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Review Article

The Interplay Between the Immune Cells and Microbial Dysbiosis in the Development of Endometriotic Lesions: Implications for Revisiting Hormonal and Surgical Treatments

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Abstract

Endometriosis is a chronic, estrogen-dependent, inflammatory and fibrotic disease characterized by endometrial-like tissue outside the uterine cavity. Although retrograde menstruation explains the presence of endometrial fragments in the peritoneal cavity, it does not explain why only a subset of women develop persistent lesions, chronic pain or infertility. Increasing evidence indicates that endometriosis emerges from a permissive immunological and microbial ecosystem in which ectopic cells evade clearance, induce angiogenesis and neurogenesis, remodel extracellular matrix and sustain chronic inflammation. Immune abnormalities include macrophage expansion and M2-like polarization, impaired natural killer cell cytotoxicity, tolerogenic dendritic cells, altered neutrophil and mast-cell activity, Th17/Treg imbalance, exhausted cytotoxic T cells, B-cell activation and autoantibody production. In parallel, microbial dysbiosis in the gut, vagina, cervix, endometrium and peritoneal cavity may influence lesion biology through lipopolysaccharide/TLR4 activation, increased intestinal permeability, estrogen recycling by the estrobolome, short-chain fatty acid depletion, altered bile acid and tryptophan metabolism, and modulation of macrophage, NK-cell and T-cell phenotypes. This review explored the bidirectional immune-microbiota interactions that may drive the implantation, survival and progression of endometriotic lesions. We propose an “immune-microbial endocrine loop” in which dysbiosis amplifies inflammation and estrogenic signaling, while endometriotic lesions reshape local and systemic microbial niches. This paradigm has implications for current treatments. Hormonal suppression reduces estrogenic stimulation and symptoms but may not fully correct immune-microbial drivers. Surgery removes visible lesions but cannot necessarily reset the inflammatory microbiome or prevent recurrence. Revisiting hormonal and surgical strategies through an immune-microbial lens supports adjunctive approaches such as perioperative microbiome profiling, anti-inflammatory nutrition, probiotics, postbiotics, selective antibiotics, estrobolome modulation, macrophage/NK-cell-targeted therapy and personalized postoperative suppression. Robust longitudinal human studies and mechanism-based trials are required before microbiome-directed interventions can be routinely integrated into care.

Keywords: *Endometriosis, Microbiota, Dysbiosis, Macrophage, Natural killer cell, Estrobolome, Inflammation, Hormonal therapy, Reproductive medicine*

Highlights

- Microbial dysbiosis, particularly of the gut, vaginal, and peritoneal microbiomes, as a critical upstream driver that amplifies local immune dysregulation and facilitates the establishment and progression of endometriotic lesions.

- The reciprocal interplay between dysbiotic microbial communities and aberrant innate and adaptive immune responses creates a self-perpetuating inflammatory niche that sustains ectopic endometrial-cell survival, invasion, and angiogenesis.

- Macrophage polarization toward a pro-inflammatory M1 phenotype, coupled with impaired natural-killer-cell cytotoxicity, is markedly exacerbated by microbial metabolites and pathogen-associated molecular patterns within the peritoneal microenvironment of endometriosis.

- Dysbiosis-induced alterations in SCFAs production and Toll-like-receptor signaling pathways directly modulate estrogen receptor activity and progesterone resistance, thereby linking microbial imbalance to the hormonal dependence of endometriotic lesions.

- Conventional hormonal therapies that solely suppress ovarian steroidogenesis leave the underlying immune–microbial axis largely unaddressed, potentially explaining high rates of treatment failure and lesion recurrence.

Abbreviations: ALA, alpha-lipoic acid; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; ASRM, American Society for Reproductive Medicine; Breg, regulatory B cell; CAF, cancer-associated fibroblast; COC, combined oral contraceptive; COX-2, cyclooxygenase-2; DC, dendritic cell; DIE/DE, deep infiltrating endometriosis/deep endometriosis; EMT, epithelial-mesenchymal transition; FMT, fecal microbiota transplantation; GAM, glioma-associated macrophage/microglia (not used here except when comparing immune biology); GnRH, gonadotropin-releasing hormone; HIF-1α, hypoxia-inducible factor 1 alpha; IDO1, indoleamine 2,3-dioxygenase 1; IL, interleukin; LNG-IUS, levonorgestrel-releasing intrauterine system; LPS, lipopolysaccharide; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NK cell, natural killer cell; NSAID, non-steroidal anti-inflammatory drug; PAMP, pathogen-associated molecular pattern; PGE2, prostaglandin E2; PR, progesterone receptor; SCFA, short-chain fatty acid; SIRPα, signal-regulatory protein alpha; TLR, toll-like receptor; TME, tissue microenvironment/tumor microenvironment (used conceptually for lesion microenvironment); TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; uNK cell, uterine natural killer cell; VEGF, vascular endothelial growth factor.

1. Introduction

Endometriosis affects approximately 5–10% of reproductive-age women and a much higher proportion of women with chronic pelvic pain or infertility. It is defined by the presence of endometrial-like glands and stroma outside the uterine cavity, most commonly on the peritoneum, ovaries and deep pelvic structures, but also in extrapelvic sites. Symptoms include dysmenorrhea, non-menstrual pelvic pain, dyspareunia, dyschezia, urinary symptoms, fatigue and infertility. The disorder has a long diagnostic delay, often 7–11 years, partly because symptoms are normalized, imaging may miss early lesions and laparoscopy was historically required for diagnosis [1-3].

The dominant historical hypothesis is Sampson's retrograde menstruation theory: menstrual fragments pass through the fallopian tubes into the peritoneal cavity and implant ectopically. Retrograde menstruation is common, but endometriosis is not. Therefore, additional factors must determine whether refluxed endometrial cells are cleared or survive. These factors include estrogen dependence, progesterone resistance, immune dysfunction, genetic and epigenetic susceptibility, stem/progenitor cell features, angiogenesis, neurogenesis, fibrosis and now increasingly microbial dysbiosis [4-7]. Endometriosis is not simply misplaced endometrium. It is a systemic inflammatory condition with local lesion ecosystems. Lesions interact with immune cells, nerves, vessels, fibroblasts, adipose tissue, peritoneal mesothelium and microbial products. They produce inflammatory mediators, prostaglandins, chemokines, neurotrophic factors and matrix remodeling enzymes. They also resist apoptosis and immune clearance. These processes sustain pain and infertility even when lesions are small.

Current treatment is centered on two pillars: hormonal suppression and surgery. Hormonal therapies reduce ovarian estrogenic stimulation and include combined hormonal contraceptives, progestins, GnRH agonists, GnRH antagonists, aromatase inhibitors and LNG-IUS. Surgery excises or ablates lesions, drains or removes endometriomas and releases adhesions. Both approaches can improve symptoms, but recurrence is common, adverse effects limit long-term use, fertility goals constrain hormonal suppression, and repeated surgery can damage ovarian reserve or pelvic organs [8,9].

A new question is emerging: should endometriosis treatment be revisited through the immune-microbial axis? If immune dysregulation and dysbiosis are not merely consequences but drivers of lesion persistence, then hormonal and surgical treatments may need adjunctive strategies that restore immune surveillance, reduce dysbiotic inflammation and reshape microbial metabolism. This review addresses that question.

2. Immune Surveillance Failure and Lesion Establishment

In women without endometriosis, refluxed endometrial debris is thought to be cleared by coordinated innate immune responses. Macrophages, NK cells, neutrophils, dendritic cells and complement participate in recognition and elimination of ectopic cells. In endometriosis, this clearance is inefficient. Peritoneal fluid often contains increased numbers of immune cells and inflammatory mediators, but these responses paradoxically support lesion survival rather than eradication [10,11]. This paradox resembles chronic inflammatory diseases in which immune activation coexists with defective resolution. Immune cells in endometriosis are not absent; they are misprogrammed. Macrophages may become pro-angiogenic and pro-fibrotic. NK cells may lose cytotoxicity. T cells may skew toward Th17 and Treg states. B cells may produce autoantibodies. Mast cells and nerves interact to produce pain. Dendritic cells may become tolerogenic. These immune states create a microenvironment in which ectopic endometrial fragments can adhere, invade, vascularize and persist. Microbial dysbiosis may further impair clearance. Bacterial products such as LPS activate TLR4 and NF-κB pathways, stimulating IL-6, IL-8, TNF-α, PGE2 and VEGF (Figure 1). Dysbiosis can also reduce microbial metabolites that normally support regulatory immunity and barrier integrity. Thus, the immune failure in endometriosis may be partly microbial-instructed.

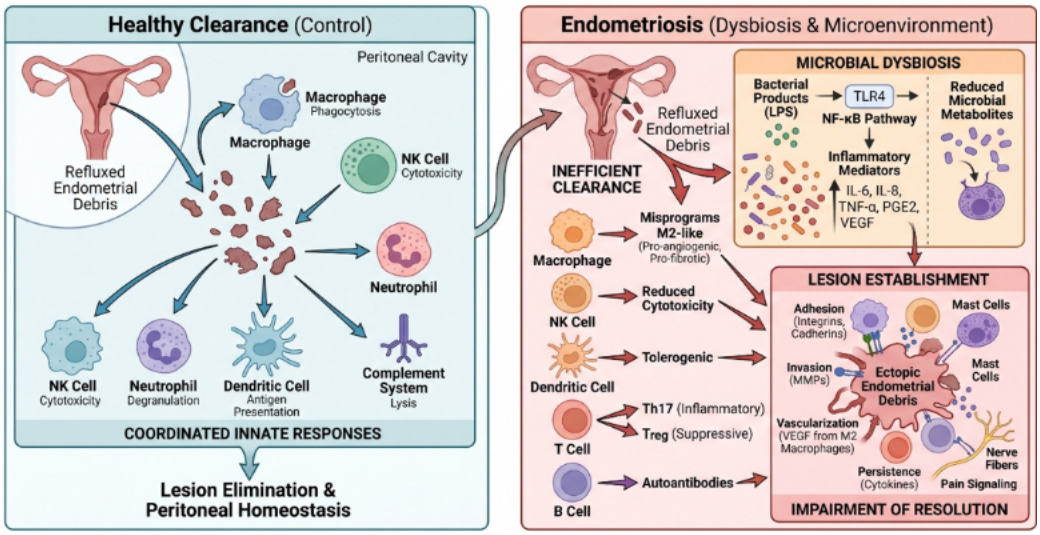


Figure 1. Endometriosis involves immune dysregulation, including altered macrophage activity, reduced NK-cell cytotoxicity, Th17/Treg imbalance, autoantibody production, and mast cell–nerve interactions contributing to chronic pain. Microbial dysbiosis further promotes inflammation through LPS–TLR4/NF-κB signalling and increased inflammatory mediators, while reducing beneficial microbial metabolites.

3. Macrophages: Central Orchestrators of Inflammation, Angiogenesis and Fibrosis

Macrophages are among the most abundant immune cells in endometriotic lesions and peritoneal fluid. They are recruited by chemokines and activated by lesion-derived factors, estrogen, hypoxia, iron, cellular debris and microbial products. Instead of clearing ectopic tissue efficiently, macrophages in endometriosis often adopt phenotypes that promote survival, angiogenesis, neurogenesis and fibrosis [10-12].

The simplistic M1/M2 dichotomy is insufficient, but it remains useful conceptually. M1-like macrophages are inflammatory and microbicidal; M2-like macrophages support tissue repair, angiogenesis and fibrosis. Endometriosis is associated with increased M2-like or pro-repair macrophage signatures. Single-cell studies have identified more nuanced subsets, including SPP1-positive lipid-associated macrophages and FOLR2-positive immunosuppressive macrophages [12].

These cells may secrete VEGF, TGF-β, IL-10, MMPs, prostaglandins and growth factors that support lesion expansion (Figure 2).

Macrophages also influence pain. They produce NGF and other neurotrophic mediators that promote nerve growth into lesions. They interact with mast cells and sensory neurons, contributing to neuroinflammation. Iron from retrograde menstruation and hemorrhagic lesions can alter macrophage polarization and oxidative stress. Microbial dysbiosis may strongly shape macrophage behavior. LPS from Gram-negative bacteria activates TLR4 on macrophages and endometrial stromal cells. Studies show that LPS and estradiol can synergistically stimulate macrophage secretion of IL-6 and TNF-α, promoting growth of eutopic and ectopic endometrial cells; anti-TNF and anti-IL-8 strategies can inhibit some LPS-induced effects in vitro [13]. Dysbiotic microbial metabolites may also influence macrophage polarization through aryl hydrocarbon receptor signaling, bile acids, SCFAs and tryptophan metabolites. Revisiting treatment through macrophage biology suggests that hormonal suppression alone may reduce estrogenic support but may not fully reprogram macrophage-driven fibrosis and neuroangiogenesis. Surgery removes macrophage-rich lesions but may cause wound inflammation and adhesion formation. Perioperative strategies that limit macrophage-driven recurrence or fibrosis may be needed.

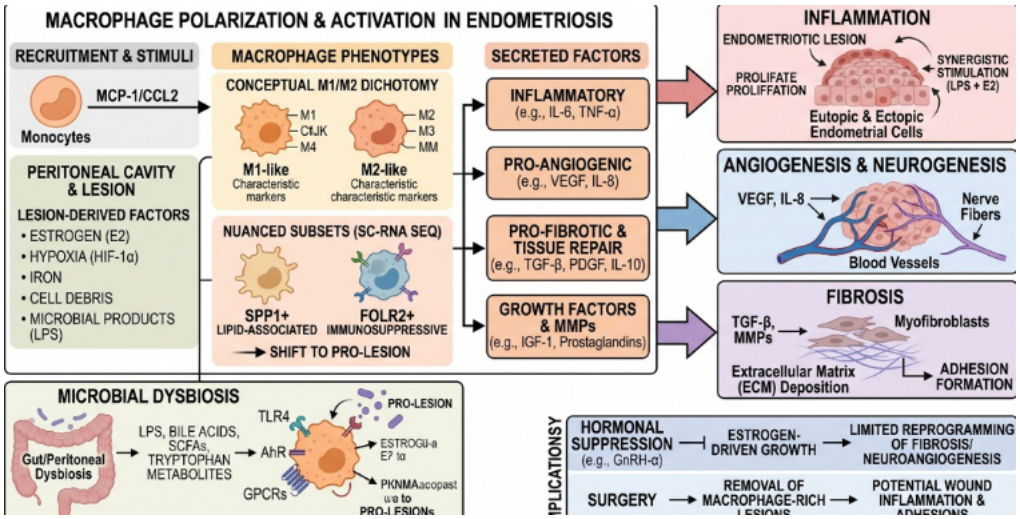


Figure 2. Endometriosis-associated macrophages exhibit diverse pro-repair and immunosuppressive phenotypes, secreting VEGF, TGF-β, IL-10, and MMPs that promote lesion growth and pain. Iron accumulation from retrograde menstruation enhances oxidative stress, while microbial dysbiosis activates LPS–TLR4 signalling and alters macrophage function through estradiol and microbial metabolites.

4. Natural Killer Cells: Failed Cytotoxicity and Immune Escape

NK cells normally recognize and eliminate stressed, abnormal or ectopic cells without prior sensitization. In endometriosis, NK cell cytotoxicity is often reduced in peripheral blood, peritoneal fluid or lesions, although findings vary by compartment and methodology [10-12]. Reduced expression of activating receptors such as NKG2D, NKp44 or NKp46 and increased inhibitory signals may contribute. Ectopic endometrial cells may evade NK killing through HLA-G, PD-L1, soluble ligands, TGF-β and IL-10. The interaction between macrophages and NK cells is important. Endometriotic stromal cells and macrophages can secrete IL-10 and TGF-β, suppressing NK cytotoxicity. Dysbiosis may worsen this by promoting tolerogenic cytokines or by chronic TLR activation that exhausts innate responses. Conversely, some probiotics may enhance NK activity (Figure 3). In mouse endometriosis models, *Lactobacillus gasseri* OLL2809 has been reported to activate NK cells and suppress lesion growth, suggesting a microbiota-immune therapeutic route [14]. For treatment, impaired NK function raises questions.

Hormonal therapy may reduce lesion proliferation but may not restore cytotoxic clearance. Surgery removes lesions but does not necessarily correct systemic NK dysfunction. Adjunctive approaches that restore NK surveillance, cytokine modulation, probiotic strategies, immune checkpoint modulation or metabolic reprogramming, could theoretically reduce recurrence, but safety is crucial because reproductive immunology requires tolerance for implantation and pregnancy.

5. T Cells: Th17/Treg Imbalance, Exhaustion and Chronic Inflammation

T-cell abnormalities in endometriosis include altered CD4+ helper subsets, increased Th17 responses, Treg enrichment in some compartments, reduced cytotoxic CD8+ function and features of exhaustion. Th17 cells produce IL-17A, which promotes neutrophil recruitment, angiogenesis, inflammation and macrophage activation. Tregs suppress immune responses and may protect ectopic lesions from clearance. CD8+ T cells may show reduced cytotoxicity or exhaustion markers such as PD-1, TIM-3 or LAG-3 in some studies [11,12]. Microbiota strongly regulates T-cell differentiation. Gut dysbiosis can shift Th17/Treg balance, especially through segmented filamentous bacteria-like signals, LPS, SCFAs, bile acids and tryptophan metabolites (Figure 3). Dysbiosis-induced increases in Th17/Treg ratio have been proposed as part of the microbiota-endometriosis axis [6,15]. Reduced SCFA production may impair Treg function and epithelial barrier integrity, while microbial LPS may favor inflammatory Th17 responses.

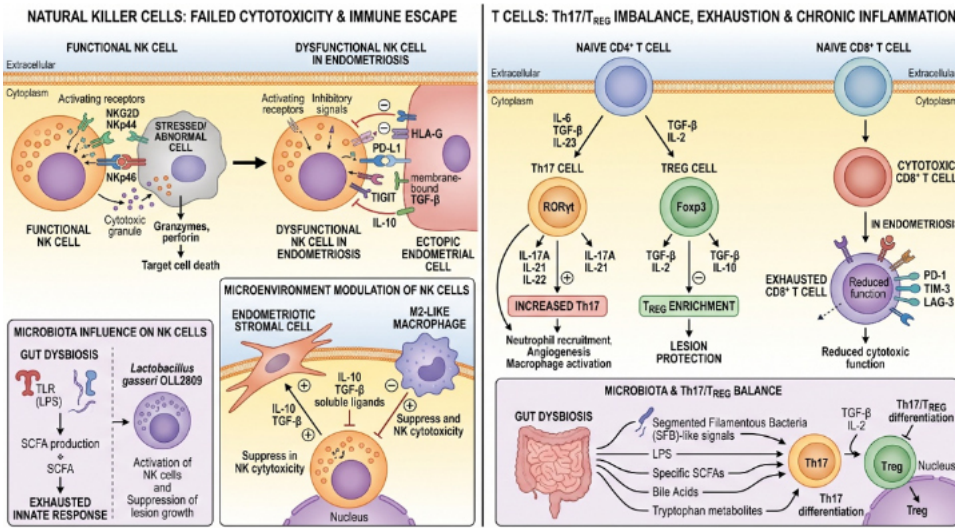


Figure 3. Gut dysbiosis may disrupt Th17/Treg balance through altered microbial metabolites, LPS, SCFAs, bile acids, and tryptophan derivatives. Increased LPS promotes Th17-mediated inflammation, while reduced SCFAs impair barrier integrity and Treg function, potentially exacerbating endometriosis-associated immune dysfunction.

T-cell biology also intersects with estrogen. Estrogen can modulate Th17, Treg and cytokine responses. Endometriosis is characterized by local estrogen production and progesterone resistance. Microbiota can alter estrogen recycling through the estrobolome, potentially reinforcing estrogen-dependent immune skewing. Therapeutically, T-cell targeting is challenging because endometriosis is benign and many patients desire fertility. Aggressive checkpoint blockade or Treg depletion would carry unacceptable risks outside experimental contexts. However, dietary, microbial and hormonal strategies that gently rebalance Th17/Treg tone may be feasible.

6. B Cells, Autoantibodies and Humoral Dysregulation

Endometriosis has autoimmune-like features: chronic inflammation, autoantibodies, association with autoimmune conditions and B-cell abnormalities. B cells and plasma cells can be enriched in lesions or eutopic endometrium in some studies. Autoantibodies against endometrial, nuclear or phospholipid antigens have been reported, although clinical utility remains limited [12,16]. B cells may promote lesions through antibody production, antigen presentation, cytokines and regulatory B-cell imbalance. IL-10-producing Bregs could suppress lesion clearance, while autoreactive plasma cells could perpetuate inflammation.

Microbial dysbiosis may stimulate B cells through TLR ligands, molecular mimicry or mucosal immune activation. Current hormonal and surgical treatments do not specifically address B-cell biology (Figure 4). This may partly explain persistent inflammatory symptoms in some patients after lesion removal. However, B-cell depletion is unlikely to become routine due to safety concerns. Instead, B-cell signatures may serve as biomarkers for immune-dominant phenotypes.

7. Neutrophils, NETs and Early Lesion Implantation

Neutrophils are rapid responders to tissue injury and infection. In endometriosis, neutrophils may contribute to early implantation by secreting inflammatory mediators, VEGF, proteases and neutrophil extracellular traps (NETs). NETs can trap cells and microbes but also promote inflammation, coagulation and tissue remodeling [12,17]. Microbial dysbiosis can activate neutrophils through LPS, formyl peptides and other bacterial products. If dysbiosis increases systemic or peritoneal neutrophil priming, retrograde endometrial fragments may encounter a pro-adhesive inflammatory environment. NETs may create extracellular scaffolds that facilitate adhesion or fibrosis. Targeting neutrophils is difficult because they are essential for host defense (Figure 4). However, excessive NET formation could be modulated by DNase, PAD4 inhibition or anti-inflammatory strategies in preclinical settings. Whether such approaches are safe in reproductive-age women remains unknown.

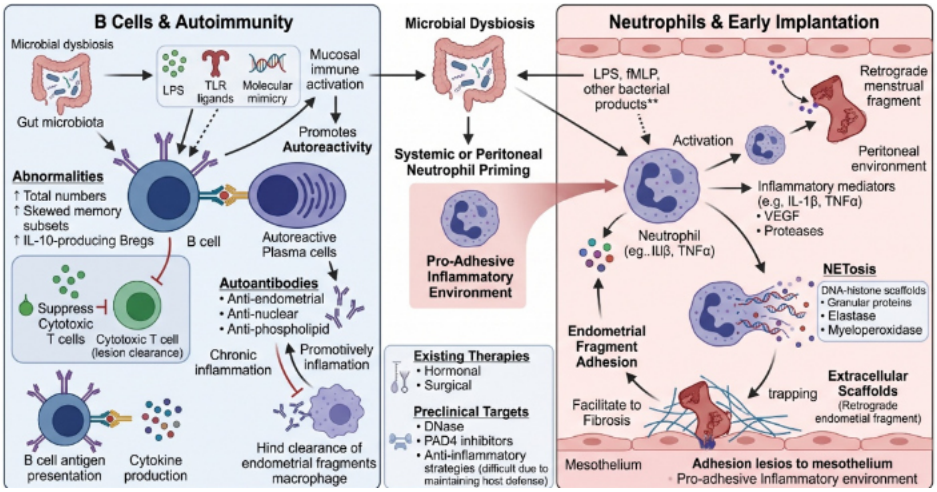


Figure 4. Neutrophils promote endometrial lesion establishment by releasing inflammatory mediators, VEGF, and tissue-remodelling proteases. NETs create an inflammatory, adhesive scaffold that supports ectopic cell attachment and survival. Microbial dysbiosis may further enhance neutrophil activation through LPS and bacterial peptides, promoting inflammation, lesion development, and fibrosis.

8. Mast Cells, Nerves and Pain-Associated Inflammation

Mast cells are increased and activated in endometriotic lesions and are closely associated with nerve fibers. They release histamine, tryptase, prostaglandins, cytokines and nerve growth factor, contributing to neurogenic inflammation, pain sensitization and fibrosis [12,18]. Mast cells can be activated by estrogen, stress, microbial products and tissue injury. Dysbiosis may influence mast cells through gut barrier permeability, LPS, histamine-producing microbes and immune mediators. Gut dysbiosis can also affect visceral pain pathways. Thus, microbiota may contribute to endometriosis-associated pain not only by lesion growth but by neuroimmune sensitization. Current hormonal therapy often reduces pain by suppressing cyclic bleeding and estrogenic stimulation, but some pain persists due to central sensitization, mast-cell-nerve interactions and fibrosis (Figure 5). Surgery may remove lesions but can also trigger nerve injury or adhesions. Mast-cell stabilization, antihistamines, neuromodulation and microbiota-targeted therapies may be adjunctive in selected pain phenotypes.

9. Dendritic Cells and Antigen Presentation

Dendritic cells bridge innate and adaptive immunity. In endometriosis, immature or tolerogenic dendritic cells may fail to activate effective cytotoxic responses against ectopic endometrial cells, while promoting angiogenesis and immune tolerance [10-12]. Dysbiosis can influence dendritic cell maturation through TLR ligands, SCFAs and tryptophan metabolites. If dendritic cells present endometrial antigens in a tolerogenic context, Tregs may expand and effector responses may decline (Figure 5). This could help ectopic cells survive. Hormonal therapy may modulate dendritic cells indirectly, but does not specifically restore antigen presentation. Future immunotherapies would need to be subtle due to reproductive tolerance concerns.

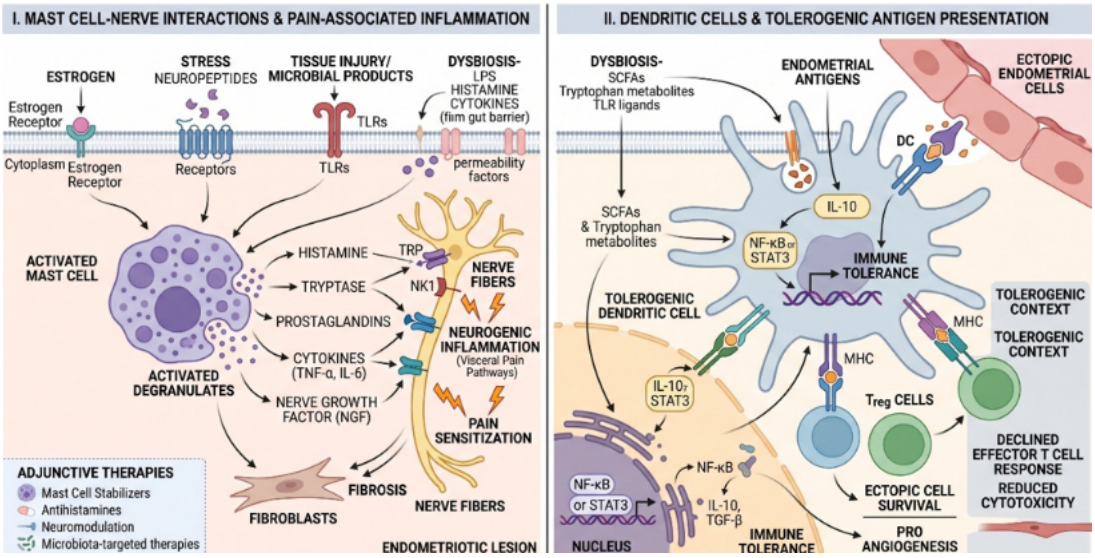


Figure 5. Activated mast cells interact with nerve fibres, releasing histamine, tryptase, prostaglandins, cytokines, and NGF, promoting neuroinflammation, pain sensitization, and fibrosis. Gut dysbiosis may further enhance mast-cell activation through increased intestinal permeability, LPS, and histamine-producing microbes. Hormonal therapy and surgery may not fully resolve established pain sensitization and fibrosis. Adjunctive approaches include mast-cell stabilizers, antihistamines, neuromodulation, and microbiota-targeted therapies. Tolerogenic dendritic cells further impair immune defence, supporting angiogenesis and ectopic lesion survival.

10. Microbial Dysbiosis in Endometriosis: Gut, Vaginal, Endometrial and Peritoneal Niches

Microbiota-endometriosis research has expanded rapidly. Alterations have been reported in gut, vaginal, cervical, endometrial and peritoneal microbiota. Findings vary, but several studies report enrichment of genera suchas *Gardnerella, Streptococcus, Atopobium, Escherichia, Prevotella, Acidovorax, Devosia, Methylobacterium* and others in specific niches of affected women [6,13,19]. Gut microbiota studies suggest altered abundance of taxa involved in inflammation, barrier integrity and estrogen metabolism. The gut microbiota may influence endometriosis through multiple routes. Dysbiosis can increase intestinal permeability, allowing LPS and microbial products to enter circulation. These products activate TLR4 and NF-κB, promoting cytokines and prostaglandins. Dysbiosis can alter estrogen metabolism through microbial β-glucuronidase activity, the so-called estrobolome, increasing enterohepatic estrogen recycling and potentially supporting estrogen-dependent lesion growth [6,13]. Dysbiosis can also reduce SCFAs, which normally support Tregs, epithelial barrier integrity and anti-inflammatory signaling (Figure 6).

Vaginal and endometrial dysbiosis may affect ascending microbial products, local uterine inflammation and endometrial receptivity. Peritoneal microbial signatures may directly interact with ectopic lesions. Whether microbes are causal, consequential or both remains under investigation. The relationship is likely bidirectional: endometriosis-associated inflammation, altered hormones and immune dysfunction may reshape microbial niches, while dysbiosis reinforces disease (Figure 6). Mendelian randomization studies have begun to explore causality. One study reported causal associations between selected gut microbiota genera and endometriosis risk or stage, implicating LPS-TLR4 inflammatory pathways [20]. Such analyses are hypothesis-generating and require biological validation.

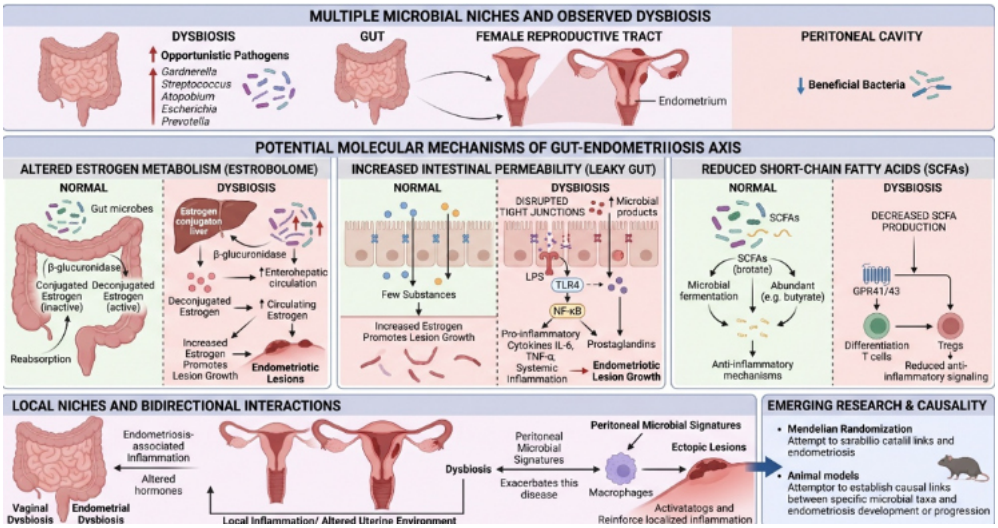


Figure 6. Gut and reproductive tract dysbiosis involves altered microbial communities, including Gardnerella, Streptococcus, Atopobium, Escherichia, and Prevotella. Microbial products may activate TLR4/NF-κB signalling and promote inflammation, while altered estrobolome activity increases estrogen recycling. Reduced SCFA production further compromises intestinal barrier integrity and Treg-mediated immune regulation, potentially contributing to endometriosis progression.

11. The Estrobolome: Microbial Regulation of Estrogenic Tone

Endometriosis is estrogen-dependent. Lesions express aromatase, produce local estrogen, resist progesterone and respond to estrogen with proliferation, inflammation and angiogenesis. Gut microbiota adds another layer through the estrobolome: microbial genes capable of metabolizing estrogens, especially through β-glucuronidase activity. Deconjugation of estrogens in the gut permits reabsorption and enterohepatic recirculation [6,21]. Dysbiosis with increased β-glucuronidase activity could increase circulating or local estrogenic tone. This may not replace ovarian estrogen production, but it may amplify it. Hyperestrogenism can further shape immunity by promoting mast-cell activation, macrophage polarization, Th17 responses and prostaglandin production. Thus, microbial estrogen metabolism links endocrine and immune mechanisms. Hormonal therapies suppress ovarian estrogen or oppose estrogen action, but they may not address microbial estrogen recycling. This raises an intriguing possibility: estrobolome modulation could enhance hormonal therapy or reduce recurrence after discontinuation. Candidate approaches include diet, prebiotics, probiotics, β-glucuronidase inhibitors and microbiome monitoring. Human evidence remains preliminary (Figure 7).

12. Microbial Metabolites: SCFAs, Bile Acids, Tryptophan and Lactate

Microbial metabolites are immune regulators. SCFAs such as acetate, propionate and butyrate support intestinal barrier integrity, Treg differentiation, anti-inflammatory macrophage phenotypes and histone deacetylase inhibition. Reduced SCFA production may promote systemic inflammation and Th17/Treg imbalance. In endometriosis, SCFA depletion could contribute to immune dysregulation, though direct human evidence is limited. Bile acids are modified by gut microbes and can regulate immunity through FXR and TGR5 pathways. Tryptophan metabolites influence aryl hydrocarbon receptor signaling, T-cell differentiation and epithelial barrier function. Lactate-producing microbes may shape vaginal and uterine immunity. A Lactobacillus-dominant vaginal microbiota is often associated with reproductive tract health, though uterine microbiome interpretation remains controversial due to low biomass and contamination concerns (Figure 7). These metabolites suggest that microbiota-targeted therapy should not focus only on bacterial names. Functional output, SCFAs, β-glucuronidase, LPS, bile acid profile, tryptophan metabolites, be more relevant than taxonomy.

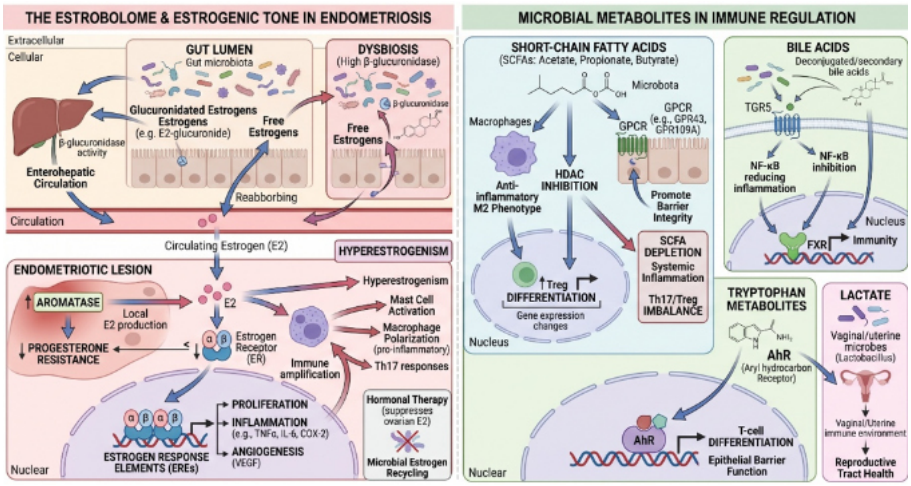


Figure 7. Reduced SCFA production may disrupt Th17/Treg balance and promote systemic inflammation, potentially contributing to endometriosis-associated immune dysfunction. Altered microbial bile acid metabolism influences immunity through FXR and TGR5 signalling, while tryptophan-derived metabolites regulate T-cell differentiation and epithelial barrier integrity through AhR activation.

13. Lesion Formation: An Immune-Microbial Sequence

A plausible sequence can be proposed. First, retrograde menstruation introduces viable endometrial fragments and heme-rich debris into the peritoneal cavity. Second, in susceptible individuals, macrophages and NK cells fail to clear fragments efficiently. Third, dysbiosis-derived LPS and inflammatory metabolites activate TLR4/NF-κB signaling in macrophages, mesothelial cells and endometrial stromal cells. Fourth, cytokines such as IL-6, IL-8, TNF-α, IL-1β and PGE2 promote adhesion, proliferation and angiogenesis. Fifth, macrophages polarize toward pro-repair phenotypes, NK cells become suppressed, Tregs and Th17 cells increase, and mast cells promote neurogenesis. Sixth, lesions produce estrogen, prostaglandins and chemokines, further reinforcing immune and microbial dysregulation (Figure 8). This sequence is not linear in all patients. Some may have primary immune defects; others may have dominant hormonal or anatomical drivers; others may have microbiota-driven inflammation. Precision medicine requires identifying the dominant loop in each patient.

14. Implications for Hormonal Therapy

Hormonal therapy remains essential because estrogen is a central driver of endometriosis. Combined oral contraceptives, progestins, dienogest, LNG-IUS, GnRH agonists and GnRH antagonists reduce pain for many patients and reduce recurrence after surgery when used long-term [8,9]. However, hormonal therapies are suppressive, not curative. Symptoms may recur after discontinuation, side effects limit adherence, and fertility-seeking patients cannot remain suppressed indefinitely. The immune-microbial model suggests several reasons hormonal therapy may be incomplete. First, lesions may persist as inflammatory fibrotic structures even under hormonal suppression. Second, dysbiosis-derived LPS and immune activation may continue to stimulate cytokines and pain pathways. Third, estrogen recycling via the estrobolome may modulate residual estrogenic tone. Fourth, progesterone resistance in lesions may reduce responsiveness to progestins. Fifth, central sensitization and mast-cell-nerve interactions may persist despite reduced lesion cycling. This does not diminish hormonal therapy; rather, it suggests adjunctive strategies. Microbiome assessment could identify patients with dysbiosis-driven inflammation who may benefit from dietary, probiotic or anti-inflammatory adjuncts (Figure 8). Estrobolome modulation might enhance hormonal suppression. Immune biomarkers could guide therapy choice: macrophage-dominant, mast-cell-dominant or Th17-dominant phenotypes may respond differently.

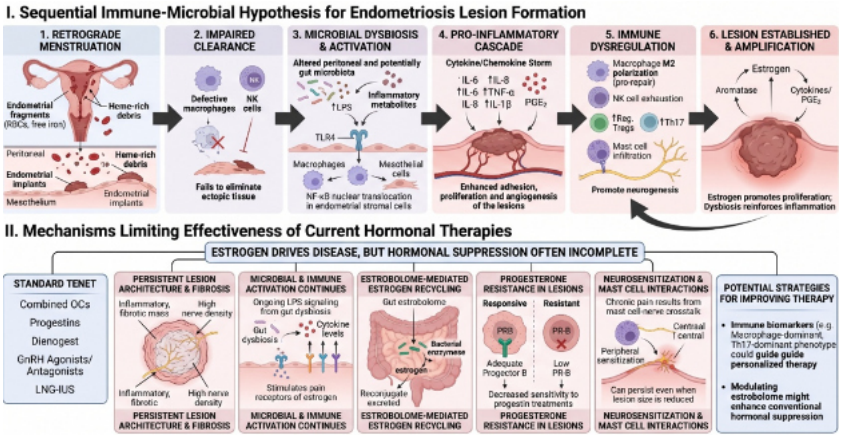


Figure 8. Although hormonal therapies reduce pain and recurrence, symptoms may return after discontinuation. Persistent lesions may be sustained by fibrosis, gut dysbiosis, estrogen recycling, progesterone resistance, and chronic immune activation. Central sensitization and mast cell–nerve interactions may further maintain pain despite hormonal suppression.

15. Implications for Surgical Treatment

Surgery can diagnose and remove visible disease, restore anatomy, treat endometriomas, relieve obstruction and improve pain or fertility in selected patients. Excision is often preferred for deep disease and endometriomas, but surgery carries risks: ovarian reserve reduction, adhesions, organ injury, neuropathic pain and recurrence. Repeated surgeries are discouraged when possible [8,9]. From an immune-microbial perspective, surgery removes established lesions but may not reset systemic drivers. If dysbiosis, macrophage polarization, NK dysfunction or estrogen recycling persist, new lesions or recurrent symptoms may develop. Surgery itself is a wound-healing event that activates inflammation, macrophages, mast cells and fibroblasts. In a dysbiotic or pro-inflammatory host, postoperative healing may favor adhesions and recurrence. This supports perioperative optimization. Preoperative assessment could include inflammatory status, bowel symptoms, vaginal infections, dysbiosis risk, diet and metabolic health. Postoperative hormonal suppression is already recommended for recurrence prevention when pregnancy is not desired [8]. In the future, postoperative microbiome modulation may be studied as a recurrence-reduction strategy. For endometriomas, preserving ovarian reserve remains critical; microbiome or immune adjuncts might reduce need for repeat surgery if proven effective.

16. Microbiome-Targeted Therapeutic Opportunities

16.1 Probiotics

Probiotics may modulate immune responses, improve barrier integrity, reduce LPS translocation and influence estrogen metabolism. *Lactobacillus gasseri* OLL2809 has shown lesion-suppressive effects in mouse models, possibly through NK-cell activation [14]. Human evidence is limited but interest is growing.

16.2 Prebiotics and Diet

Prebiotics increase beneficial microbial metabolites such as SCFAs. Anti-inflammatory dietary patterns rich in fiber, omega-3 fatty acids, polyphenols and low in ultra-processed foods may improve gut barrier and inflammatory tone. Diet may also influence estrogen metabolism. Clinical trials are needed.

16.3 Postbiotics and SCFAs

Postbiotics, microbial metabolites or inactivated microbial products, offer more controlled immunomodulation than live bacteria. Butyrate and other SCFAs could theoretically support Treg function and reduce inflammation.

16.4 Antibiotics

Antibiotics can alter lesion growth in animal models, and broad-spectrum antibiotics may reduce dysbiosis-associated inflammation. However, indiscriminate antibiotics risk resistance, microbiome damage and recurrence. Precision antibiotics targeting specific pathobionts would be preferable.

16.5 Fecal, Vaginal or Uterine Microbiota Transplantation

FMT is established for recurrent *Clostridioides difficile* infection, but its role in endometriosis is speculative. Vaginal or uterine microbiota transplantation is even more experimental. Safety, donor screening and reproductive implications are major concerns.

17. Immune-Targeted Adjunctive Therapies

Several immune targets are being explored preclinically: macrophage reprogramming, CSF1R inhibition, PI3Kγ modulation, CD47-SIRPα blockade to enhance phagocytosis, NK-cell activation, IL-12 therapy, IL-17 modulation, mast-cell stabilization, NET inhibition and dendritic cell reprogramming [12,22]. These approaches could complement hormonal therapy by restoring immune clearance rather than only suppressing lesion stimulation. However, endometriosis is benign and often affects women seeking pregnancy. Immune interventions must avoid impairing implantation, fetal tolerance or host defense. Local or time-limited approaches may be safer than systemic immune modulation. Biomarker-defined subgroups will be essential.

18. Revisiting Treatment Algorithms

A revised algorithm could classify patients by dominant biological phenotype: (i) Hormone-dominant phenotype: cyclic symptoms, estrogen-responsive lesions, good response to suppression. (ii) Inflammatory-microbial phenotype: bowel symptoms, dysbiosis markers, high inflammatory cytokines, recurrent pain despite suppression. (iii) Fibrotic-deep phenotype: organ distortion, fibrosis, nerve involvement, surgical expertise needed. (iv) Pain-sensitization phenotype: persistent pain disproportionate to lesion burden, mast-cell/nerve and central sensitization features. (v) Infertility-immune phenotype: implantation failure, altered uterine immune environment, endometrial microbiome concerns. Treatment could then be personalized. Hormonal therapy remains foundational for hormone-dominant disease. Surgery is prioritized for obstructive or fibrotic lesions. Microbiome and immune adjuncts are studied for inflammatory-microbial and recurrence-prone phenotypes. Pain neuroscience interventions are integrated when sensitization dominates.

19. Biomarkers and Precision Medicine

Potential biomarkers include gut microbiome signatures, vaginal/endometrial microbiota profiles, LPS-binding protein, intestinal permeability markers, β-glucuronidase activity, SCFAs, inflammatory cytokines, macrophage markers, NK cytotoxicity, Th17/Treg ratios, mast-cell mediators, prostaglandins and estrogen metabolites. Imaging and lesion phenotyping should be integrated with biomarkers. A major challenge is contamination in low-biomass reproductive tract microbiome studies. Rigorous controls are essential. Another challenge is variability across menstrual cycle, sexual activity, antibiotics, hormones and geography. Longitudinal within-patient designs may be more informative than cross-sectional comparisons.

20. Research Gaps

Key gaps include causality, standardization and phenotype specificity. Does dysbiosis precede endometriosis or result from it? Which microbial communities are causal? Which immune alterations are primary? Do microbiome interventions reduce lesions or only symptoms? How do hormonal therapies alter microbiota? Does surgery reset or worsen microbial-immune states? Can postoperative dysbiosis predict recurrence? Animal models are useful but imperfect. Human lesions are heterogeneous: superficial peritoneal, ovarian endometrioma and deep infiltrating disease may have different immune-microbial dynamics. Future studies must stratify by lesion type, stage, pain phenotype and fertility status.

21. Ethical and Clinical Caution

Patients with endometriosis often face delayed diagnosis and may seek alternative therapies. Microbiome-based claims are proliferating faster than evidence. Clinicians should avoid dismissing patient interest, but also avoid overpromising. Probiotics, diets and supplements may help some patients but are not substitutes for evidence-based hormonal, surgical, pain or fertility care. Microbiome testing is not yet standardized for routine endometriosis management. FMT or reproductive tract microbiota transplantation should not be used outside research. Antibiotic use should be cautious. The goal is rigorous integration, not replacement of established care.

22. Methodological Challenges in Studying the Microbiota-Endometriosis Axis

Microbiome studies in endometriosis face several methodological challenges. The female reproductive tract contains low-biomass niches, particularly the endometrium and peritoneal cavity, where contamination from reagents, sampling devices, skin, vagina or laboratory environment can distort results. Rigorous negative controls, standardized sampling, quantitative bacterial load assessment and careful interpretation are essential. Detection of microbial DNA does not necessarily prove viable bacteria or active microbial function. Another challenge is compartment specificity. Stool microbiota does not equal vaginal microbiota; vaginal microbiota does not equal endometrial microbiota; and endometrial microbiota does not necessarily represent the peritoneal cavity. Each compartment has different oxygen tension, immune exposure, mucus, hormones and microbial biomass. Endometriosis may affect each niche differently. For example, deep infiltrating disease involving bowel may have stronger gut microbial associations than isolated superficial peritoneal disease. Ovarian endometriomas may have distinct inflammatory and iron-rich microenvironments.

Timing also matters. Microbiota and immune profiles vary across the menstrual cycle, hormonal therapy exposure, sexual activity, antibiotic use, bowel function, diet and surgery. Many studies include women already using hormonal therapy, which may alter both immune and microbial states. Others compare surgical patients with different indications, introducing confounding by pain, infertility, fibroids or ovarian cysts. Longitudinal designs before treatment, during treatment and after surgery are needed to distinguish cause, consequence and treatment effect. Functional analysis is more informative than taxonomy alone. 16S rRNA sequencing identifies bacterial composition but cannot reliably measure β-glucuronidase activity, LPS structure, SCFA output, tryptophan metabolism or virulence factors. Shotgun metagenomics, metatranscriptomics, metabolomics and culture-based validation will be necessary. Integration with immune phenotyping—macrophage polarization, NK cytotoxicity, Th17/Treg ratio, mast-cell mediators—should become standard.

23. Fertility, Implantation and the Immune-Microbial Interface

Endometriosis-associated infertility is multifactorial. Distorted pelvic anatomy, adhesions, endometriomas, reduced ovarian reserve, chronic inflammation, altered folliculogenesis, impaired oocyte quality, sperm dysfunction, tubal transport abnormalities and impaired implantation may all contribute. The immune-microbial axis may influence several of these mechanisms. At the ovarian level, endometriomas create an iron-rich, inflammatory environment that may impair follicular function. Macrophages, oxidative stress and microbial products could influence granulosa cells and oocyte competence. Surgical removal of endometriomas may improve access or reduce inflammation but can reduce ovarian reserve, especially in bilateral or recurrent disease. If immune-microbial inflammation contributes to endometrioma recurrence or ovarian injury, adjunctive non-surgical strategies could be valuable.

At the endometrial level, implantation requires a carefully timed immune tolerance state, involving uterine NK cells, macrophages, dendritic cells, Tregs and cytokines. Endometriosis may impair endometrial receptivity through progesterone resistance, inflammatory cytokines and altered immune cell maturation. Endometrial or vaginal dysbiosis may further alter implantation through local inflammation, epithelial barrier disruption or microbial metabolites. However, the uterine microbiome remains controversial because of low biomass and contamination risk. For assisted reproduction, the implications are complex. Hormonal suppression before ART may improve outcomes in selected patients, but prolonged suppression delays conception. Surgery before ART is not universally beneficial and may harm ovarian reserve. Microbiome-directed interventions are not yet evidence-based for improving ART outcomes in endometriosis, but future trials could test whether correcting dysbiosis or inflammatory signatures improves implantation or reduces miscarriage.

24. Pain Phenotypes and Microbial-Immune Neurobiology

Pain in endometriosis is not explained solely by lesion size or location. Some women with extensive disease have modest pain, while others with minimal lesions have severe pain. This discrepancy reflects neuroimmune mechanisms, central sensitization, mast-cell activation, nerve fiber growth, pelvic floor dysfunction and comorbid pain syndromes such as irritable bowel syndrome, bladder pain syndrome and vulvodynia. Microbial dysbiosis may contribute to pain through several pathways. Gut dysbiosis can increase intestinal permeability and visceral sensitivity. LPS and inflammatory metabolites can activate macrophages and mast cells, which release prostaglandins, histamine, tryptase and NGF. These mediators sensitize nociceptors. Dysbiosis may also alter tryptophan metabolism, serotonin signaling and vagal pathways, influencing mood and pain perception.

This may explain overlap between endometriosis and gastrointestinal symptoms. In some patients, bowel symptoms may reflect deep bowel lesions; in others, they may reflect dysbiosis, visceral hypersensitivity or irritable bowel syndrome. Hormonal therapy may reduce cyclic pelvic pain but not fully address gut-brain-immune pain loops. Surgery may remove lesions but not central sensitization. Therefore, treatment should include pain phenotyping, pelvic floor therapy, dietary assessment, gut symptom evaluation and psychological support. Microbiome-directed pain therapy remains investigational, but plausible strategies include probiotics, prebiotics, low-inflammatory dietary patterns, mast-cell stabilization, SCFA restoration and reduction of LPS-producing dysbiosis. Trials should measure pain subtypes, not only lesion size.

25. Reconsidering Recurrence: Residual Lesions or Residual Ecology?

Endometriosis recurrence is often described anatomically: residual lesions remain after incomplete excision, or new lesions arise after surgery. This is true, but incomplete. Recurrence may also represent persistence of the ecological conditions that allowed lesions to form in the first place. If macrophage polarization, NK-cell dysfunction, estrogen recycling, intestinal permeability and microbial dysbiosis persist, the pelvis remains permissive for lesion re-establishment. This ecological view explains why postoperative hormonal suppression reduces recurrence: it removes estrogenic fuel from a permissive system. But if suppression is discontinued for pregnancy or due to side effects, recurrence can occur. It also explains why repeated surgery alone may fail: surgery removes lesions but can intensify adhesions, inflammation and tissue injury while leaving systemic drivers unchanged. A recurrence-prevention model should therefore combine excellent surgical technique, ovarian reserve preservation, long-term hormonal suppression when appropriate, and future immune-microbial adjuncts. Perioperative microbiome modulation could aim to reduce LPS-driven inflammation, support barrier integrity and improve immune clearance. Anti-adhesion strategies may need to consider macrophage and mast-cell biology. Postoperative monitoring could include symptoms, imaging, inflammatory markers and, eventually, microbial-metabolic signatures.

26. Digital, Omics and AI-Driven Precision Endometriosis Care

Endometriosis precision medicine will require integration of diverse data. Imaging defines lesion location and anatomy. Surgical findings classify lesion phenotype. Histology confirms diagnosis. Single-cell and spatial omics reveal immune and stromal states. Microbiome profiling defines dysbiosis. Metabolomics measures estrobolome and inflammatory metabolites. Patient-reported outcomes capture pain, fatigue, bowel symptoms, sexual function and quality of life. Artificial intelligence may help identify patterns invisible to clinicians. For example, a model could identify a phenotype combining bowel symptoms, high *Prevotella* abundance, elevated LPS-binding protein, Th17 skewing and poor response to progestins. Another phenotype might combine deep fibrosis, mast-cell activation and neuropathic pain features. Such models could guide therapy: hormonal suppression, surgery, microbiome intervention, immune modulation or pain neuroscience care. However, AI is only as good as its data. Endometriosis datasets are fragmented, biased toward surgical patients and inconsistent in definitions. Future registries should collect standardized imaging, surgical staging, lesion subtype, medication history, microbiome samples, immune biomarkers and longitudinal outcomes. Patient privacy and consent are especially important because reproductive and microbiome data are sensitive.

27. Future Directions

Future research should include longitudinal cohorts from adolescence to diagnosis, multi-omics profiling of gut/vaginal/endometrial/peritoneal microbiota, immune phenotyping, estrogen metabolomics and lesion single-cell analysis. Trials should test probiotics, prebiotics, postbiotics and dietary interventions as adjuncts to hormonal or surgical treatment. Perioperative trials could evaluate whether microbiome modulation reduces recurrence or adhesions. Mechanistic studies should identify how microbial metabolites regulate macrophages, NK cells, T cells and mast cells in lesion environments. The field also needs practical clinical endpoints. Microbiome interventions should be tested against pain, recurrence, fertility, bowel symptoms, inflammatory biomarkers and quality of life. Studies should stratify by lesion subtype and hormonal therapy status. Importantly, microbiome therapies should be evaluated as adjuncts, not replacements, for established care until strong evidence exists.

28. An Integrated Immune-Microbial Endocrine Loop Model

We propose a loop model: (i) **Microbial dysbiosis** increases LPS, alters estrogen metabolism and reduces anti-inflammatory metabolites. (ii) **Immune dysregulation** impairs NK clearance, polarizes macrophages, activates Th17/Tregs and mast cells. (iii) **Endocrine amplification** through estrogen and progesterone resistance supports lesion growth and inflammatory signaling. (iv) **Lesion remodeling** produces angiogenesis, neurogenesis, fibrosis and pain. (v) **Feedback** from lesions and inflammation reshapes microbial communities and systemic immunity. Hormonal therapy interrupts endocrine amplification. Surgery removes lesion burden. Microbiome and immune therapies may interrupt upstream and feedback drivers. Combined, phenotype-guided care may be more durable than any single modality.

29. Conclusion

Endometriosis is best understood as an immune-microbial-endocrine disease rather than a purely hormonal or surgical condition. Immune cells determine whether retrograde endometrial fragments are cleared or become lesions. Microbial dysbiosis may regulate this immune environment through LPS/TLR4 signaling, intestinal permeability, estrobolome activity, SCFA depletion and systemic inflammation. Lesions then perpetuate immune dysfunction, estrogenic signaling, pain and microbial shifts. This paradigm does not replace hormonal or surgical treatments; it reframes them. Hormonal therapy remains essential but may need adjunctive immune-microbial modulation. Surgery remains indispensable for many patients but should be integrated with strategies that reduce recurrence and inflammatory persistence. The future of endometriosis management lies in precision phenotyping: identifying the dominant hormonal, immune, microbial, fibrotic and pain mechanisms in each patient and tailoring treatment accordingly.

Clinical Trial Number

Not applicable.

Conflict of Interest

The authors declare no competing interests that may have influenced in this manuscript.

Generative AI statement

The authors declare that Gen AI and large language models (LLMs) were used in this manuscript. Generative AI items like “QuillBot” and “DeepL” were used for structural editing and improve handwriting of the text. Also, the “NOAH AI” platform was used for some parts of figures illustrations.

Author Agreement

This paper is submitted with the agreement of all its co-authors and the author list has been approved by all authors.

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Author Contribution

We agree that the author list and order is correct and complete. We understand that any changes to the author list (additions, deletions, order changes) after submission will require a formal request to the editor signed by all authors. Order list include:

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