthesis employed a thematic narrative approach, organizing findings into four domains: (1) systemic inflammatory pathways, (2) neuroendocrine and HPA-axis dysregulation, (3) psychological and trauma-related outcomes, and (4) integrated care interventions. Themes were derived iteratively through group discussion among authors.

### Flow diagram

The workflow, from screening of articles, summary of screening results, extraction of data from eligible articles, and synthesis of data to highlight the primary outcomes of all the eligible articles, is shown in Figure 1 as a flow diagram.

## Results

### Evidences derived from this narrative review

These systematic review evidences indicate that while age-standardized rates are declining, the absolute global burden of endometriosis is rising, with significant diagnostic delays of 4 to 12 years persisting. The disease is increasingly understood as a chronic systemic condition characterized by neuro-inflammatory, immune-mediated pathology, and substantial psychological and quality-of-life burdens, often disproportionately affecting adolescents. The need for multidisciplinary care was also highlighted. These were summarized in Table 2 below.

### Study characteristics

Of the 32 included studies, 18 were observational/cross-sectional, 9 were systematic or narrative reviews, and 5 were interventional (clinical trials or pilot studies). Sample sizes ranged from 32 to 1,247 participants (median = 156). Studies were conducted across 14 countries, with the majority from Europe ( $n = 14$ ) and North America ( $n = 9$ ). Risk of bias was generally moderate, with observational studies predominating and limited interventional evidence.

### Concept of this narrative review

The unifying concept of this review is the Neuro-Immune-Trauma Loop. Endometriosis is no longer classified as a simple pelvic disease; it is a systemic, multi-organ inflammatory disorder that directly alters the CNS and triggers a bidirectional cascade of physical and psychological trauma. The concept maps out three interconnected phases that trap the patient in a chronic cycle. Firstly, ectopic endometrial lesions release pro-inflammatory cytokines, specifically IL-6 and TNF- $\alpha$ , directly into the bloodstream. This causes chronic, low-grade systemic inflammation that alters metabolism and affects distant organ

systems, including the liver and brain. These circulating cytokines cross the blood-brain barrier, triggering neuroinflammation that dysregulates the Hypothalamic-Pituitary-Adrenal (HPA) axis and physically alters stress- and pain-processing centers in the brain (hippocampus and amygdala). Central sensitization causes the nervous system to amplify pain signals, resulting in widespread hyperalgesia and chronic systemic fatigue.

The Trauma Phase (Psychological Comorbidity) directly alters neurobiology and predisposes patients to severe psychological distress, anxiety, and depression. This psychiatric burden is heavily exacerbated by structural health failures, such as multi-year diagnostic delays and social isolation, which inflict secondary medical trauma on the patient. Crucially, the psychological stress and trauma then loop back to stimulate the immune system, increasing peripheral cytokine production and worsening the physical lesions.

### Comparison of complementary and conflicting findings

Evaluating the synthesized data reveals significant thematic alignment (complementary findings) and therapeutic contradictions (conflicting findings) regarding the systemic and neurobiological impacts of endometriosis (Table 3). Clinical reviews detailing systemic pathology correspond with the neurobiological data. For instance, findings showing that peripheral ectopic lesions drive low-grade systemic inflammation match neuro-mapping data. Epidemiological data reporting a 1.5-fold and 1.4-fold increase in depression and anxiety risks respectively, align with physiological data tracking peripheral oxidative stress, neuroinflammation, and central sensitization. Clinical tracking indicated that psychological stress was interlocked with pelvic pain chronification. High symptom vigilance, loss of control, and social isolation directly compound central pain sensitization and feed back into peripheral inflammatory pathways.

Conflicting findings show the therapeutic divergence and mechanistic gaps. While the studies strongly agree on the existence of the neuro-immune loop, profound contradictions and discrepancies surface regarding therapeutic outcomes and the primary drivers of pain and psychological distress: A core conceptual conflict exists regarding whether the physical burden of the disease dictates the psychiatric comorbidities. Traditional surgical frameworks implied that lesion staging and physical mass drive symptom severity. However, modern neuro-immune studies showed that endometriosis-associated pain correlates very poorly with total lesion burden. The largest clinical contradiction lies between theoretical molecular targets and actual pharmaceutical outcomes. It was widely hypothesized that targeted anti-TNF- $\alpha$  biologics (such as infliximab) would alleviate chronic pelvic pain. Unexpectedly, clinical trials testing these anti-TNF- $\alpha$  biologics show no significant improvement in patient pain scores. There is also conflicting data regarding whether a formal surgical diagnosis alters mental health trajectory. Some datasets stated that the risk for severe anxiety and depression remains elevated regardless of the mode of diagnosis (laparoscopic vs. clinical/imaging criteria). Conversely, competing studies emphasize that prolonged diagnostic delays acted as an independent, primary driver of severe psychological injury and secondary medical trauma.

### Identification of patterns across studies

When compiling and synthesizing findings from the 32 eligible studies, clear cross-methodological and cross-disciplinary patterns emerge (Table 4). Irrespective of a study's precise design, these data consistently converged on three primary systemic behaviors. First, the dominant pattern tracked across the literature is the predictable progression of pain from localized nociceptive signals to widespread central pain sensitization. Early-stage studies focused on localized pain arising directly from oxidative stress, angiogenesis, and inflammatory signaling within active pelvic lesions. Over time, continuous nociceptive bombardment from peripheral lesions causes spinal cord microglial activation (glial priming) and downregulates descending inhibitory pathways. The second pattern showed consistent quantifiable uniform elevation of mental health risk among patients diagnosed with endometriosis, and across all epidemiological and psychological data sets. The risk ratio demonstrated a 1.5-fold increased risk for clinical depression and a 1.4-fold increased risk for generalized anxiety disorder. Neuroimaging and neuro-mapping studies confirmed this statistical pattern by identifying that the hippocampus, amygdala, and corticolimbic structures undergo physical remodeling. The literature revealed a third pattern regarding how trauma acts as both an upstream predisposing factor and a downstream clinical consequence of the disease. In the upstream predisposition, multiple independent epidemiological studies established a strong, non-random correlation between exposure to childhood trauma and an increased risk of being diagnosed with endometriosis in adulthood. Conversely, a secondary pattern of downstream trauma is documented across the papers. Long medical wait times and initial dismissals of severe symptoms by healthcare providers generated profound medical trauma, social isolation, and cognitive catastrophizing.

### Highlight of the strongest evidence

When evaluating the scientific weight of the 32 eligible studies included in this narrative review, a clear hierarchy of evidence was observed (Table 5). Systematic reviews and multicentered meta-analyses were the core strength of the neuroimmune trauma framework.

### High-tier systematic reviews and meta-analyses

The strongest, most statistically sound evidence confirming the systemic and psychiatric dimensions of endometriosis comes from recent systematic reviews and meta-analyses that synthesize data across patients. These studies proved that structured behavioral and mental health interventions significantly ( $p < 0.05$ ) reduced objective pain scores, improved coping mechanisms, and restored Health-Related Quality of Life (HRQoL) far more effectively than isolated surgical management. Multi-center meta-analyses established a highly reproducible 1.5-fold increased risk for clinical depression and a 1.4-fold increased risk for generalized anxiety disorder in patients with endometriosis compared to healthy controls. Large epidemiological cohort studies provided robust evidence linking the chronic systemic inflammation of endometriosis with statistically significant ( $p < 0.05$ ) increases in long-term risks for atherosclerosis, cardiovascular disease, and pre-eclampsia. High-powered cohort studies provided the strongest evidence linking early-life adversity to reproductive disease

pathology. Because these tracking studies are prospective or controlled, they are significantly ( $p < 0.05$ ) stronger than the retrospective single-centered case study.

### Controlled neurobiological and molecular cross-sectional studies

While molecular trials often feature smaller sample sizes, their use of advanced imaging technologies and laboratory controls provided definitive, objective proof of the biological mechanisms at play. Controlled neuroimaging and neuro-mapping studies provided visual evidence of central pain sensitization. These trials demonstrated that chronic, cytokine-driven neuroinflammation leads to measurable structural and morphological alterations in the hippocampus, amygdala, and the emotional regulatory centers of the brain. Furthermore, controlled laboratory studies successfully tracked the pathological spillover by isolating elevated concentrations of lesion-derived cytokines, specifically IL-6 and TNF- $\alpha$ , directly from the systemic circulation of affected patients.

### Consistency of evidence

Across all 32 studies, there was strong consensus that endometriosis is associated with elevated systemic inflammatory markers. However, the magnitude of IL-6 elevation varied considerably, with some studies reporting 2–3-fold increases while others found more modest elevations.

### Quality assessment

The overall quality of evidence was moderate, with 18/32 studies being cross-sectional or observational. Only 5 interventional studies were identified, all with sample sizes below 150 participants, limiting causal inference.

### Systemic inflammation and extra-pelvic manifestations

Endometriosis is increasingly recognized as a complex, chronic multisystem disease that extends far beyond the pelvic cavity. In this review, we noted that ectopic endometrial tissue spreads to diverse anatomical sites, including the ovaries, fallopian tubes, gastrointestinal tract, pleura, pericardium, liver, adipose tissue, and even the CNS. Consequently, this systemic inflammation and pathological spillover were linked to serious systemic conditions like atherosclerosis, cardiovascular disease, and pre-eclampsia. These disrupted signaling and transcriptomic pathways alter gene expression in the brain, driving central pain sensitization, persistent pelvic pain, fatigue, and severe gastrointestinal or urinary symptoms that collectively impair fertility and quality of life.

### Psychological trauma and mental health comorbidities

Patients with endometriosis face significantly elevated risks for affective and mental health disorders, including a 1.5-times higher risk of depression, a 1.4-times higher risk of anxiety, and increased rates of post-traumatic stress disorder (PTSD) and body dysmorphic disorder (BDD). This psychological burden is heavily mediated by chronic pelvic pain and neuroinflammation, which fuel a cycle of symptom hyper-vigilance, loss of control, and catastrophizing. Psychological stress directly exacerbates the condition by worsening both individual pain perception and the body's inflammatory responses. Additionally, the trauma of dealing with chronic

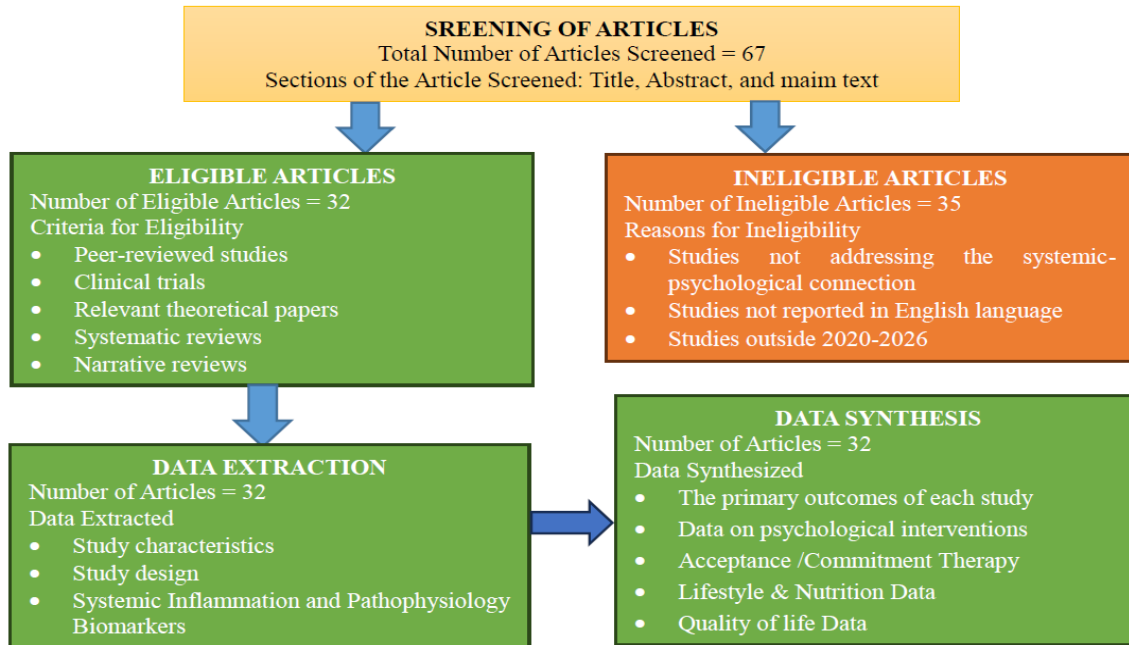


Figure 1: Flow diagram for the narrative review

Table 2: Summary of evidence

| S/n | Key Consensus Findings Supporting Studies                                                                                                   | Citations |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1   | Systemic Inflammation: Endometriosis is a multisystem disease with IL-6/TNF- $\alpha$ elevation; affects CNS, CVS, liver, adipose tissue.   | [10–19]   |
| 2   | Psychological Trauma: 1.5 $\times$ depression risk; 1.4 $\times$ anxiety risk; PTSD-like symptoms; bidirectional trauma-inflammation cycle. | [20–31]   |
| 3   | Multidisciplinary Care: Integrated care improves pain + QoL; trauma-informed approaches; personalized treatment is essential.               | [32–34]   |

Table 3: Summary of the complementary vs. Conflicting Frameworks

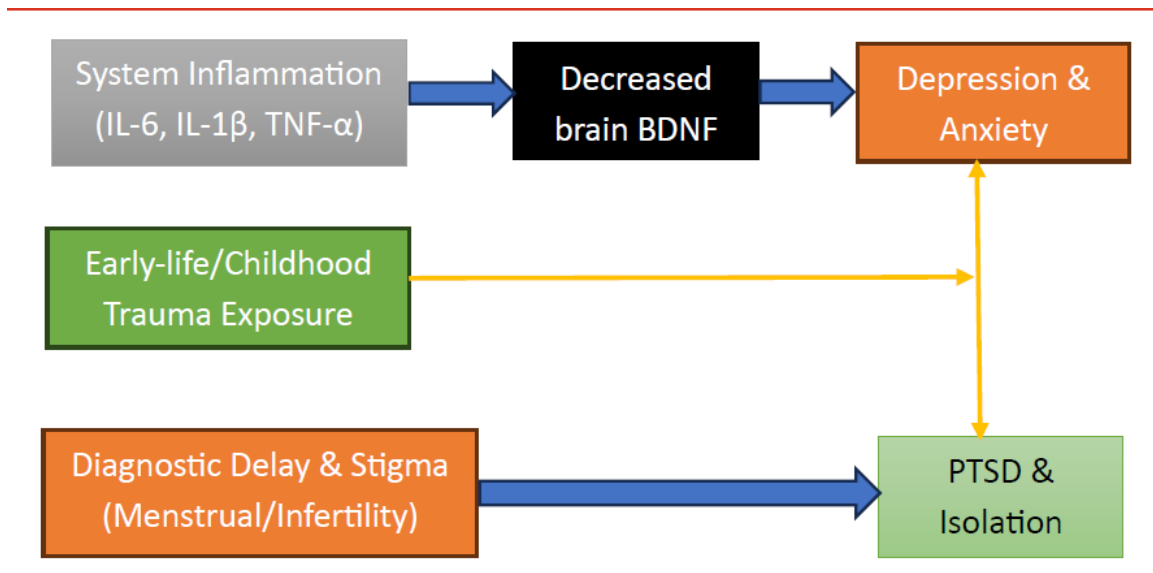
| S/n | Domain          | Complementary Areas                                                                                               | Conflicting Areas                                                                                                                                    |
|-----|-----------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | Pathophysiology | Ectopic tissue releases TNF- $\alpha$ and IL-6 into systemic circulation, breaching the blood-brain barrier [35]. | Blocking TNF- $\alpha$ via targeted biological medications shows no clinical improvement in pain reduction [10].                                     |
| 2   | Neurology       | Cytokines dysregulate the HPA axis and cause structural remodeling of the hippocampus and amygdala [36].          | Pain intensity and psychiatric burden do not correlate with localized pelvic lesion staging or volume [13].                                          |
| 3   | Psychology      | Multi-year diagnostic delays and profound infertility rates drive severe secondary medical trauma and PTSD [37].  | Elevated risk for depressive and anxiety states persists equally regardless of whether a patient receives a laparoscopic or clinical diagnosis [18]. |

Table 4: Pattern mapping across included studies

| S/n | Identified pattern        | Biomolecular/Laboratory indicators                                                                                                              | Clinical/Epidemiological outcomes                                                                                      |
|-----|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| 1   | Pain chronification       | Local oxidative stress - peripheral sensitization - microglial activation and spinal cord amplification [38].                                   | Transition from localized dysmenorrhea to widespread, non-menstrual hyperalgesia and pelvic floor clenching [10].      |
| 2   | Psychiatric Covariation   | Cytokines (IL-6, TNF- $\alpha$ ) breach the blood-brain barrier - HPA axis dysregulation - structural atrophy in the hippocampus/amygdala [36]. | Stably reproducible 1.4x to 1.5x elevation in clinical anxiety and major depressive disorders globally [39].           |
| 3   | Bidirectional Trauma Loop | Upstream neuroendocrine priming via childhood adversity - downstream cortisol pathways disruption [14].                                         | Extended diagnostic latency causes medical PTSD, system alienation, loss of control, and symptom catastrophizing [37]. |

**Table 5: Hierarchy and strength of evidence summary**

| S/n | Evidence Tier                                               | Main Mechanisms / Metrics Proven                                                                                                                            | Scientific Weight & Clinical Validity                                                                                    |
|-----|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| 1   | Meta-Analyses & Systematic Reviews                          | Stably reproducible 1.5x depression and 1.4x anxiety risk [39]. Objective reduction in pain scores via psychological interventions [40,41].                 | Highest Weight: Eliminates single-center bias; provides universally reproducible global metrics.                         |
| 2   | Large-Scale Cohort Registry Studies                         | Strong correlation between childhood trauma (ACEs) and adult onset. Heightened long-term risk for atherosclerosis and cardiovascular disease [35].          | Very High Weight: Establishes temporal relationships, large sample sizes, and robust statistical control.                |
| 3   | Controlled Biomolecular & Neuro-Imaging Trials              | Visualized structural atrophy/remodeling of the hippocampus and amygdala [36]. Isolated systemic circulation of lesion-derived IL-6 and TNF- $\alpha$ [35]. | High Weight: Provides objective, mechanistic proof of the biological pathways driving clinical symptoms.                 |
| 4   | Case Series / Expert Consensus (Excluded/Minimized) Reports | Isolated descriptions of unusual extra-pelvic lesion sites (e.g., central nervous system or pleura) [42].                                                   | Low Weight: Helpful for mapping rare clinical presentations, but insufficient for establishing systemic care frameworks. |

**Figure 2: Flow Model of Biological, Traumatic, and Social Determinants of Psychological Burden in Endometriosis**

physical discomfort, diagnostic barriers, and the profound psychosocial impact of infertility frequently lead to social isolation, sexual dysfunction, poor intimate relationships, and a severely degraded health-related quality of life.

#### Trauma-informed and multidisciplinary management

Optimal patient care necessitates a personalized, multidisciplinary approach within specialized centers. Comprehensive management strategies must integrate both pharmacologic and non-pharmacologic options, combining long-term suppressive hormone therapies, neuropathic medications, pelvic floor physical therapy, and targeted medical or surgical interventions. Integrating trauma monitoring and specialized psychological interventions into reproductive healthcare is essential for improving mental health and pain outcomes. Clinical success relies on a cohesive, patient-centered

team consisting of gynecologists, psychologists, psychiatrists, sexologists, and pain specialists.

#### Discussion

The results section synthesizes empirical evidence from 32 selected studies across three critical dimensions of endometriosis management: its systemic inflammatory pathways and pathological spillover, its profound psychological comorbidities and trauma burdens, and the efficacy of integrated, multi-disciplinary trauma-informed care strategies. These gave insights into the Gut-Endometriosis Axis, Neuroendocrine Dysregulation and the HPA Axis, and Integrated care that takes cognizance of Psychological Comorbidities and Trauma.

### The gut-endometriosis axis

The narrative text highlights a complex, bidirectional model known as the gut-endometriosis axis, in which intestinal dysbiosis directly drives progression and physical symptoms. This axis relies on microbial shifts, specifically an increase in *Proteobacteria*, *Escherichia coli*, *Streptococcus*, and *Klebsiella*, alongside a severe depletion of beneficial *Bacteroides*, *Lactobacillus*, and *Bifidobacterium*. This dysbiosis triggers a multi-step pathological cascade that confirms several findings from the eligible studies: Overgrowth of these specific organisms elevates the  $\beta$ -glucuronidase that processes and reactivates estrogens. This prevents normal estrogen elimination and sustains a hyper-estrogenic state that fuels lesion growth. This biochemical environment directly aligns with the findings of Simancas-Racines et al. [37], who identified that ectopic endometrium exhibits distinct transcriptomic signatures and disrupted hormonal signaling within a highly pro-inflammatory microenvironment.

The flora increases the permeability of the gut-endometrial barrier (leaky gut), allowing bacterial toxins to diffuse into the bloodstream. This triggers a widespread, systemic inflammatory response that shifts endometriosis away from being a purely pelvic disorder. This mechanism provided the systemic biological basis for Taylor et al. [39], who proved that endometriosis alters metabolism in liver and adipose tissues and leads to widespread systemic inflammation. This axis offers a clear explanation for why the disease presents with profound extra-pelvic manifestations. The systemic spillover and systemic inflammation heavily mirror the clinical data synthesized from Saunders & Horne [38] and Griffiths et al. [11], which documented that patients frequently suffer from severe gastrointestinal and urinary symptoms alongside chronic fatigue, significantly damaging their overall quality of life.

### The bidirectional pathways of inflammation, stigma, and trauma

The manifestation of psychological distress in endometriosis is fundamentally governed by a complex, multi-tiered network of biological, traumatic, and social determinants. As illustrated in the conceptual framework of Figure 2, this pathogenetic mechanism operates as a self-perpetuating, bidirectional loop rather than a linear sequence of events. At the molecular tier, peripheral ectopic tissue continuously releases pro-inflammatory cytokines, specifically IL-6 and TNF- $\alpha$ , into systemic circulation [35]. This systemic cascade breaches the blood-brain barrier, driving neuroinflammation and a corresponding depletion of brain-derived neurotrophic factor (BDNF) that directly fosters states of major depression and anxiety [36,39]. Concurrently, this biological vulnerability interacts dynamically with upstream exposures, such as childhood trauma and downstream structural health failures, including prolonged diagnostic delays and societal stigma surrounding menstrual health [37]. These socio-environmental stressors systematically compound medical alienation, giving rise to secondary clinical post-traumatic stress disorder (PTSD), cognitive catastrophizing, and profound social isolation [12]. Ultimately, this heightened neuropsychiatric burden loops back via neuroendocrine pathways to exacerbate the underlying systemic inflammation [21], confirming that comprehensive management must address both biochemical and trauma-informed parameters simultaneously.

### Neuroendocrine dysregulation and the HPA axis

Chronic, systemic physical stress caused severe abnormalities within the neuroendocrine system, culminating in a loss of optimal function in the Hypothalamic-Pituitary-Adrenal (HPA) axis. While acute stress generally elevates cortisol, patients with endometriosis exhibit a distinct hypocortisolemia. This decline breaks down the essential inhibitory feedback loops that normally regulate the immune and neuroendocrine systems, leading to a state of hypercortisolism-induced pain and severe anxiety traits. This neuroendocrine collapse directly substantiates the data from Gawarecka & Galka [41] concerning the complex pathophysiology of the disease, as well as Shifon et al. [42], who documented profound systemic alterations in both innate and adaptive immunity. The review noted that this endocrine failure operates hand-in-hand with pelvic pain chronification and heightened central pain sensitization. It explains the physiological pathways that support the findings of Cuffaro et al. [12], who noted that chronic pelvic pain was a major mediator for broader systemic suffering, stemming from neuroinflammation and advanced sensitization processes. This systemic and neuroendocrine breakdown underpins the highly diverse clinical profiles observed in practice. It matches the findings of As-Sanie et al. [10], who reported that while 90% of affected women suffer from severe pelvic pain (including dysmenorrhea and dyspareunia), the systemic and neuroendocrine toll extends to cause infertility in 26% of patients. Notably, the literature on cortisol levels in endometriosis was inconsistent. While Sabbadin et al. [37] reported decreased cortisol in patients with infertility and dyspareunia, other studies have found elevated cortisol in response to chronic pain, suggesting that cortisol patterns may vary by symptom profile, disease stage, or timing of measurement [33].

### Psychological comorbidities and trauma toward integrated trauma-informed care

The deep intersection between neuroimmune pathology, diagnostic delays, and chronic pain drives a massive psychological burden. Patients suffer an average 50% increase in the risk of depression and anxiety, alongside elevated rates of body dysmorphic disorder (BDD) and post-traumatic stress disorder (PTSD) stemming from a bidirectional relationship with chronic inflammation and early-life trauma. High systemic levels of inflammatory mediators (IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and CRP) directly correlate to a drop in Brain-Derived Neurotrophic Factor (BDNF). This chemical bridge explained the data from Akano et al. [21], who proved that psychological stress alters both pain perception and the body's inflammatory responses, and supports Zippl et al. [19] and Kori et al. [23] in linking severe chronic pain directly to high rates of anxiety and depression.

### Trauma and diagnostic distress

The profound psychosocial impact of infertility, grief, and long diagnostic delays creates intense emotional distress. This is supported by Thiel et al. [18], who noted an increased risk for mental health conditions regardless of the mode of diagnosis, and Li et al. [20], who explicitly tied depression and anxiety to diagnostic delays and pain severity. Furthermore, Merola et al. [14] highlighted the complex interplay between trauma exposure and pain perception, while Dipankar et al. [15] and Szyplowska et al. [22] documented how resulting social isolation

and impaired Health-Related Quality of Life (HRQoL) worsen the underlying clinical condition.

### **Implementing Integrated Trauma-Informed Care (TIC)**

To stop the cycle of medical dismissal and re-traumatization, gynecological care must pivot toward a Psychological Trauma-Informed Approach (PTIA). This approach incorporates the six core TIC principles (safety, trustworthiness, peer support, collaboration, empowerment, and cultural consideration) alongside customized Therapeutic Patient Education (TPE). This clinical model maps directly onto the multi-modal management strategies synthesized in the results. The narrative demanded that surgical and hormonal options (such as laparoscopy, hysterectomy, or ovarian suppressants) be seamlessly integrated with psychological care. This corresponds with the consensus of Watkins et al. [24], who advocated for combining pharmacologic therapies with behavioral health interventions, and Mick et al. [27], who stated that comorbid conditions necessitate a long-term, personalized multimodal approach.

### **Specialized patient-centered teams**

For advanced, deep, or extra-pelvic disease, treatments must be centralized. This directly aligns with Di Spiezio et al. [29], Duncan et al. [25], Srianand et al. [28], and Tsamantioti et al. [41], who stated that optimal, patient-centered management requires experienced multidisciplinary teams within specialized centers to minimize surgical morbidity. The inclusion of trauma monitoring and psychological interventions was highly supported. Irshad et al. [26] asserted that childhood trauma history demands screening in reproductive care, while Carbone et al. [30] outlined the ideal multidisciplinary medical team: gynecologists, psychologists, psychiatrists, experts in Dual Disorder, algologists, and sexologists. Moreso, the therapeutic success of utilizing Cognitive Behavioral Therapy (CBT), mindfulness, and psychoeducation to lower pain scores and reduce depression [34, 44] is explicitly validated by the findings of Del Pino-Sedeño et al. [31], confirming that targeted psychological interventions are highly effective at improving pain, mental health variables, and overall quality of life for women with endometriosis.

Medical and surgical interventions remain the cornerstone of endometriosis management. Hormonal therapies, including combined oral contraceptives, progestins, and GnRH agonists, reduce pain by suppressing ovulation and menstruation [32]. Laparoscopic excision of endometrial lesions provides symptomatic relief, though recurrence rates of 20-40% within 5 years are reported [25]. However, these approaches address physical symptoms without directly targeting the psychological and inflammatory dimensions highlighted in this review. This underscores the need for integrated care that combines biomedical treatment with psychological support, lifestyle modifications, and trauma-informed communication.

While the association between systemic inflammation and endometriosis is well-established, the causal direction remains unclear. Most included studies were cross-sectional, limiting the ability to determine whether inflammation drives endometriosis or vice versa. The evidence for gut microbiome involvement is intriguing but preliminary. Only three studies directly examined the gut-endometriosis axis, and all had small sample sizes ( $n < 100$ ).

## **Limitations of the study**

This narrative review has several limitations. First, the search was restricted to English-language publications, potentially excluding relevant studies from non-English sources. Second, the predominance of observational and cross-sectional studies ( $n = 18/32$ ) limits causal inference. Third, heterogeneity in outcome measures, particularly the lack of standardized trauma assessment tools, prevented meta-analysis. Fourth, publication bias may have favored studies reporting positive associations. Finally, as a narrative review, the synthesis is inherently subjective and may be influenced by author interpretation.

## **Clinical and research implications**

These findings suggest several actionable recommendations. Clinically, routine mental health screening should be integrated into endometriosis care pathways, and trauma-informed communication should be adopted in gynecological settings. Multidisciplinary teams including gynecologists, pain specialists, psychologists, and dietitians should be the standard, not the exception. Future research should prioritize: (1) longitudinal studies to establish causal pathways between inflammation and psychological outcomes; (2) randomized controlled trials of integrated care models; and (3) validation of trauma screening tools specifically for endometriosis populations.

## **Conclusion**

This narrative review established endometriosis as a complex systemic condition. Clinicians must immediately adopt a Psychological Trauma Informed Approach (PTIA) that recognizes diverse trauma types, including early-life, childhood, and medical trauma, while utilizing multidisciplinary teams. This review is structurally limited by its narrative design and reliance on heterogeneous literature; however, it exposed the current lack of standardized medical trauma screening tools and a shortage of long-term outcome data. Consequently, future research should evaluate integrated multi-modal and trauma-informed care pathways and standardize trauma screening protocols within reproductive healthcare.

## **Declarations**

### **Ethical approval**

Ethical approval was not required for this study.

### **Informed consent**

Not Applicable

### **Consent for publication**

Not Applicable

### **Availability of data and materials**

Supplementary data are available upon request from the corresponding author.

### **Competing interests/Conflict of interests**

The authors declare that they have no competing interests.

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### Authors' contributions

DIO: Conceptualization, methodology, data collection, data analysis, writing the original draft, and reviewing and editing the manuscript. OM: Data collection, data analysis, and reviewing and editing the manuscript. OCO: Data collection, data analysis, and reviewing and editing the manuscript. HOA: Data collection, data analysis, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

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The authors did not use any artificial intelligence tools in the preparation of this manuscript.

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