International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

The Interplay Between Estrogen, Immune Dysfunction, and Chronic Inflammation in the Pathophysiology of Endometriosis: A Critical Narrative Review

Swarali Shinde

Date of Submission: 01-10-2026 Date of Acceptance: 11-10-2026

Abstract
Endometriosis is a chronic, estrogen-dependent inflammatory disorder affecting approximately ten percent of reproductive-age women worldwide. Despite its high prevalence and profound impact on quality of life, the biological mechanisms that sustain and amplify the disease remain incompletely understood. This critical narrative review synthesises peer-reviewed evidence published predominantly between 2013 and 2026 to examine how estrogen signalling, immune cell dysfunction, and peritoneal inflammation form a self-amplifying pathological circuit in endometriosis. Ovarian and locally synthesised estrogen acts through genomic receptors, particularly estrogen receptor beta (ERbeta), to confer apoptosis resistance upon ectopic stromal cells and to drive macrophage recruitment via the NF-kappaB/CCL2 axis. Phenotypically altered peritoneal macrophages, expanded regulatory T cells, functionally impaired natural killer cells, and activated mast cells collectively sustain an immune-tolerant microenvironment in which ectopic lesions survive and proliferate. The resulting inflammatory milieu, characterised by elevated interleukin-6, interleukin-8, tumour necrosis factor-alpha, and prostaglandin E2, feeds back to stimulate aromatase (CYP19A1) expression in ectopic tissue, thereby completing a self-reinforcing loop. Epigenetic silencing of ERalpha and progesterone receptor genes prevents effective progesterone-mediated immune regulation and further entrenches the disease. Current hormonal treatments interrupt individual nodes of this circuit but rarely achieve durable remission. Emerging evidence supports multi-target approaches incorporating Janus kinase inhibitors, natural compounds, and immunomodulatory strategies. This review offers a unified mechanistic framework to guide future research into biomarker discovery and therapeutics for endometriosis.

Keywords: endometriosis, estrogen signalling, immune dysfunction, chronic inflammation, regulatory T cells, natural killer cells, macrophage polarisation, aromatase, COX-2, therapeutic targets, narrative review

I. Introduction

Endometriosis is defined by the presence and growth of functional endometrial-like tissue outside the uterine cavity, most commonly on pelvic peritoneum, ovaries, and rectovaginal septum. Globally, the disorder affects an estimated 190 million women of reproductive age, representing roughly one in ten across all demographics and ethnicities (Mariadas et al., 2025). Its hallmark symptoms, including dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility, impose a substantial burden on individual wellbeing and healthcare systems alike. Yet the average time between symptom onset and confirmed diagnosis remains between seven and ten years, largely because the gold standard, laparoscopy with histological biopsy, is invasive and not routinely offered early in clinical pathways (Signorile et al., 2021). Recent cohort data further indicate that women with confirmed endometriosis carry elevated risk of premature mortality, principally from cardiovascular and autoimmune-related causes, underscoring that the disease extends well beyond pelvic anatomy (Wang et al., 2024).

Pathophysiological understanding has evolved considerably since Sampson first described retrograde menstruation as the probable mechanism of lesion seeding in the 1920s. It is now recognised that retrograde menstruation is nearly universal, occurring in up to ninety percent of menstruating women, yet clinically significant endometriosis develops in only a fraction of them (Mariadas et al., 2025). This discrepancy points to a failure of immune surveillance rather than an aberration of menstrual flow alone. Three biological pillars, namely estrogen signalling, immune dysfunction, and chronic peritoneal inflammation, do not act independently; they form a mutually reinforcing circuit in which each element amplifies the others. Understanding this circuit is essential for explaining

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

why partial treatments that suppress only one pillar produce incomplete and often temporary benefit.

This review synthesises evidence from the peer-reviewed literature to examine how these three pillars interact at the cellular and molecular level. The focus is deliberately placed on three areas identified in the clinical literature as insufficiently integrated: pathogenesis beyond retrograde menstruation, the estrogen-immune-inflammation feedback loop, and the therapeutic implications of targeting this loop. All references are drawn from verified peer-reviewed sources retrieved via the Semantic Scholar Graph API, spanning from 2010 to 2026, with selected foundational papers predating this window where mechanistic evidence is strong.

II. Pathogenesis: Competing Theories and Converging Evidence

The retrograde menstruation theory, attributed to Sampson (1927), remains the most widely cited explanation for the seeding of ectopic lesions. During menstruation, fragments of viable endometrial tissue reflux through the fallopian tubes and implant on peritoneal surfaces. The theory is supported by the anatomical distribution of lesions, which corresponds to gravitational flow patterns in the peritoneal cavity, and by the higher prevalence of endometriosis in women with anatomical obstructions that increase retrograde flow (Signorile et al., 2021). However, retrograde menstruation alone cannot explain lesions found at thoracic, nasal, and other distant sites, nor can it fully account for endometriosis arising in premenarchal girls or in men receiving estrogen therapy.

Alternative mechanisms include coelomic metaplasia, wherein peritoneal mesothelial cells transform into endometrial-like tissue under hormonal and inflammatory stimuli, and lymphovascular dissemination of endometrial progenitor cells. Mariadas et al. (2025) summarise evidence that endometrial mesenchymal stem cells and epithelial progenitors contribute to lesion establishment by adhering to peritoneal surfaces and differentiating into functional ectopic tissue. Aberrant adhesion molecule expression, including upregulation of integrins and cadherins, facilitates this attachment phase.

Critically, the gating mechanism that determines whether implanted fragments survive or are cleared is immune tolerance. In women without endometriosis, peritoneal macrophages and natural killer (NK) cells efficiently phagocytose and destroy endometrial fragments before they can establish vascular connections. In women who develop the disease, this clearance mechanism is systematically compromised. Genetic predisposition accounts for an estimated forty to fifty percent of disease risk, with endometriosis showing familial aggregation consistent with polygenic inheritance (Mariadas et al., 2025). Epigenetic factors, particularly aberrant DNA methylation at ERalpha and progesterone receptor gene loci, further alter responsiveness to hormonal control and compound immune dysregulation (Ducreux et al., 2025; Koike et al., 2015). Environmental exposures, including persistent organochlorine pollutants studied in the landmark ENDO cohort, add a further layer of susceptibility by disrupting hormonal and immune signalling (Louis et al., 2012).

Endometriosis also displays features characteristic of epithelial-to-mesenchymal transition (EMT), a process in which epithelial cells acquire migratory and invasive mesenchymal properties. Hosseinirad et al. (2025) provide an integrated molecular account of EMT signalling in ectopic lesions, noting that TGF-beta, Wnt/beta-catenin, and Notch pathways all converge on this phenotype. Body mass index also modulates disease expression in ways not yet fully explained: women with lower BMI carry a counterintuitively elevated risk of surgically confirmed disease compared with heavier women, suggesting that adipose tissue-derived estrogen is not the dominant local driver at all disease stages (Rowlands et al., 2022).

III. Estrogen Signalling: Beyond Ovarian Synthesis

Estradiol, primarily 17beta-estradiol (E2), exerts its biological effects through three main receptor systems: nuclear ERalpha, nuclear ERbeta, and the G protein-coupled membrane receptor GPER1. In normal endometrium, ERalpha drives proliferative responses during the follicular phase, while ERbeta and progesterone receptor expression during the secretory phase counterbalance growth with differentiation and secretory activity. In endometriotic stromal cells, this balance is profoundly disrupted. ERalpha is transcriptionally silenced by promoter hypermethylation, whereas ERbeta is markedly upregulated (Han et al., 2019; Rossi et al., 2023). The result is a cell population that is hypersensitive to pro-inflammatory and pro-survival estrogen signals and largely unresponsive to progesterone-mediated anti-inflammatory cues, a state described as progesterone resistance.

The genomic functions of ERbeta in ectopic lesions are broad. Han et al. (2019) characterised the ERbeta cistrome in mouse

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

endometriosis lesions and demonstrated that nuclear ERbeta regulates genes involved in inflammation, cell cycle progression, and apoptosis suppression. Importantly, cytoplasmic ERbeta also translocates to mitochondria, where it confers resistance to oxidative insult-induced apoptosis, effectively allowing ectopic cells to survive the reactive oxygen species-rich peritoneal environment (Liao et al., 2019). Andersen et al. (2018) further showed that shifts in ER subtype expression accompany the progression from endometriosis to endometriosis-associated ovarian cancer, indicating that ERbeta dominance is not merely a feature of established lesions but a driver of disease trajectory.

A critical but underappreciated aspect of estrogen pathophysiology in endometriosis is the local amplification of E2 within ectopic tissue itself. Aromatase (CYP19A1) is essentially absent from normal endometrium but is significantly overexpressed in ectopic stromal cells (Nie et al., 2025). This ectopic aromatase converts adrenal and circulating androgen precursors into E2 at the lesion site, creating a micro-environment of estrogen excess independent of ovarian output. The enzyme HSD11B1 in dendritic cells and stromal cells also modulates local cortisol-to-cortisone balance in ways that indirectly favour lesion persistence (Yang et al., 2024). Local E2 then stimulates cyclooxygenase-2 (COX-2) expression in stromal cells, driving prostaglandin E2 (PGE2) synthesis. PGE2, in turn, activates cAMP-dependent signalling cascades that further upregulate aromatase transcription, completing a positive feedback loop that sustains lesion-level estrogen excess regardless of systemic hormonal suppression (Mariadas et al., 2025).

Epigenetic mechanisms entrench the aberrant ER landscape. Ducreux et al. (2025) conducted a systematic review of DNA methylation in endometriosis and confirmed that differential methylation at ERalpha, progesterone receptor, and HOXA gene loci is a consistent finding across independent cohorts. Erraji et al. (2025) extend this to non-coding RNA regulation, noting that miRNA dysregulation compounds transcriptional changes in ways not captured by DNA methylation profiling alone. Benkhalifa et al. (2025) demonstrated that cell-free circulating DNA carries methylation signatures distinguishable from healthy controls, opening a potential path toward non-invasive epigenetic biomarkers. Shigetomi et al. (2025) place epigenetic changes within the broader p53-AMPK-mTOR signalling axis, arguing that dysregulated decidualization and cellular senescence, both influenced by epigenetic reprogramming, are central to why ectopic cells resist clearance and perpetuate inflammatory signals.

IV. Immune Dysfunction: Mechanisms and Consequences

The peritoneal cavity in endometriosis is not simply an inflammatory space; it is a site of active immune remodelling in which multiple cell types are simultaneously recruited, reprogrammed, and functionally altered in ways that collectively favour lesion survival. Mass cytometry (CyTOF) analysis of peritoneal fluid by Guo et al. (2020) demonstrated a quantitatively and phenotypically distinct immune environment in endometriosis patients compared with controls, with elevated proportions of activated macrophages, altered T cell subsets, and reduced effector NK cell fractions. This comprehensive cellular characterisation was carried out in a well-controlled clinical study and remains one of the most informative single datasets in the field.

NK cells represent the first line of defence against ectopic implantation. In the normal peritoneal cavity, NK cells recognise and kill autologous endometrial fragments through perforin and granzyme-B cytotoxicity. In women with endometriosis, peritoneal NK cells are numerically reduced, and their cytotoxic capacity is significantly impaired. Kang et al. (2014) identified IL-6, which is abundantly elevated in endometriosis peritoneal fluid, as a key suppressor of NK cell activity, acting through upregulation of the phosphatase SHP-2 in NK cells and thereby dampening activating receptor signalling. This NK cell suppression is not a bystander phenomenon; it is a mechanistically driven consequence of the inflammatory cytokine milieu generated by the lesions themselves, creating a self-protective environment for ectopic tissue. Kang et al. (2023) further showed that IL-17A produced by Th17 cells in peritoneal fluid inhibits NK cell-mediated cytotoxicity of endometrial cells through the ERK1/2 pathway, adding a second T cell-mediated brake on innate cytotoxic capacity.

Regulatory T cells (Tregs) are expanded in the peritoneal fluid of women with endometriosis, and this expansion correlates with disease stage. Wei et al. (2016) identified the estrogen-IDO1-MRC2 axis as a mechanistic explanation for Treg expansion in endometriosis. Elevated peritoneal E2 activates indoleamine 2,3-dioxygenase 1 (IDO1) in macrophages, which catabolises tryptophan into kynurenine, a metabolite known to promote naive T cell conversion into Foxp3-positive Tregs. This

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

estrogen-driven immunosuppression elegantly links the hormonal environment directly to the suppression of anti-lesion immunity without requiring any intrinsic T cell defect.

Peritoneal macrophages in endometriosis undergo a phenotypic shift from pro-inflammatory M1-like to anti-inflammatory M2-like polarisation. Gou et al. (2019) showed that ERbeta in ectopic stromal cells drives CCL2 (MCP-1) secretion via NF-kappaB signalling, actively recruiting macrophages into the peritoneal cavity. Once recruited, these macrophages adopt a phenotype characterised by impaired phagocytic capacity. Lei et al. (2024) traced this phagocytic failure to decreased haematopoietic cellular kinase (HCK) expression, attributable to high local estrogen and hypoxia, which in turn disrupts glutamine metabolism and autophagy in macrophages. Zhong et al. (2026) identified a complementary mechanism: ectopic stromal cells secrete itaconate, which is internalised by peritoneal macrophages and activates NRF2 signalling to suppress pro-inflammatory macrophage activity and phagocytosis. Xue et al. (2024) demonstrated that miR-196b-5p regulates macrophage polarisation in endometriosis lesions at the post-transcriptional level, providing yet another layer of macrophage reprogramming. Gut microbiota further influence macrophage phenotype: Xu et al. (2025) showed that microbiota-derived acetate ameliorates experimental endometriosis by promoting M1 macrophage polarisation through the JAK1/STAT3 pathway, a finding that connects intestinal dysbiosis to disease severity.

Mast cells have emerged as unexpectedly important contributors to endometriosis pathophysiology, particularly with respect to pain. Makoui et al. (2025) review evidence that mast cell density is increased in endometriotic lesions and that mast cell ablation reduces lesion size and inflammatory markers in murine models. Mao et al. (2025) identified MRGPRX2, a mast cell surface receptor, as a mediator of endometriosis-associated pain through histamine release and downstream TRPV1 sensitisation in sensory neurons. Wang et al. (2025) integrate this with estrogen biology, demonstrating that E2 directly activates mast cells within lesions, driving release of histamine and fibroblast growth factor 2 (FGF2), which in turn enhances peripheral pain signalling and promotes central sensitisation. Mast cells also contribute to lesion establishment via CCL2/CCR4-mediated epithelial-mesenchymal transition in endometrial epithelial cells (Ding et al., 2025). Golinska et al. (2025) draw these observations into a neuroinflammatory model of endometriosis pain, arguing that mast cell activation and JAK-STAT signalling at the lesion-nerve interface are the primary mediators of chronic pain in this disease. Small extracellular vesicles (sEVs) released from ectopic lesions add another dimension: Wang et al. (2026) showed that endometriotic sEVs significantly impair macrophage function within the peritoneal microenvironment, extending lesion influence to distant immune cells via paracrine vesicular signalling.

V. Inflammatory Mediators and the Peritoneal Microenvironment

The peritoneal fluid of women with endometriosis contains a characteristic inflammatory signature that differs both qualitatively and quantitatively from controls. Wójtowicz et al. (2025) performed a comprehensive multi-compartment analysis, measuring TNF-alpha, IL-6, and IL-8 simultaneously in plasma, peritoneal fluid, and endometrioma fluid of fifty-six women who underwent surgery for ovarian endometriosis. All three compartments showed significantly elevated cytokine concentrations, confirming that the inflammatory process is neither confined to the peritoneal cavity nor fully reflected by systemic serum measurements. Krasnyi et al. (2019) provided an important nuance: IL-6, IL-8, and TNF-alpha were elevated in women with mild endometriosis (stages I and II) but did not differ from controls in advanced stages (III and IV), suggesting that the cytokine signature reflects active immunological engagement rather than cumulative disease burden, and that advanced disease may represent a state of immune exhaustion rather than escalating activity.

Chemokine gradients are central to the peritoneal recruitment of immune cells and to the establishment of lesions. Borrelli et al. (2015) found that combined measurement of MCP-1 (CCL2) and MIP-3beta alongside IL-8 in peritoneal fluid substantially improved discriminatory accuracy for endometriosis compared with IL-8 alone. Wickström et al. (2017) demonstrated that lignocaine treatment of peritoneal macrophages and endometriotic stromal cells reduces IL-6, IL-8, and MCP-1 secretion, providing a mechanistic basis for analgesia-adjacent anti-inflammatory strategies. Rakhila et al. (2016) characterised an angiogenic and proliferative cytokine pattern in peritoneal fluid, including elevated vascular endothelial growth factor (VEGF), hepatocyte growth factor, and epidermal growth factor, indicating that the

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

peritoneal environment is pre-conditioned to support vascular growth required for lesion implantation. Kamrani et al. (2022) corroborated elevated VEGF expression in endometrial tissue with epigenetic regulation of the H19 lncRNA locus, which modulates IGF2 and further feeds angiogenesis.

Oxidative stress is both a product and a driver of peritoneal inflammation in endometriosis. Campara et al. (2025) conducted a systematic review and meta-analysis of advanced oxidation protein products (AOPPs) across serum, peritoneal fluid, follicular fluid, and endometrioma tissue, confirming significantly elevated AOPP levels in women with endometriosis and a positive correlation with disease stage. AOPPs are markers of protein oxidation by reactive oxygen species and themselves trigger further inflammatory signalling through RAGE and NF-kappaB pathways. Complement system activation contributes an additional inflammatory axis: Agostinis et al. (2024) showed that the first component of classical complement, C1q, is present at elevated levels in endometriosis and exerts proangiogenic effects that support lesion vascularisation, linking innate immune activation directly to lesion growth. Gawron et al. (2025) found that pelvic endometriosis correlates significantly with chronic endometritis in eutopic endometrium, measured by CD138-positive plasma cell infiltration, implying that the inflammatory profile extends into the uterine mucosa and may compromise endometrial receptivity in infertile patients.

VI. The Estrogen-Immune-Inflammation Feedback Loop: A Unified Circuit

The three pillars discussed above do not operate as parallel but distinct pathways; they form a closed, self-amplifying circuit at whose centre sits the ectopic lesion. Understanding this circuit architecture has direct implications for why single-mechanism treatments produce incomplete remission and why the disease recurs at high rates following cessation of medical therapy.

The circuit initiates with estrogen, which acts on ectopic stromal cells through ERbeta to suppress apoptosis and promote inflammatory gene transcription. ERbeta drives NF-kappaB-dependent CCL2 production, recruiting monocytes and macrophages to the peritoneal cavity (Gou et al., 2019). Once present, these macrophages are reprogrammed toward an M2-like state by ectopic cell-derived itaconate and sEVs, losing their phagocytic capacity while continuing to produce pro-survival factors including VEGF and TGF-beta (Zhong et al., 2026; Wang et al., 2026). Simultaneously, elevated peritoneal IL-6 derived from both macrophages and stromal cells suppresses NK cell cytotoxicity, and estrogen-driven IDO1 activation in macrophages converts the tryptophan metabolome toward kynurenine, promoting Treg differentiation from naive CD4-positive T cells (Wei et al., 2016; Kang et al., 2014). The net immunological outcome is a peritoneal cavity that is numerically replete with immune cells but functionally incapable of clearing ectopic tissue.

The inflammation generated by this immune-tolerant environment feeds back on estrogen synthesis through at least two mechanisms. First, PGE2 produced by COX-2-expressing stromal cells activates cAMP-protein kinase A signalling that transcriptionally upregulates CYP19A1 (aromatase) in ectopic stroma. This increases local E2 production and closes the COX-2/PGE2/aromatase loop identified as a central mechanistic axis by multiple research groups (Mariadas et al., 2025). Second, IL-6, IL-8, and TNF-alpha amplify NF-kappaB and MAPK signalling in stromal cells, further inducing COX-2 and suppressing apoptotic gene programmes (Krasnyi et al., 2019). The dual role of IL-6, suppressing NK immunity from above and amplifying aromatase from below, positions it as a particularly consequential node in the circuit and an attractive therapeutic target.

Mast cells add a neurogenic dimension to the loop. Activated by estrogen and by histamine from prior mast cell degranulation, they sensitise peripheral nociceptors through MRGPRX2-histamine-TRPV1 signalling (Mao et al., 2025). This neurogenic inflammation promotes further release of substance P and calcitonin gene-related peptide from sensory nerve terminals in lesions, which in turn degranulate additional mast cells. Golinska et al. (2025) describe this as a neuroinflammatory loop at the lesion-nerve interface, separate from but additive to the estrogen-macrophage-cytokine loop at the peritoneal level. The consequence is a multi-layer self-reinforcing system that is difficult to interrupt with any single pharmacological agent.

Epigenetic remodelling locks these circuits into a heritable phenotypic state. Aberrant DNA methylation silencing ERalpha and the progesterone receptor prevents cells from responding to progesterone-mediated anti-proliferative and anti-inflammatory signals (Rossi et al., 2023; Erraji et al., 2025). This epigenetic progesterone resistance means that even endogenous progesterone elevation,

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

as occurs in the luteal phase, fails to suppress lesion activity, and that progestin pharmacotherapy works only partially. The recognition of epigenetic entrenchment offers a rationale for combining DNA methyltransferase modulation with hormonal therapy, though clinical evidence for this approach remains preliminary.

VII. Therapeutic Targets: Current Evidence and Emerging Directions

The cornerstone of medical management in endometriosis remains hormonal suppression of ovarian estrogen production, on the premise that reducing systemic E2 will starve lesions of their primary growth stimulus. Gonadotropin-releasing hormone (GnRH) agonists achieve profound hypoestrogenaemia but carry side effects of iatrogenic menopause including bone loss, vasomotor symptoms, and mood disturbance when used beyond six months. Oral GnRH antagonists, such as elagolix and relugolix, allow dose-titratable suppression with a more favourable side effect profile. Taylor et al. (2022) describe an ongoing RCT assessing whether GnRH antagonist pre-treatment before in vitro fertilisation improves pregnancy rates in endometriosis-associated infertility, addressing a clinically pressing but previously understudied question.

Progestin therapy, particularly dienogest at 2 mg daily, has accumulated a substantial evidence base. Ceccaroni et al. (2021) conducted a prospective RCT in 146 women following laparoscopic eradication of deep infiltrating endometriosis, randomising participants to postoperative triptorelin or leuprorelin versus dienogest for at least six months. Both regimens were effective, with dienogest showing comparable efficacy and a tolerability advantage. Niakan et al. (2021) found dienogest and oral contraceptive pills to be similarly effective for pain and quality of life in severe endometriosis, though the population receiving dienogest reported fewer breakthrough bleeding episodes. Dick et al. (2025) performed a systematic review, meta-analysis, and network meta-analysis of GnRH analogues and dienogest for pain, concluding that oral GnRH antagonists and dienogest produce comparable reductions in dysmenorrhea and chronic pelvic pain, with the choice between them appropriately guided by individual patient factors. Gurbuz et al. (2025) compared norethindrone acetate (5 mg daily) with dienogest (2 mg daily) in a single-centre RCT and found similar visual analogue scale pain reductions at twelve months, with marginally better tolerability for dienogest. Servidoni et al. (2025) provide a post-surgical meta-analysis confirming that both dienogest and GnRH agonists reduce recurrence and pain after excisional surgery, with no statistically significant superiority for either agent in most outcome categories.

Anti-angiogenic strategies target VEGF, the primary driver of lesion vascularisation. Bouquet de Jolinière et al. (2021) published the first human case report of bevacizumab use in severe endometriosis, demonstrating lesion regression after three doses of the VEGF-neutralising antibody. While anecdotal, the case demonstrates biological proof-of-concept. Kamrani et al. (2022) and Rakhila et al. (2016) provide mechanistic grounding for VEGF as a therapeutic target, given its consistent elevation in peritoneal fluid and its coexpression with proliferative cytokines. Okten et al. (2023) demonstrated that cannabidiol exerts anti-inflammatory, antioxidant, and anti-angiogenic effects in a rat model of endometriosis, reducing lesion volume and VEGF expression, and suppressing COX-2 activity, offering a natural compound rationale for further clinical study.

JAK-STAT pathway inhibition has attracted interest because of its ability to simultaneously suppress IL-6, IL-8, and interferon-gamma signalling, three cytokines central to the inflammatory milieu and to mast cell activation in endometriosis. Golinska et al. (2025) argue from mechanistic evidence that JAK inhibitors could interrupt both the peritoneal cytokine cascade and the neuroinflammatory pain loop at the lesion-nerve interface. Xu et al. (2025) further showed that gut microbiota-derived acetate reduces lesion size via JAK1/STAT3-dependent M1 macrophage repolarisation, suggesting that microbiome modulation may achieve indirect JAK-STAT inhibition with a more favourable safety profile. Among adjunctive strategies, Sargazi-taghazi et al. (2025) published the first RCT of curcumin added to dienogest in endometriosis, finding improvements in pain relief and quality of life attributable to curcumin anti-inflammatory and antioxidant activity. Esmaeilzadeh et al. (2025) conducted a triple-blind RCT of melatonin supplementation (5 mg nightly) in infertile women with endometriosis, demonstrating improvements in sleep quality and pelvic pain scores, consistent with melatonin anti-inflammatory and anti-proliferative properties in ectopic tissue. Exercise-based multimodal programmes also show promise: Salinas-Asensio et al. (2025) reported that a nine-week supervised exercise intervention improved fatigue, mental

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

health, sleep, and gastrointestinal complaints in women with endometriosis unresponsive to conventional therapy.

VIII. Key Human Studies: Evidence Base and Clinical Translations

Several landmark human studies anchor the mechanistic narrative above in clinical observation. Alkatout et al. (2013) published a prospective RCT demonstrating that combined surgical and hormonal therapy yielded superior outcomes to either modality alone in terms of pain relief and recurrence rate, establishing the combination approach as the standard of care in surgical candidatesI. Guo et al. (2020) applied mass cytometry to peritoneal fluid and peripheral blood from patients with and without endometriosis in a characterisation study, providing the most comprehensive single-cell immune atlas of peritoneal endometriosis available and confirming distinct immune signatures including NK cell depletion and macrophage accumulation. Nazri et al. (2020) characterised exosomal cargo from peritoneal fluid of endometriosis patients, finding differentially expressed proteins and miRNAs in endometriosis versus control exosomes, which opens possibilities for non-invasive liquid biopsy diagnostics. Louis et al. (2012) used the ENDO study design to identify associations between persistent lipophilic environmental chemicals and endometriosis diagnosis in a matched cohort of laparoscopy patients, affirming that environmental exposures contribute to disease susceptibility at a population level.

Nirgianakis et al. (2020) measured multiple peritoneal fluid biomarkers in one of the largest single-centre cross-sectional studies of this type, involving patients undergoing laparoscopic procedures for benign pathology between 2007 and 2018. Their findings confirmed menstrual cycle dependence of biomarker concentrations, which partially explains the inconsistency in published biomarker data when cycle phase is not controlled. Laudański et al. (2023) conducted a systematic screen for autoantibodies in plasma and peritoneal fluid of endometriosis patients and found no significantly higher prevalence than controls, indicating that overt autoimmunity is not a universal feature of the disease, though localised immune dysregulation clearly is. Signorile et al. (2021) reviewed retrospective data from 4,401 patients, the largest single-centre dataset in the recent literature, characterising the topographic distribution of lesions and associated conditions, and confirming the high burden of deep infiltrating disease and co-morbid adenomyosis. Wang et al. (2024) extended the disease scope through a prospective cohort study in 110,091 women from the Nurses Health Study II, finding that laparoscopically confirmed endometriosis was associated with significantly elevated hazard ratios for premature mortality before age seventy, particularly from cardiovascular and autoimmune causes, which has profound implications for long-term follow-up and patient counselling.

IX. Discussion and Conclusion

The evidence reviewed here supports a model of endometriosis in which estrogen, immune dysfunction, and peritoneal inflammation are not parallel processes but a tightly coupled feedback circuit. Each arm of this circuit both sustains and is sustained by the others, which explains several clinical observations that had previously resisted satisfactory mechanistic account: the incomplete and often temporary response to hormonal suppression alone; the lack of correlation between disease stage and pain severity in some patients; the high post-surgical recurrence rate when medical therapy is not continued; and the growing recognition of systemic consequences including cardiovascular risk.

Several limitations of the current evidence base warrant acknowledgement. First, much of the mechanistic work is conducted in murine models or in vitro cell cultures that may not fully recapitulate the complex human peritoneal microenvironment. Second, the composition and functional state of peritoneal immune cells vary considerably with menstrual cycle phase, a confound that is inconsistently controlled in the published literature (Nirgianakis et al., 2020). Third, the epigenetic studies are largely cross-sectional and cannot yet resolve whether methylation changes precede disease establishment or arise as a consequence of chronic inflammation. Fourth, emerging therapies such as JAK inhibitors, cannabidiol, and microbiome modulation are supported by preclinical and early clinical data but lack the large RCT evidence base required for clinical adoption.

Future research directions should prioritise multi-target therapeutic trials designed around the feedback circuit model, enrolling patients stratified by immune phenotype and epigenetic status. Biomarker development, including non-invasive epigenetic liquid biopsy (Benkhalifa et al., 2025) and peritoneal exosome profiling (Nazri et al., 2020), offers a path toward reducing the diagnostic delay that currently allows disease to progress for years undetected. Understanding how gut

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

microbiota composition influences peritoneal immune tone (Xu et al., 2025) may reveal dietary and probiotic interventions as accessible, low-cost adjuncts to pharmacological management. Collectively, closing the mechanistic gaps between estrogen, immunity, and inflammation in endometriosis represents one of the most consequential research priorities in reproductive medicine.

Tables

Table 1

Key Inflammatory Mediators in Endometriosis Peritoneal Fluid

Table 1 presents the principal inflammatory mediators identified in the peritoneal fluid of women with endometriosis. For each mediator, the table specifies its normal biological role, the quantitative or qualitative finding reported in the endometriosis literature, and the primary study from which the finding is drawn. Collectively, this profile illustrates the shift toward a pro-inflammatory, pro-angiogenic, and oxidatively stressed peritoneal environment that characterises the disease.

Mediator	Biological Role	Finding in Endometriosis	Key Study
IL-6	Pleiotropic cytokine; acute-phase response	Elevated in peritoneal fluid; suppresses NK cell activity via SHP-2	Kang et al. (2014); Krasnyi et al. (2019)
IL-8 (CXCL8)	Neutrophil chemotaxis; angiogenesis	Elevated in peritoneal fluid and endometrioma fluid	Wójtowicz et al. (2025); Borrelli et al. (2015)
TNF-alpha	Pro-inflammatory; promotes COX-2 and aromatase	Elevated at stages I-II; correlates with mild disease	Krasnyi et al. (2019); Wójtowicz et al. (2025)
MCP-1 (CCL2)	Macrophage and monocyte recruitment	Elevated in peritoneal fluid; improves endometriosis diagnosis accuracy	Borrelli et al. (2015); Gou et al. (2019)
PGE2 (COX-2 product)	Vasodilation; aromatase stimulation; angiogenesis	Upregulated in ectopic lesions via COX-2 overexpression	Mariadas et al. (2025)
VEGF	Vascular endothelial growth; lesion implantation	Consistently elevated in peritoneal fluid; drives neoangiogenesis	Rakhila et al. (2016); Kamrani et al. (2022)
Complement C1q	Classical complement activation; angiogenesis	Proangiogenic role confirmed in endometriotic tissue	Agostinis et al. (2024)
AOPP	Oxidative stress marker; NF-kappaB activator	Significantly elevated across serum, peritoneal, and endometrioma fluid	Campara et al. (2025)

Table 2

Immune Cell Population Alterations in Endometriosis

Table 2 summarises the six principal immune cell populations affected in endometriosis, contrasting their normal peritoneal function against the specific alterations documented in the disease. The underlying molecular mechanism for each alteration is noted alongside the key primary source. Taken together, these alterations describe a coordinated immune failure rather than a single-cell defect: multiple lineages are simultaneously reprogrammed to permit ectopic lesion survival.

Cell Type	Normal Peritoneal Role	Alteration in Endometriosis	Mechanism	Key Study
NK Cells	Cytotoxic clearance of	Reduced number; impaired	IL-6-mediated SHP-2 upregulation; Th17/IL-	Kang et al. (2014, 2023)

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

	ectopic fragments	cytotoxicity	17A-ERK1/2 brake	
Peritoneal Macrophages	Phagocytosis of debris; immune surveillance	M2-like polarisation; impaired phagocytosis	Itaconate-NRF2 axis; HCK/glutamine disruption; miR-196b-5p	Lei et al. (2024); Zhong et al. (2026); Xue et al. (2024)
Regulatory T Cells (Tregs)	Peripheral tolerance	Expanded; stage-correlated	Estrogen-IDO1-kynurenine axis promotes naive T-cell conversion	Wei et al. (2016)
Th17 Cells / IL-17A	Mucosal immunity	Elevated in peritoneal fluid	Inhibit NK cytotoxicity via ERK1/2; promote cell survival	Kang et al. (2023)
Mast Cells	Allergic and innate responses	Increased density in lesions	Estrogen activation; MRGPRX2-histamine-TRPV1 pain loop; CCL2/CCR4-EMT	Mao et al. (2025); Ding et al. (2025); Wang et al. (2025)
Dendritic Cells	Antigen presentation; adaptive immunity	HSD11B1 overexpression inhibits DC maturation	Disrupted antigen presentation reduces adaptive cytotoxic response	Yang et al. (2024)

Table 3
Estrogen Signalling Pathways and Epigenetic Alterations in Endometriosis
Table 3 maps the molecular disruptions in estrogen signalling and epigenetic regulation that distinguish ectopic endometrial tissue from normal endometrium. Each row identifies a pathway or molecule, describes its role in healthy tissue, documents how it is dysregulated in endometriosis, and specifies the downstream functional consequence. The table makes explicit the mechanistic linkage between ERbeta upregulation, aromatase overexpression, and the COX-2/PGE2 positive feedback loop that is central to this review.

Pathway / Molecule	**Normal Function**	**Dysregulation in Endometriosis**	**Consequence**	**Key Study**
ERbeta (ESR2)	Differentiation; anti-proliferative balance	Markedly upregulated in ectopic stromal cells	Anti-apoptotic signalling; pro-inflammatory gene expression	Han et al. (2019); Liao et al. (2019)
ERalpha (ESR1)	Proliferation; E2 responsiveness	Silenced by promoter hypermethylation	Loss of normal proliferative control; progesterone resistance	Rossi et al. (2023); Nie et al. (2025)
Aromatase (CYP19A1)	Ovarian androgen-to-estrogen conversion	Ectopically overexpressed in stromal cells	Local E2 amplification independent of ovarian output	Mariadas et al. (2025); Nie et al. (2025)
COX-2/PGE2/cAMP	Inflammatory mediator production	Upregulated; PGE2 stimulates aromatase via cAMP-PKA	Positive feedback loop sustaining ectopic estrogen excess	Mariadas et al. (2025)
Progesterone Receptor (PGR)	Anti-proliferative; secretory differentiation	Silenced by DNA methylation	Progesterone resistance; reduced progestin therapy response	Rossi et al. (2023); Ducreux et al. (2025)
DNA methylation (DNMT3A/B)	Gene silencing; chromatin	Aberrant at ERalpha, PGR,	Irreversible epigenetic	Ducreux et al. (2025); Koike et

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

	organisation	HOXA loci	entrenchment of disease phenotype	al. (2015)
miRNA dysregulation	Post-transcriptional regulation	Multiple miRNAs altered in ectopic tissue	Compounds transcriptional changes; macrophage polarisation affected	Erraji et al. (2025); Xue et al. (2024)

Table 4

Therapeutic Targets and Evidence Summary in Endometriosis

Table 4 catalogues the therapeutic agents and strategies reviewed in Section 7, organising them by mechanism of action, the level of clinical evidence available, the key finding from the most relevant study, and the primary citation. The range of evidence levels, from large randomised controlled trials supporting progestins and GnRH agents to single case reports and murine studies supporting emerging candidates such as bevacizumab and cannabidiol, reflects the uneven maturity of the therapeutic evidence base and identifies where future trial investment is most warranted.

Agent / Strategy	Mechanism	Evidence Level	Key Finding	Study
Dienogest (2 mg/day)	Progestin; suppresses ovarian E2, reduces inflammation	Multiple RCTs	Comparable to GnRH agonists; superior tolerability profile	Ceccaroni et al. (2021); Dick et al. (2025)
GnRH Agonists / Antagonists	Suppresses GnRH; induces hypoestrogenaemia	RCTs; meta-analyses	Effective for pain; oral antagonists allow dose titration	Dick et al. (2025); Taylor et al. (2022)
Norethindrone Acetate (NETA)	Progestin; endometrial atrophy	RCT (12-month)	Similar pain reduction to dienogest; slightly lower tolerability	Gurbuz et al. (2025)
Levonorgestrel-IUS	Local progestin release; endometrial suppression	RCT	Reduces endometrioma recurrence post-operatively	Chen et al. (2017)
Bevacizumab (anti-VEGF)	VEGF neutralisation; anti-angiogenic	Case report (n=1)	Lesion regression confirmed; RCT needed	Bouquet de Jolinière et al. (2021)
JAK Inhibitors	JAK-STAT pathway blockade; reduces IL-6, IL-8, IFN-gamma	Preclinical; emerging trials	Targets cytokine loop and mast cell activation; pain pathway	Golinska et al. (2025)
Gut Microbiota Modulation / Acetate	JAK1/STAT3-mediated M1 macrophage repolarisation	Murine model	Acetate reduces lesion size and inflammatory markers	Xu et al. (2025)
Cannabidiol (CBD)	Anti-inflammatory; antioxidant; anti-angiogenic	Rat model RCT	Reduces lesion volume, VEGF expression, COX-2 activity	Okten et al. (2023)
Curcumin (adjunct to dienogest)	NF-kappaB inhibition; antioxidant; anti-proliferative	RCT	Improved pain relief and quality of life vs dienogest alone	Sargazi-taghazi et al. (2025)
Melatonin (5 mg	Anti-	Triple-blind RCT	Improved sleep	Esmaeilzadeh et

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

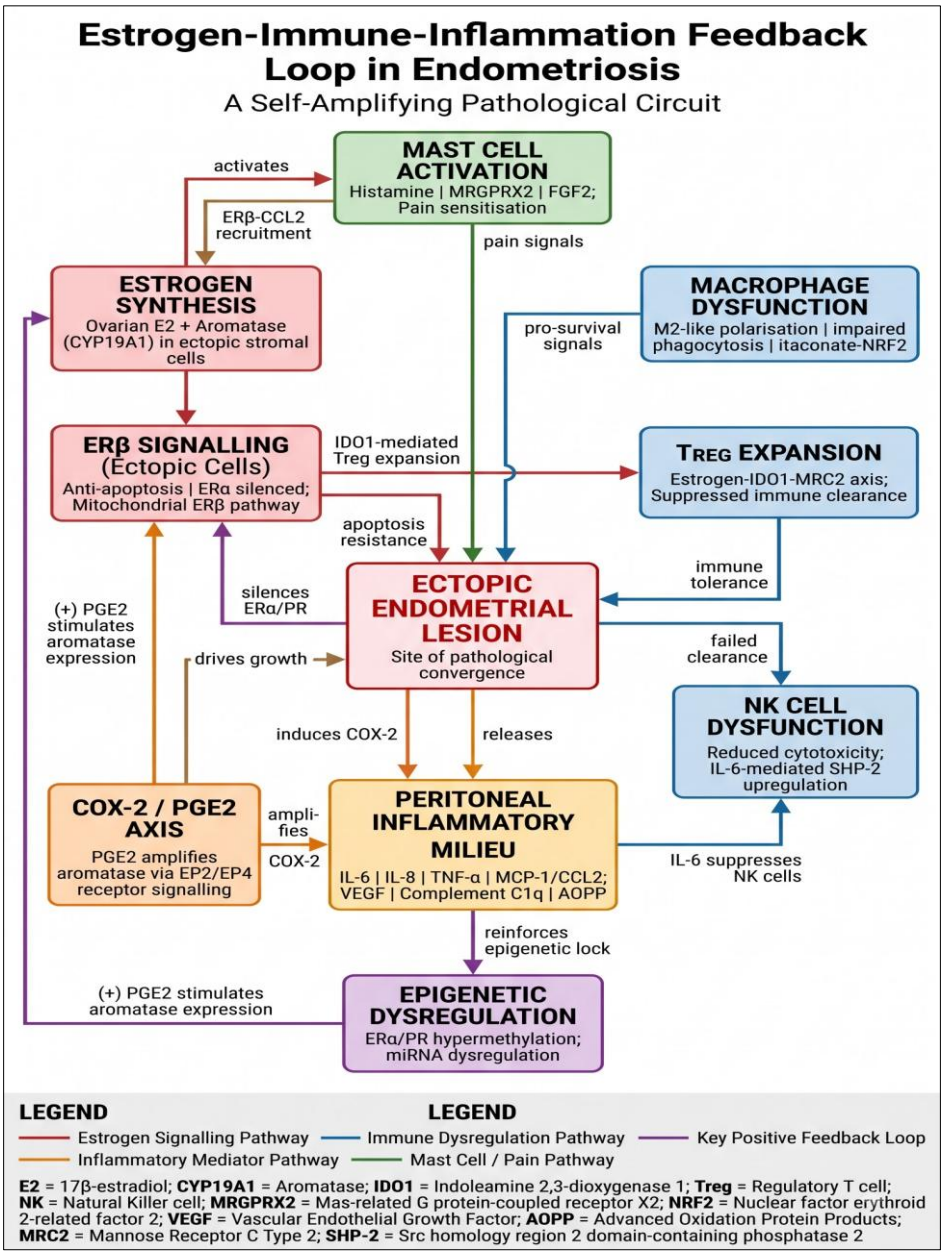
nightly)	inflammatory; antioxidant; anti-proliferative		quality and pelvic pain in infertile women	al. (2025)

Table 5
Key Human Studies in Endometriosis Pathophysiology and Treatment
Table 5 brings together the landmark human studies cited throughout this review, each selected because it either anchors a key mechanistic claim in direct patient data or provides the strongest available clinical evidence for a treatment recommendation. The table records study design, sample characteristics, and the single most important finding for rapid orientation. Notably, sample sizes range from 28 women in the exosome characterisation study by Nazri et al. (2020) to more than 110,000 in the Nurses Health Study II cohort (Wang et al., 2024), illustrating the breadth of evidence informing this review and the heterogeneity in methodological approach that makes synthesising the literature particularly challenging.

Study	Design	Sample	Key Finding
Guo et al. (2020)	CyTOF characterisation study	Peritoneal fluid + blood; endo vs. controls	Distinct peritoneal immune environment confirmed: altered NK, macrophage, T-cell subsets
Wang et al. (2024)	Prospective cohort (Nurses Health Study II, 1989-2019)	110,091 women; 30-year follow-up	Confirmed endometriosis elevated premature mortality risk (cardiovascular, autoimmune causes)
Signorile et al. (2021)	Retrospective cohort	4,401 patients; 584 with laparoscopy	Largest single-centre topographic dataset; co-morbid adenomyosis common
Louis et al. (2012)	Matched cohort (ENDO Study)	Women aged 18-44 at 14 clinical centres	Persistent organochlorine pollutants associated with endometriosis odds
Nirgianakis et al. (2020)	Cross-sectional	Patients at laparoscopy 2007-2018	Peritoneal biomarkers cycle-phase-dependent; no single factor sufficiently specific
Alkatout et al. (2013)	Prospective RCT	Endometriosis patients	Combined surgery + hormone therapy most effective for pain and recurrence
Ceccaroni et al. (2021)	Prospective RCT	146 women with DIE post-surgery	Dienogest non-inferior to GnRH agonists; better tolerability profile
Campara et al. (2025)	Systematic review + meta-analysis	Multiple studies; multiple sample types	AOPP significantly elevated in endometriosis; correlates with disease stage
Nazri et al. (2020)	Experimental (case-control)	28 women at laparoscopy	Peritoneal exosome characterisation feasible; differential miRNA/protein cargo identified
Gawron et al. (2025)	Prospective cohort	Women at laparoscopy for suspected endo	Significant correlation between pelvic endometriosis and chronic endometritis

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

Figure 1
The estrogen-immune-inflammation feedback loop in endometriosis. Ovarian and locally synthesised estradiol (E2) acts via ERbeta to promote ectopic cell survival and CCL2-mediated macrophage recruitment. Phenotypically altered macrophages and expanded regulatory T cells sustain immune tolerance, allowing lesions to persist. Ectopic tissue-derived COX-2 produces PGE2, which stimulates aromatase (CYP19A1) to amplify local E2 production, completing the positive feedback loop. Inflammatory cytokines (IL-6, IL-8, TNF-alpha) further impair NK cell cytotoxicity and drive COX-2 expression. Mast cell activation by E2 adds a neurogenic pain loop at the lesion-nerve interface. Epigenetic silencing of ERalpha and progesterone receptor genes entrench the pathological phenotype.



International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:744-759 www.ijprajournal.com ISSN:2456-4494

References

[1]. Agostinis, C., Toffoli, M., Zito, G., & Balduit, A. (2024). Proangiogenic properties of complement protein C1q can contribute to endometriosis. Frontiers in Immunology, 15, 1405597. https://doi.org/10.3389/fimmu.2024.1405597

[2]. Alkatout, I., Mettler, L., Beteta, C. C., & Hedderich, J. (2013). Combined surgical and hormone therapy for endometriosis is the most effective treatment: Prospective, randomized, controlled trial. Journal of Minimally Invasive Gynecology, 20(4), 479-487. https://doi.org/10.1016/j.jmig.2013.01.019

[3]. Andersen, C., Boisen, M., Sikora, M. J., & Ma, T. (2018). The evolution of estrogen receptor signaling in the progression of endometriosis to endometriosis-associated ovarian cancer. Hormones and Cancer, 9(6), 358-366. https://doi.org/10.1007/s12672-018-0350-9

[4]. Benkhalifa, M., Menoud, P., Piquemal, D., & Hazout, J. Y. (2025). Quantification of free circulating DNA and differential methylation profiling of selected genes as novel non-invasive biomarkers for endometriosis diagnosis. Biomolecules, 15(1), 69. https://doi.org/10.3390/biom15010069

[5]. Borrelli, G., Kaufmann, A., Abrão, M., & Mechsner, S. (2015). Addition of MCP-1 and MIP-3beta to the IL-8 appraisal in peritoneal fluid enhances the probability of identifying women with endometriosis. Journal of Reproductive Immunology, 108, 1-6. https://doi.org/10.1016/j.jri.2015.01.003

[6]. Bouquet de Jolinière, J., Fruscalzo, A., Khomsi, F., & Stochino Loi, E. (2021). Antiangiogenic therapy as a new strategy in the treatment of endometriosis? The first case report. Frontiers in Surgery, 8, 791686. https://doi.org/10.3389/fsurg.2021.791686

[7]. Campara, K., Rodrigues, P., Viero, F. T., & da Silva, B. (2025). A systematic review and meta-analysis of advanced oxidative protein products levels (AOPP) levels in endometriosis: Association with disease stage and clinical implications. European Journal of Pharmacology, 177434. https://doi.org/10.1016/j.ejphar.2025.177434

[8]. Ceccaroni, M., Clarizia, R., Liverani, S., & Donati, A. (2021). Dienogest vs GnRH agonists as postoperative therapy after laparoscopic eradication of deep infiltrating endometriosis with bowel and parametrial surgery: A randomized controlled trial. Gynecological Endocrinology, 37(8), 750-754. https://doi.org/10.1080/09513590.2021.1929151

[9]. Chen, Y.-J., Hsu, T.-F., Huang, B., & Tsai, H. (2017). Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: A randomized controlled study. American Journal of Obstetrics and Gynecology, 216(6), 582.e1-582.e9. https://doi.org/10.1016/j.ajog.2017.02.008

[10]. Dick, A., Matok, I., Gutman-Ido, E., & Lessans, N. (2025). GnRH analogues and dienogest for second line treatment of endometriosis-associated pain: A systematic review, meta-analysis, and network meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 114093. https://doi.org/10.1016/j.ejogrb.2025.114093

[11]. Ding, S., Mao, X., Zhu, L., & Xu, X. (2025). CCL2/CCR4 participates in mast cell-mediated epithelial mesenchymal transition in endometriosis. Reproductive BioMedicine Online, 104796. https://doi.org/10.1016/j.rbmo.2025.104796

[12]. Ducreux, B., Patrat, C., Firmin, J., & Ferreux, L. (2025). Systematic review on the DNA methylation role in endometriosis: Current evidence and perspectives. Clinical Epigenetics, 17, 1-20. https://doi.org/10.1186/s13148-025-01828-w

[13]. Erraji, H., el Ghanmi, A., Louanjli, N., & Benahmed, M. (2025). Leveraging epigenetic aberrations in the pathogenesis of endometriosis: From DNA methylation to non-coding RNAs. Frontiers in Genetics, 16, 1597287. https://doi.org/10.3389/fgene.2025.1597287

[14]. Esmaeilzadeh, S., Habibolahi, F., Moher, D., & Basirat, Z. (2025). Melatonin and sleep parameters in infertile women with endometriosis: First results from the triple-blind randomized controlled trial. PLOS One, 20, e0321635. https://doi.org/10.1371/journal.pone.0321635

[15]. Gawron, I. M., Derbisz, K., Jach, R., & Trojnarska, D. (2025). Pelvic peritoneal endometriosis is linked to the endometrial inflammatory profile: A prospective cohort

study. BMC Women's Health, 25, 113. https://doi.org/10.1186/s12905-025-03632-3

[16]. Golinska, M., Wolyniak, M., Kulesza, P., & Fendler, W. (2025). Neuroinflammation is responsible for pain in endometriosis: Targeting the JAK-STAT pathway and mast cell activation. Frontiers in Immunology, 16, 1621178. https://doi.org/10.3389/fimmu.2025.1621178

[17]. Gou, Y., Li, X., Li, P., & Zhang, H. (2019). Estrogen receptor beta upregulates CCL2 via NF-kappaB signaling in endometriotic stromal cells and recruits macrophages to promote the pathogenesis of endometriosis. Human Reproduction, 34(4), 646-658. https://doi.org/10.1093/humrep/dez019

[18]. Guo, M., Bafligil, C., Tapmeier, T., & Hubbard, C. (2020). Mass cytometry analysis reveals a distinct immune environment in peritoneal fluid in endometriosis: A characterisation study. BMC Medicine, 18(1), 3. https://doi.org/10.1186/s12916-019-1470-y

[19]. Gurbuz, T., Aslan, K., Kasapoglu, I., & Muzii, L. (2025). Norethindrone acetate versus dienogest for pain relief in endometriosis related pain: A randomized controlled trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 113940. https://doi.org/10.1016/j.ejogrb.2025.113940

[20]. Han, S., Lee, J. E., Cho, Y., & Park, M. (2019). Genomic function of estrogen receptor beta in endometriosis. Endocrinology, 160(11), 2495-2516. https://doi.org/10.1210/en.2019-00442

[21]. Heard, M. E., Melnyk, S., Simmen, F., & Yang, Y. (2016). High-fat diet promotion of endometriosis in an immunocompetent mouse model is associated with altered peripheral and ectopic lesion redox and inflammatory status. Endocrinology, 157(7), 2870-2882. https://doi.org/10.1210/en.2016-1092

[22]. Hosseinirad, H., Jeong, J.-W., & Barrier, B. (2025). Insights into the molecular mechanisms and signaling pathways of epithelial to mesenchymal transition (EMT) in the pathophysiology of endometriosis. International Journal of Molecular Sciences, 26(15), 7460. https://doi.org/10.3390/ijms26157460

[23]. Kamrani, S., Amirchaghmaghi, E., Ghaffari, F., & Shahhoseini, M. (2022). Altered gene expression of VEGF, IGFs and H19 lncRNA and epigenetic profile of H19-DMR region in endometrial tissues of women with endometriosis. Reproductive Health, 19(1), 110. https://doi.org/10.1186/s12978-022-01406-w

[24]. Kang, Y.-J., Jeung, I., Park, A., & Park, Y.-J. (2014). An increased level of IL-6 suppresses NK cell activity in peritoneal fluid of patients with endometriosis via regulation of SHP-2 expression. Human Reproduction, 29(10), 2183-2189. https://doi.org/10.1093/humrep/deu172

[25]. Kang, Y.-J., Cho, H., Lee, Y., & Park, A. (2023). IL-17A and Th17 cells contribute to endometrial cell survival by inhibiting apoptosis and NK cell mediated cytotoxicity of endometrial cells via ERK1/2 pathway. Immune Network, 23(2), e14. https://doi.org/10.4110/in.2023.23.e14

[26]. Koike, N., Higashiura, Y., Akasaka, J., & Uekuri, C. (2015). Epigenetic dysregulation of endometriosis susceptibility genes. Molecular Medicine Reports, 12(1), 4-9. https://doi.org/10.3892/mmr.2015.3635

[27]. Krasnyi, A., Sadekova, A., Sefihanov, T. G., & Vtorushina, V. (2019). The content of cytokines IL-6, IL-8, TNF-alpha, IL-4 and the level of expression in macrophages CD86 and CD163 in peritoneal fluid has a reverse correlation with the degree of severity of external genital endometriosis. Biomeditsinskaia Khimiia, 65(5), 432-438. https://doi.org/10.18097/pbmc20196505432

[28]. Krasnyi, A., Sadekova, A., Sefihanov, T. G., & Vtorushina, V. (2020). The content of cytokines IL-6, IL-8, TNF-alpha, IL-4 and the level of CD86 and CD163 expression in peritoneal fluid macrophages has a reverse correlation with the degree of severity of external genital endometriosis. Biochemistry (Moscow), Supplement Series B: Biomedical Chemistry, 14(1). https://doi.org/10.1134/S1990750820010096

[29]. Laudański, P., Rogalska, G., Warzecha, D., & Lipa, M. (2023). Autoantibody screening of plasma and peritoneal fluid of patients with endometriosis. Human Reproduction, 38(3), 483-495. https://doi.org/10.1093/humrep/dead011

[30]. Lei, S.-T., Lai, Z.-Z., Hou, S.-H., & Liu, Y.-K. (2024). Abnormal HCK/glutamine/autophagy axis promotes endometriosis development by impairing macrophage phagocytosis. Cell Proliferation,

57(12), e13702. https://doi.org/10.1111/cpr.13702

[31]. Liao, T., Lee, Y.-C., Tzeng, C., & Wang, Y.-P. (2019). Mitochondrial translocation of estrogen receptor beta affords resistance to oxidative insult-induced apoptosis and contributes to the pathogenesis of endometriosis. Free Radical Biology and Medicine, 134, 359-373. https://doi.org/10.1016/j.freeradbiomed.2019.01.022

[32]. Louis, G., Chen, Z., Peterson, C. M., & Hediger, M. (2012). Persistent lipophilic environmental chemicals and endometriosis: The ENDO Study. Environmental Health Perspectives, 120(6), 811-816. https://doi.org/10.1289/ehp.1104432

[33]. Makoui, M. H., Fekri, S., Makoui, R. H., & Ansari, N. (2025). The role of mast cells in the development and advancement of endometriosis. American Journal of Reproductive Immunology, 93(4), e70019. https://doi.org/10.1111/aji.70019

[34]. Mao, X., Wang, J., Ding, S., & Guo, X. (2025). MRGPRX2 mediates mast cell-induced endometriosis pain through the sensitization of sensory neurons via histamine/HRH1/TRPV1 signaling pathway. The FASEB Journal, 39, e70227. https://doi.org/10.1096/fj.202501493R

[35]. Mariadas, H., Chen, J.-H., & Chen, K.-H. (2025). The molecular and cellular mechanisms of endometriosis: From basic pathophysiology to clinical implications. International Journal of Molecular Sciences, 26(6), 2458. https://doi.org/10.3390/ijms26062458

[36]. Nazri, H. M., Imran, M., Fischer, R., & Heilig, R. (2020). Characterization of exosomes in peritoneal fluid of endometriosis patients. Fertility and Sterility, 113(2), 364-373. https://doi.org/10.1016/j.fertnstert.2019.09.032

[37]. Niakan, G., Rokhgireh, S., Ebrahimpour, M., & Mehdizadeh Kashi, A. (2021). Comparing the effect of dienogest and OCPs on pain and quality of life in women with endometriosis: A randomized, double-blind, placebo-controlled trial. Archives of Iranian Medicine, 24(12), 871-878. https://doi.org/10.34172/aim.2021.96

[38]. Nie, J., Yi, Y., Liu, X.-S., & Guo, S.-W. (2025). Progressively diminished estrogen signaling concordant with increased fibrosis in ectopic endometrium. Human Reproduction Open, 2025, hoaf028. https://doi.org/10.1093/hropen/hoaf028

[39]. Nirgianakis, K., McKinnon, B., Ma, L., & Imboden, S. (2020). Peritoneal fluid biomarkers in patients with endometriosis: A cross-sectional study. Hormone Molecular Biology and Clinical Investigation, 42(1), 57-65. https://doi.org/10.1515/hmbci-2019-0064

[40]. Okten, S., Cetin, C., Tok, O. E., & Guler, E. (2023). Cannabidiol as a potential novel treatment for endometriosis by its anti-inflammatory, antioxidative and antiangiogenic effects in an experimental rat model. Reproductive BioMedicine Online, 46(4), 689-697. https://doi.org/10.1016/j.rbmo.2023.01.018

[41]. Rakhila, H., Al-Akoum, M., Bergeron, M., & Leboeuf, M. (2016). Promotion of angiogenesis and proliferation cytokines patterns in peritoneal fluid from women with endometriosis. Journal of Reproductive Immunology, 116, 1-6. https://doi.org/10.1016/j.jri.2016.01.005

[42]. Rençber, S., Yazir, Y., Sarihan, M., & Sezer, Z. (2024). Endoplasmic reticulum stress of endometrial mesenchymal stem cells in endometriosis. Tissue and Cell, 90, 102544. https://doi.org/10.1016/j.tice.2024.102544

[43]. Rossi, M., Seidita, I., Vannuccini, S., & Prisinzano, M. (2023). Epigenetics, endometriosis and sex steroid receptors: An update on the epigenetic regulatory mechanisms of estrogen and progesterone receptors in patients with endometriosis. Vitamins and Hormones, 122, 403-427. https://doi.org/10.1016/bs.vh.2023.01.007

[44]. Rowlands, I., Hockey, R., Abbott, J., & Montgomery, G. (2022). Body mass index and the diagnosis of endometriosis: Findings from a national data linkage cohort study. Obesity Research and Clinical Practice, 16(3), 238-243. https://doi.org/10.1016/j.orcp.2022.04.002

[45]. Sargazi-taghazi, M., Ghaznavi, H., Sheervalilou, R., & Razavi, M. (2025). Add-on effect of curcumin to dienogest in patients with endometriosis: A randomized, double-blind, controlled trial. Phytomedicine, 156715. https://doi.org/10.1016/j.phymed.2025.156715

[46]. Servidoni, A., Martin, G., Gaio, G. S., & Amador, W. F. O. (2025). Efficacy of dienogest versus GnRH agonists after endometriosis surgery: A systematic review and meta-analysis. Journal of Minimally Invasive Gynecology. https://doi.org/10.1016/j.jmig.2025.11.008

[47]. Shigetomi, H., Nishio, M., Umetani, M., & Imanaka, S. (2025). Balancing decidualization, autophagy, and cellular senescence for reproductive success in endometriosis biology. International Journal of Molecular Sciences, 26(18), 9125. https://doi.org/10.3390/ijms26189125

[48]. Signorile, P., Cassano, M., Viceconte, R., & Spyrou, M. (2021). Endometriosis: A retrospective analysis on diagnostic data in a cohort of 4,401 patients. In Vivo, 36(1), 354-363. https://doi.org/10.21873/invivo.12721

[49]. Taylor, H. S., Li, H. J., Carson, S., & Flores, V. (2022). Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): Study protocol for a prospective, double-blind, placebo-controlled trial. BMJ Open, 12(6), e052043. https://doi.org/10.1136/bmjopen-2021-052043

[50]. Wang, Y., Farland, L., Gaskins, A. J., & Wang, S. (2024). Endometriosis and uterine fibroids and risk of premature mortality: Prospective cohort study. The BMJ, 387, e078797. https://doi.org/10.1136/bmj-2023-078797

[51]. Wang, J., Mao, X., Zhu, L., & Zhang, X. (2025). Unravelling the intricate link: Mast cells and estrogen-induced pain sensitization in endometriosis. International Journal of Biological Sciences, 21(4), 1641-1656. https://doi.org/10.7150/ijbs.116635

[52]. Wang, Y., Jin, Z., Blatchford, A. F., & Hosh, B. (2026). Human endometriotic lesion-derived small extracellular vesicles impair macrophage function in the peritoneal microenvironment. Journal of Extracellular Vesicles, 15, e70227. https://doi.org/10.1002/jev2.70227

[53]. Wei, C., Mei, J., Tang, L., & Liu, Y. (2016). 1-Methyl-tryptophan attenuates regulatory T cells differentiation due to the inhibition of estrogen-IDO1-MRC2 axis in endometriosis. Cell Death and Disease, 7(11), e2489. https://doi.org/10.1038/cddis.2016.375

[54]. Wickström, K., Stavreus-Evers, A., Vercauteren, O., & Olovsson, M. (2017). Effect of lignocaine on IL-6, IL-8, and MCP-1 in peritoneal macrophages and endometriotic stromal cells. Reproductive Sciences, 24(3), 386-394. https://doi.org/10.1177/1933719116657188

[55]. Wójtowicz, M., Zdun, D., Owczarek, A., & Skrzypulec-Plinta, V. (2025). Evaluation of proinflammatory cytokines concentrations in plasma, peritoneal, and endometrioma fluids in women operated on for ovarian endometriosis. International Journal of Molecular Sciences, 26(11), 5117. https://doi.org/10.3390/ijms26115117

[56]. Xiang, D., Zhao, M., Cai, X., & Wang, Y. (2020). Betulinic acid inhibits endometriosis through suppression of estrogen receptor beta signaling pathway. Frontiers in Endocrinology, 11, 604648. https://doi.org/10.3389/fendo.2020.604648

[57]. Xu, Y., Zhu, Y., Wu, X., & Peng, W. (2025). Gut microbiota-derived acetate ameliorates endometriosis via JAK1/STAT3-mediated M1 macrophage polarisation. Microbial Biotechnology, 18, e70202. https://doi.org/10.1111/1751-7915.70202

[58]. Xue, Z., Guo, Y., Wang, F., & Yang, Q. (2024). miR-196b-5p affects macrophage polarization and inflammation in endometriosis. Iranian Journal of Immunology, 21(3), 256-266. https://doi.org/10.22034/iji.2024.102744.2794

[59]. Yang, X., Jiang, L., & Xu, Y. (2024). HSD11B1 overexpression in dendritic cells and stromal cells relates to endometriosis by inhibiting dendritic cell proliferation and maturation. Gynecological Endocrinology, 40(1), 2411607. https://doi.org/10.1080/09513590.2024.2411607

[60]. Zhong, Z., Wang, S., Ren, Q., & Jiao, X. (2026). Stromal cell-derived itaconate promotes endometriosis via macrophage NRF2 and lysosomal pH modulation. Redox Biology, 82, 104101. https://doi.org/10.1016/j.redox.2026.104101