

Gut microbiome and endometriosis: a bidirectional interaction

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ABSTRACT

Background. Endometriosis is a chronic estrogen-dependent inflammatory disease with a multifactorial pathogenesis. Increasing evidence suggests that the gut microbiome contributes to disease development through interactions involving immune regulation, intestinal barrier integrity, microbial metabolites, and estrogen metabolism, while endometriosis may also alter microbial composition.

Aim. To summarize current evidence on the relationship between the gut microbiome and endometriosis, focusing on pathogenic mechanisms, microbial alterations, diagnostic potential, and microbiome-directed therapies.

Material and methods. A narrative literature review with a structured search strategy was conducted using PubMed, Embase, the Cochrane Library, and Google Scholar. Search terms included endometriosis, gut microbiome, dysbiosis, estrobolome, intestinal permeability, inflammation, oxidative stress, probiotics, and fecal microbiota transplantation.

Results. Current evidence supports a bidirectional relationship between gut dysbiosis and endometriosis. Microbial alterations may promote immune dysregulation, increased intestinal permeability, oxidative stress, lipopolysaccharide-mediated inflammation, and enhanced estrogen recirculation via the estrobolome, facilitating lesion establishment and persistence. Conversely, chronic inflammation, hormonal treatment, surgery, and bowel involvement may further modify the gut microbiome. Although no consistent microbial signature has been identified, several taxa and functional pathways have been associated with disease phenotype and severity.

Conclusions. The gut microbiome is an important modifier of endometriosis rather than a single causative factor. Microbiome-derived biomarkers and targeted therapies show promise but require validation in prospective studies before routine clinical use.

Key words: *endometriosis, gut microbiome, dysbiosis, estrobolome, intestinal permeability, inflammation.*

1. Endometriosis as a clinical and inflammatory disease

Endometriosis is defined by the presence of endometrial-like glands and stroma outside the uterine cavity. Lesions most often involve the pelvic peritoneum, ovaries, uterosacral ligaments, and rectovaginal septum, but may also occur in the bowel, bladder, ureters, diaphragm, lungs, or surgical scars. This distribution supports the view that endometriosis is not a purely local disease, but a chronic condition involving hormone-dependent proliferation, inflammation, tissue remodeling, fibrosis, pain sensitization, and, in many patients, infertility [30].

Endometriosis is estimated to affect about 5–10% of women of reproductive age, although this likely underestimates the true burden because many patients remain undiagnosed. It may also occur in adolescents and, less commonly, after menopause. Among infertile women, estimates reach 30–50%, which explains why endometriosis is treated both as a pain disorder and a fertility-related condition [11,58]. The clinical picture is highly variable: patients may report dysmenorrhea, dyspareunia, chronic pelvic pain, painful ovulation, heavy bleeding, dysuria, dyschezia, or gastrointestinal complaints, while others are diagnosed during infertility evaluation or incidental imaging [58,70]. This variability contributes to diagnostic delay and supports the search for non-invasive markers.

Clinically, endometriosis is usually divided into superficial peritoneal disease, ovarian endometrioma, and deep infiltrating endometriosis. Deep infiltrating disease is particularly important because it may invade the rectovaginal septum, uterosacral ligaments, urinary tract, or bowel wall [1,43]. Intestinal endometriosis directly links gynecology with gastroenterology. Bowel involvement is estimated in roughly 3–37% of women with endometriosis, depending on the population and diagnostic method [24]. Lesions most often occur near the rectosigmoid junction, followed by the sigmoid colon and appendix, although other gastrointestinal or even hepatobiliary sites have also been reported [2]. Patients may describe constipation, diarrhea, cyclic rectal bleeding, dyschezia, obstructive symptoms, or vague abdominal pain. Because these complaints overlap with irritable bowel syndrome and inflammatory bowel disease, intestinal endometriosis is especially relevant to microbiome-focused research [10,24].

Modern diagnostic practice no longer treats laparoscopy as the only acceptable starting point. The ESHRE guideline emphasizes symptoms, transvaginal ultrasound, and MRI, especially when deep disease is suspected [7]. TVUS may reveal hypoechoic or mixed-echogenicity bowel wall lesions, while signs such as the comet sign, tail sign, Indian headdress, or moose antler sign reflect how nodules, fibrosis, and adhesions alter the muscularis propria and surrounding tissues [9,13,16,23]. MRI provides a wider field of view, helps assess the depth of infiltration, and supports surgical planning when lesions involve the rectum, bladder, ureters, or

multiple pelvic compartments [10,42]. The ENZIAN classification further allows radiologists and surgeons to describe deep infiltrating endometriosis in a structured way [60].

2. Origin, genetics, and hormonal background

No single theory fully explains the origin of endometriosis. Sampson's theory of retrograde menstruation remains the most intuitive explanation for many pelvic lesions: menstrual blood enters the peritoneal cavity through the fallopian tubes, carrying viable endometrial cells that may attach, survive, and proliferate [37]. However, this model cannot explain all extrapelvic lesions or the fact that retrograde menstruation occurs in many women who never develop the disease. Other hypotheses, including coelomic metaplasia and stem/progenitor cell models, suggest that peritoneal or coelomic epithelial cells, bone-marrow-derived cells, or endometrial progenitors may transform or migrate under specific hormonal, inflammatory, or developmental conditions and contribute to lesion formation [45,67,69].

Genetic, epigenetic, environmental, and nutritional factors further modify disease susceptibility. Family and twin studies indicate that inherited predisposition plays an important role, while genome-wide and epigenetic studies point to pathways related to estrogen signaling, progesterone resistance, cell adhesion, chromatin regulation, and proliferation [1,44,31]. Epigenetic dysregulation is particularly relevant because endometriotic tissue may behave differently from eutopic endometrium despite related developmental origins [31]. Diet probably acts as a modifying rather than causal factor: vegetables, fruit, omega-3 fatty acids, and selected micronutrients may reduce inflammatory tone, whereas alcohol, red meat, trans fats, and saturated fats may promote inflammation in susceptible patients [55,59]. This is biologically plausible because long-term dietary patterns can influence the gut microbiome, intestinal barrier function, estrogen metabolism, and systemic inflammation [17].

Estrogen drives much of endometriosis biology. Lesions rely on local and systemic estrogenic stimulation and often show altered estrogen and progesterone receptor signaling. Endometriotic tissue may increase local estrogen production through aromatase and 17 β -hydroxysteroid dehydrogenase-1 activity, while progesterone resistance weakens the anti-proliferative control that normally limits endometrial growth [66]. ER α and ER β have different roles, and ER β has been linked to cell survival, invasion, adhesion, and inflammatory signaling in endometriotic lesions [12,66]. Experimental studies also show that estrogen receptor signaling contributes to the establishment of endometriosis-like lesions in mouse models [51]. Additional pathways, including SGK1 and RERG, connect estradiol and prostaglandin E2 with the survival and proliferation of endometriotic cells [48,50].

3. Immune escape, oxidative stress, and the bowel microenvironment

The immune system does not simply react to endometriosis after lesions appear. It participates in lesion survival from the earliest stages. Neutrophil levels increase in peritoneal fluid, while IL-8, epithelial neutrophil-activating peptide-78, and human neutrophil peptides 1-3 recruit and activate these cells. These markers correlate with pain and dysmenorrhea in some studies, whereas animal experiments have shown that early neutrophil depletion reduces lesion formation [21, 52, 53, 64]. Neutrophil extracellular traps (NETs) appear particularly relevant in deep infiltrating endometriosis, where researchers have reported elevated circulating NET levels and a more pronounced inflammatory state [73].

Macrophages represent another central component of the immune response. They produce MCP-1, IL-1 β , IL-6, and TNF- α , promote angiogenesis, and create a microenvironment that supports tissue repair, fibrosis, and immune tolerance rather than efficient clearance of ectopic cells [65]. Single-cell studies have described coordinated transcriptional programs that promote immunotolerance and angiogenesis across eutopic and ectopic tissues [71]. Other studies have linked macrophage phenotypes with impaired phagocytosis and persistence of endometriotic debris or cells, helping to explain why retrograde menstrual tissue survives in some patients but not in others [22].

Macrophages also contribute to pain generation. Nerve fibers produce CSF-1 and MCP-1/CCL2, while estradiol promotes macrophage migration toward these fibers. Macrophages subsequently release nerve growth factor, brain-derived neurotrophic factor, and other neurotrophins, which intensify neuroinflammation

and peripheral sensitization [34, 68]. This mechanism provides a tissue-level explanation for chronic pelvic pain and links immune activation with the symptoms that most profoundly affect quality of life.

Natural killer (NK) cells normally eliminate abnormal cells, but this defense is impaired in endometriosis. Studies have described reduced expression of activating receptors together with increased expression of inhibitory receptors. Platelets, IL-6, and TGF- β may suppress NK-cell activity, while ectopic stromal cells can use IL-15 and other signaling pathways to inhibit degranulation, IFN- γ release, granzyme B activity, and perforin-mediated cytotoxicity [3, 20, 75]. This immune escape resembles a controlled yet persistent failure of immune surveillance: the immune system remains sufficiently active to sustain inflammation but not effective enough to eliminate ectopic lesions.

Oxidative stress further amplifies this process. Retrograde bleeding introduces iron into the peritoneal cavity, and endometriotic lesions can accumulate iron through transporters such as DMT1. Excess iron promotes the generation of hydroxyl radicals and iron-mediated oxidative stress, resulting in tissue damage and altered cell survival pathways [61]. Patients with deep infiltrating endometriosis, especially those with intestinal involvement, may exhibit higher levels of advanced oxidation protein products and nitrates or nitrites than patients with other forms of the disease [47]. Nitric oxide and shifts in TH1/TH2 may further promote lesion growth in experimental models [39]. At the same time, signaling pathways such as MAPK/ERK and mTOR/AKT link oxidative stress to cellular proliferation and survival [49].

The bowel microenvironment adds another layer of complexity. When inflammation disrupts intestinal tight junctions, intestinal permeability may increase. The source manuscript referred to this phenomenon as a “leaky gut” phenotype and associated it to zonulin, claudin-1, claudin-2, and myosin IXB. Pilot studies suggest that intestinal permeability may be altered in some patients with endometriosis, although larger, well-controlled studies are still required to confirm these findings [74]. A compromised intestinal barrier can allow bacterial products, endotoxins, and microbial metabolites to enter the systemic circulation. Although current evidence does not demonstrate that increased intestinal permeability causes endometriosis, it supports a biologically plausible link between gastrointestinal symptoms, dysbiosis, immune activation, and pelvic inflammation [41].

4. Gut microbiome, dysbiosis, and the gut-reproductive axis

The microbiota comprises bacteria, viruses, fungi, protozoa, and archaea that inhabit specific ecological niches. The microbiome refers to the collective genetic material of these microorganisms. In the gut, they contribute to nutrient digestion, maintenance of the mucosal barrier, metabolite synthesis, immune system education, and the prevention of pathogen overgrowth [6,8,19]. Short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, support epithelial integrity and modulate immune signaling. They also participate in communication among the gut, the nervous system, and the endocrine organs [62]. When microbial diversity declines or pathobionts expand, eubiosis shifts toward dysbiosis. Dysbiosis can increase intestinal permeability, reduce colonization resistance, alter metabolite production, and activate inflammatory pathways [38].

Endometriosis frequently overlaps clinically with gastrointestinal symptoms, and many patients undergo evaluation for IBS-like complaints before receiving the gynecological diagnosis. This clinical overlap encouraged researchers to investigate the gut-reproductive axis. The concept does not claim that the gut microbiome acts in isolation. Rather, it integrates microbial metabolites, endotoxins, cytokines, estrogen metabolism, vagal signaling, and the hypothalamic-pituitary-gonadal axis into a complex regulatory network [17]. Within this network, bacterial products can influence immune homeostasis and sensory pathways, while reproductive hormones can, in turn, reshape microbial niches.

Several mechanisms support the biological plausibility of this relationship. First, dysbiosis can enrich Gram-negative bacteria and increase exposure to lipopolysaccharide (LPS). LPS activates macrophages and other innate immune cells, which then release TNF- α , IL-1 β , IL-6, and chemokines that promote inflammation, stromal cell proliferation, and angiogenesis. This mechanism is consistent with the bacterial contamination hypothesis, which proposes that microbial products prime immune cells and reinforce peritoneal inflammation [63]. Second, dysbiosis may reduce the abundance of beneficial taxa, such as *Lactobacillus* or

Bifidobacterium, thereby weakening the mucosal barrier, and decreasing the anti-inflammatory metabolite production. Third, microbial enzymes can influence estrogen recirculation through the estrobolome, a mechanism particularly relevant to endometriosis because the disease is strongly dependent on estrogen signaling [4,17].

Researchers have also linked dysbiosis to neuroimmune pathways. Gut microorganisms and their metabolites can influence serotonin, gamma-aminobutyric acid (GABA), glutamatergic signaling, and SCFA-mediated pathways. These mechanisms may contribute to visceral hypersensitivity and chronic pelvic pain in addition to lesion growth [62]. The original manuscript cited studies on chronic pelvic pain to demonstrate that reduced microbial diversity has been observed in several pain syndromes. However, these findings should be interpreted cautiously, as evidence derived from conditions such as chronic prostatitis, migraine, or IBS cannot be directly extrapolated to endometriosis.

5. Microbial patterns reported in endometriosis

Human studies have not yet identified one consistent microbial signature for endometriosis. However, several recurring patterns have emerged. Svensson and colleagues compared women with endometriosis with healthy participants and found lower alpha- and beta-diversity in the endometriosis group. They also reported higher abundances of *Bacteroides*, *Parabacteroides*, *Oscillospira*, and *Coprococcus*, together with lower abundances of *Paraprevotella*, *Lachnospira*, and *Turicibacter* [25]. Ata and colleagues compared the vaginal, cervical, and gut microbiota in women with stage III/IV endometriosis and healthy controls. They observed lower abundances of *Sneathia*, *Barnesiella*, and *Gardnerella* in the endometriosis group, while two patients with deep bowel involvement exhibited a gut dominant *Escherichia-Shigella* microbiome profile; both subsequently required segmental colon resection [5]. Although this observation does not establish a clinically useful prediction tool, it highlights the importance of evaluating bowel endometriosis as a distinct entity in microbiome analysis and research.

Animal studies further support the concept that endometriosis can alter the gut microbiota. Hantschel and colleagues induced endometriosis in mice and observed increased abundances of *Escherichia* and *Shigella* during the acute phase of lesion formation [28]. Bailey and Coe studied rhesus macaques and found lower levels of *Lactobacillus* and higher abundance of Gram-negative bacteria in animals with endometriosis, accompanied by greater intestinal inflammation [26]. These models are valuable because they reduce several confounding factors present in human studies. Nevertheless, they do not eliminate the challenge of translation as lesion biology, microbial ecology, and hormonal conditions differ between animal models and human disease.

Studies examining the microbiota of peritoneal fluid, stool, and endometrial lesions provide additional local insights. Huang and colleagues reported that gut microbiota profiling outperformed the cervical microbiota profiling in the early diagnostic classification of endometriosis and identified increased abundances of Gram-negative bacteria, including *Pseudomonas* and *Prevotella*, in affected patients [76]. Hernandez and colleagues analyzed deep infiltrating lesions and found higher levels of *Alishewanella*, *Enterococcus*, and *Pseudomonas*, together with lower levels of *Lactobacillus*, within endometriotic tissue. In contrast, vaginal or eutopic endometrial samples demonstrated fewer microbial differences [14]. These findings suggest that the local microbiota associated with deep lesions may differ from that of the vagina or eutopic endometrium, particularly in deep infiltrating disease.

The Firmicutes/Bacteroidetes ratio has been reported repeatedly, although it should be interpreted with caution. Yuan and colleagues induced endometriosis in mice and observed an increased Firmicutes/Bacteroidetes ratio after 42 days, whereas the control and endometriosis groups were more similar at earlier time points [40]. Chadchan and colleagues treated mice with antibiotics and found that metronidazole reduced lesion burden while altering the gut microbiome, including a reduction in the Firmicutes/Bacteroidetes ratio [15]. These findings support a role of the gut microbiota in disease activity, but the ratio itself is not a specific clinical biomarker, as it also varies in obesity, inflammatory bowel disease, and other metabolic or inflammatory conditions.

Mendelian randomization and large-cohort studies have further advanced the field. Liu and colleagues reported that a higher genetically abundance of *Clostridiales_vadin_BB60_group*, *Oxalobacteraceae*, *Desulfovibrio*, *Haemophilus*, and *Holdemania* was associated with lower risk of endometriosis, whereas *Porphyromonadaceae* and *Anaerotruncus* emerged as potential risk-associated taxa [57]. Pérez-Prieto and colleagues analyzed a large cohort and found that gut microbial functions related to fatty acid biosynthesis and long-chain fatty acid metabolism were more pronounced in women with endometriosis. They linked these functional pathways to fatty acid synthase, an estrogen-modulated enzyme that promotes endometrial cell proliferation [36]. This functional perspective may ultimately prove more useful than genus-level taxonomic comparisons, as microbial metabolic pathways are often more stable than the exact taxa that encode them.

Overall the current literature points toward a recurring pattern rather than a single causative microorganism: reduced microbial diversity in some cohorts, enrichment of Gram-negative and pro-inflammatory taxa in others, reduced *Lactobacillus* abundance in animal models and lesion-based studies, altered Firmicutes/Bacteroidetes dynamics in mouse models, and changes in microbial metabolic pathways linking gut microorganisms with estrogen metabolism, lipid metabolism, and inflammation. Future research should therefore move beyond the search for a single universal bacterial marker and instead integrate clinical phenotype, menstrual cycle phase, hormonal treatment, lesion location, dietary factors, antibiotic exposure, surgical history, and sequencing methodology when characterizing the microbiome in endometriosis.

6. Estrobolome and beta-glucuronidase as a mechanistic mediators

The estrobolome represents one of the most compelling mechanistic frameworks linking the gut microbiome to the pathophysiology of endometriosis. It encompasses the collective repertoire of microbial genes involved in estrogen biotransformation, among which β -glucuronidase has received the greatest attention. Under physiological conditions, estrogens undergo hepatic glucuronidation to facilitate biliary excretion. Within the intestinal lumen, microbial β -glucuronidases hydrolyze estrogen glucuronides, regenerating biologically active estrogens that can be reabsorbed via enterohepatic circulation, thereby modulating systemic estrogen exposure [4,72]. Consequently, alterations in the taxonomic composition and functional potential of the gut microbiota may substantially influence estrogen bioavailability, with important implications for endocrine homeostasis and the progression of estrogen-dependent disorders.

Rather than functioning as a uniform metabolic entity, the estrobolome comprises a diverse repertoire of enzymes with distinct structural and catalytic properties. Pollet et al. systematically characterized the human intestinal β -glucuronidase landscape, demonstrating marked heterogeneity in enzyme architecture and substrate specificity across bacterial taxa [57]. These findings suggest that interindividual differences in microbial community composition may translate into substantial variation in the metabolism of estrogen conjugates, xenobiotics, and other glucuronidated metabolites. Consistent with this concept, Komorowski and Pezo proposed that the functional capacity of the estrobolome, rather than microbial taxonomy alone, represents a key determinant of susceptibility to hormone-dependent diseases and therapeutic responsiveness [36]. Although their discussion primarily focused on oncological conditions, the underlying biological principles are highly relevant to endometriosis, given its pronounced dependence on estrogen signaling, chronic inflammatory milieu, and invasive tissue remodeling.

Experimental evidence further supports the pathological relevance of this pathway. Wei et al. demonstrated increased expression of GUSB, the gene encoding β -glucuronidase, in both the serum and ectopic endometriotic lesions, including bowel and uterosacral disease, with expression levels positively correlating with circulating estradiol concentrations [72]. Functional analyses revealed that GUSB enhances the proliferative, migratory, and invasive capacities of endometrial stromal cells while promoting macrophage polarization toward an M2 phenotype. This was accompanied by increased expression of NGF, TNF- α , and BDNF, implicating β -glucuronidase in the coordinated regulation of inflammation, neuroangiogenesis, and lesion progression [32]. Collectively, these findings support a mechanistic model in which microbiome-derived β -glucuronidase augments estrogen reactivation and inflammatory signaling, establishing a self-perpetuating microenvironment that favors ectopic lesion survival, tissue remodeling, and pain generation.

Despite these observations, β -glucuronidase is unlikely to function as an independent driver of disease. Instead, its biological effects should be considered within the broader network of pathogenic processes that characterize endometriosis, including dysregulated steroidogenesis, aberrant estrogen receptor signaling, altered immune cell polarization, oxidative stress, epithelial barrier dysfunction, and neuroimmune interactions. Taken together, these observations position the estrobolome as a central interface between microbial metabolism and estrogen signaling. Whether these alterations represent a primary pathogenic mechanism or arise secondary to disease progression remains an area of active investigation.

7. Does dysbiosis cause endometriosis, or does endometriosis cause dysbiosis?

Current evidence suggests that the relationship between intestinal dysbiosis and endometriosis is bidirectional, with the relative contribution of each pathway likely depending on disease stage, lesion phenotype, and host characteristics. On one hand, microbial dysbiosis may precede lesion establishment by promoting intestinal barrier dysfunction, increasing lipopolysaccharide (LPS) translocation, enhancing Th17/IL-17 signaling, stimulating macrophage activation, and augmenting estrogen recirculation through the estrobolome. Together, these alterations create a pro-inflammatory peritoneal microenvironment that favors the implantation and persistence of refluxed endometrial tissue rather than its immune-mediated clearance. Experimental studies support this sequence, demonstrating that antibiotic-induced microbiota depletion attenuates lesion growth, whereas fecal microbiota transplantation from endometriosis-bearing donors restores inflammatory responses and promotes lesion development in recipient animals [35,56].

Conversely, endometriosis itself may drive secondary alterations in the intestinal microbiome. Clinical studies have identified distinct microbial signatures associated with advanced disease, including enrichment of *Escherichia-Shigella* in patients with deep bowel involvement [5]. Similarly, longitudinal animal studies demonstrated progressive microbiome remodeling during lesion development, while spontaneous endometriosis in non-human primates was associated with both intestinal dysbiosis and local gastrointestinal inflammation [26,40]. In clinical settings, this reciprocal relationship is likely further influenced by disease-related factors, including chronic inflammation, surgical intervention, hormonal therapies, antibiotic exposure, altered gastrointestinal motility, dietary modifications, and reduced physical activity.

Recognition of this bidirectional interaction provides a plausible explanation for the substantial heterogeneity observed across microbiome studies. Many investigations analyze biologically diverse populations comprising superficial peritoneal endometriosis, ovarian endometriomas, deep infiltrating disease, and post-surgical cases despite their distinct pathophysiological characteristics. Additional sources of variability, including menstrual cycle phase, endogenous hormonal status, hormonal treatment, body mass index, dietary habits, and coexisting gastrointestinal disorders such as irritable bowel syndrome, further complicate the identification of reproducible microbial signatures and likely contribute to inconsistencies between studies.

From a clinical perspective, these findings suggest that microbiome profiling is unlikely to replace established diagnostic modalities such as imaging, clinical examination, or histopathological confirmation. Nevertheless, functional or taxonomic microbial biomarkers may ultimately complement current diagnostic strategies, particularly in patients with nonspecific symptoms or when imaging findings do not adequately explain gastrointestinal manifestations. Supporting this possibility, Khan et al. reported higher *Escherichia coli* abundance in the menstrual blood of women with both ovarian endometriomas and superficial peritoneal lesions compared with those presenting ovarian endometriomas alone [33]. Other studies have similarly proposed that gut and peritoneal microbial signatures may facilitate disease stratification and phenotypic classification [76]. Although these observations remain preliminary and require validation in large prospective cohorts, they address an important unmet clinical need, as delayed diagnosis and the limited detectability of early or superficial lesions continue to represent major challenges in the management of endometriosis. Beyond their diagnostic potential, these findings also provide the rationale for exploring microbiome-directed interventions as adjunctive therapeutic strategies.

8. Therapeutic implications and limits of microbiome modulation

The growing recognition of microbiome involvement in endometriosis has stimulated considerable interest in microbiome-directed therapeutic strategies. Unlike surgery or prolonged hormonal suppression, these approaches seek to modify disease-associated microbial and immunometabolic pathways while minimizing systemic adverse effects. Nevertheless, the available evidence remains preliminary, with most data derived from preclinical models and small clinical studies.

Antibiotic-based approaches have provided important proof of concept for microbial involvement in disease progression but are not currently supported as therapeutic strategies. In experimental models, metronidazole attenuated lesion development while simultaneously reshaping gut microbial composition [56]. Similarly, Khan et al. demonstrated that preoperative levofloxacin, particularly when combined with a GnRH agonist, reduced the abundance of endometriosis-associated bacteria, including *Gardnerella*, *Prevotella*, and *Atopobium*, and produced greater reductions in chronic endometritis, inflammatory activity, cellular proliferation, and angiogenesis than hormonal treatment alone [70]. Although these findings reinforce the contribution of microbial dysbiosis to endometriosis pathogenesis, they should not be interpreted as justification for routine antibiotic therapy, given the well-recognized risks of antimicrobial resistance, disruption of commensal microbial communities, and further exacerbation of dysbiosis.

Probiotic supplementation represents a more targeted strategy aimed at restoring microbial homeostasis and regulating host immune responses. A randomized placebo-controlled pilot trial demonstrated that oral *Lactobacillus* supplementation reduced pain severity in women with endometriosis after several weeks of treatment [35]. Consistent with these clinical observations, experimental studies have shown that *Lactobacillus gasseri* OLL2809 suppresses ectopic lesion development through mechanisms involving natural killer cell activation [29], while *Lactobacillus acidophilus* has been reported to modulate cytokine production by peripheral blood monocytes from affected individuals [46]. These immunomodulatory effects are consistent with the broader biological functions of *Lactobacillus* species in maintaining epithelial barrier integrity, limiting pathogen expansion, and regulating mucosal immunity. However, considerable strain-specific variation precludes extrapolation of these findings to probiotic formulations in general, emphasizing the need for rigorous strain-specific clinical evaluation.

The complexity of host–microbiome interactions is further illustrated by *Akkermansia muciniphila*. Although frequently regarded as beneficial in metabolic disorders, its mucin-degrading activity may be detrimental in individuals with impaired intestinal barrier function or concomitant inflammatory bowel disease [18]. Given the high prevalence of gastrointestinal symptoms and intestinal dysfunction among women with endometriosis, future microbiome-based interventions should adopt a precision medicine approach, incorporating careful patient stratification rather than assuming universal therapeutic benefit.

Dietary modulation represents another potential avenue for influencing microbiome-mediated disease mechanisms. Omega-3 polyunsaturated fatty acids, including α -linolenic acid, have demonstrated anti-inflammatory properties together with the capacity to reshape microbial communities in experimental endometriosis. Ni et al. reported that α -linolenic acid altered gut microbiota composition while simultaneously attenuating inflammatory responses in a murine model [54]. Short-chain fatty acids also represent attractive therapeutic candidates because of their established roles in maintaining epithelial barrier integrity, regulating immune homeostasis, and suppressing inflammatory signaling, although clinical evidence in endometriosis remains limited and is largely extrapolated from other chronic inflammatory disorders [27]. Consequently, dietary interventions should currently be regarded as supportive components of multidisciplinary management rather than disease-modifying therapies.

Among microbiome-based interventions, fecal microbiota transplantation (FMT) remains the most experimental. Preclinical studies indicate that microbiota-derived metabolites can influence lesion establishment and progression, suggesting that restoration of a healthy microbial ecosystem may modify disease behavior [35]. However, the absence of robust clinical evidence precludes its application in routine practice. Future clinical trials will require standardized donor selection, comprehensive phenotypic characterization, longitudinal microbiome analyses, validated clinical and imaging endpoints, and extended follow-up to establish both safety and therapeutic efficacy. Overall, accumulating evidence supports an

important contribution of the gut microbiome to the pathophysiology of endometriosis through interconnected endocrine, immune, inflammatory, and metabolic mechanisms. Although microbiome-based interventions remain investigational, continued integration of metagenomics, metabolomics, and carefully phenotyped clinical cohorts is expected to refine our understanding of disease heterogeneity and facilitate the development of personalized diagnostic and therapeutic strategies.

9. Diagnostic implications and research priorities

The diagnostic value of microbiome profiling in endometriosis depends on its incremental utility beyond standard imaging and clinical examination. This approach is promising for mitigating diagnostic delays caused by symptomatic overlap with conditions like IBS or IBD. While TVUS and MRI effectively detect endometriomas and deep infiltrating disease, superficial and early-stage lesions frequently elude non-invasive screening. Rather than identifying a single pathogen, a viable diagnostic tool would utilize a multi-omic signature integrating altered gut diversity, Gram-negative enrichment, menstrual *E. coli* load, elevated bacterial beta-glucuronidase activity, and inflammatory metabolite profiles.

Khan and colleagues' menstrual blood work gives a useful example because it samples a biologically relevant fluid without surgery [29]. If future studies confirm that *E. coli* or endotoxin-related signatures differ by lesion type, menstrual blood could support risk stratification in patients with pelvic pain and equivocal imaging. Huang and colleagues took a different approach and compared gut, cervical, and peritoneal microbial data; their finding that the gut microbiota exceeded the cervical microbiota in early diagnostic classification suggests that clinicians should not focus solely on the vaginal tract when studying endometriosis [76]. Hernandez and colleagues add another warning: deep lesions may harbor a microbial profile that is not readily apparent in vaginal or eutopic endometrial samples [26]. Therefore, future biomarker studies should decide in advance whether they want to detect endometriosis in general, bowel involvement, deep infiltrating disease, pain severity, infertility risk, or treatment response. These endpoints may require different microbial markers.

Current studies are limited more by poor methodology than a lack of hypotheses. Many cohorts remain small, mix lesion subtypes, and collect samples at different menstrual phases. Hormonal contraception, progestins, GnRH analogs, antibiotics, bowel preparation before surgery, previous laparoscopy, diet, BMI, and comorbid IBS can all alter the microbiome. Without accounting for these variables, researchers might mistake the effects of treatments or lifestyle for the actual biology of the disease. Therefore, future studies need to standardize their sampling, record the menstrual cycle phase and medication history, and analyze superficial, ovarian, deep, and intestinal disease as completely separate groups while tracking patients' surgical and gut health histories.

Functional analysis may provide more reliable and consistent answers than simple lists of bacterial genera. Because of bacterial functional redundancy, two women can carry entirely different species but share the same microbial functions, such as high beta-glucuronidase activity, increased LPS synthesis, altered bile acid metabolism, or upregulated fatty acid biosynthesis. The findings of Pérez-Prieto and colleagues regarding lipid metabolism and FASN clearly show why this direction matters [36]. Endometriosis depends on proliferation, inflammatory lipid mediators, and estrogen signaling. A pathway-level approach can connect microbial data more directly to tissue behavior than a list of taxa does, which varies across sequencing platforms.

Clinical translation requires rigorous caution. Observed Gram-negative enrichment does not justify empirical antibiotic therapy, nor should probiotics be integrated into routine care without strain-specific efficacy data, standardized dosing, and long-term follow-up. At present, microbiome research serves a more immediate clinical purpose: it underscores the necessity of evaluating dietary habits, antibiotic exposure, and gastrointestinal comorbidities like IBS or IBD. Ultimately, this framework supports a multidisciplinary approach when endometriosis manifests as concurrent pelvic pain and gastrointestinal dysfunction.

10. Conclusion

The reviewed evidence supports a bidirectional relationship between the gut microbiome and endometriosis. Dysbiosis can plausibly promote endometriosis through barrier dysfunction, LPS exposure, immune activation, oxidative stress, and altered estrogen recirculation. Endometriosis can also reshape the gut through chronic inflammation, bowel involvement, pain-related lifestyle changes, hormonal treatment, surgery, and altered intestinal motility. This circular relationship helps explain why researchers do not find one stable bacterial marker across all studies.

The most useful current interpretation treats the microbiome as a modifier of disease expression rather than a single cause. Specific details from the literature strengthen this view: lower diversity in some human cohorts, *Escherichia-Shigella* dominance in severe bowel cases, reduced *Lactobacillus* in animal and lesion studies, altered *Firmicutes/Bacteroidetes* ratios in mouse models, Gram-negative enrichment in peritoneal and stool samples, and functional changes in fatty acid metabolism and beta-glucuronidase activity. The estrobolome offers one of the clearest mechanistic links, as beta-glucuronidase can increase active estrogen recirculation and modulate macrophage and stromal cell behavior.

This framework is critical for intestinal endometriosis, where lesions sit directly adjacent to the gut microbiome, mucosal immune cells, and enteric neural networks. Symptoms such as rectosigmoid involvement, cyclic dyschezia, constipation, diarrhea, and rectal bleeding are pathophysiologically linked rather than isolated events: tissue infiltration disrupts local motility and immunity, while microbial products and barrier dysfunction exacerbate pelvic inflammation. This complex interaction justifies treating intestinal endometriosis as a distinct biological entity rather than a minor epidemiological detail.

The same caution applies to treatment. Microbiome modulation looks attractive because it offers a less invasive approach, but clinicians need stronger evidence before adopting it as standard therapy. Antibiotics, probiotics, dietary fatty acids, and FMT influence patients differently. A patient with dominant bowel symptoms, recent antibiotics, and deep infiltrating disease may not respond like a patient with an ovarian endometrioma, no bowel involvement, and long-term progestin therapy. Future trials should therefore combine microbial endpoints with pain scores, bowel symptom scores, imaging findings, lesion phenotype, and inflammatory markers. Without that level of detail, the field may produce statistically significant associations that do not help patients in daily care.

Future research must analyze endometriosis phenotypes separately, while accounting for patient variables like cycle phase, hormones, diet, BMI, antibiotics, surgery, and GI comorbidities. Only with this precision can microbiome analysis become useful for risk stratification, diagnosis, and therapy. Currently, the gut-endometriosis axis is a promising framework, but it cannot replace careful clinical assessment, expert imaging, and individualized treatment.

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