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Review

Endometriosis as a systemic disease with neuroimmunological and tumor-like features: A review of current pathophysiological mechanisms

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ABSTRACT

Endometriosis is among the most common gynecological disorders, affecting an estimated 10% of women of reproductive age. In clinical practice, it primarily manifests as chronic pelvic pain and infertility, significantly impairing patients' daily functioning. Its pathophysiology is complex and involves both local and systemic processes. The mechanisms underlying pain in endometriosis are multifaceted and not limited solely to the presence of ectopic lesions. Both peripheral sensitization and alterations within the central nervous system play a crucial role, often accompanied by neurogenic inflammation and the development of new blood vessels and nerve fibers. Increasing attention is being paid to immunological mechanisms, particularly the role of macrophages with high phenotypic plasticity, which contribute to the persistence of chronic inflammation and support the growth and invasion of endometriotic cells. Endometriosis exhibits numerous features in common with neoplastic processes, including the ability to proliferate under hypoxic conditions, invasiveness, and the induction of angiogenesis and neurogenesis. A better understanding of these mechanisms may, in the future, enable the development of therapies targeting the underlying causes of the disease rather than merely alleviating its symptoms.

KEYWORDS

macrophages, endometriosis, chronic pelvic pain, women's quality of life, chronic inflammation, central sensitization, neuroangiogenesis

Introduction

Endometriosis is a chronic, estrogen-dependent gynaecological condition in which tissue similar to the endometrium grows outside the uterine cavity. This ectopic tissue, consisting of both glandular and stromal components, can appear in different parts of the body. It is most often found in the ovaries and peritoneum, but may also involve the gastrointestinal and urinary systems, and in rarer cases the thoracic cavity [1,2,3]. Although located outside the uterus, these cells remain hormonally active and respond to the cyclical changes of the menstrual cycle. This can result in repeated bleeding, ongoing inflammation, progressive fibrosis, and the development of adhesions and scar tissue over time. Consequently, the disease is multifocal, polymorphic, and progressive in nature, while its ethology remains incompletely understood. In clinical practice, endometriosis is estimated to affect approximately 10% of women of reproductive age, corresponding to over 190 million women worldwide [4]. In Europe, the prevalence is similar; however, the true scale of the problem may be underestimated due to a large number of undiagnosed cases. The incidence is higher in selected patient groups-particularly among women with dysmenorrhea, infertility, and chronic pelvic pain [5]. Despite its high prevalence, endometriosis remains a challenging condition

to diagnose. A characteristic feature is a delay in diagnosis, which may range from several to even more than a decade after the onset of symptoms. The delay in diagnosing endometriosis is influenced by several factors. Symptoms are often non-specific and vary widely in intensity, which can lead to them being overlooked or mistaken as “normal” menstrual discomfort. This is further reinforced by persistent social and cultural beliefs that tend to normalise or minimise period pain. Another challenge is the absence of reliable, non-invasive diagnostic markers [6]. As a result, a definitive diagnosis frequently requires surgical confirmation, even though lesions may also be present in women without any symptoms. It is estimated that endometriosis is identified in up to 50% of patients investigated for infertility [6]. Traditional explanations of its development mainly focus on the theory of retrograde menstruation, where endometrial cells travel backwards through the fallopian tubes and implant outside the uterus. However, this theory does not fully account for the wide range of clinical manifestations, particularly chronic pain and the frequent coexistence of other conditions [7]. More recently, endometriosis has increasingly been viewed as a systemic disorder rather than a purely local one. Research highlights the role of neuroimmunological dysregulation, altered pain perception, and biological processes that in some ways resemble tumour-like behaviour, helping to better explain its complexity. These include, among others, uncontrolled cellular proliferation and angiogenesis. In this context, peripheral and central sensitisation phenomena are of particular importance, as they contribute to pain persistence and disease progression [8]. At the same time, endometriosis shares several characteristics with neoplastic processes, including tissue invasiveness, the ability to establish a distinct local microenvironment, and mechanisms of immune evasion. For this reason, it is sometimes described as a pseudoneoplastic condition. The disease also has a profound impact on patients’ daily functioning. It can significantly reduce quality of life, limit professional and social activity, and increase the risk of developing emotional disorders [9]. Despite many years of research, endometriosis remains conceptually fragmented, which highlights the need for a more coherent and integrative framework. In response to this gap, we propose a unified model that views endometriosis as a neuroimmunoendocrine systemic disorder, driven by self-sustaining feedback loops between inflammation, neural sensitisation, and hormonal dysregulation.

Methodology

This narrative review aims to discuss current knowledge regarding the pathophysiological mechanisms of endometriosis, with particular emphasis on its potential systemic nature and the role of neuroimmunological and pseudoneoplastic processes in disease development and progression. Particular attention was given to the interactions between chronic inflammation, immune dysregulation, hormonal alterations, and mechanisms of central and peripheral

sensitisation, as well as their influence on the persistence of ectopic endometrial lesions and the development of chronic pain. The review also explores the potential involvement of the hypothalamic-pituitary-adrenal (HPA) axis, gut–brain interactions, and cancer-like biological behaviour in the broader understanding of endometriosis as a multi-system disorder. The literature analysed in this review was identified through searches of the PubMed, Scopus, and Google Scholar databases. Publications from 2008 to 2024 were considered, with particular emphasis placed on studies published after 2020 due to the growing body of research concerning the molecular, neuroimmunological, and systemic mechanisms of endometriosis. Earlier publications were included primarily to provide historical background and establish the foundations of currently accepted theories of pathogenesis. The literature search was conducted between 3 and 7 April 2026 using combinations of the following keywords: endometriosis, central sensitisation, immune system, chronic pelvic pain, macrophages, multi-system disease, quality of life, IBS, cancer, gut–brain axis, HPA axis, meta-analysis, and pathophysiology review. Additional relevant publications were identified through manual screening of the reference lists of selected articles. Only peer-reviewed articles published in English and available in full-text form were considered. The inclusion criteria were defined according to the PICO framework as illustrated in Figure 1. The review included original research articles, clinical and observational studies, review articles, systematic reviews, and meta-analyses addressing the pathophysiological mechanisms of endometriosis. Studies unrelated to disease mechanisms or focused on unrelated medical conditions without a clear connection to endometriosis were excluded. Due to the narrative nature of this review, a formal systematic selection process and quantitative risk-of-bias assessment were not performed. Instead, the included studies were evaluated qualitatively based on their relevance, methodological transparency, scientific contribution, and consistency with the scope of the review. The collected literature was analysed thematically. The findings were organised into major conceptual areas, including inflammatory and immunological mechanisms, neuroimmune interactions, central pain sensitisation, endocrine dysregulation, gut–brain axis involvement, and pseudoneoplastic features of endometriosis. Particular emphasis was placed on identifying recurring biological patterns, overlaps between different pathophysiological pathways, and current gaps in understanding the systemic nature of the disease. This review has several limitations. The search was limited to three databases and to English-language full-text publications, which may have resulted in the omission of potentially relevant studies. Furthermore, the heterogeneity of the included literature and the narrative nature of the review may introduce a degree of interpretative subjectivity. Nevertheless, this approach enabled a broad and integrative discussion of the multifactorial mechanisms involved in endometriosis.

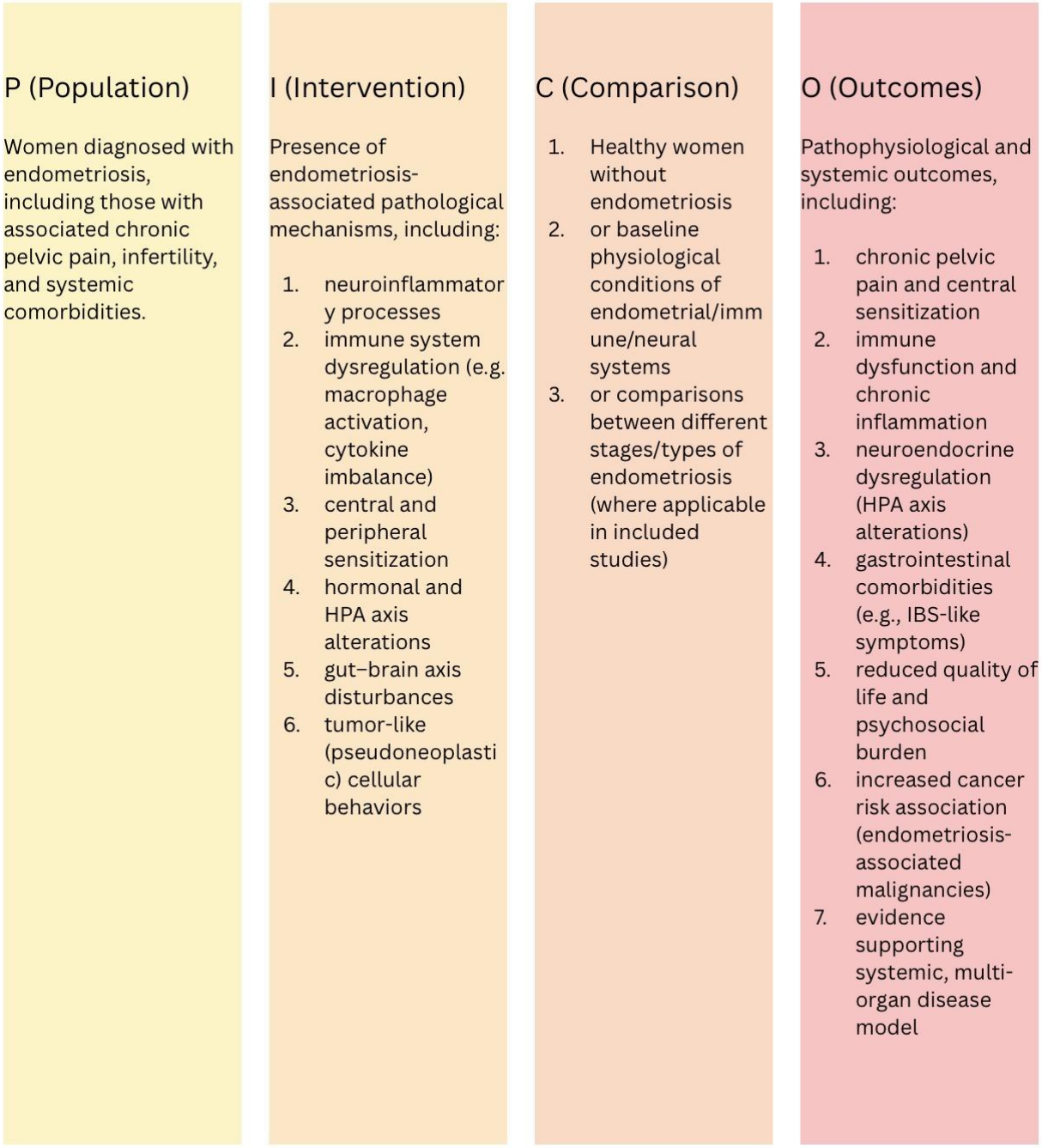

Fig. 1. PICO framework used to structure the research question on the pathophysiological mechanisms of endometriosis

Pathogenesis of endometriosis – biological basis

Endometriosis is a disease with a complex and multifactorial ethology, strongly dependent on estrogen, and characterised by the presence of endometrium-like tissue outside the uterine cavity [6,10]. Contemporary models of pathogenesis indicate that it is not a single disease entity, but rather a spectrum of processes involving migration of endometrial cells, metaplastic transformation, and the involvement of progenitor cells [10,11]. The most widely cited pathogenic

model is retrograde menstruation, which posits that viable endometrial cells are refluxed through the fallopian tubes into the peritoneal cavity during menses, where they can adhere, invade, and establish ectopic lesions [10,12]. However, because retrograde menstruation occurs physiologically in a substantial proportion of menstruating individuals, its presence alone is insufficient to explain disease development. This discrepancy implicates additional contributory mechanisms, including impaired immune surveillance and clearance, genetic susceptibility, and intrinsic molecular or phenotypic abnormalities of eutopic endometrial tissue that enhance ectopic implantation and survival [10,12]. The characteristic distribution of lesions in pelvic compartments-particularly the pouch of Douglas, uterosacral ligaments, and ovarian fossa-further supports the hypothesis of gravitational and fluid-dynamic deposition of refluxed cells in dependent peritoneal regions where peritoneal fluid tends to accumulate [10]. An alternative hypothesis is coelomic metaplasia, which proposes that multi-potent cells within the coelomic epithelium or peritoneum may undergo metaplastic transformation into endometrial-like tissue in response to hormonal signalling or other local microenvironmental stimuli [6,12]. This mechanism may explain the presence of lesions in locations where retrograde transport is unlikely; however, it does not account for all clinical forms of the disease [12]. Increasing importance is also attributed to the stem cell hypothesis, according to which lesions may originate from endometrial progenitor cells or bone marrow-derived cells [10,11]. Stem cells have the capacity for self-renewal and differentiation, which may allow them to survive in ectopic sites and contribute to the formation of stable endometriotic lesions [11]. This model may help explain both the biological heterogeneity of endometriotic lesions and their presence in distant anatomical locations outside the pelvis [11].

Another explanatory framework is the “tissue injury and repair” (TIAR) hypothesis (Figure 2). According to this model, endometriosis may originate from repeated injury to the junctional zone between the endometrium and myometrium, often associated with abnormal uterine peristalsis [13]. This tissue damage can trigger a local inflammatory response, increase aromatase expression, and enhance estrogen production, thereby promoting the proliferation and persistence of endometrial tissue [13]. Hypoxia-related pathways, including activation of hypoxia-inducible factor 1-alpha (HIF-1α), may further support tissue remodelling, angiogenesis, and lesion survival [13]. Endometriosis is also strongly shaped by the hormonal environment, particularly by oestrogens, which stimulate the growth of ectopic endometrial tissue and amplify inflammatory processes [6,11]. In many lesions, estrogen can be produced locally, resulting in increased tissue-level estrogen activity that is partly independent of the hypothalamic-pituitary-ovarian (HPO) axis [11]. At the same time, progesterone resistance reduces the normal anti-inflammatory and anti-

proliferative effects of progesterone, thereby favouring the persistence of biologically active ectopic tissue [11]. According to newer concepts, endometriosis may represent a systemic disease in which lesions spread via lymphatic and hematogenous routes, rather than exclusively through local implantation [13]. The presence of lesions in lymph nodes and distant organs supports this hypothesis [13]. It has been demonstrated that endometriotic lesions contain not only endometrial cells but also smooth muscle cells, giving them characteristics of structures resembling “miniature uteri” responsive to steroid hormones [13]. This suggests the involvement of pluripotent cells and processes of smooth muscle metaplasia in disease pathogenesis [13]. Genetic and epigenetic factors also play a significant role in susceptibility to endometriosis and its clinical course [6,13]. Familial aggregation of the disease has been observed, along with numerous genetic variants associated with increased risk [13]. Environmental factors, particularly exposure to endocrine-disrupting chemicals, may further modulate gene expression through epigenetic mechanisms [13]. Dysfunction of the immune system plays a pivotal role in this context, serving as a central nexus that integrates inflammatory, hormonal, and molecular processes. Impaired immune surveillance not only facilitates the survival of ectopic endometrial cells but also actively sculpts the disease microenvironment, thereby driving progression and sustaining chronic inflammation.

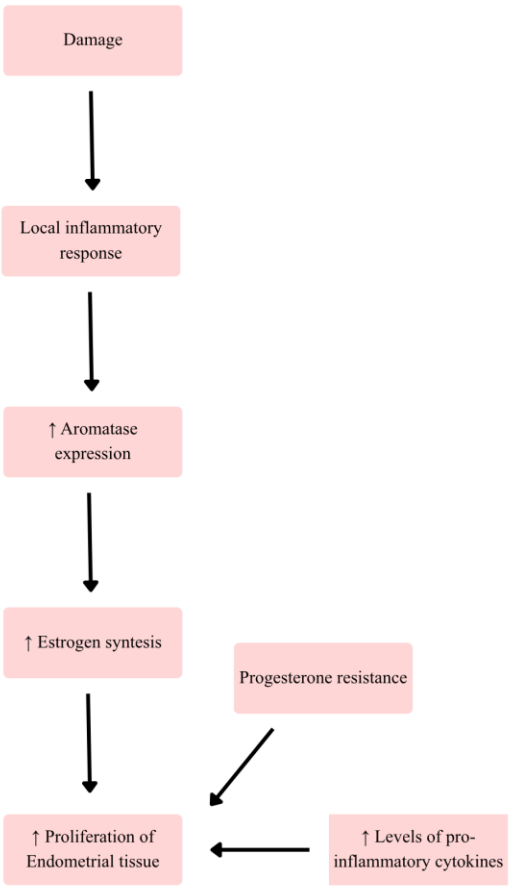

Fig. 2. Mechanism of the "tissue injury and repair" model. Simplified representation of the local hormonal-inflammatory mechanism in endometriosis

The role of the immune system in the pathogenesis of endometriosis

Current evidence demonstrates that hormonal mechanisms alone are insufficient to explain the development of the disease, and that dysfunction of the immune system plays a significant role, leading to abnormal interactions between endometrial cells and immune cells [14,15]. In the peritoneal cavity, a state of chronic activation of inflammatory cells is maintained, accompanied by increased production of mediators that promote the survival and implantation of endometrial cells in ectopic locations [14]. A particularly important role is attributed to macrophages, which undergo functional reprogramming in the endometriotic environment. They exhibit both increased secretory activity and a reduced capacity for phagocytosis. This leads to a weakening of their protective functions and a shift toward supporting disease processes. These cells also participate in tissue remodelling and angiogenesis, thereby promoting the persistence and progression of endometrial lesions. They may also acquire properties of long-term immune memory, which may

contribute to the chronicity of inflammation [16,17]. Reduced cytotoxic activity of natural killer (NK) cells limits the effectiveness of natural mechanisms for eliminating ectopic cells and enables their continued survival [14,15]. In endometriosis, disturbances in adaptive immunity are also observed, including impaired activity of T lymphocytes. A shift in the balance between Th1, Th2, and Th17 responses is noted, resulting in the predominance of an environment that promotes chronic inflammation and weakens the effector mechanisms of the immune response [14]. Increased activity of regulatory T cells (Treg) contributes to suppression of the immune response against endometrial cells, facilitating their survival in ectopic locations [15]. A key element of endometriosis pathogenesis is also the dysregulation of cytokine function. Elevated levels of pro-inflammatory cytokines sustain inflammation, support cell proliferation, and enhance angiogenesis [15]. Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) are involved in maintaining chronic inflammatory activation and support the survival of endometrial cells, while interleukin-8 (IL-8) plays a role in angiogenesis. At the same time, immunosuppressive cytokines such as IL-10 and transforming growth factor-beta (TGF-β) promote the formation of a tolerogenic environment [14,15]. Endometriosis is also associated with mechanisms that enable endometrial cells to evade immune responses. This includes both impaired function of effector cells and increased activity of immunosuppressive mechanisms, including Treg cells and anti-inflammatory cytokines [14,15]. Additionally, macrophages with an altered phenotype support angiogenesis and tissue remodelling processes [16,17]. As a result, the immune system, instead of eliminating ectopic cells, contributes to the creation of an environment that favours disease development. Chronic inflammation and persistent activation of immune cells significantly affect the nervous system. Inflammatory mediators present in the endometriotic microenvironment may act on nerve fibres, increasing their excitability and initiating sensitisation processes. Immunological mechanisms thus link disease pathogenesis with the development of chronic pain.

Neurobiological mechanisms of pain in endometriosis

The primary symptom that reduces the quality of life in patients with endometriosis is chronic pelvic pain [18]. The clinical presentation of pain is heterogeneous and includes, among others, dysmenorrhea, dyspareunia, and pain associated with urination or defecation [18]. The severity of pain symptoms is often not proportional to the extent of pathological lesions, suggesting the involvement of mechanisms beyond the mere presence of disease foci [19]. The frequent coexistence of other chronic pain syndromes, such as IBS or vulvodynia, suggests a shared pathophysiological basis related to dysfunction in pain processing [19]. Persistence of pain leads to secondary changes in the central nervous system [20]. Central sensitisation is a key mechanism responsible for the chronic nature of pain and involves increased reactivity of neurones within the

central nervous system [20]. This results in enhanced transmission of pain stimuli in the dorsal horns of the spinal cord and a lowered activation threshold [19]. It induces plastic changes in brain structures responsible for pain perception, such as the somatosensory cortex, insula, and components of the limbic system [18]. The consequence of these changes is the occurrence of allodynia and hyperalgesia [20]. Central sensitisation may persist despite the removal of lesions, which explains the persistence of symptoms after surgical treatment [18]. The nature of pain in endometriosis is complex and includes both nociceptive and neuropathic components [19]. Damage or abnormal functioning of nerve fibres within disease lesions promotes the generation of spontaneous pain impulses [18]. An increased presence of nerve fibres has been observed in endometrial tissue, which may be directly associated with symptom severity [18]. The process of neuroangiogenesis further enhances pain signal transmission [19]. Symptoms such as burning, stabbing, or radiating pain indicate the involvement of neuropathic mechanisms [20]. Another mechanism is cross-sensitisation, in which stimulation of one pelvic organ affects pain perception in other organs [19]. Neuroinflammation is a direct consequence of chronic immune system activation observed in endometriosis and plays a key role in pain modulation. In this context, interactions between immune cells and the nervous system are important, leading to the release of inflammatory mediators and increased excitability of nociceptors [18]. Inflammatory cells present in lesions secrete mediators such as cytokines and prostaglandins, which increase the excitability of pain receptors [18]. Activated nerve fibres release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which intensify local inflammation and pain transmission [19]. As a result, peripheral sensitisation occurs, manifested by a lowered activation threshold of nociceptors and an increased response to stimuli [20]. Chronic inflammation promotes the persistence of changes in the nervous system and the transition of pain into a chronic form [18]. This creates a vicious cycle in which inflammation and pain reinforce each other [19]. Available data indicate that the extent of endometrial lesions does not correlate with the severity of pain [18]. In some patients, small lesions may cause severe symptoms, whereas in advanced cases symptoms may be relatively mild [19]. This phenomenon is explained by the dominant role of neurobiological mechanisms, such as central and peripheral sensitisation [20]. Pain perception is also influenced by psychological factors, including stress and anxiety, acting through the HPA axis [18]. Individual differences in pain processing further determine variability in clinical presentation [19]. Therefore, effective pain management in endometriosis requires a holistic approach that takes into account both biological mechanisms and neuropsychological factors [18].

Neuroimmunological and neuroendocrine regulatory mechanisms

The neuroimmunological axis in endometriosis is a system of interconnections between hormonal regulation, the stress response, and immune system activity, in which the HPA axis and the HPO axis play a key role [21]. Under normal conditions, hormonal impulses regulating the secretion of gonadotropins, such as luteinising hormone (LH), remain in balance with stress-related mechanisms. Chronic activation of the HPA axis may disrupt this homeostasis and affect the functioning of the reproductive system [21]. Studies on women with endometriosis indicate that chronic psychological stress and pain may lead to activation of the HPA axis and increased cortisol secretion, which exerts an inhibitory effect on the HPO axis [22]. Cortisol may influence the secretion of gonadotropin-releasing hormone (GnRH), which in turn may modulate the secretion of LH and follicle-stimulating hormone (FSH). This leads to disturbances in hormonal balance essential for ovarian function [22]. Such changes may be significant in the pathophysiology of endometriosis, as disrupted hormonal regulation affects the hormonal environment that promotes the persistence of disease lesions [22]. Additionally, it has been shown that patients with endometriosis exhibit alterations in diurnal cortisol levels, which may include abnormal morning values and an impaired stress response [23]. These changes are associated with increased chronic pain and reduced quality of life, suggesting that dysregulation of the HPA axis is not merely a consequence of the disease but may also contribute to its maintenance [23]. Cortisol functions as a stress hormone but also as a factor linking neuroendocrine and immune responses [23]. The significance of LH and other gonadotropins in the context of endometriosis results from their role in regulating the ovarian cycle and estrogen production, which influence the activity of endometrial lesions [21]. Disturbances in the HPO axis, resulting from chronic activation of the HPA axis, may lead to alterations in LH secretion, indirectly affecting the estrogen–progesterone balance [21]. Cortisol also affects the immune system by modulating the inflammatory response [24]. Under physiological conditions, it exerts anti-inflammatory effects; however, its chronic dysregulation may lead to impaired control of inflammatory processes and sustained immune activation [24]. As a result, this may promote intensified local inflammatory reactions within endometrial lesions and their continued biological activity [24]. Disruptions in the neuroimmunological axis indicate that the pathologies present in endometriosis are not solely local in nature but involve multilevel regulatory mechanisms of the organism. Consequently, endometriosis may be viewed as a systemic disease in which immunological, hormonal, and neurobiological disturbances are integrated.

Endometriosis as a systemic disease

Key importance is attributed to chronic low-grade inflammation and an abnormal immune response. Additionally, alterations in pain processing led to the persistence and generalization of symptoms [8,10]. Genetic data indicate shared molecular mechanisms between endometriosis and other inflammatory and pain-related diseases, confirming its multi-system nature [25]. The clinical presentation of endometriosis is heterogeneous and includes numerous non-gynaecological symptoms, which often dominate the disease course and may obscure its actual origin (Figure 3) [9]. Particularly significant are gastrointestinal symptoms, such as chronic abdominal pain, bloating, altered bowel habits, and painful defecation, which often show cyclically associated with the menstrual cycle [9]. Special attention should be paid to the frequent coexistence of endometriosis with irritable bowel syndrome (IBS), which constitutes a significant diagnostic and therapeutic challenge [9,25]. The overlap of symptoms between these two conditions may result from shared pathophysiological mechanisms, including disturbances in the gut–brain axis, hypersensitivity, and chronic activation of the immune system [25]. Additionally, the phenomenon of central sensitisation leads to a lowered threshold for pain perception, which promotes the persistence of both intestinal and pelvic symptoms [8]. As a consequence, some patients may initially be diagnosed and treated for IBS, which delays the correct diagnosis of endometriosis [9]. In addition to gastrointestinal symptoms, urological complaints are also frequently observed, such as urinary frequency, urgency, bladder pain, and dysuria, which may mimic bladder pain syndrome [9]. Systemic symptoms are also present in the clinical picture, including chronic fatigue, sleep disturbances, headaches, and generalised hypersensitivity to pain stimuli [8]. Neurobiological mechanisms play a key role in the spread of pain beyond the pelvic region and in maintaining its chronic nature [8,10]. Comorbidity of endometriosis with IBS and other pain syndromes, such as fibromyalgia or migraine, leads to a significant increase in overall disease burden and worsens prognosis [25]. Patients with overlapping disorders are characterised by greater symptom severity, a broader spectrum of symptoms, and a poorer response to standard treatment methods [9]. The shared background of these conditions includes both genetic factors and dysregulation of the neuroimmunological axis, further emphasising the need for a systemic approach to diagnosis and therapy [25]. Endometriosis affects multiple aspects of life, including physical, psychological, and social functioning [9,26]. Chronic pain and accompanying somatic symptoms lead to limitations in daily activity and reduced work capacity [9]. Gastrointestinal and urological symptoms further impact quality of life, often causing embarrassment and limiting participation in social life [9]. Results of multicenter studies indicate a significant reduction in work productivity, resulting both from absenteeism and from reduced efficiency while at work [26]. Loss of productivity may

constitute a substantial burden for both patients and healthcare systems [26]. The disease also negatively affects mental health and interpersonal relationships, including sexual activity, which is often impaired due to discomfort [9]. The chronic nature of symptoms, diagnostic delays, and limited effectiveness of causal treatment promote the development of depressive and anxiety disorders [9]. These factors contribute to reduced quality of life and a sense of social isolation [9]. Considering endometriosis as a disorder involving the entire organism allows for integration of observed clinical and pathophysiological phenomena [10,27]. The disease is associated with simultaneous dysregulation of immune, hormonal, and nervous system axes, and its course may be modulated by environmental factors, including lifestyle and diet [27]. Such an approach explains both the multi-organ nature of symptoms and the frequent coexistence of functional disorders [27]. Optimal therapeutic management requires a multidisciplinary approach, taking into account not only gynaecological treatment but also interventions targeting the gastrointestinal system, pain management, and psychological support [9,27].

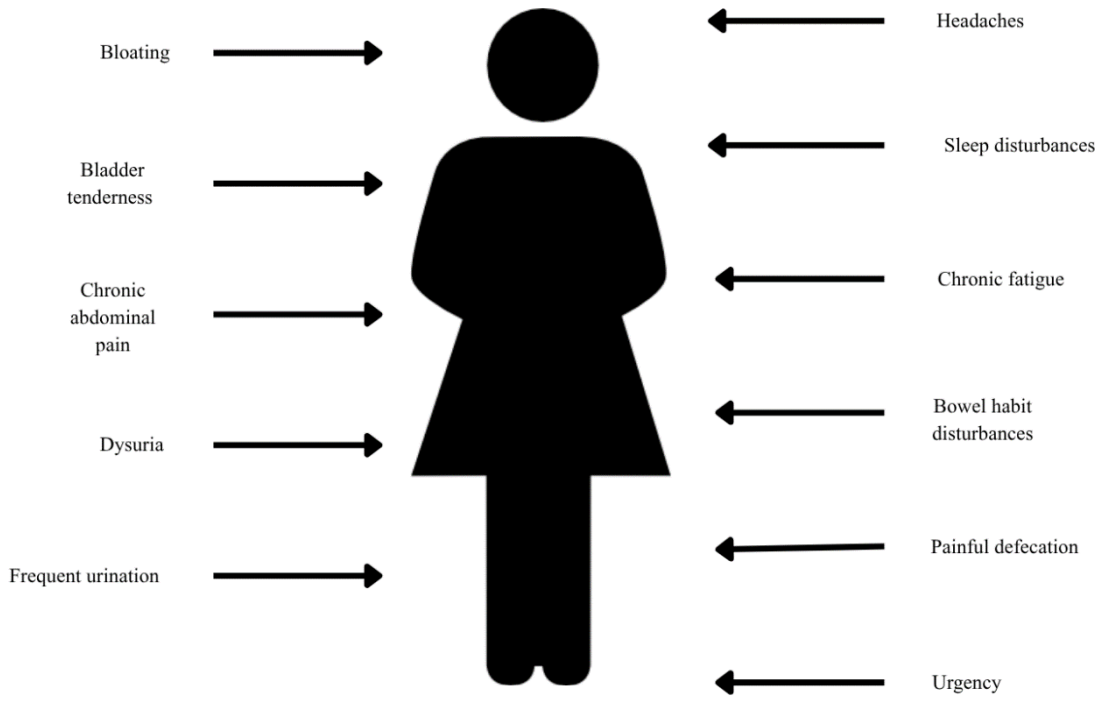

Fig. 3. Symptoms of endometriosis

Pseudoneoplastic nature of endometriosis

In endometriosis, particular emphasis is placed on its “pseudoneoplastic” character, resulting from the presence of mechanisms such as uncontrolled cellular proliferation [28,29]. In this context, the term “tumour-like disease” is increasingly used, which does not strictly imply neoplastic transformation, but indicates biological and molecular similarities to oncogenic processes [30]. A particularly important area of research involves somatic mutations detected in endometriotic

lesions, especially in the ovarian region. Numerous molecular analyses have demonstrated the presence of alterations in genes crucial for regulating cell proliferation and survival, such as *ARID1A*, *PIK3CA*, and *KRAS* [29,31]. These mutations are not merely passive markers of DNA damage but actively influence signalling pathways, including PI3K/AKT/mTOR and RAS/MAPK, leading to dysregulation of the cell cycle, increased cell survival, and enhanced proliferative potential [29,31]. Some of these genetic mutations are shared with ovarian cancers associated with endometriosis, which strengthens the hypothesis of a link between endometriosis and specific types of cancer [31]. However, the presence of somatic mutations does not unequivocally indicate neoplastic transformation but rather reflects the mosaic nature of lesions and the biological variability of endometrial foci. In certain cases, these mutations may represent an initial step in carcinogenesis. For full transformation to occur, additional microenvironmental disturbances as well as further genetic and epigenetic alterations are required [29]. Consequently, endometriosis is progressively being examined as a potential precursor condition, especially concerning ovarian endometriosis [31]. Beyond genetic changes, the inflammatory microenvironment holds considerable importance, as it may facilitate the selection of cells exhibiting more aggressive characteristics. Persistent immune stimulation, elevated levels of pro-inflammatory cytokines, and impaired macrophage function establish conditions that support the survival of cells possessing altered molecular features [17,32]. Within this framework, macrophages additionally amplify the "tumour-like" characteristics [17]. The question of malignant transformation potential in endometriosis continues to be a central subject of scientific debate. The most robust epidemiological links involve ovarian cancer, particularly the endometrioid and clear cell variants, which are categorised as endometriosis-related malignancies [31,33]. Population-based cohort research indicates that endometriosis correlates with elevated risk of developing these malignancies, though the absolute risk at the population level remains comparatively modest [31,33]. Genomic studies have additionally revealed partial commonality between genetic variants associated with endometriosis and ovarian cancer susceptibility, pointing to shared biological mechanisms [34]. Current theoretical frameworks tend to propose the existence of a continuum of alterations, wherein certain endometrial lesions may persist unchanged for extended periods, while others through accumulation of somatic genetic changes and microenvironmental influences may advance toward precancerous states and eventually malignant transformation [29,31,35]. Endometriosis does not represent a singular disease entity but rather a diverse collection of processes demonstrating variable biological potential [28,35] as summarised in Table I. The strongest correlations pertain to ovarian cancer; nevertheless, certain epidemiological investigations also indicate a modest elevation in endometrial cancer and breast

cancer risk among endometriosis patients, although these associations remain less definitive and may be influenced by numerous variables, including hormonal factors [36]. The "tumour-like disease" conceptualisation carries important clinical significance, as it redirects the understanding of endometriosis from merely a hormonal-inflammatory disorder toward recognition as a condition with a distinctive molecular dimension, necessitating treatment approaches that address not only symptomatic manifestations but also the fundamental biological mechanisms involved [28,35]. Nevertheless, the detection of shared mutations should not be interpreted as direct evidence that endometriosis constitutes a precancerous condition in a universal or deterministic sense. Somatic mutations are increasingly recognised in many benign tissues and may reflect clonal expansion, chronic inflammation, oxidative stress, or local tissue adaptation rather than inevitable malignant transformation [30,31]. Current evidence suggests that the majority of endometriotic lesions remain biologically stable and do not progress to cancer [29,35]. Therefore, molecular overlap between endometriosis and ovarian cancer should be interpreted cautiously and primarily as evidence of partially shared biological pathways rather than proof of direct oncogenic progression. The inflammatory microenvironment characteristic of endometriosis is considered another important factor contributing to these tumour-like features. Chronic exposure to pro-inflammatory cytokines, oxidative stress, altered immune surveillance, and dysregulated macrophage activity may support cellular survival and persistence of ectopic lesions [31,32]. These mechanisms may create conditions favouring the accumulation of additional molecular alterations over time, particularly in ovarian lesions repeatedly exposed to cyclical haemorrhage and iron-induced oxidative stress [31,35]. However, the presence of such mechanisms alone remains insufficient for malignant transformation, which is understood as a complex, multistep process requiring additional genetic, epigenetic, and microenvironmental events [29,30,31].
Epidemiological studies demonstrate that women with endometriosis may have an increased relative risk of specific ovarian cancer histotypes, most notably endometrioid and clear cell ovarian carcinoma [28,29,31,35]. These malignancies are frequently described as endometriosis-associated ovarian cancers. Nonetheless, although relative risk may be elevated, the absolute lifetime risk of ovarian cancer among patients with endometriosis remains comparatively low at the population level [29,31,35]. This distinction is clinically important, as relative associations may overestimate perceived cancer risk when not interpreted in the context of absolute incidence.
Current genomic and epidemiological data suggest the existence of partially overlapping molecular mechanisms between endometriosis and certain ovarian cancer subtypes, rather than a direct linear progression from benign disease to malignancy in most patients [28,30,35]. It has been proposed that only a limited subgroup of lesions, particularly ovarian endometriomas displaying

specific molecular alterations and prolonged inflammatory exposure, may possess increased susceptibility to neoplastic transformation [31,35]. Even within this subgroup, progression to malignancy appears to remain uncommon. Associations between endometriosis and other malignancies, including breast and endometrial cancer, are less consistent. Available meta-analyses indicate that these relationships are generally weaker and may be influenced by shared hormonal, reproductive, genetic, or environmental factors rather than direct causal mechanisms [33]. Consequently, current evidence does not support the interpretation of endometriosis as a broadly premalignant condition. The concept of endometriosis as a tumour-like disorder therefore primarily reflects selected similarities in cellular behaviour and molecular signalling pathways rather than equivalence to malignant disease. Recognition of these shared biological features may nevertheless contribute to improved understanding of lesion persistence, recurrence, and therapeutic resistance, while also supporting the development of more targeted molecular and anti-inflammatory treatment strategies [30,31,35].

Table I. Key pathophysiological mechanisms in endometriosis

Pathway	Key mechanisms	Main consequences	Interactions
Immunological	Macrophages lose ability to clear ectopic cells and switch to pro-inflammatory, pro-angiogenic mode [16,17]. NK cells show reduced cytotoxic activity [14,15]. Immune balance shifts toward chronic inflammation (↑ IL-6, TNF-α, IL-8) and immune tolerance (↑ IL-10, TGF-β, Treg cells) [14,15]	Ectopic cells survive and implant. Chronic inflammation is maintained. New blood vessels form to sustain lesions [14,15,16,17]	Inflammatory mediators stimulate nerve fibres → pain sensitisation → stress response → hormonal disruption [14,18,19]
Neurobiological	Peripheral and central sensitisation develop over time [19,20]. Lesions become increasingly innervated (neuroangiogenesis) [18,19]. Neuropeptides (substance P, CGRP) amplify local inflammation [19]. Brain	Chronic pelvic pain independent of lesion size [18,19]. Hyperalgesia and allodynia [20]. Pain persists even after surgery [18].	Persistent pain activates the HPA axis → cortisol dysregulation → hormonal and immune imbalance → worsening

	structures involved in pain processing undergo plastic changes [18]	Co-occurrence of IBS, fibromyalgia, migraine [19,25]	sensitisation [21,22,23]
Endocrine	Local oestrogen overproduction via ↑ aromatase in lesions [11,13]. Progesterone resistance reduces anti-inflammatory effects [11]. Chronic stress dysregulates HPA axis → abnormal cortisol levels [22,23]. HPA activation suppresses HPO axis → altered LH and FSH secretion [21,22]	Oestrogen-driven lesion growth [6,11]. Reduced response to hormonal treatments [11]. Reproductive dysfunction [36]. Worsening systemic symptoms [22,23]	Oestrogens fuel inflammation and cell proliferation → reinforce immune dysregulation and neural sensitisation [11,13,24]
Molecular/ Pseudoneoplastic	Somatic mutations (*ARID1A*, *PIK3CA*, *KRAS*) activate pro-survival signalling pathways (PI3K/AKT/mTOR, RAS/MAPK) [29,31]. Oxidative stress from cyclical bleeding promotes further molecular damage [31,35]. Epigenetic changes alter gene expression [13]. Lesions share molecular features with certain ovarian cancers [28,31,35]	Lesion persistence and resistance to apoptosis [30]. Capacity for distant spread via lymphatic and blood vessels [13]. Modestly elevated risk of endometrioid and clear-cell ovarian cancer (relative risk elevated; absolute risk remains low) [29,31,33,35]	Chronic inflammation and oestrogen excess drive molecular alterations → further sustain inflammation and angiogenesis → reinforce all other pathways [17,31,32,35]

DISCUSSION

The available evidence indicates that endometriosis is a complex, systemic, and inherently heterogeneous disorder that cannot be fully explained by the classical theory of retrograde menstruation. In light of this, we propose an integrative model that conceptualises endometriosis as a neuroimmunoendocrine systemic disorder sustained by self-reinforcing feedback loops involving inflammation, neural sensitisation, and hormonal dysregulation. Although the traditional retrograde menstruation model has been historically influential, it does not adequately account for the multi-system involvement, the wide diversity of clinical phenotypes, or the frequently observed disconnect between lesion burden and symptom severity. It is increasingly recognised that endometriosis should be considered a spectrum of related pathological conditions rather than a single disease entity. This redefinition is not merely semantic; it reflects the underlying biological reality. The absence of a single unifying pathogenic model should be viewed not as a lack of knowledge, but as a consequence of genuine biological heterogeneity. This heterogeneity constitutes a central challenge to achieving reliable diagnosis, consistent treatment responses, and

therapeutic innovation. Among the mechanisms implicated, immune dysregulation appears to play a particularly important role in disease persistence. Impaired macrophage function, characterised by reduced phagocytic capacity and increased pro-angiogenic activity, is thought to sustain the inflammatory microenvironment that supports lesion survival. Concurrently, T-cell imbalance and enhanced regulatory immune responses may facilitate immune evasion by ectopic endometrial tissue. Nevertheless, it remains unclear whether these immune alterations represent a primary driver of the disease or a secondary adaptation, highlighting a significant gap in current mechanistic understanding. Neurobiological processes, particularly central sensitisation, are equally critical. Chronic pain in endometriosis cannot be explained solely by the physical presence of lesions. Rather, it appears to involve altered central pain processing maintained by persistent neuroplastic changes. This mechanism helps explain why pain frequently persists despite surgical or hormonal interventions. In addition, neuroangiogenesis and increased innervation of lesions may create a self-perpetuating cycle between inflammation and nociception, contributing to a chronic pain state that is often independent of ongoing peripheral pathology. Endocrine-immune interactions further increase the complexity of the disorder. Dysregulation of the HPA and HPO axes may promote hormonal instability and sustained inflammatory signalling. The persistence of symptoms despite hormonal suppression challenges the traditional estrogen-dependent paradigm and suggests that additional mechanisms, including epigenetic reprogramming and autonomous cellular behaviour, are likely to be involved. These elements are not yet sufficiently integrated into existing disease models. Endometriotic lesions also exhibit tumour-like features. The presence of somatic mutations (including *ARID1A*, *PIK3CA*, *and KRAS*), together with angiogenic and invasive properties, indicates shared molecular pathways with oncogenic processes. Although this does not imply that endometriosis is a premalignant condition, it underscores the importance of examining the disorder within a broader biological context. These overlaps may partly explain the observed increased risk of certain ovarian cancer subtypes and represent an area requiring further mechanistic investigation. Despite substantial progress in understanding disease mechanisms, a significant translational gap remains. Mechanistic insights have not been effectively translated into clinically actionable therapeutic strategies. This is reflected in the limited number of high-quality clinical trials targeting specific pathogenic pathways. Consequently, current treatment approaches remain largely symptom-suppressive rather than disease-modifying. Although hormonal therapies and surgical interventions are often necessary, they are associated with high recurrence rates and variable efficacy, indicating that they do not adequately address the underlying drivers of disease progression. Diagnostic limitations are equally important. The continued dependence on invasive laparoscopy for definitive diagnosis highlights the urgent need for reliable non-invasive

biomarkers. The resulting diagnostic delays, which frequently span several years, have well-documented negative consequences for disease progression and patient quality of life. Collectively, these observations support the conclusion that heterogeneity is not a peripheral feature of endometriosis but its defining characteristic. Management strategies based on uniform approaches are therefore inherently limited. Future progress will require the development of phenotype-driven classification systems and truly personalised therapeutic strategies. We propose that meaningful advancement depends on the construction of integrative, mechanism-based models capable of addressing immune dysfunction, neuroangiogenesis, central sensitisation, and endocrine imbalance in a coordinated manner. A shift from primarily symptomatic management toward causative, biology-driven interventions is essential if the field is to convert scientific progress into tangible clinical benefit.

CONCLUSIONS

1. Current evidence indicates that endometriosis is characterised by complex and multifactorial pathophysiological mechanisms involving inflammatory, immunological, hormonal, and neurobiological pathways.
2. Despite substantial advances in research, the pathogenesis of endometriosis remains incompletely understood, with existing data demonstrating considerable biological and clinical heterogeneity among patients and disease phenotypes.
3. The development of reliable non-invasive biomarkers for endometriosis remains an important area of ongoing research. Delayed diagnosis continues to be associated with increased disease burden and impaired quality of life.
4. Contemporary therapeutic strategies are primarily directed towards symptom control, particularly pain reduction and suppression of lesion activity. However, challenges related to disease recurrence and long-term treatment effectiveness remain significant clinical concerns.
5. Phenotype-based classification systems have increasingly been proposed as a means of improving patient stratification and facilitating more individualised therapeutic approaches.
6. Experimental, molecular, and translational studies have contributed substantially to the current understanding of endometriosis pathophysiology; nevertheless, implementation of these findings in routine clinical practice remains limited.
7. Further interdisciplinary research integrating molecular, immunological, neurobiological, and clinical perspectives is required to advance understanding of endometriosis and support the development of more targeted diagnostic and therapeutic strategies.

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Conflict of interest

The authors declare that there is no conflict of interest.

Use of AI tools statement

OpenEvidence was used to search and select scientific literature and to aid in identifying current publications. ChatGPT was used for linguistic and stylistic proofreading and translation into English.

Authors' contribution

Study design – K. Gawarecka, K. Gałka
Data collection – K. Gawarecka
Manuscript preparation – K. Gawarecka, K. Gałka
Literature research – K. Gawarecka
Final approval of the version to be published – K. Gawarecka, K. Gałka

REFERENCES

1. Giudice LC. Clinical practice. Endometriosis. N Engl J Med. 2010;362(25):2389–2398. doi: 10.1056/NEJMcp1000274.

2. Maniglio P, Ricciardi E, Meli F, Vitale SG, Noventa M, Vitagliano A, et al. Catamenial pneumothorax caused by thoracic endometriosis. Radiol Case Rep. 2017;13(1):81–85. doi: 10.1016/j.radcr.2017.09.003.

3. Tsakiridis K, Triantafilopoulou K, Minadakis G, Zatagias A, Sapalidis K, Kosmidis C, et al. Catamenial pneumothorax recurrence due to endometriosis. Respir Med Case Rep. 2020;30:101036. doi: 10.1016/j.rmcr.2020.101036.

4. Endometriosis. World Health Organization, 15 October 2025 [online] https://www.who.int/news-room/fact-sheets/detail/endometriosis [accessed on 22 July 2026].

5. Falcone T, Flyckt R. Clinical Management of Endometriosis. Obstet Gynecol. 2018;131(3):557–571. doi: 10.1097/AOG.0000000000002469.

6. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell. 2021;184(11):2807–2824. doi: 10.1016/j.cell.2021.04.041.

7. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). Int J Mol Sci. 2021;22(19):10554. doi: 10.3390/ijms221910554.

8. Maddern J, Grundy L, Castro J, Brierley SM. Pain in Endometriosis. Front Cell Neurosci. 2020;14:590823. doi: 10.3389/fncel.2020.590823.

9. Della Corte L, Di Filippo C, Gabrielli O, Reppuccia S, La Rosa VL, Ragusa R, et al. The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. Int J Environ Res Public Health. 2020;17(13):4683. doi: 10.3390/ijerph17134683.

10. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012;98(3):511–519. doi: 10.1016/j.fertnstert.2012.06.029.

11. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. F1000Res. 2019;8:F1000 Faculty Rev-529. doi: 10.12688/f1000research.14817.1.

12. Wang Y, Nicholes K, Shih IM. The Origin and Pathogenesis of Endometriosis. Annu Rev Pathol. 2020;15:71–95. doi: 10.1146/annurev-pathmechdis-012419-032654.

13. Gruber TM, Mechsner S. Pathogenesis of Endometriosis: The Origin of Pain and Subfertility. Cells. 2021;10(6):1381. doi: 10.3390/cells10061381.

14. Abramiuk M, Grywalska E, Małkowska P, Sierawska O, Hrynkiewicz R, Niedźwiedzka-Rystwej P. The Role of the Immune System in the Development of Endometriosis. Cells. 2022;11(13):2028. doi: 10.3390/cells11132028.

15. Bedaiwy MA. Endometrial cytokines, endometriosis and infertility: a deeper dive into the endometrial immune microenvironment. Fertil Steril. 2022;117(3):641–642. doi: 10.1016/j.fertnstert.2022.01.023.

16. Jeljeli M, Riccio LGC, Chouzenoux S, Moresi F, Toullec L, Doridot L, et al. Macrophage Immune Memory Controls Endometriosis in Mice and Humans. Cell Rep. 2020;33(5):108325. doi: 10.1016/j.celrep.2020.108325.

17. Artemova D, Vishnyakova P, Khashchenko E, Elchaninov A, Sukhikh G, Fatkhudinov T. Endometriosis and Cancer: Exploring the Role of Macrophages. Int J Mol Sci. 2021;22(10):5196. doi: 10.3390/ijms22105196.

18. Song SY, Jung YW, Shin W, Park M, Lee GW, Jeong S, et al. Endometriosis-Related Chronic Pelvic Pain. Biomedicines. 2023;11(10):2868. doi: 10.3390/biomedicines11102868.

19. McNamara HC, Frawley HC, Donoghue JF, Readman E, Healey M, Ellett L, et al. Peripheral, Central, and Cross Sensitization in Endometriosis-Associated Pain and Comorbid Pain Syndromes. Front Reprod Health. 2021;3:729642. doi: 10.3389/frph.2021.729642.

20. Zheng P, Zhang W, Leng J, Lang J. Research on central sensitization of endometriosis-associated pain: a systematic review of the literature. J Pain Res. 2019;12:1447–1456. doi: 10.2147/JPR.S197667.

21. Quiñones M, Urrutia R, Torres-Reverón A, Vincent K, Flores I. Anxiety, coping skills and hypothalamus-pituitary-adrenal (HPA) axis in patients with endometriosis. J Reprod Biol Health. 2015;3:2. doi: 10.7243/2054-0841-3-2.

22. Ortiz R, Gemmill JAL, Sinaii N, Stegmann B, Khachikyan I, Chrousos G, et al. Hypothalamic-Pituitary-Adrenal Axis Responses in Women with Endometriosis-Related Chronic Pelvic Pain. Reprod Sci. 2020;27(10):1839–1847. doi: 10.1007/s43032-020-00201-x.

23. Petrelluzzi KF, Garcia MC, Petta CA, Grassi-Kassisse DM, Spadari-Bratfisch RC. Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. Stress. 2008;11(5):390–397. doi: 10.1080/10253890701840610.

24. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 2022;23(3):333–355. doi: 10.1007/s11154-021-09666-w.

25. Habib N, Buzzaccarini G, Centini G, Moawad GN, Ceccaldi PF, Gitas G, et al. Impact of lifestyle and diet on endometriosis: a fresh look to a busy corner. Prz Menopauzalny. 2022;21(2):124–132. doi: 10.5114/pm.2022.116437.

26. Rahmioglu N, Mortlock S, Ghiasi M, Møller PL, Stefansdottir L, Galarneau G, et al. The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. Nat Genet. 2023;55(3):423–436. doi: 10.1038/s41588-023-01323-z.

27. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011;96(2):366–373.e8. doi: 10.1016/j.fertnstert.2011.05.090.

28. Mortlock S, Corona RI, Kho PF, Pharoah P, Seo JH, Freedman ML, et al. A multi-level investigation of the genetic relationship between endometriosis and ovarian cancer histotypes. Cell Rep Med. 2022;3(3):100542. doi: 10.1016/j.xcrm.2022.100542.

29. Barnard ME, Farland LV, Yan B, Wang J, Trabert B, Doherty JA, et al. Endometriosis Typology and Ovarian Cancer Risk. JAMA. 2024;332(6):482–489. doi: 10.1001/jama.2024.9210.

30. Terzic M, Aimagambetova G, Kunz J, Bapayeva G, Aitbayeva B, Terzic S, et al. Molecular Basis of Endometriosis and Endometrial Cancer: Current Knowledge and Future Perspectives. Int J Mol Sci. 2021;22(17):9274. doi: 10.3390/ijms22179274.

31. Adilbayeva A, Kunz J. Pathogenesis of Endometriosis and Endometriosis-Associated Cancers. Int J Mol Sci. 2024;25(14):7624. doi: 10.3390/ijms25147624.

32. Králíčková M, Losan P, Vetvicka V. Endometriosis and cancer. Womens Health (Lond). 2014;10(6):591–597. doi: 10.2217/whe.14.43.

33. Ye J, Peng H, Huang X, Qi X. The association between endometriosis and risk of endometrial cancer and breast cancer: a meta-analysis. BMC Womens Health. 2022;22(1):455. doi: 10.1186/s12905-022-02028-x.

34. Di Spiezio Sardo A, Becker CM, Renner SP, Suvitie PA, Tarriel JE, Vannuccini S, et al. Management of women with endometriosis in the 21st century. Curr Opin Obstet Gynecol. 2025;37(3):149–157. doi: 10.1097/GCO.0000000000001027.

35. Steinbuch SC, Lüß AM, Eltrop S, Götte M, Kiesel L. Endometriosis-Associated Ovarian Cancer: From Molecular Pathologies to Clinical Relevance. Int J Mol Sci. 2024;25(8):4306. doi: 10.3390/ijms25084306.

36. Stilley JA, Birt JA, Sharpe-Timms KL. Cellular and molecular basis for endometriosis-associated infertility. Cell Tissue Res. 2012;349(3):849–862. doi: 10.1007/s00441-011-1309-0.