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The role of the gut and reproductive tract microbiota in the development, diagnosis, and treatment of endometriosis

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ABSTRACT

Endometriosis is an inflammatory disorder. Caused by the proliferation of endometrial tissue outside the uterine mucosa. Progression results from elaborate interactions among hormonal, immunological, and environmental factors. Growing evidence indicates that the gut and reproductive tract microbiota play a key role in the pathogenesis of endometriosis. In patients with endometriosis, an increase in potentially pathogenic taxa, including *Escherichia*, *Gardnerella*, and *Streptococcus*, is observed. Dysbiosis leads to the translocation of bacterial endotoxins (Lipopolysaccharide (LPS)), activation of the TLR4/NF-κB pathway, and increased production of pro-inflammatory cytokines (IL-6, IL-8, TNF-α), which promote angiogenesis and the proliferation of endometrial foci. Furthermore, disturbances in the activity of the enzyme β-glucuronidase, part of the oestrobolome, increase the pool of active oestrogens, playing a role in disease progression. Despite the growing number of studies, further prospective studies involving larger populations are needed to standardise diagnostic methods and confirm the therapeutic potential of microbiome modulation in treating endometriosis.

Keywords: endometriosis, gut microbiota, reproductive tract microbiota, estrabolome

1. INTRODUCTION

Endometriosis is an inflammatory disease involving the growth of the uterine lining outside the uterus. Depending on the location, different names and forms of the disease can be distinguished. Adenomyosis is a type of endometriosis located within the uterine wall. Superficial endometriosis is characterised by foci on the surface of the peritoneum. Deep endometriosis is a condition in which endometrial cells grow beyond the female reproductive organs. A case of deep endometriosis has even been described in which endometrial foci were in the central nervous system (Meggyesy et al., 2020). It most commonly affects young women of reproductive age, affecting 10% of women.

Sampson's theory is the most popular among the existing theories (Konickx et al., 2019), which claims that in a new environment, retrograde menstrual blood flow may facilitate the transplantation and growth of endometrial fragments. This theory supports the typical locations of endometriosis foci, such as the adnexal region, uterosacral ligaments, or the pouch of Douglas. Nevertheless, the anatomical obstruction to menstrual blood outflow or proven retrograde flow is not always associated with endometriosis. Risk factors include: disturbances in menstrual blood flow, anatomical defects, prolonged oestrogen exposure, short menstrual cycles, low birth weight, or exposure to toxins (Konickx et al., 2019; Caporossi et al., 2021). Recently, increasing significance has been attributed to the role of dysbiosis in the gut and vaginal microbiota, which has the potential to amplify inflammation and disrupt hormonal balance (Molina et al., 2020).

As endometrial implants shed just like the normal endometrium, they naturally correspond with the menstrual cycle. An intensified inflammatory process occurs, nerve-receptor transmission increases, and patients' perception of pain is heightened. This is the first and most common symptom of endometriosis. What is more, the heavy menstrual bleeding and painful sexual intercourse (dyspareunia) occur as well. In the long term, endometriosis can be a factor playing a role in an ectopic pregnancy, premature birth, or even infertility. The well-established standard for its diagnosis is laparoscopy. The treatment for endometriosis includes pharmacological, surgical, and with supportive methods, depending on symptoms, the location of changes, and the patient's future reproductive plans. The pharmacotherapy is mainly based on hormonal drugs. In refractory cases or deep infiltrating endometriosis, surgical treatment (most commonly laparoscopic) is used, aimed at removing the disease outbreaks. Supportive treatment includes physiotherapy, a specific diet therapy, probiotic therapy, and psychological support.

Currently, all treatment methods are symptomatic. Recently established treatment approaches include examining the gut and reproductive tract microbiota as potential targets for causal treatment. Nonetheless, the therapy should be individualised and long-term-oriented. Henceforth, the aim of this paper is to present the current state of research and knowledge on the role of the gut and reproductive tract microbiota in the pathogenesis and treatment of endometriosis, with particular emphasis on immunological, hormonal, and inflammatory mechanisms.

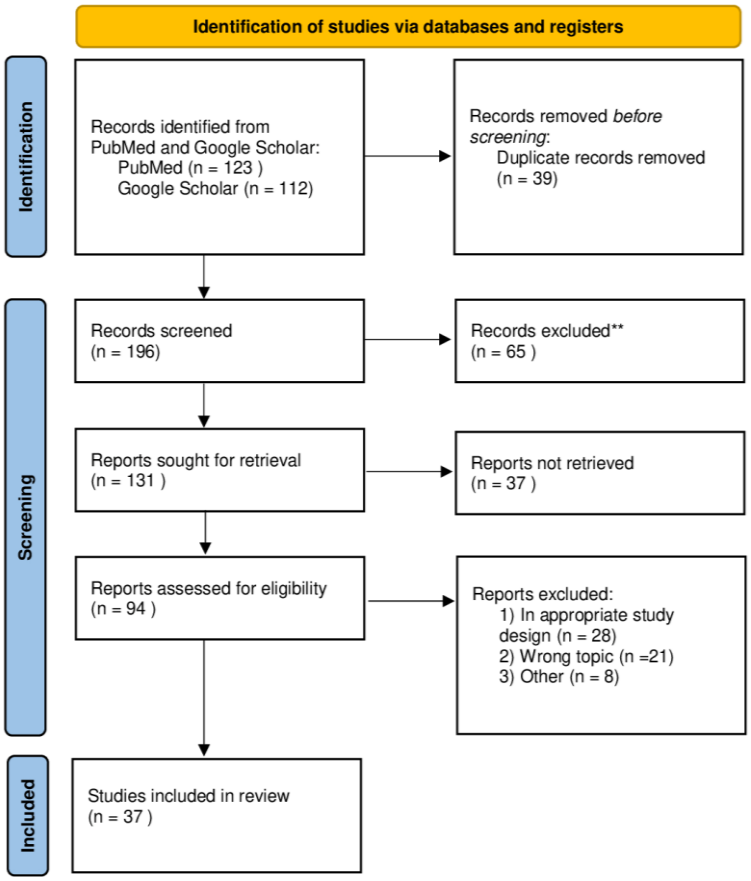

Figure 1. Prisma Flowchart

2. REVIEW METHODS

For this review, we searched PubMed and Google Scholar for articles published. Electronic literature searches were performed with a restriction to particular publication years (January, 1999 – July, 2025), using the following English search terms: endometriosis, gut microbiota, reproductive tract microbiota, oestrobolome. Inclusion criteria included literature treating clinical trials, systematic reviews, and original papers, as well as meta-analyses concerning the influence of the microbiome on the development of endometriosis, all published in English. Exclusion criteria, however, included studies with weak methodology and publications written in languages other than English (Figure 1).

3. RESULTS & DISCUSSION

Recent publications clearly indicate dysbiosis in the intestinal microbiota and reproductive organs. The disease develops as a result of colonisation by pathogenic *Escherichia*, *Gardnerella*, *Prevotella* and a decrease in the number of protective *Lactobacillus* and *Bifidobacterium* bacteria. This disequilibrium promotes activation of the TLR4 and NF-kB pathways by LPS, leading to chronic inflammation. In turn, elevated concentrations of IL-6, IL-8, and TNF-alpha promote the growth of ectopic endometrial foci outside the uterine cavity. Increased β-glucuronidase activity increases serum estrogen levels. Under the influence of estrogen, the endometrium undergoes increased proliferation. In a short time, this can lead to clinical symptoms and exacerbation of the disease. The microbiome varies depending on lesion stage and anatomical location, with some bacterial taxa exhibiting protective effects and others increasing disease risk. Animal models have confirmed a causal link, as transplantation of microbiota from affected individuals induced endometriotic lesions in healthy animals. Modulation of the microbiota, including increased levels of short-chain fatty acids (SCFAs), reduced lesion growth by influencing macrophage polarisation. The diversity of substances secreted by the microbiome and its composition enables the development of diagnostic methods and screening tests in the future. To this end, diagnostics should be improved, and funding for clinical trials should be increased (Table 1).

Table 1: The impact of gut and reproductive tract microbiome on the development, diagnosis, and treatment of endometriosis.

Study	Aspect	Key findings	Pathophysiological relevance
Hicks et al., 2025	Microbiota dysbiosis	Decrease concentration: *Lactobacillus*, *Bifidobacterium* Increase concentration: Escherichia, Prevotella, Gardnerella	Induction of inflammation
Khan et al., 2010	Inflammatory pathways	↑ LPS ↑ TLR4/NF-κB	Chronic inflammatory response
Machado et al., 2022 Wang et al., 2021	Inflammatory mediators	↑ IL-6 ↑ IL-8 ↑ TNF-α	Progression and persistence of endometriotic lesions
Kwa et al., 2016	Estrobolome	↑ β- glucuronidase	Increased levels of estrogens
Ji et al., 2023 Wang et al., 2025).	Angiogenesis	↑ pro-angiogenic factors	Vascularization and survival of ectopic lesions
Quaranta et al., 2019 Liu et al., 2024	Causal evidence	Microbiota transplantation induces lesions (animal models)	Confirms microbiota involvement
Li et al., 2024	Microbiota modulation	↑ SCFAs-macrophage polarization	Reduced lesion growth
Toffoli et al., 2025	Clinical potential	Microbiome profiles as biomarkers	Targeted diagnosis and therapy

Current State of Research and Knowledge

The Physiological Role of the Gut Microbiome

A description of the physiological role of the gut microbiome's all functions is beyond the scope of this publication; nevertheless, to highlight the enormous role it plays in our body, it is worth recalling that the number of cells making up the gut microflora is several times greater than the number of cells in our body. We now know that its role goes beyond the digestive system as it includes influences on the immune, hormonal, and nervous systems, as well as on the pathogenesis of gynaecological diseases such as

endometriosis (Polycystic Ovary Syndrome – (PCOS)) and fertility disorders. It additionally plays an important role in the metabolism of nutrients and the production of (Short-Chain Fatty Acids (SCFA)). The compound exhibits anti-inflammatory properties by sealing the intestinal membrane. It mobilises the immune system and activates dendritic cells, Th17 lymphocytes, and Treg cells (Li et al., 2024). Dysbiosis then leads to excessive immune activation and a chronic inflammatory state, which ultimately promotes the development of inflammatory, metabolic, autoimmune, and neoplastic diseases.

The Physiological Role of the Female Reproductive Tract Microbiome

The microbiota of the female reproductive tract, notably of the vagina, is dominated under physiological conditions by bacteria of the *Lactobacillus* genus (L. *crispatus*, L. *iners*, L. *gasseri*, L. *jensenii*). They produce lactic acid, they maintain an acidic environment (pH < 4.5), which serves as protection for them from infections and a support for local mucosal immunity. A stable vaginal microbiome serves as a barrier against pathogens while also ensuring immunological tolerance to natural bodily changes, such as during the menstrual cycle or pregnancy. Disturbances in this state of balance result in dysbiosis. Most commonly referred to as bacterial vaginosis, it is characterised by a decrease in *Lactobacillus* abundance and a predominance of anaerobic bacteria (*Gardnerella*, *Prevotella*, *Atopobium*) (Wang et al., 2021).

Clinically, this is associated with increased susceptibility to reproductive and urinary tract infections. Modern sequencing techniques have shown the presence of specific bacteria in the uterine cavity and peritoneal fluid (Chen et al., 2017). This has raised new questions about their role in the initiation and progression of endometrial changes.

Gut and genital dysbiosis can lead to the translocation of bacterial endotoxins (e.g., LPS), which activate the TLR4/NF-κB pathway. The result is the production of pro-inflammatory cytokines (IL-6, IL-8, TNF-α), promoting angiogenesis and the proliferation of endometrial foci. Studies have long unravelled the differences in the composition of the gut, vaginal, and endometrial microbiota in women with endometriosis compared to healthy women. Among other findings, there was a decrease in beneficial (e.g., *Lactobacillus* and *Bifidobacterium*) and an increase in the proportion of potentially pathogenic bacteria (e.g. *Escherichia*, *Streptococcus*, *Gardnerella*). More and more attention is being drawn to the increased prevalence of *Phascolarctobacterium* in patients' faeces, which serves as a possible diagnostic biomarker (Hicks et al., 2025). Initial attempts at microbiota modulation, probiotics, diet, antibiotics, and, in animal models, faecal microbiota transplantation. Suggest that influencing the microbiome may reduce inflammation, limit the development of foci, and relieve pain symptoms.

Gut Microbiota and Endometriosis

In recent years, the gut microbiota has gained particular significance as a potential factor modulating the development and progression of endometriosis. A growing body of data indicates that its composition and functions can influence the immune response. The primary factor associated with endometriosis development is increased intestinal permeability to pathogenic bacteria, which interferes with the normal microbiome. These disturbances lead to chronic inflammatory states, which are a risk factor for disease development. This leads to an accumulation of inflammatory cytokines (including TNF-α, IL-6, IL-8) and Vascular Growth Factors (VEGF).

Angiogenesis and inflammation enable the survival of endometrial implants in a new location. As early as 1999, Garcia-Velasco and Arici conducted in vitro studies showing that IL-8 significantly increases the adhesion of cells to fibronectin, the main extracellular matrix protein, in a dose-dependent manner, and further, the neutralisation of IL-8 with monoclonal antibodies partially blocked this effect, corroborating its important role in this process. The authors suggest that IL-8 is present in elevated concentrations. May function as an autocrine and paracrine factor, supporting the adhesion, proliferation, and angiogenesis of endometrial foci (1999), which overall s that the peritoneal inflammatory microenvironment promotes the initiation of endometriosis, strengthening the early stages of endometrial cell implantation (Garcia-Velasco and Arici,1999).

Currently, there is no way to determine exactly what causes endometriosis. Many hypotheses have arisen on this topic, one of which is the bacterial contamination hypothesis. The authors demonstrated that (LPS) – the main component of the cell membrane of Gram-negative bacteria, notably from *Escherichia coli*, can enter the peritoneal cavity with menstrual blood as a result of retrograde menstruation. Studies have found that *E. coli* contamination in the control group was larger. (LPS) activates the TLR4 and NF-kB pathways, augmenting the inflammatory response. Active macrophages secrete TNF-alpha, IL-6, and IL-8. This process supports angiogenesis, followed by endometrial proliferation of ectopic endometrial lesions. Clinical studies have demonstrated gut dysbiosis, and several taxa have been identified as more abundant in the study group, including the classes *Bacilli*, *Clostridia*, *Coriobacteriia*, and *Gammaproteobacteria* (Ji et al., 2023; Wang et al., 2025).

Nevertheless, a change in the microbiome does not always favour disease development. *Anaerotruncus*, *Olsenella*, and *Ruminococcaceae* may increase the risk of developing endometriosis, whereas *Eubacterium ruminantium*, *Holdemania*, and *Sutterella* have a protective effect (Dang et al., 2024). The evidence of animal experiments supports this thesis (Chadchan et al., 2023), as it has been proven that transplanting faecal microbiota from mice with endometriosis to healthy animals induces the development of lesions.

A correlation has been discovered between bacterial species and the location of endometriosis. Carriage of *Blantia*, *Oscillospira*, and *Adlercreutzia* increases the risk of ovarian and peritoneal disease (Tang et al., 2024). The microbiomes of female patients at different stages of disease progression were compared. Taxonomic analysis showed that in the early stage, bacteria such as *Saccharofermentans*, *Prevotella*, or *Bacteroides* predominated; however, in the late stage, *Bartonella* and *Snodgrassella* were the ones to show greater abundance. As a result of the findings overall, *Prevotella ruminicola* and *Bacteroides caecimuris* were associated with a milder clinical course (Xu et al., 2025; Cai et al., 2025).

A study including 38 patients with endometriosis and 20 healthy women was conducted, focusing on assessing levels of Mannose-Binding Lectin (MBL), the activity of the lectin pathway (LP), and associated changes in the endometrial microbiota. The authors demonstrated that elevated plasma (MBL) levels correlate with disease advancement, but they were not linked to polymorphisms in the MBL2 gene. Patients with elevated LPS concentrations were more likely to be carriers of pathogenic Gardnerella and Prevotella bacteria (Wang et al., 2025). However, Lactobacillus significantly reduced LPS concentration. This was noted by the team (Toffoli et al., 2025) in their study. They suggest that LPS may serve as a marker of disease progression in the future. They noted that this requires further research.

Some substances secreted by bacteria have protective properties, e.g., SCFA. It alleviates inflammation and reduces disease symptoms (Su et al., 2024). Faecal microbiota transplantation (FMT), from healthy donors increases SCFA concentration. This results in the activation of the tyrosine kinases JAK1/STAT3 pathway within the lesions. The consequence of this was the polarisation of macrophages towards the M1 phenotype (Quaranta et al., 2019; Liu et al., 2024).

The oestrobolome is a term introduced by Plottel and Blaser in 2011, defining the set of bacterial genes in the gut microbiota whose enzymatic products participate in oestrogen metabolism. The key enzyme in this process is β-glucuronidase, produced by bacterial species (e.g., *Escherichia coli*, *Bacteroides*, *Clostridium*). Oestrogens are metabolised and conjugated with glucuronic or sulphuric acid in the liver. Next, it is then excreted with bile into the intestines. In the intestine, bacteria producing β-glucuronidase can break down conjugated oestrogens. Restoring their active form. Active oestrogens are reabsorbed into the circulation (enterohepatic circulation). Regular oestrobolome activity facilitates the maintenance of the appropriate level of oestrogens in the body, as shown in studies (Kwa et al., 2016), and disturbances in this process can appear as hypooestrogenaemia or hyperoestrogenaemia. The latter can also directly influence endometrial growth in other locations or the development of oestrogen-dependent tumours (Hu et al., 2023).

Plottel and Blaser analysed faecal and urine samples from 51 patients (27 with endometriosis, 24 healthy). In the faeces of patients with endometriosis, elevated levels of oestrogen metabolites were found: oestriol, 16-epioestriol, 16α-hydroxyoestrone, and 2-methoxyoestradiol. On the contrary, such differences were not observed in urine samples. The authors emphasise that despite the lack of clear signs of gut dysbiosis, the altered microbiota composition and increased concentrations of active oestrogen metabolites in faeces may indicate subtle interactions between the gut microbiome and the oestrobolome in the pathogenesis of endometriosis. This evidence shows a role for the microbiota in locally modulating oestrogen metabolism, which may further support disease development. This data support the hypothesis that the gut oestrobolome can truly impact the pool of active oestrogens in the enterohepatic circulation, consequently facilitating the progression of endometriosis (Pai et al., 2023). Studies on mouse models have confirmed that administration of β-glucuronidase causes an increase in LPS concentration and macrophage infiltration. This leads to an increase in the inflammatory response and disease progression (Wei et al., 2023).

Reproductive Tract Microbiota and Endometriosis

For a long time, it was believed that the cervical barrier provided adequate protection of the uterine cavity against colonisation by microorganisms from the vagina and the external environment. However, thanks to advances in sequencing techniques and the expansion of diagnostic methods. We know that the microflora of the reproductive tract consists of many species of bacteria (Hugerth et al., 2024). In patients with chronic endometritis, there was a significant decrease in the dominance of *Lactobacillus* bacteria in both the vagina and the uterus. What is essential is that transplanting vaginal microbiota from such patients into animal models results in endometrial inflammation, a risk factor for endometriosis. A reverse trial was conducted, in which the introduction of the protective strain *Lactobacillus murinus* showed an anti-inflammatory effect in animals. This way, a link was proven between infection of the lower

reproductive tract, including the vagina, and an increased risk of endometriosis (Elizur et al., 2014). Female reproductive tract dysbiosis also increases the risk of infertility, ectopic pregnancy, and endometrial cancer (Wessels et al., 2021).

Patients are marked by decreased levels of Lactobacillus bacteria. This is typical for a healthy vaginal microbiome. In addition, there is colonisation by species that increase the risk of endometriosis: *Gardnerella*, *Atopobium*, *Prevotella*, or *Megasphaera* (Sessa et al., 2024). In patients with endometriosis, Escherichia coli was more frequently detected in menstrual blood and endometrial smears, a finding that is significant given the presence of LPS bacterial endotoxins capable of activating TLR4 receptors and intensifying local inflammatory reactions (Khan et al., 2010). Higher levels of endotoxins and (Heat Shock Proteins (HSP70)) were found in the menstrual and peritoneal fluid of patients with endometriosis, which increases the chances of survival and proliferation of endometrial cells via the TLR4 signalling pathway (Khan et al., 2013).

Due to diagnostic difficulties and the lack of a specific disease marker, considerable funding has been allocated to research on this topic, resulting in the creation of a specialised predictive model. The algorithm created enables differentiation between the microbiome of the vagina and the reproductive tract in sick and healthy patients with an accuracy of 81% sensitivity and 88% specificity (MacSharry et al., 2024). The significance of the microbiome in the pathogenesis of endometriosis is also supported by studies examining its composition in sick patients. Specific patterns of IgG glycosylation in serum and urine may be another marker of the disease (MacSharry et al., 2024; Li et al., 2025). Currently, however, the tests have not found any clinical application due to high diagnostic costs and the complexity of the process.

The inoculation with *Fusobacterium* in animal models resulted in exacerbation of endometriosis, whereas antibiotic treatment significantly decreased the number and mass of disease foci (Muraoka et al., 2023). Due to the lack of causal treatment, however, much attention is devoted to new methods and hopes for the future are placed in probiotics.

Progress in observations indicates a high therapeutic potential targeted at the microbiome *Lactobacillus spp*, as the dominant component of healthy vaginal flora, not only strengthens the mucosal barrier but also limits the colonisation of pathogens (e.g., *Gardnerella vaginalis*, *E. coli*), consequently lowering the production of pro-inflammatory cytokines (IL-6, IL-8, TNF-α). It inhibits the action of endotoxins, which is notably important in treatment (Machado et al., 2022; Wang et al., 2021). Given current evidence, the female reproductive tract microbiome is no longer associated solely with infections requiring antibiotic treatment; it is now a source of knowledge for future diagnostic and therapeutic methods.

4. CONCLUSION

More and more studies indicate that dysbiosis promotes the development of the disease. Both intestinal and reproductive tract microbiome disorders promote the progression of endometriosis through particular mechanisms. Activation of TLR4 receptors by LPS molecules and the subsequent activation of the NF-κB inflammatory pathway lead to the proliferation of ectopic endometrial foci. An additional influence is the increased concentration of estrogens, which is affected by the estrobolome. Currently, pathogenic and protective bacteria have been identified. In the future, this division may allow for greater precision and earlier diagnosis of patients. Animal studies indicate that disruption of the microbiota may influence the development or inhibition of disease lesions. Researchers emphasise the future therapeutic impact of disease regression in animals.

The studies describe molecules secreted by bacteria that may have the potential to alleviate the development of the disorder. SCFAs have immunomodulatory effects, reduce inflammation, and limit the activation of immune system cells. Their low concentration correlated with the development of endometriosis. Promising results and evidence from animal models deliver a meaningful understanding of future diagnostic and clinical therapies. However, further research is required to completely understand these relationships and their potential clinical applications.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the Corresponding Author.

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