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REVIEW

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Microbiota insights in endometriosis

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Abstract

Endometriosis affects approximately 10% of women of reproductive age and is characterized by the presence of endometrial-like tissue outside the uterine cavity, leading to chronic pelvic pain, infertility, and a significant reduction in quality of life. Beyond its local manifestations, endometriosis is increasingly recognized as a systemic, immune-mediated condition with multifactorial origins. In this narrative review, we provide an updated and comprehensive overview of the disease, including its pathophysiology, clinical features, and evolving conceptual frameworks. Considering the frequent digestive symptoms observed in affected patients, we summarize key findings from both animal and human studies that investigate alterations in the gut microbiota. We also review the profound immune dysregulation associated with endometriosis and explore its potential bidirectional relationship with the microbiota. Furthermore, we examine recent insights into the endometrial microbiota—an emerging field of interest given its early involvement in the disease process and its strong interconnection with the vaginal microbiome. Lastly, we highlight studies exploring the gynecological microbiota and present an updated discussion of novel therapeutic strategies, including microbiota-targeted approaches that may shape future management of this complex disease.

Keywords Endometriosis, Host-microbe interaction, Gut microbiota, Gynecological microbiota, Metabolites

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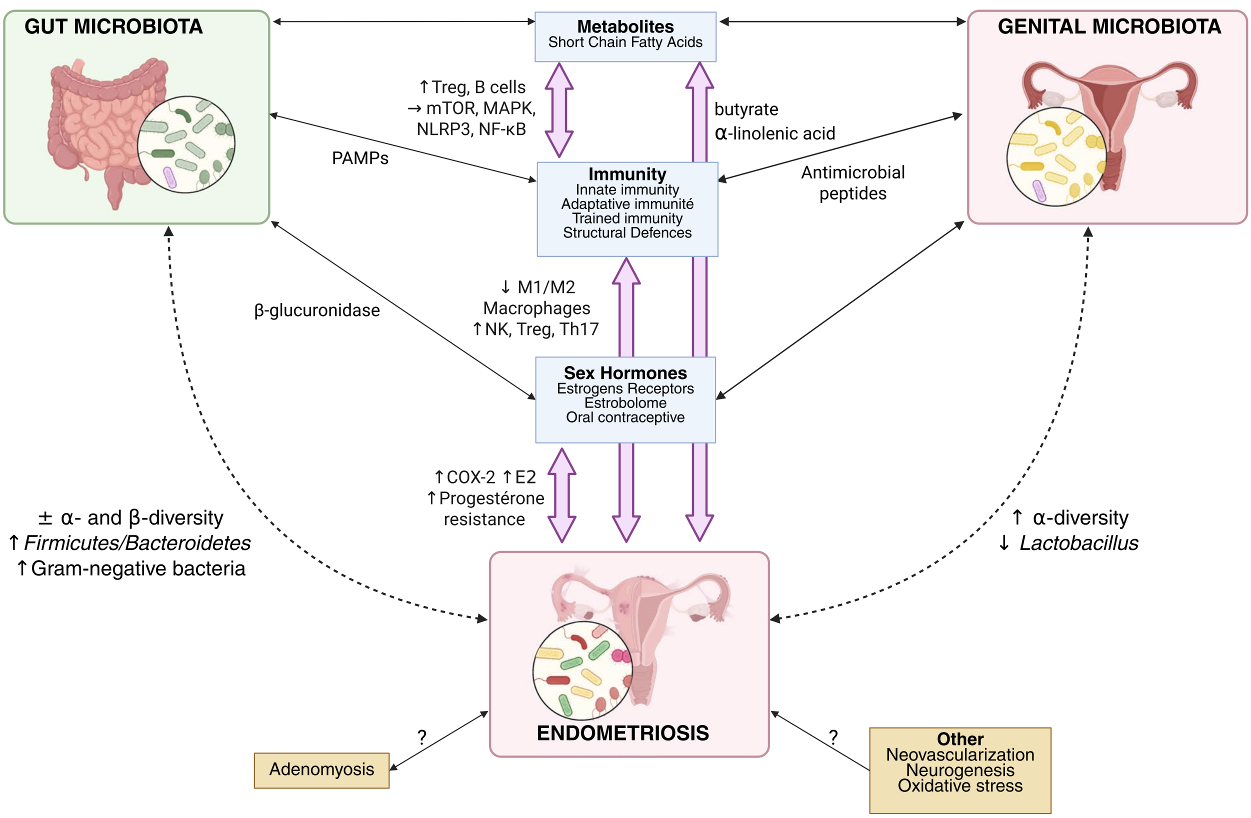
Graphical Abstract

Abbreviations: Treg: T regulatory cells, MAPK: mitogen-activated protein kinases, mTOR: mammalian target of rapamycin, NLRP3: NOD-like receptor family pyrin domain containing 3, NF-κB: nuclear factor-kappa B, NK: natural killer, Cox-2: cyclooxygenase-2, E2: estradiol



Revisiting endometriosis: from established pathways to microbiota-driven perspectives

Endometriosis is a chronic, estrogen-dependent, gynecological condition characterized by the presence of endometrial-like tissue outside the uterine cavity [1, 2]. Endometriosis likely results from the convergence of multiple biological mechanisms. The leading theory—retrograde menstruation—suggests that endometrial cells flow backward through the fallopian tubes during menstruation and implant in the peritoneal cavity [3]. Approximately 10% of reproductive-age women are afflicted with endometriosis, but the discrepancy between this prevalence and the quasi-systematic retrograde menstruations in cycling women (80%) suggests other susceptibility factors are implicated at the individual level [4]. This suggests the involvement of additional mechanisms [5]. The implantation of ectopic endometrial cells appears to be facilitated by: (i) alterations in local immunity, particularly within the peritoneal cavity, including impaired macrophage clearance and dysregulation of pro-inflammatory cytokines [6]; (ii) a hormonal environment marked by relative hyperestrogenism and progesterone resistance, which promotes ectopic lesion survival and growth [7]; and (iii) neovascularization and tissue invasion, driven by growth factors and matrix metalloproteinases, contributing to lesion progression [8]. Although the retrograde menstruation theory explains the typical pelvic distribution of lesions, it fails to account for extrapelvic forms of endometriosis, such as inguinal or pulmonary involvement [9]. Alternative hypotheses include Müllerian remnants [10], coelomic metaplasia, and lymphovascular dissemination [3, 11], which account for cases in non-menstruating women and distant lesion sites. More recently, the role of endometrial stem cells has gained attention, suggesting their aberrant migration and differentiation at ectopic locations [12]. Together, these theories underscore the multifactorial nature of endometriosis pathogenesis.

Endometriosis is classically responsible for pain and infertility, thus significantly impacting quality of life [13]. A correlation between the location of lesions and patients' symptoms was first demonstrated during surgical treatment of endometriosis [14], then thanks to the considerable development of medical imaging techniques [15]. Some classifications of the disease have sought to link the intensity of painful symptoms to the anatomical staging of lesions. Severe stages (III and IV) and mild to moderate stages (I and II) have thus been defined by the American Society for Reproductive Medicine [16]. In some cases, this correlation was not accurate, as shown by patients with a severe stage on imaging but no painful symptoms or infertility [17]. The concept of disease defined by the location of lesions and their correlation with symptoms has progressively evolved. Surgical removal of endometriosis lesions could result in residual pain, such as neuropathic pain [18]. The discovery of an association between endometriosis and autoimmune or inflammatory diseases (systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome and inflammatory bowel disease) [19, 20], the presence of migraine [21] or cardiovascular comorbidities [22] argues in favour of a systemic feature to endometriosis.

Recent studies have revealed a modulatory effect of training innate immunity in endometriosis, suggesting a role for environmental factors, especially the effects of bacterial stimulation [23]. The influence of the microbiome on the development of various inflammatory diseases is well established, implicating bacteria in enhanced immune responses and the perpetuation of chronic inflammation [24, 25]. Unique intestinal microbiota signatures and distinct associated immune cell profiles in peripheral blood and endometrium, characterized by an enhanced Th17/Treg ratio, have been observed in a baboon model of endometriosis, thus highlighting the importance of bacteria–immune system interaction in this chronic disorder [26]. Focusing on the intestinal mucosa, factors such as lipopolysaccharide (LPS), antimicrobial peptides, mucins, short-chain fatty acids (SCFAs), and immunoglobulins are thought to play a role, but their precise contributions have not yet been clearly defined. Furthermore, the discovery of an endometrial microbiota through next-generation sequencing (NGS), particularly targeting 16S ribosomal RNA, has opened new avenues for investigation in many gynecological conditions such as endometriosis and infertility [27, 28]. Focusing on endometriosis, the exact mechanisms of interaction between the endometrial microbiota and the endometrium, as well as the exact impact on the disease process, remain unknown.

This review aims to provide a comprehensive understanding of the mechanisms by which the digestive and gynecological microbiota may participate in endometriosis pathogenesis. By elucidating these mechanisms, new diagnostic, and therapeutic strategies for managing this multifactorial disease can be explored.

Gut microbiota and endometriosis

The study of the gut microbiota has emerged as a pivotal area of research for elucidating the pathophysiology of endometriosis for several compelling reasons. Firstly, the digestive microbiota represents the most abundant microbial community in the human body, and these symbionts express approximately 10 times more unique genes than the host's genome, underscoring their substantial genetic diversity and potential impact [29]. Secondly, the field of immunology has experienced a paradigm shift with the recognition of the pivotal role played by the microbiota in shaping and modulating the induction, education, and functioning of the immune system [30]. Thirdly, individuals afflicted with endometriosis exhibit a threefold higher incidence of intestinal functional disorders, which have been linked to intestinal dysbiosis [31, 32]. These converging factors highlight the significance of investigation of the interplay between the gut microbiota and endometriosis.

Human studies

Human studies focusing on the gut microbiota in endometriosis-affected patients compared to controls have also revealed a wide discrepancy in results, summarized in Table 1 [40, 41]. Patients with stage III or IV (moderate to severe) endometriosis ($n=14$) were more likely to have abundant *Shigella* and *Escherichia* than healthy participants ($n=14$) [33]. An observational cross-sectional pilot study to characterize the gut microbiome profiles among endometriosis patients ($n=35$) and healthy controls ($n=24$) did not detect significant differences between groups [34]. The microbiota is often analyzed using α-diversity (representing the bacterial richness of an individual) and β-diversity (bacterial diversity between two groups) or using ratios such as Firmicutes/Bacteroidetes, which has an important influence in maintaining normal intestinal homeostasis [42]. A large study found that β-diversity was different in healthy controls ($n=198$) compared to patients with endometriosis ($n=66$), with a lower α-diversity in endometriosis patients [37]. Authors reported the abundance of 12 bacteria belonging to the classes Bacilli, Bacteroidia, Clostridia, Coriobacteriia, and Gammaproteobacteria that differed significantly between stool samples from endometriosis patients ($n=66$) and those from matched healthy controls ($n=198$).Two bacteria from the class

Table 1 Gut microbiota modification in human endometriosis

Study	Material and Methods	Design	Results (EMS vs controls)
Ata et al. 2019 [33]	Human Feces RNA 16S V3-V4	14 EMS vs. 14 controls	↑ Proteobacteria (BGN): *Escherichia, Shigella*
Perrota et al. 2020 [34]	Human Feces RNA 16S V4	21 EMS stage I-II vs. 14 EMS stage III-IV	Similar α and β-diversity
Shan et al. 2021 [35]	Human Feces RNA 16S V3-V4	12 EMS stage III-IV vs. 12 controls	Different relative abundance (PCoA) ↑ Firmicutes/Bacteroidetes ratio ↑ *Actinobacteria, Saccharibacteria, Acidobacteria, Cyanobacteria, Fusobacteria and Prevotella*
Huang et al. 2021 [36]	Human Feces RNA 16S V4	21 EMS vs. 20 controls	Different relative abundance (PCoA) ↓ α-diversity ↑ *Eggerthella lenta, Eubacterium dolichum* ↓ *Clostridia Clostridiales, Lachnospiraceae Ruminococcus, Clostridiales Lachnospiraceae, Ruminococcaceae Ruminococcus*
Svensson et al. 2021 [37]	Human Feces RNA 16S V1-V3	66 EMS vs. 198 controls	Different relative abundance (PCoA) ↓ α-diversity ↑ *Clostridia* ↓ Bacteroidia, Coriobacteriia ↑ Gammaproteobacter, Bacilli
Huang et al. 2021 [36]	Human Feces RNA 16S V3-V4	18 EMS vs. 18 controls	Different relative abundance (PCoA) ↓ α-diversity ↑ Proteobacteria ↓ Bacteroidota and Firmicutes
Pérez-Prieto et al. 2024 [38]	Human Feces DNA Shotgun	136 EMS vs. 864 controls	Similar α and β-diversity
Cai et al. 2025 [39]	Human Feces RNA 16S V3-V4	39 EMS stage I-II vs. 36 EMS stage III-IV	Different relative abundance (PCoA) Similar α-diversity Different relative abundance in subgroupe analysis of patients with dysmenorrhea

Abbreviations: D day, *EMS* endometriosis, *PCoA* Principal Coordinates Analysis

Bacteroidia (*Bacteroides* and *Parabacteroides*) and two belonging to the class Clostridia (*Oscillospira* and *Coprococcus*) were present in higher abundances in endometriosis patients, whereas two bacterial species from the classes Bacteroidia (*Paraprevotella* and one unidentified) and Clostridia (*Lachnospira* and one unidentified) were present at lower abundances compared to in individuals without endometriosis [37]. On the other hand, another study found that patients with stage III or IV endometriosis ($n = 12$) had a higher Firmicutes/Bacteroidetes ratio than the healthy controls, the two groups nevertheless exhibited differences in β-diversity [35]. A recent study compared patients with stage I-II versus III-IV, showing a significant difference in the composition of the gut microbiota. In addition, the digestive microbiota of the most severe patients (stage III-IV with dysmenorrhoea) had a significantly different composition [39]. The largest study to date by Pérez Prieto et al., comparing 136 women with endometriosis to 864 controls, found no significant differences between groups. However, it is important to note that the control group lacked radiological or surgical confirmation to rule out endometriosis [38]. Variability in the findings across these studies points to the need for larger studies in which potential confounders (e.g., age, race/ethnicity, other health conditions, medication, and diet) are taken into account. In addition, while the changes in microbiota may be due to endometriosis, they may also be due independently to the inflammation it triggers. These different studies allow us to explore a phenomenon of association without being able to distinguish whether it is the endometriosis itself or the inflammation or dysimmunity that it causes.

Another interesting yet overlooked aspect of clinical studies concerns the digestive symptoms reported by patients. It is estimated that more than a half of individuals with endometriosis experience debilitating digestive symptoms, including bowel movement disorders, digestive pain, and bloating [43]. The main hypothesis generally put forward is the presence of digestive tract lesions responsible for these symptoms. However, in most cases, these signs occur in the absence of any visible digestive lesions [44]. This suggests that alterations in the gut microbiota—despite their variability—may be linked to these disorders. To date, no study has specifically explored the relationship between digestive symptoms and microbiota variation. Further studies are therefore needed and should be conducted longitudinally across the menstrual cycle to account for the known exacerbation of digestive symptoms in the premenstrual phase. It has indeed been shown that both gut microbiota composition and intestinal gas production are influenced by hormonal fluctuations—particularly those associated with the menstrual cycle and the use of oral contraceptives, the latter being especially relevant in endometriosis due to their widespread therapeutic use [45].

Animal models

The main advantage of studying the intestinal microbiota in animal models lies in the strict control of the various parameters that can modify the microbiota, of which diet is the most important. In mouse models, studies of the potential role played by the intestinal microbiota in endometriosis have yielded heterogenous results, summarized in Table 2. Feces samples were found with lower gut α and β diversities and abundances in mice with endometriosis compared to those of control mice [54]. Another study conducted on feces reported no difference in the α- and β-diversities between mice with and without endometriosis [48]. However, it should be noted that their experiment ended 21 days after the surgical induction of endometriosis and that the feces samples were taken from the cage and not by surgical means from the colon [48]. In a third study, dysbiosis of the gut microbiota was observed 42 days after endometriosis induction, with an elevated Firmicutes/Bacteroidetes ratio and an elevated abundance of *Bifidobacterium* [47]. The same results were observed in another study of mice [47], while an elevated Firmicutes/Bacteroidetes ratio and decreased abundance of *Ruminococcaceae* were observed in feces samples from female rats with endometriosis [50]. Three studies found higher gut microbiota diversity and an increased Firmicutes/Bacteroidetes ratio [35, 46, 47, 49], which is a marker of dysbiosis [55]. These data support the presupposed interrelation between endometriosis and the microbiota, but they also raise two critical questions: the impact of inflammation related to endometriosis on the microbiota, and the impact of microbiota on the endometriosis pathogenesis.

Unraveling the causal link between gut microbiota and endometriosis

In the study of the microbiota—particularly the gut microbiota—in endometriosis, a recurring question is whether endometriosis alters the microbiota or whether a pre-existing dysbiosis contributes to the development of the disease. Several experimental mouse studies support the latter hypothesis, showing that the microbiota may participate in the initiation or progression of endometriosis. For example, fecal microbiota transfer (FMT) from mice with endometriosis to healthy mice resulted in larger lesions compared to transfers from healthy donors [56]. Similarly, induction of dysbiosis through a Western diet also worsened lesion severity [52]. These findings support the emerging view of the microbiota as a functional "last organ" [57] and suggest that it may contribute to the pathogenesis of endometriosis—an argument that further supports its classification as a systemic disease. It should be noted that endometriosis most commonly originates from retrograde menstruation, and that the microbiota likely serves as a co-factor in lesion development and symptom expression, rather than as a primary cause. On the other hand, endometriosis has been shown to alter the gut microbiota in both human and mouse models—suggesting a potential reverse causality. Dysbiosis may help explain the high prevalence of digestive symptoms in affected patients, as these symptoms could arise secondarily from microbiota alterations triggered by the onset of endometriosis. The use of probiotics, and their effects on gut microbiota composition and clinical symptoms, warrant further investigation in this context.

Metabolites: a promising direction for research

The gut microbiota produces an extremely diverse metabolite repertoire by anaerobic fermentation of dietary components [58, 59]. The main metabolic end products are SCFAs, including butyrate, acetic acid, butyric acid, and propionic acid. These SCFAs interact with host cells via epithelial cells to influence the immune response. They induce the overexpression of Treg lymphocytes and myeloid cells [60]. The immune responses mediated by SCFAs consist of the regulation of Treg inhibition, histone-deacetylases, and B cells by regulation of the mitogen-activated protein kinases (MAPK) and mammalian target of rapamycin (mTOR) pathways [61]. SCFAs have been shown to be involved in various pathologies, exerting either a deleterious or protective effect [5, 62, 63]. SCFAs have been described as activators of the pro-inflammatory pathway as NOD-like receptor family, pyrin domain containing 3 (NLRP3), and Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and the production of interleukins (IL)−1β and IL-18 [64, 65].

Other SCFA with anti-inflammatory properties, Such as n-butyrate, are decreased in endometriosis, as reported by Chadchan et al. In a mouse model of endometriosis the authors demonstrated that 1) endometriosis alters the gut microbiome, resulting in reduced production of the n-butyrate, and 2) n-butyrate, but not acetate or propionate, inhibits endometriotic lesion growth [66]. Once translocated into the systemic circulation, these molecules can be further recognized by pattern recognition receptors (PRR) including Toll-like receptors (TLR) and NOD-like receptors (NLRs), which

Table 2 Gut microbiota modification in animal endometriosis

Study	Material et Methods	Design	Results (EMS vs controls)
Bailey et al. 2002 [46]	Rhesus monkey Selective and differential agars	8 EMS vs. 10 controls	↓ *Lactobacillus* species ↑ Aerobic and gram negative bacteria
Yuan et al. 2018 [47]	Mice Feces D7, D14, D28, D42 ARN 16S V4	22 EMS vs. 20 controls	Different relative abundance (PCoA) ↑ *Firmicutes/Bacteroidetes* ratio
Hantschel et al. 2019 [48]	Mice Feces D21 ARN 16S V4-V5	8 EMS vs. 8 controls	Similar relative abundance ↑ *Bacteroidales, Lactobacillus* species, *Prevotellaceae* and *Lachnospiraceae*
Chadchan et al. 2019 [49]	Mice Feces D21 ARN 16S	5 EMS vs. 5 controls	Different relative abundance (PCoA) ↑ α-diversity ↓ *Firmicutes/Bacteroidetes* ratio
Cao et al. 2020 [50]	Mice Feces D56 ARN 16S V3-V4	8 EMS vs. 8 controls	Different relative abundance (PCoA) ↓ α-diversity ↓ *Ruminococcaceae*
Ni et al. 2020 [51]	Mice Feces D21 ARN 16S V3-V4	6 EMS vs. 6 controls	Different relative abundance (PCoA) ↓ α-diversity ↑ *Proteobacteria* and *Verrucomicrobia* ↓ *Firmicutes/Bacteroides* ratio
Parpex et al. 2024 [52, 53]	Mice Feces W7 ARN 16S V3-V4	30 EMS vs. 28 controls	Different relative abundance (PCoA) Similar α-diversity and *Firmicutes/Bacteroides* ratio ↓ *Akkermansia*

Abbrevations: *D* day, *W* week, *EMS* endometriosis, *PCoA* Principal Coordinates Analysis

are able to recognize certain patterns of microbial molecules and activate innate immune pathways, then modifying the growth of lesions [67]. Dysbiosis of the gut microbiota leads to reduced butyrate production and impaired metabolism, as seen in inflammatory bowel disease [68]. While butyrate is present in the diet, its levels may be insufficient to counteract inflammation in the gut. Oral butyrate Supplementation has shown dose-dependent anti-inflammatory effects in both preclinical and clinical studies, with significant benefits observed at doses of 100 mg/kg/day [69]. Although butyrate is rapidly absorbed in the duodenum, its use as a dietary supplement—assuming it can reach the colon—represents an interesting therapeutic avenue.

A study investigating the correlation between fecal metabolomics and gut microbiota in a mouse model of endometriosis revealed significant alterations in bile acid and fatty acid profiles, including an increase alpha-linolenic acid levels [51, 70]. In a subsequent study by the same group, alpha-linolenic acid supplementation was shown to attenuate the inflammatory response by reducing nitrite and prostaglandin E2 accumulation, key mediators of inflammation [54]. Furthermore, alpha-linolenic acid has been shown to suppress the pro-inflammatory activity of M1 macrophages, notably by reducing the secretion of IL-1β and IL-6 [71]. It also contributes to improving the peritoneal inflammatory environment in endometriosis by decreasing lipopolysaccharide (LPS) levels [54].

Other gut microbiota–derived SCFAs and related metabolites have also been implicated in endometriosis. Recent research explored the combined gut microbiota and metabolomic profiles in stool samples from women with endometriosis, identifying novel bioactive metabolites with therapeutic potential [72]. Among them, 4-hydroxyindole, a compound derived from bacterial tryptophan metabolism, emerged as a promising candidate. This metabolite was shown to prevent the formation of endometriotic lesions, promote lesion regression, and significantly reduce pain in experimental models.

Microbiota of the female genital tract in endometriosis

Lower genital tract microbiota

The lower genital tract corresponds to the vagina and the external part of the cervix. It contains a relatively large microbial abundance dominated by the gram-positive bacillus *Lactobacillus* species. Bacterial vaginal communities can be clustered into five community state types (CSTs). Four of these CSTs are dominated by *Lactobacillus* species: *Lactobacillus crispatus* (CST I), *Lactobacillus gasseri* (CST II), *Lactobacillus iners* (CST III), or *Lactobacillus jensenii* (CST V). The fourth CST (CST IV), however, has lower proportions of lactobacilli and higher proportions of strictly anaerobic organisms, such as *Prevotella*, *Dialister*, *Atopobium*, and *Gardnerella* among others [73]. The possible association between these bacterial clusters and susceptibility to gynecological pathologies, including endometriosis, was assessed in several works. Perrotta et al. found a higher vaginal CST I microbiota ratio in endometriosis patients compared with the controls [34]. Other bacteria are associated with endometriosis phenotypes, such as gram-positive (*Anaerococcus*, Firmicutes, Actinobacteria, and *Atopobium*) and gram-negative bacillus (Bacteroidetes, *Gardnerella*). A strong relation between the presence of *Anaerococcus* species in the vaginal microbiota and severe endometriosis stage (III et IV) was described [16, 34]. Ata et al. compared vaginal and cervical microbiota from 14 women with Surgically proven stage 3/4 endometriosis and 14 controls without endometriosis. They evidenced that *Gardnerella* increased in the cervical microbiota in the endometriosis group compared with the control group. By studying the cervical microbiota in Taiwanese endometriosis patients (11 patients with stage I/II, 12 with stage III/IV), a tendency of increased Firmicutes with decreased Actinobacteria and Bacteroidetes was found during endometriosis progression, although the concept of endometriosis progression remains controversial [74]. Wei et al. compared vaginal and cervical samples for 36 patients with endometriosis and 14 controls. They found that the proportion of *Lactobacillus* species in endometriosis patients in vaginal samples was lower than that in the control cases, and the case number of non-*Lactobacillus*-dominated microbiota significantly increased in cervical samples [75]. These various studies show that in cases of endometriosis, vaginal bacterial diversity appears to be unchanged or increased to the detriment of *Lactobacillus* species, a known marker of healthy flora balance, especially in the external part of the cervix. A recent Italian study showed higher bacterial diversity in endometriosis cases, with an overrepresentation of *E. coli* [76]. However, few studies to date have obtained reproducible results, and potential confounding factors (i.e. hormonal, environmental and/or sexual) are not thoroughly assessed (Table 3).

Upper genital tract microbiota

The upper female genital tract (endocervix, uterus, and oviduct) is thought to contain a much lower bacterial biomass compared to the lower genital tract [79]. Until recently, the endometrial cavity was considered to be sterile, but this concept has been repetitively challenged [27]. Upper genital tract colonization is suspected of being linked to the ascension of microorganisms from the vagina through the cervix [80–82]. In 1989, Hemsell et al. first evidenced the existence of upper reproductive tract bacteria, with 55 positive cultures of endometrium in asymptomatic women with no history of previous pelvic infection [83]. With the development of NGS, especially of 16S ribosomal RNA, abundant studies have confirmed these results and further suggested the existence of an endometrial microbiota. The endometrium contains a much lower microbial biomass—approximately 1,000-fold less than that of the vagina [79].

Thus, the concept of an endometrial microbiota remains controversial. Several authors have claimed that endometrial bacteria are the result of sample contamination rather than an actual microbiota. As suggested by Molina et al., two pitfalls remain problematic. Firstly, individual factors must be considered and require subgroup analysis with several samples. Indeed, in addition to the presence of endometrial disease, menstrual cycle, ethnicity, sexual activities, and diet are all potential biases that should be included in the analysis of the female reproductive tract, especially for the endometrial microbiota with its low biomass. Secondly, the performance of endometrial sampling is at high risk of contamination, either as a result of the passage through the cervix or by contamination of the material, which is likely to be more impactful due to the low biomass [84, 85]. Briefly, three types of genomic analyses evaluating microbial communities can be performed. Marker gene analysis (mainly 16S RNA sequencing) is appropriate with low-biomass and highly host-contaminated samples (due to highly conserved regions) but does not discriminate between alive and dead. Metagenomic analysis (shotgun sequencing) can directly infer the relative abundance of microbial functional genes but still does not discriminate live versus dead bacteria, although it is less sensitive to contamination. The most expensive technique, focusing on the transcriptional activity of bacteria, favoring alive over dead bacteria, is referred to as a metatranscriptomics approach [86]. A recent study compared the vaginal and endometrial microbiota of 10 patients with a culturomics-based approach combining bacterial culture and 16S RNA sequencing [87]. On average, 28% of species were found in both the endometrial biopsy and vaginal swab of a given patient. The remaining bacteria, therefore, came exclusively from the vagina or the endometrium. Finally, studies using NGS technology are based on the detection of microbial DNA sequences. With the novel metatranscriptomics approach, Sola-Leyva et al. mapped the entire live microbiota comprising > 5300 microorganisms within the endometrium of healthy women, with significant differences in the microbial abundances in the secretory and proliferative phases [88]. The identification of endometrial bacterial populations is becoming more precise. However, there are still considerable challenges in defining a bona fide microbiota and its healthy and pathological state.

Studies analyzing endometrial microbiota from women affected or not by endometriosis are summarized in Table 4. The study involving the highest number

Table 3 Studies comparing the cervicovaginal microbiota of patients with and without endometriosis based on 16S RNA gene sequencing

Study	Material et Methods	Design	Results (EMS vs controls)
Ata et al. 2019 [33]	Vaginal et cervical swab RNA 16S V3-V4	14 EMS vs. 14 controls	Similar α- and β-diversity in vaginal and cervical samples ↑ *Atopobium* in vaginal sample ↑ *Atopobium, Gardnerella, Streptococcus, Escherichia, Shigella*, and *Ureoplasma* in cervical sample
Perrota et al. 2020 [34]	Vaginal swab RNA 16S V4	21 EMS stage I-II vs. 14 EMS stage III-IV	*Anaerococcus* species predictive of stage III-IV
Wei et al. 2020 [75]	Vaginal et cervical swab RNA 16S V4-V5	36 EMS vs. 14 controls	↓ *Lactobacillus* species in cervical and vaginal sample
Sessa et al. 2024 [76]	Vaginal swab ARN 16S V3-V4	24 EMS vs. 99 controls	Different relative abundance (PCoA) ↓ α-diversity ↑ *Escherichia*, *Megasphaera*, and *Sneathia* ↓ *Pseudomonas*, *Bifidobacterium*, *Novispirillum* and *Sphingomonas*
Chao et al. 2021 [77]	Vaginal swab ARN 16S V4	37 EMS vs. 66 controls	Different relative abundance (PCoA) ↑ α-diversity ↓ *Lactobacillus* species ↑ *Clostridium butyricum, Clostridium disporicum, Alloscardovia omnicolens, and Veillonella montpellierensis*
Akiyama et al. 2019 [78]	Cervical swab ARN 16S V5-V6	30 EMS vs. 39 controls	Similar relative abundance (PCoA) ↑ α-diversity ↑ *Lactobacillus* species, *Corynebacterium*, *Enterobacteriaceae*, *Flavobacterium*, *Pseudomonas*, and *Streptococcus*

Abbrevations: *EMS* endometriosis, *PCoA* Principal Coordinates Analysis

of women assessed 73 women with endometriosis and 55 controls, and—importantly—it revealed a significant increase of *Enterococcus*, *Escherichia coli*, *Gardnerella*, and *Streptococcus* in the endometriosis patients compared with the control group [92]. However, the bacterial identification method was based on culture. Using 16S RNA sequencing, the same authors found that *Streptococcaceae*, *Moraxellaceae*, *Staphylococcaceae,* and *Enterobacteriaceae* families were significantly increased while *Lactobacillus* species decreased in samples obtained from women with endometriosis [89]. Another study investigating women with endometriosis identified the presence of *Pseudomonas*, *Acinetobacter*, *Vagococcus,* and *Sphingobium* in the uterus and revealed that the uterine microbiota composition was significantly different in infertile women due to endometriosis [28]. In summary, due to the heterogeneous results, these studies mostly indicate an increase in bacterial diversity, often at the expense of the *Lactobacillus* species [28, 75, 89–92].

To ensure robustness in human studies investigating the link between the gynecological microbiota and endometriosis, it is essential to carefully control for clinical and reproductive history, which may confound microbiota composition. Future studies should systematically collect and report variables such as history of pelvic inflammatory disease, sexually transmitted infections, prior pregnancies, and mode of delivery (vaginal vs. cesarean section), as these factors have all been shown to influence both the immune environment and microbial communities of the reproductive tract. In addition, previous surgical procedures—including hysteroscopy, curettage, intrauterine device—may also impact local microbiota through alterations of the mucosal barrier or introduction of antibiotics. Finally, sexual activity should also be taken into account. Heterosexual intercourse involving penetration creates direct contact between the vaginal and penile microbiota. Standardizing the collection of these clinical data will be crucial for enabling meaningful comparisons across cohorts and avoiding misleading associations. The integration of these variables into multivariate analyses should become a standard practice in microbiome research related to endometriosis. As a consequence, studies that adequately account for a large number of these potential confounding factors remain scarce, due to the substantial number of patients required for meaningful inclusion.

Defenses of the female genital tract in endometriosis

Structural defenses by mucus and mucins

The cervix acts as a crucial barrier, exhibiting a distinct microbiota composition compared with the endometrium. These differences suggest that the cervix plays a pivotal role in bacterial clearance within the female reproductive tract. Cervicovaginal mucus, an essential component of this barrier, is a complex secretion composed of water, electrolytes, lipids, and proteins. During the ovulation phase, mucus selectively restricts sperm

Table 4 Studies comparing the endometrial microbiota of patients with and without endometriosis based on 16S RNA gene sequencing

Reference	Design	Endometrial sample	Results for endometrial microbiota with endometriosis	Potential biases for endometrial microbiota analysis
Khan et al., 2016 [89]	32 EMS vs. 32 control	Transcervical swab	↑*Streptococcaceae*, *Moraxellaceae*, *Staphylococcaceae,* and *Enterobacteriaceae* families ↓ *Lactobacillus* species	Age (between 21 and 52 years old), antibiotics, sexual habits, douching effect Control group: ovarian cysts, uterine fibroids
Chen et al., 2017 [28]	32 EMS vs. 16 control	Transcervical swab	Appearance of *Pseudomonas*, *Acinetobacter*, *Vagococcus,* and *Sphingobium*	Time of menstrual cycle Control: uterine fibroids, adenomyosis, tubal disorders
Hernandes et al. 2020 [90]	10 EMS vs. 11 control	Transcervical curettage	No difference in α- and β-diversity	Time of menstrual cycle, sexual habits, douching effect Control group: unspecified benign gynecologic diseases or elective tubal ligation
Wei et al. 2020 [75]	26 EMS vs. 11 control	Transcervical uterine wash	↑ α-Diversity ↑ *Prevotella*, *Veillonella*, *Atopobium*, and *Veillonellaceae*	Sexual habits, douching effect Control group: ovarian teratoma, serous cystadenoma, uterine fibroids
Wessels et al. 2021 [91]	12 EMS vs. 9 control	Transcervical endometrial biopsy (Cornier)	↑ α-Diversity ↑ Actinobacteria, *Oxalobacteraceae* and *Streptococcaceae* species, and *Tepidimonas* species ↓ *Burkholderiaceae* and *Ralstonia* species	Antibiotics, sexual habits, douching effect Control group: unspecified benign gynecological conditions

Abbreviations: EMS endometriosis

transport [93] and prevents the colonization of unwanted vaginal microorganisms [94].

Cervicovaginal mucus contains many immunomodulatory and antimicrobial molecules, such as IgA, mucins, defensins, and lysozyme [95–98]. Mucus appears to be a relevant area to study alongside microbiota, as it is in direct contact with bacteria that use the sugars attached to mucins as an energy reserve. Functionally, two major types of mucins can be distinguished: transmembrane mucins and gel-forming mucins [99]. By binding water with their O-linked glycans, mucins impart gel-like properties to mucus. Gel-forming mucins are the backbone of mucus. Glycosylation of mucins has a major impact on their function, affecting their structure [100]. Interestingly, it has been shown that the hyposialylation pattern of endometriotic cells appears to be associated with the enhancement of their migratory abilities in case of endometriosis, a mechanism that could explain the invasion of lesions [101]. Despite the lack of systematic mapping of endometrial mucins, their close association with the microbiota, as observed in the intestinal barrier, is evident. In vitro fermentation models have demonstrated that the addition of mucins leads to altered bacterial profiles, favoring mucin-degrading bacteria (Bacteroidetes, *Akkermansia,* and *Lachnospiraceae* species) while decreasing the abundance of *Lactobacillus* species and *Bifidobacterium* [102]. Studies have identified the expression of several mucins, including MUC1 (with the known CA19-9 epitope) [103], MUC2, MUC4, MUC5AC, MUC6 [104], and MUC16 (with the known CA125 epitope) [105], in the endometrial epithelium. However, investigations of mucin polymorphisms in endometriosis have primarily focused on MUC2 and MUC4, linking specific single-nucleotide polymorphisms (SNPs) to the development of endometriosis and associated infertility [106, 107]. Functional studies regarding the involvement of mucins in endometriosis and the link with the endometrial or vaginal microbiota are lacking, however.

Immunological defenses

A large number of studies have suggested a degree of crosstalk between the gut microbiota and the immune system [30, 108]. This dialogue begins at the tissular level, with the combined action of bacteria, epithelial barrier, mucus, and immune cells [109]. The correct functioning of this relationship results in homeostasis. It is the sensor that enables both tolerance to healthy microbiota and response to diseased microbiota. The immune system plays a vital role in the interaction between the host and the microbiota.

Innate immunity

Peritoneal macrophages play a central role in the development and maintenance of endometriotic lesions. Macrophages function as innate immune cells by phagocytosing and sterilizing foreign substances such as bacteria and play a central role in defending the host against infection. Increased in numbers in the peritoneal cavity as well as in the lesions, they participate in chronic inflammation and the recruitment and activation of other immune cells through their secretion of cytokines [110, 111]. Their role in eliminating endometrial debris by phagocytosis is severely impaired, whereas the number of macrophages and their activation is greatly increased in endometriosis [112, 113]. A reduced phagocytotic capacity of peritoneal macrophages in endometriosis has been described in association with decreased levels of protein and matrix metalloproteinase-9 enzyme activity [114]. Emani et al. found that leakage of bacterial products from the gut results in increased numbers of macrophages in the peritoneal cavity [115]. According to their activation status, macrophages are divided into two populations: classically activated (M1) and alternatively activated (M2). This activation state is highly dependent on the cellular environment, and macrophages can switch from one type to another.

M1 macrophages are capable of pro-inflammatory responses. In contrast, M2 macrophages are involved in angiogenesis, and they are capable of anti-inflammatory responses and repair of damaged tissues [116, 117]. In infected tissues, macrophages are first polarized to the pro-inflammatory M1 phenotype to assist the host against pathogens. Subsequently, macrophages are polarized to the M2 phenotype to mount an anti-inflammatory response and repair damaged tissue. A shift from M1 to M2 within eutopic endometrium is observed in association with endometriosis [118]. In a mouse model of endometriosis, analysis of the immune cell populations in the peritoneal fluid of vehicle versus antibiotic-induced microbiota-depleted mice found fewer total and CD206+(M2-like) macrophages in the peritoneum [56]. Finally, at the endometrial level, no study to date has investigated the impact of the endometrial microbiota on macrophage activation or differentiation [119].

The implication of neutrophils in the modulation of microbiota in endometriosis has not been studied. However, neutrophils cells in endometriosis are known to generate inflammation as it is demonstrated by an increase level of chemotactic factors, such as IL-8 in the plasma or in peritoneal fluid of affected women [120]. Neutrophil infiltration and migration can be promoted by their own IL-17 production and by estrogen [121, 122]. Their modulation by the microbiota in endometriosis has not been studied to date.

The involvement of natural killer (NK) cells in the disturbance of microbiota in endometriosis women has not been clearly elucidated. Their low cytotoxic activity against ectopic endometrial cells may be due to the consequences of chronic disease-induced inflammation [123]. Macrophages-secreted IL-6, IL-10, and transforming growth factor β in the peritoneal environment have been shown to reduce the cytolytic activity of NK cells [124, 125]. It has been shown that butyrate (e.g., microbial short-chain fatty acids) has a strong anti-inflammatory effect on NK cells. Co-culture of NK cells with butyrate has been shown to decrease cytokine production (interferon-γ, tumor necrosis factor-α, and IL-22) and to downregulate mTORC1 activity [126]. The impact of NK and neutrophil cells on variations in the microbiota deserves further investigation.

Training innate immunity

Given the central role of macrophages in endometriosis, the trained immunity associated with macrophages and its role in bacterial dialogue should be discussed. Briefly, macrophages can be reprogrammed to acquire memory-like characteristics after antigenic challenge to reinforce or inhibit a subsequent immune response, a phenomenon called trained immunity [127]. Jeljeli et al. trained peritoneal macrophages in a mouse model of endometriosis. When exposed to bacillus Calmette–Guérin (BCG), macrophages enhance the growth of lesions. Conversely, with repeated exposure to low doses of LPS, immunotolerance was observed, resulting in smaller lesions and less production of the pro-inflammatory cytokine IL-10 [23]. This model is fully adaptable to bacterial exposure; LPS is contained in the membrane of gram-negative bacteria. Exposure to higher doses of LPS produces opposite effects, with larger lesions [128]. The bacterial biomass studied in the microbiota is closer to the doses used in trained immunity.

Adaptative immunity

B and T lymphocytes play an essential role in the survival and proliferation of endometrial cells. Indeed, endometriosis is characterized by reduced activity of cytotoxic T cells, modulation of cytokine secretion by T helper cells, and autoantibody production by B lymphocytes [129]. Le et al. studied a baboon model for endometriosis that presents several advantages such as natural menses, development of spontaneous endometriosis [130], and adequate animal body size for repeated sampling of sufficient size. They noticed alteration of the gut microbiota in baboons after induction of endometriosis. These changes were accompanied by an increase in the Tregs/Th17 cell ratio in peripheral blood [26]. Regulatory T cells (Tregs) are potent suppressors of inflammatory immune responses. Th17 cells are a pro-inflammatory effector CD4 T cell population that initiates an inflammatory response mainly through recruitment, activation, and migration of neutrophils [131]. Interestingly, they found a correlation between certain bacterial species and these T-cell populations. The phyla Bacteroidetes, Firmicutes, and Proteobacteria were negatively correlated with the level of peripheral Treg cells; while *Prevotella* and *Sutterella* were positively correlated with the level of Th17 cell populations. No data are available for other T and B cells and their interaction with microbiota in the context of endometriosis.

More generally, the most studied form of homeostatic immunity to the gut microbiota is the one associated with IgA specific for commensal-derived antigen responses secreted by T cells in Peyer's patches [132]. At steady state, most Th17 and Th1 cells are found at barrier sites, and their frequencies are severely reduced in the context of antibiotic-induced depletion of microbiota [133].

Pattern recognition receptors and antimicrobial peptides

The endometrial defenses against bacteria involve their recognition by receptors. These receptors are found on the surface of endometrial immune cells and comprise TLRs [134] and several NLRs [135], which bind molecules specific to microbial organisms, which are often called pathogen-associated molecular patterns (PAMPs). No relationship between the microbiota and the expression of these receptors in endometrium has been documented to date in endometriosis.

While bacteria can colonize the mucosa, the endometrium can also defend itself against these bacteria by producing antimicrobial peptides [136]. Antimicrobial peptides are effective against bacteria, fungi, enveloped viruses, and protozoa. Transcription of antimicrobial peptides is increased when pattern recognition receptors are activated and in response to cytokines [137]. In addition to direct inhibition of microorganisms, antimicrobial peptides also help protect epithelia against microbial proteases and help in resolving inflammation. The endometrium has a unique set of antimicrobial peptides that are mainly secreted by epithelial cells and leukocytes: β-defensin 1–4, α-defensin (human defensin 5), elafin, and secretory leukocyte protease inhibitor [138]. β-Defensins are the most common endometrial defensins. Activated by NF-kB transcription factors, they are known to have an antibacterial effect and the ability to neutralize LPS [139]. Intriguingly, these antimicrobial peptides were identified in a physiological setting prior to the discovery of an endometrial microbiota. To date, there are no data linking the expression of these antimicrobial peptides to endometrial microbiota or endometriosis.

Microbiota and oxidative stress in endometriosis

The role of oxidative stress in endometriosis as a driver of lesion proliferation is well established [140, 141] and is reflected by increased levels of advanced oxidation protein products, protein carbonyls and nitrates/nitrites, in perioperative peritoneal fluid of patients with endometriosis [142]. Marcellin et al. found that redox-sensitive Nrf2 is deregulated in eutopic and ectopic endometrium towards increased growth and fibrogenic processes [143]. Interestingly, *Lactobacillus* species release reactive oxygen species (ROS) which maintains an acid pH that is unfavorable to the growth of certain non-commensal bacteria [144]. According to Riganelli et al., the presence of *Lactobacillus* species in endometrial microbiota were exclusively detected in a group of infertile patients in which in vitro fertilization was unsuccessful [145].In a mouse model of non-alcoholic steatohepatitis, it has been shown that treatment with *Lactobacillus* species could improve the molecular pathological alterations via upregulation of the expression of Nrf2 and downregulation of the TLR4/NF-kB signaling pathways [146]. These data suggest that there appears to be a link between the production of ROS and the presence of bacterial patterns associated with unfavorable outcomes.

Microbiota and sex hormones in endometriosis

Endometriosis lesions, as infiltration of ectopic endometrium, are by definition hormone-dependent [147]. Lesions mainly sensitive to estrogen and progesterone express both estrogen (ER) and progesterone receptors (PR). This makes hormonal treatments such as oral contraceptives the first-line treatment for pain caused by endometriosis which consists of reversing menstrual cycles, through a mechanism of hormonal blockade by saturation of these receptor [13, 148].

Both ERα and the ERβ isoforms are required for the growth of endometriosis-like lesions [7]. Endometriosis mouse models using receptor knockout mice exhibit very low levels of lesion proliferation [149, 150]. Yilmaz et al. recently found that endometriotic stromal cells exhibit an abnormally low ERα/ERβ (ER1/ER2 in human) ratio due to excessive levels of ERβ (ER2) [151], which mediates an estrogen-driven inflammatory process triggering the activation of cyclooxygenase-2 (COX-2) [152, 153]. Moreover, endometriotic lesions have the ability to synthesize E2 de novo. Finally, a positive feedback cycle sustaining the inflammation and estrogen production in endometriosis are linked by a positive feedback cycle in which the chronic overexpression of aromatase and COX-2 supports the sustained production of estradiol and PGE2 [154, 155]. The activation of COX-2 expression interacts with the inflammasome to increase IL-1β in uterine endothelial cells [156]. Progesterone resistance is the second well-known hormonal signature of endometriosis [157]. Progesterone receptor signaling leads to downregulation of estrogen receptors. Progestins, a class of synthetic hormone drugs that mimic the endogenous hormone progesterone, inhibit cell proliferation, inflammation, neovascularization, and neurogenesis in endometriosis. However, progesterone receptor expression is reduced and disrupted in endometriotic lesions, with a predominance of the less active isoform [158].

Sex hormones have a significant impact on the composition of the gut microbiota, with a sex-specific effect on the composition of the gut microbiota after puberty [159]. Compared with males, the gut microbiota of females has higher α-diversity but lower abundance of Bacteroides species [160]. One possible explanation lies in the ability of certain bacteria to influence the circulation of sex hormones. The estrobolome is defined as the set of enteric bacterial genes for which the products are able to metabolize estrogens [161]. Hepatically conjugated estrogens excreted in the bile can be deconjugated in the gut by bacterial species with β-glucuronidase activity [162, 163]. Dysregulation of estrogen metabolism disrupts the spectrum of hormone-dependent pathologies, including steroid-dependent cancers, polycystic ovary syndrome, and endometriosis [164, 165]. The study by Pérez-Prieto et al. found no significant differences in estrobolome-associated enzyme sequence reads between women with endometriosis ($n=136$) and controls ($n=864$), based on metagenomic analysis [38]. Outside of metagenomic approaches, another compared 24 control women and 27 with endometriosis and found that although gut β-glucuronidase activity was similar between groups, fecal samples from endometriosis patients showed increased levels of four estrogen or estrogen-related metabolites [166]. Another study combining human and mouse models showed that β-glucuronidase, derived from gut dysbiosis, promotes endometriosis progression by enhancing endometrial stromal cell proliferation and inducing macrophage polarization toward the M2 phenotype. These findings suggest that β-glucuronidase contributes to lesion development both directly and indirectly, highlighting its potential as a therapeutic target in endometriosis [167].

It therefore seems important to take hormonal fluctuations into account when analyzing genital microbiota. The vaginal microbiota varies according to the estrogen level and, therefore, also the menstrual cycle [168]. Chen et al. found that endometrial bacterial proliferation was increased in the proliferative phase of the menstrual cycle, in contrast to the secretory phase [28]. Mechanistically, the elevation of estrogen levels induces thickening of the vaginal epithelium and resulted in an accumulation of glycogen [169, 170]. This could allow the proliferation of *Lactobacillus* species whose function is to regulate the acidity of the vagina and thus modify certain non-*Lactobacillus* species [171]. During the pre-ovulatory period, when estrogens are elevated, an increase has been found in the production of some antimicrobial peptides, such as secretory leukocyte peptidase inhibitor, β-defensin 1–2, and elafin [172]. This theory implies constant and Substantial turnover of the bacterial biomass. To date, this bacterial clearance has been observed within 48 h through phagocytosis of bacteria as well as the presence of antimicrobial products [172]. Importantly, butyrate has been shown to regulate the synthesis of progesterone and estradiol in porcine granulosa cells via the cAMP signaling pathway [173]. The estrobolome hypothesis, described in the digestive system, has not been documented in the endometrium. It may participate in the known abnormal in situ production of estrogen in the endometrium of patients with endometriosis.

Neurogenesis and the microbiota in endometriosis

Neurogenesis is defined as the generation of new neurons, glial cells, and other neural lineages. Endometriosis-associated pain is complex. It is widely accepted that no correlation exists between the extent of endometriosis seen at laparoscopy or radiology and the degree of pain symptoms [174]. The experience of pain is complex and involves many mechanisms and interactions between the peripheral and the central nervous systems [175]. This involves the activation of nociceptors [176] and neurogenesis of lesions activated by neurophils [177]. No data are available on a possible interaction between the microbiota and neurogenesis at both the digestive and endometrial sites. The release of inflammatory mediators by the gut microbiota can lead to neuroinflammation [178]. In addition, microbiota-derived short-chain fatty acids can induce the proliferation and differentiation of human neural progenitor cells [179]. Although the relationship between microbiota and neurogenesis has not been specifically explored in the context of endometriosis, the role of the gut microbiota in modulating visceral pain is well documented [180], particularly in irritable bowel syndrome. Studies in germ-free mice have shown that the absence of commensal gut microbes leads to enhanced visceral pain sensitivity, a phenotype that can be reversed upon microbial colonization [181]. This pain-related sensitivity has also been shown to be transmissible via fecal microbiota transplantation (FMT), and attenuated by antibiotic treatment [182]. Mechanistically, these effects appear to involve inflammasome signaling pathways [183], suggesting that microbial composition may shape nociceptive pathways through immune–neural interactions.

Microbiota in adenomyosis

Adenomyosis, characterized by the presence of endometrium in the myometrial tissue, is a significant threat to women's health due to its high incidence [184]. Adenomyosis, which is frequently associated with endometriosis (~30%), causes pain, infertility, and abnormal uterine bleeding [185]. Diffuse internal adenomyosis (in relation to the myometrium) is the most common form, compared to focal external adenomyosis, which shares more characteristics with deep infiltrating endometriosis [186]. Chen et al. recently investigated the impact of adenomyosis on the gut microbiota [187]. They found an increase in the ratio of Firmicutes/Bacteroidetes and the relative abundance of *Lactobacillus* species in cases of adenomyosis. In a study of 38 patients with adenomyosis—89% of whom also had deep infiltrating endometriosis—and 46 controls, 16S rRNA sequencing revealed significantly reduced gut microbial α-diversity and distinct gut and vaginal microbiota compositions in patients with adenomyosis. Several bacterial taxa were differentially represented in the gut and endometrial microbiota, with specific profiles associated with internal versus external adenomyosis phenotypes. Data are available regarding the association between adenomyosis and imbalance in the vaginal microbiota. Kunaseth et al. found an increase in microbial richness in patients with adenomyosis, with abundant *Alloscardovia*, *Oscillospirales*, *Ruminococcaceae*, *Oscillospiraceae*, *Enhydrobacter*, *Megamonas*, *Selenomonadaceae*, and *Faecalibacterium* [188, 189]. Interestingly, *Atopobium* is a known biomarker of vaginal microbiota in patients with endometriosis combined with adenomyosis [190]. Lin et al. studied the endometrial microbiota in 38 women with ($n = 21$) and without ($n = 17$) adenomyosis. In contrast with the results for patients with endometriosis, patients with adenomyosis had a significantly lower richness than the control group. Their findings identified *Lactobacillus zeae*, *Burkholderia cepacia*, *Weissella confusa*, *Prevotella copr*i, and *Citrobacter freundii* as potential biomarkers for adenomyosis [191]. A recent systematic review concluded that adenomyosis is associated with significant microbial alterations, including a depletion of protective vaginal *Lactobacillus* species and an enrichment of vaginal and endometrial opportunistic anaerobic bacteria rich in virulent cell wall components such as LPS [192]. It has also been shown that these microbial differences are cycle-dependent and more pronounced during the luteal phase [193]. The proximity of adenomyosis lesions to the uterine cavity and the vagina makes them a potential therapeutic target for vaginal probiotics.

Perspectives

A bacterial contribution to the pathophysiology of endometriosis

Inflammation and aberrant immune responses are well-known factors involved in the pathophysiology of endometriosis. Both can be triggered by bacterial endotoxins, which promote the secretion of inflammatory cytokines and chemokines. The bacteria found in the microbiota are sources of pathogen-associated molecular patterns and metabolites. Pathogen-associated molecular patterns are mainly represented by LPS (a component of the outer cell wall of gram-negative bacteria), lipoteichoic acid, and flagellin. These highly conserved structural motifs serve as ligands that are recognized by PRRs to trigger immune responses. Bacterial adaptive changes including modulation of LPS synthesis and structure are conserved processes in infections. Activation of macrophages and dendritic cells was found to occur by the binding of LPS to the membrane surface of certain gram-negative bacteria, to its TLR4 receptor, resulting in nuclear translocation of NF-kB, which induces the expression of inflammatory cytokines (IL-6 and TNFα) [194]. In patients with endometriosis, Khan et al. found a higher colony formation of *Escherichia coli* in menstrual blood and endotoxin levels in menstrual fluid [195]. The hypothesis that *E. coli* is a key pathogenic bacterium in endometriosis has been reinforced by a recent publication from our team focusing on the only pathognomonic infection of the disease: endometrioma infections. An ecological analysis of aspirated fluid from infected endometriomas revealed that the majority of infections were caused by *E. coli* [53]. Several studies have shown that intraperitoneal LPS injected into mice increases endometriosis lesions through activation of the NF-kB pathway [128, 196]. Moreover, the use of antibiotics before or after induction of endometriosis in rodent models results in a decrease in lesion size and inflammation. It is not possible to know whether the antibiotic action was induced by modification of the microbiota, by inhibition of certain inflammatory pathways, or by both [197]. A recent study revealed that infection of endometrial cells with *Fusobacterium* led to a transition from quiescent fibroblasts to myofibroblasts, with an increase in their proliferation, adhesion, and migration [198]. These results were confirmed by *Fusobacterium* inoculation in a syngeneic mouse model of endometriosis, which resulted in an increase in the number and weight of endometriotic lesions. This effect was also reversible with antibiotic treatment.

Interestingly, Lin et al. conducted a nationwide prospective cohort study to determine whether lower genital tract infections increase the risk of endometriosis. A total of 79 512 patients were included in the lower genital tract infection group, with an equal number of controls. The incidence of endometriosis (HR = 2.01; $p < 0.001$) was higher in patients than in the controls [199]. Concerning upper genital tract infection, a strong association has been found between endometriosis and chronic endometritis [200]. Pelvic inflammatory disease was shown to be a major risk factor (three-fold) for developing endometriosis within 10 years in another nationwide retrospective cohort study involving a total of 141 460 patients [201]. Several questions remain unanswered, however, and are likely to be key to understanding the bacterial hypothesis in the pathophysiology of endometriosis. Do the bacteria responsible for these infections come from the endometrium? Are they responsible for the alteration of the endometrium, from eutopic to ectopic, and do they then promote the implantation of lesions in the peritoneal cavity?

Hope for treatment

Modulating the microbiota could be beneficial for patients (Fig. 1). In a mouse model of endometriosis, oral administration of *Lactobacillus* reduced the size of lesions by activating NK cells, mimicking their stimulation by IL12 [202]. Furthermore, treatment with one or two probiotics (*Saccharomyces boulardii* and/or *Lactobacillus acidophilus*) has been reported to exert favorable effects on clinical, immune, and physiologic parameters in a mouse model of endometriosis [203]. In patients with severe endometriosis (Stages III and IV), a randomized placebo-controlled trial showed some beneficial effects of oral administration of *Lactobacillus* on endometriosis-related pain [204]. In addition to modulating the microbiota, the use of broad-spectrum antibiotics has been tested in a mouse model of surgically-induced endometriosis, with the important observation of reduction of the development of lesions [49]. Finally, as demonstrated in the mouse study by Parpex et al., the marked depletion of *Akkermansia* in the gut, observed in association with the most severe endometriotic lesions, highlights its potential as a candidate for probiotic-based therapeutic strategies [52].

A potential lead lies in the effect of dietary modifications on these symptoms. The low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) diet was introduced in 2005 to group together certain poorly absorbed fermentable carbohydrates responsible for intestinal symptoms, particularly in patients with irritable bowel syndrome [205]. Clinical studies confirmed the effectiveness of the low-FODMAP diet in irritable bowel syndrome patients, which reduces pain, bloating, and bowel movement disorders by limiting the osmotic and fermentative effects of these sugars in the gut [206]. This dietary approach is based on well-defined pathophysiological mechanisms, including incomplete intestinal absorption, rapid fermentation by the microbiota, and visceral hypersensitivity, all of which vary depending on the type of FODMAP and individual sensitivity. Moore et al. evaluated the efficacy of this diet on gastrointestinal symptoms in 160 female patients diagnosed with irritable bowel syndrome. Among them, 59 (37%) had a confirmed diagnosis of endometriosis. After one month on the diet, improvement defined as a > 50% reduction in gastrointestinal symptoms was more pronounced in patients with both endometriosis and irritable bowel syndrome [207]. A randomized controlled trial conducted by the same team further explored this effect by comparing the low-FODMAP diet to both the patients' baseline diet and a control diet based on national Australian dietary guidelines [208]. The study used a crossover design with three 4-week periods (including a 4-week washout). A significant improvement in quality of life was observed after 4 weeks on the low-FODMAP diet, compared to both the baseline diet group ($p < 0.001$) and the control diet group ($p = 0.004$). Additional clinical symptoms such as abdominal pain, stool consistency, and abdominal bloating were also significantly improved. This is the first study providing robust evidence that a dietary intervention can significantly enhance the quality of life of patients with endometriosis. The changes in gut microbiota before, during, and after implementation of the low-FODMAP diet need to be investigated in patients with endometriosis. This promising diet in endometriosis is known to induce long-lasting changes in the gut microbiota of patients with irritable bowel syndrome (lower *Bifidobacteria*) [209]. If a sustained improvement in symptoms associated with microbiota alterations were also observed in endometriosis, this would constitute strong evidence for considering the gut microbiota as an effective therapeutic target.

Dysbiosis has been associated with increased intestinal permeability ("leaky gut"), allowing the translocation of antigens and bacteria, which may promote chronic inflammation and contribute to endometriosis progression [210]. A pilot study by Mohling et al. found that nearly half of patients with laparoscopically confirmed endometriosis had impaired intestinal permeability, compared to none in the control group, suggesting a possible link between barrier dysfunction and the disease [211]. Zonulin, a key regulator of tight junctions, is overexpressed in states of dysbiosis and may facilitate immune activation, potentially explaining gastrointestinal symptoms commonly reported in endometriosis, even in the absence of bowel involvement [212]. Future studies should investigate zonulin as a biomarker of gut

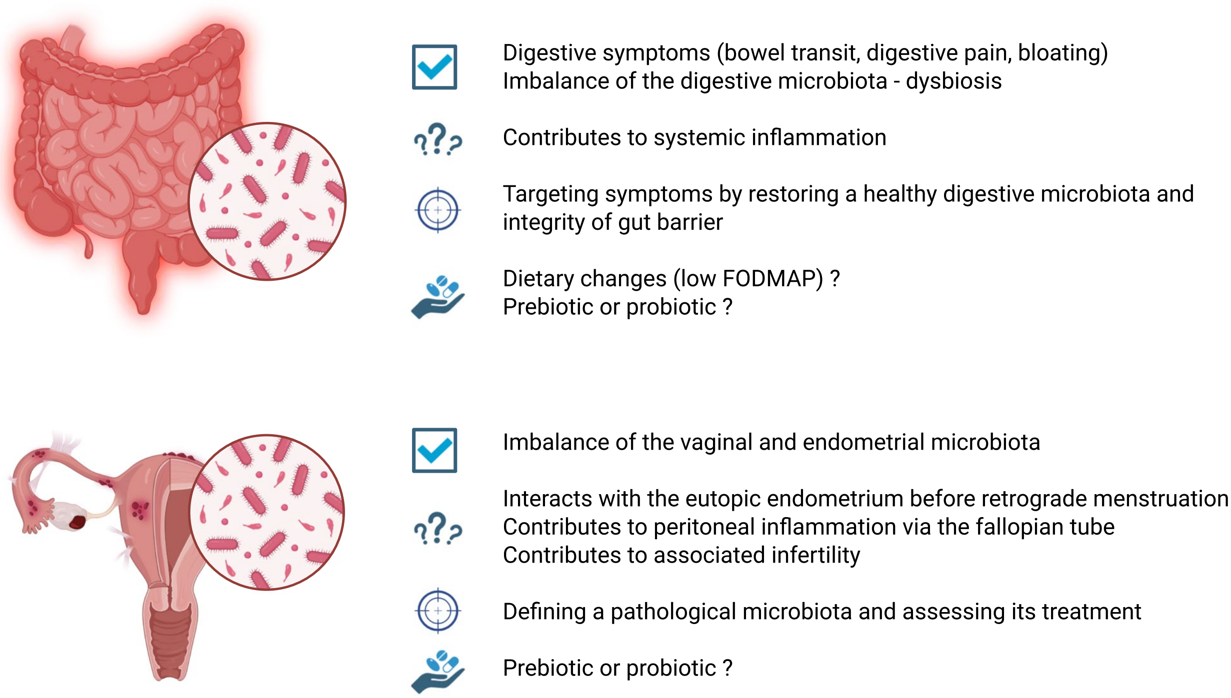


Fig. 1 Gut and Gynecological Microbiota in Endometriosis: Current Knowledge and Future Directions

permeability and explore probiotic interventions to alleviate symptoms and improve quality of life in affected patients.

The role of the gynecological microbiota—both vaginal and endometrial—in endometriosis remains less well characterized to date. However, several hypotheses can be proposed, starting from a consistent observation: most studies report alterations in the vaginal and endometrial microbiota. While the composition of a healthy vaginal microbiota is well defined, the endometrial microbiota is less understood and likely originates from the vaginal tract. This endometrial microbiota warrants further investigation, as it is in direct contact with the eutopic endometrium prior to retrograde menstruation and may contribute to lesion establishment in the peritoneal cavity. Consequently, it could be involved in peritoneal inflammation through its anatomical continuity via the fallopian tubes and may also play a role in infertility mechanisms through the presence of pathogenic bacteria (subclinical endometritis) and associated cervical mucus dysregulation.

Conclusion

Endometriosis, a chronic disease predominantly affecting women of childbearing age, has garnered increasing attention in the context of microbiota research. Investigations into the digestive and gynecological microbiota in relation to endometriosis have provided valuable insights. Notably, the interplay between the immune system and bacterial interactions has demonstrated promising outcomes concerning lesion development and the potential for microbiota modulation as a therapeutic approach for patients. These findings highlight the significance of understanding the intricate connections between the microbiota, immune system, and endometriosis pathogenesis, paving the way for innovative treatment strategies. However, great caution must be exercised regarding various potential biases, such as the menstrual cycle, lifestyle habits, sexual habits, and precise selection of control groups. Further exploration of this complex interplay holds immense potential for improving the management and outcomes of individuals affected by endometriosis.

Abbreviations

ASRM	American Society for Reproductive Medicine
cAMP	Cyclic AMP pathway
COX-2	Cyclooxygenase-2
CST	Community state type
ER	Estrogen receptor
IL	Interleukine
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear factor kappa-light-chain-enhancer
NGS	Next-generation sequencing

NK Natural killer
NLR NOD-like receptor
NLRP3 NOD-like receptor family, pyrin domain containing 3
NrF2 Nuclear factor 2
PAMP Pathogen-associated molecular patterns
PPR Pattern recognition receptor
PR Progesteron receptor
ROS Reactive oxygen species
SCFA Short-chain fatty acid
SNP Single-nucleotide polymorphisms
TLR Toll-like receptor

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