Medical Science

To Cite:
Hassan S, Bienia S, Hassan A, Hassan K. Endometriosis and the Microbiome: A Hidden Link in the Female Reproductive Ecosystem. *Medical Science* 2025; 29: e104ms3605
doi: https://doi.org/10.54905/disssi.v29i161.e104ms3605

Authors' Affiliation:
[1]Medical University of Silesia, 18 Medyków Street, 40-752 Katowice, Poland; Email: sara.hassan2605@gmail.com; ORCID: 0009-0009-3297-8250
[2]Medical University of Silesia, 18 Medyków Street, 40-752 Katowice, Poland; Email: szymonbienia1@gmail.com; ORCID: 0009-0000-7632-5125
[3]Cardinal Stefan Wyszyński University in Warsaw, Wóycickiego 1/3, 01-938 Warsaw, Poland; Email: 114039@student.uksw.edu.pl; ORCID: 0009-0001-5078-7724
[4]Social Academy of Sciences in Łódź, Henryka Sienkiewicza 9, 90-113 Łódź, Poland; Email: hassimma99@gmail.com; ORCID: 0009-0008-3207-4836

[*]**Corresponding author**
Szymon Bienia
Medical University of Silesia, 18 Medyków Street, 40-752 Katowice, Poland
Email: szymonbienia1@gmail.com
ORCID: 0009-0000-7632-5125

Peer-Review History
Received: 03 June 2025
Reviewed & Revised: 07/June/2025 to 05/July/2025
Accepted: 07 July 2025
Published: 12 July 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Endometriosis and the Microbiome: A Hidden Link in the Female Reproductive Ecosystem

Sara Hassan[1], Szymon Bienia[2*], Aisha Hassan[3], Kamil Hassan[4]

ABSTRACT

Endometriosis involves the persistent presence of endometrial-like tissue growing outside the uterus. These lesions respond to hormones, break down, and cause inflammation. This disease mainly affects women of reproductive age and is often accompanied by unpleasant symptoms such as pain and infertility. To this day, the actual cause of endometriosis has not been identified. There are many theories, such as coelomic metaplasia or retrograde menstruation, but they do not offer a complete picture of the cause. In recent years, research has emerged concerning the gut microbiome's potential role as a contributing factor to the development of endometriosis. Results show that women with endometrial lesions exhibit a modified gut microbial composition, with an overgrowth of harmful bacteria (such as Pseudomonas) and a reduction in those with more beneficial effects (such as Ruminococcus). These changes may impact hormone metabolism and immune function, contributing to disease development. This has led to the "gut-reproductive tract axis" hypothesis — the idea that the digestive and reproductive systems interact via immune and hormonal pathways. Microbial imbalances in one system may trigger inflammation in the other. Laparoscopy remains the gold standard for diagnosis, but it's invasive and often delayed due to overlapping symptoms. If microbial patterns are strongly linked to endometriosis, they could lead to non-invasive diagnostic methods. The gut microbiome is also being explored as a therapeutic target. While human data are limited, probiotics might one day support standard treatments. Large-scale clinical trials are needed to validate these findings.

Keywords: endometriosis, gut microbiota, dysbiosis, probiotics, inflammation

1. INTRODUCTION

Endometriosis is a chronic, estrogen-dependent condition characterized by the presence of functional endometrial-like tissue outside the uterine cavity. These ectopic lesions, composed of both glands and stroma, exhibit cyclical activity in response to hormonal fluctuations, mirroring the behavior of the eutopic endometrium. However, in the absence of a physiological outflow pathway, this activity results in localized inflammation, fibrosis, and the formation of adhesions,

contributing to the hallmark symptoms of the disease: pelvic pain, dysmenorrhea, dyspareunia, abnormal uterine bleeding, and infertility (Moïse et al., 2025).

Epidemiological data suggest that endometriosis affects approximately 10% of women of reproductive age, with markedly higher prevalence among individuals experiencing reproductive disorders (20–50%) and those with chronic pelvic pain (up to 80%) (Parasar et al., 2017). Although most commonly diagnosed in women in the 20-40 age group, the disease has also been documented in adolescents and postmenopausal women, underscoring its complex and multifactorial pathophysiology.

The exact etiology of endometriosis remains unknown to this day. Several mechanistic theories have been proposed, including retrograde menstruation, coelomic metaplasia, Müllerian remnant activation, and stem cell involvement (Lamceva et al., 2023). More recent hypotheses emphasize the role of uterine microtraumas and inflammatory processes at the endometrial-myometrial junction, which may facilitate the proliferation and ectopic implantation of endometrial cells (Zhai et al., 2020). Yet, none of these models fully capture the heterogeneity of clinical presentation, disease progression, or patient response to treatment. These doubts regarding the correctness of the diagnosis significantly prolong the time to diagnosis and treatment.

Over the past decade, growing interest has emerged in the potential role of the human microbiome, particularly the gut microbiota, in the pathogenesis and symptomatology of endometriosis. The gut microbiome represents a complex and varied ecosystem made up of trillions of microorganisms that collectively perform essential functions, including nutrient metabolism, immune regulation, epithelial barrier maintenance, and hormone modulation. Disruption of this balance, known as dysbiosis, has been implicated in a wide range of inflammatory and autoimmune conditions (Zhang et al., 2025).

An additional, recently discovered fact, beyond the influence of the gastrointestinal tract, is a broader interaction between the gut and the female reproductive tract, which has been termed the "gut-reproductive tract axis." This theory sheds light on the two-way interaction between the gastrointestinal and gynecological systems, driven by immune and hormonal factors. The close anatomical relationship between these systems, along with additional vascular and lymphatic connections, further supports the validity of this hypothesis (Escorcia et al., 2025).

Many women with endometriosis report gastrointestinal complaints that mimic irritable bowel syndrome (IBS), including bloating, constipation, and altered bowel habits (Malin et al., 2015). These symptoms often lead to misdiagnosis or delayed recognition of endometriosis. Searching for new biomarkers associated with changes in the microbiome may enable earlier and much less invasive diagnosis of endometriosis compared to laparoscopy (Imperale et al., 2023).

Early-stage studies have shown notable differences in the microbial composition of stool, cervical mucus, and peritoneal fluid between women with endometriosis and healthy controls (Xholli et al., 2023). Reductions in anti-inflammatory genera such as Lactobacillus and Ruminococcus, along with an increase in potentially pathogenic species like Pseudomonas and Escherichia coli, have been documented in affected patients (Ser et al., 2023). These findings, although preliminary, suggest a possible diagnostic role for microbial profiling and, in the future, a therapeutic one as well.

In animal models, specific probiotic strains—particularly Lactobacillus gasseri—have demonstrated immunomodulatory effects capable of reducing lesion volume and enhancing NK cell activation (Itoh et al., 2011). Although clinical trials in humans remain scarce, such evidence raises the possibility of incorporating microbiota-directed therapies into individualized endometriosis management strategies, complementing hormonal or surgical interventions.

Unfortunately, the diagnostics of endometriosis are currently minimal due to its chronic and recurrent nature. Therefore, its proper treatment requires the discovery of its factual basis. One of the hypothesis assumes the key role of the microbiome and its influence on immunological and hormonal pathways, knowledge of which could enable effective and rapid diagnosis of endometriosis, as well as its treatment.

In our review, we examined existing scientific papers related to the topic of endometriosis and its association with changes in the microbiome, specifically gut microbial dysbiosis and its systemic impact. As a result of analyzing the current state of knowledge, we aim to highlight the diagnostic potential of microbiota analysis, as well as potential treatment options primarily related to changes in the microbiota, which simultaneously influence the development of endometriosis.

2. REVIEW METHODS

This review was conducted through a comprehensive and systematic search of peer-reviewed literature focused on the relationship between endometriosis and the microbiome, with particular emphasis on gut dysbiosis and its potential role in disease development, progression, and treatment. A search was conducted using open-access medical databases, including PubMed, with keywords such as

"endometriosis," "gut health," and "inflammation" to identify relevant studies published between January 2009 and May 2025. Articles were selected based on their direct connection to the topic, as determined by title and abstract screening. This review examines current evidence on the gut microbiome in endometriosis to inform clinical diagnosis and treatment. The goal of this review is to highlight the diagnostic and therapeutic potential of microbiota-based approaches and to underscore the need for further research in this promising and rapidly evolving field.

3. RESULTS AND DISCUSSION

3.1. Concepts on the etiology of endometriosis

One of the frequently cited theories is based on the phenomenon of reverse flow of menstrual blood through the fallopian tubes, which occurs in the majority of women, potentially causing the transplantation of fragments of the uterine lining into the new environment (Weber et al., 2023). An alternative theory, coelomic metaplasia, refers to the ability of cells to undergo metaplasia and form endometrial-like tissue, including both glands and stroma (Lamceva et al., 2023). Another theory proposes that endometriosis can be activated by excessive uterine peristalsis, which leads to micro-injuries between the endometrium and the myometrium, releasing pro-inflammatory mediators that induce the expression of aromatase. Locally released estrogen further stimulates endometrial proliferation and angiogenesis. During the healing process, stem cells are released that migrate to the abdominal cavity, where they contribute to the development of endometriosis. They can also invade the myometrium, causing adenomyosis (Gruber et al., 2021). However, it cannot be stated with complete certainty that any of the known theories represents the actual mechanism underlying the development of endometriosis, which hinders the identification of an effective therapeutic option.

3.2. Current clinical strategies used to identify endometriosis

The current scientific consensus is that there are three main types of endometriosis, which can be distinguished by their localization, endometrial lesions, and pathological structure: superficial peritoneal endometriosis (SPE), ovarian endometrioma (OMA), and deep infiltrating endometriosis (DIE). Regardless of location, all of them are associated with similar symptoms (Hsu et al., 2010). In the mentioned cases, collecting a thorough medical history and a physical examination are the basis for a correct diagnosis and implementing appropriate treatment. Besides symptoms suggesting a gynecological issue, patients might also show signs commonly linked to gastrointestinal or urinary tract disorders. For this reason, other possible causes must be ruled out before concluding that the symptoms are due to endometriosis. Unfortunately, the detection of peritoneal endometriotic lesions still relies on laparoscopy, as no current imaging technique matches its sensitivity and specificity (Imperale et al., 2023).

3.3. Microbiome-endometriosis correlation

The microbiome consists of all the microorganisms present in a given environment, such as bacteria, fungi, viruses, and archaea. The human body harbors a microbiome that varies extensively by location, depending on factors such as pH, oxygenation, and the presence of particular nutrients (Blum, 2017). For instance, the gastric microbiome, being highly acidic, supports acid-tolerant genera such as Prevotella, Streptococcus, and Veillonella. The colon, however, being more neutral and anaerobic, harbors a more abundant and diverse microbial population, including species of the genus Lactobacillus, Akkermansia, and Enterobacter, among many others (Hollister et al., 2014).

The gut microbiota has a key function in several essential physiological activities. These involve breaking down and absorbing nutrients, as well as vitamin production, the regulation of metabolic activity, the stimulation of angiogenesis, and the promotion of repair and regeneration of epithelial tissue (Ramakrishna, 2013). Besides these local effects, there is mounting evidence that the gut microbiome exerts a systemic influence, most prominently through its interaction with the immune system. Disruptions in microbial balance, or dysbiosis, have been linked to the development of various chronic diseases, including autoimmune diseases, metabolic syndrome, and inflammatory diseases (Durack et al., 2019). Much of this effect is thought to originate from the microbiota's capacity to regulate inflammatory signaling pathways and guide immune responses at both mucosal and systemic levels (Costello et al., 2015).

This is particularly relevant in the context of endometriosis, where immune dysregulation and chronic inflammation are firmly established as central features of the disease pathology. Interestingly, heightened levels of pro-inflammatory cytokines have been universally demonstrated in the peritoneal fluid of women with endometriosis, indicating an aberrant immune response in the pelvic environment. Since gut microbes have been shown to affect cytokine production and immune cell function, it is not illogical to implicate dysbiosis in the initiation or perpetuation of inflammatory processes in endometriosis.

Furthermore, microbial flora of the lower genital tract, specifically the vaginal and cervical environments, has also been of interest. These communities are typically dominated by Lactobacillus species, which establish a stable, low-pH niche that confers protection against pathogenic organisms. Vaginal microbiota profiles are categorized based on the Community State Type (CST) model, and CST types I to III and V are considered healthy, predominantly dominated by Lactobacillus crispatus, gasseri, iners, and jensenii. In contrast, CST IV is associated with bacterial vaginosis and contains a higher proportion of anaerobic species such as Gardnerella, Atopobium, and Mobiluncus (Molina et al., 2022; Dong et al., 2024).

These microbiological changes are not constant and vary throughout a woman's life, depending on hormonal disorders, sexual activity, menstruation, and other behavioral or environmental factors. The dynamic nature of the microbiome suggests that it not only responds to physiological changes but may also regulate disease risk. With immune-modulatory functions of numerous microbial species—some promoting inflammation, while others dampening it—ongoing research continues to investigate whether the microbiome plays an active role in endometriosis pathogenesis and development, or whether it simply mirrors an underlying dysbiosis brought about by the disease process itself.

3.4. Probiotics as a supportive strategy in Endometriosis management

Although clinical trials in humans are still limited, promising results have been obtained from preclinical studies in animal models. One of the best-known examples is a study published in 2011, in which mice with induced endometriosis were orally administered the inactivated L. gasseri OLL2809 for 21 days. (Itoh et al., 2011). The effects were compared with a control group and a group receiving interleukin-12 (IL-12), known to activate NK cells. In the study, it was observed that the administration of L. gasseri OLL2809 significantly reduced the development of endometrial lesions, achieving an effect comparable to that of IL-12. Although no significant changes were observed in peritoneal fluid cytokine levels or NK cell cytotoxicity, gene expression analysis revealed increased transcription of IL-2 and NCR1 genes in peritoneal cells, suggesting NK cell activation. Based on this study, the conclusion emerged that L. gasseri may inhibit the development of endometrial lesions by acting as an immunomodulatory agent.

3.5. Available treatments for endometriosis

Unfortunately, as of today, there is no way to cure endometriosis completely, but there are ways to alleviate the symptoms associated with it, such as pain and infertility. There are various treatment methods available, including hormone therapy, pain medications, and surgery (table 1).

3.5.1. Hormonal therapy

Hormonal therapy is a standard approach in managing pain associated with endometriosis. Since endometriotic lesions respond to hormonal fluctuations in a way similar to the endometrium, suppressing hormone production can reduce symptoms and lesion activity (Vannuccini et al., 2022). Hormonal treatment may help prevent the formation of new lesions and adhesions, but it will not dissolve existing adhesions.

3.5.2. Pain medications

Analgesic effectiveness is based mainly on non-steroidal anti-inflammatory drugs. Since evidence of the efficacy of these medications for relieving endometriosis-associated pain is limited, further research is needed on the use and effectiveness of different types of analgesics in pain relief in endometriosis (Allen et al., 2009).

3.5.3 Surgical treatments

The gold standard in surgical treatment of endometriosis is laparoscopy. It enables the assessment of the extent of endometrial changes, the collection of a sample for histological and pathological examination, and the removal of endometrial foci. Possible interventions for endometriosis include diagnostic laparoscopy, excision and/or ablation of lesions, conscious pain-mapping laparoscopy, microlaparoscopy, and adhesiolysis (surgical removal of adhesions). In some cases, procedures targeting nerve pathways, such as uterosacral nerve ablation (UNA) or presacral neurectomy, may be performed to reduce chronic pelvic pain. Additional options include pelvic vein ligation (via surgery or interventional radiology), hysterectomy (total or subtotal), oophorectomy, and ventrosuspension (Leonardi et al., 2021).

Patients need a complete understanding of surgical treatment because the effects of some procedures are irreversible and may have a significant impact on future fertility. This is why it is crucial for patients to discuss available treatment options with their healthcare team before making definitive decisions.

Table 1. Endometriosis Treatment Methods Overview

Treatment Method	Description	Effectiveness/Limitations	Key references
Hormonal therapy	Suppresses hormone production to reduce endometriotic lesion activity. Mimics endometrial suppression to manage pain.	Helps reduce symptoms and prevent new lesions or adhesions; does **not** remove existing ones.	Vannuccini et al., 2022
Pain Medication (NSAIDs)	Primarily uses non-steroidal anti-inflammatory drugs to alleviate pelvic pain.	Limited clinical evidence for long-term effectiveness; further studies needed to assess optimal pain management.	Allen et al., 2009
Surgical Treatments	Laparoscopy is the gold standard: allows for direct visualization, biopsy, and removal of lesions.	Procedures include lesion excision, ablation, microlaparoscopy, adhesiolysis, and pain-mapping surgery. Can also involve more invasive steps like hysterectomy or nerve pathway interventions.	Leonardi et al., 2021
Nerve-Targeting Procedures	May include uterosacral nerve ablation (UNA), presacral neurectomy.	Aim to reduce chronic pelvic pain; some procedures are irreversible and may impact fertility.	Leonardi et al., 2021

3.6. Can microbiota be a diagnostic marker?

Due to the nonspecific symptoms of endometriosis, identification can take over a dozen years. The gold standard – laparoscopic diagnosis – is an invasive procedure. There is growing speculation that examining the microbiome may facilitate the diagnosis of endometriosis. However, to develop non-invasive diagnostic tools based on the microbiome, it is essential to characterize the microbial profiles typically observed in individuals with endometriosis and to distinguish them from those found in healthy individuals (Iavarone et al., 2023). The study by Khan et al., (2010) presents the correlation between the significant increase in E. coli bacteria levels in the menstrual blood of women with ovarian endometriomas and superficial peritoneal lesions compared to women with ovarian endometriomas alone.

Huang et al., (2021) conducted a study of 41 women, 21 with endometriosis and 20 healthy volunteers as a control group. Samples were collected from all participants at three sites: stool, cervical mucus, and peritoneal fluid. The study aimed to compare the composition of the microbiota between groups and different body locations. Research has identified notable variations in the microbiota of patients with endometriosis and healthy individuals, with the most pronounced changes observed in fecal and peritoneal fluid samples.

Among the bacterial genera identified as promising biomarkers were Pseudomonas in the peritoneal fluid and Ruminococcus in the gut. As a result of advanced analyses, scientists created models based on key microbiota taxa. As of today, research results indicate that gut microbiota has a higher diagnostic value than cervical microbiota in the diagnosis of endometriosis (Huang et al., 2021).

4. CONCLUSIONS

The relationship between the microbiota of the gastrointestinal system and the formation of endometrial lesions has been documented in numerous studies. Dysbiosis specific to endometriosis has been identified in both fecal and peritoneal fluid samples, with distinguishing features that accompany the illness. These include the expansion of some harmful bacterial taxa at the expense of anti-

inflammatory bacteria, which is quite protective. Evidence suggests that Ruminococcus from the gut and Pseudomonas from the peritoneal fluid may serve as potential antagonistic microbial markers that could assist the development of non-invasive diagnostic methods for endometriosis in the future. The data suggest that changes in the microbiome may underlie, modulate, or sustain the pathophysiological processes in endometriotic lesions, particularly with regard to immunomodulatory factors and estrogen interactions on metabolism and biological actions.

There is an emerging trend in the so-called gut reproductive tract axis, which prompts scientists to consider that some regions of the body may have a potential means of communicating with each other. Considering anatomical proximity and shared borders of the gastrointestinal tract with the reproductive system, scientists believe that a state of dysbiosis in the bowel leacan lto an impairment in the body's immune balance and local environment.

In conclusion, the gut microbiome represents a positive perspective on understanding and treating endometriosis. Although further work is needed to translate laboratory findings into clinical applications, the integration of microbiome science into gynecological research holds great potential to improve diagnosis, guide treatment, and ultimately enhance quality of life for women living with this condition.

Author's Contributions

Conceptualization: Sara Hassan, Szymon Bienia
Methodology: Szymon Bienia, Aisha Hassan
Formal analysis: Sara Hassan
Resources, data curation: Kamil Hassan
Investigation: Sara Hassan, Szymon Bienia
Writing – original draft: Sara Hassan, Szymon Bienia
Writing – review & editing: Sara Hassan, Szymon Bienia
All authors have read and agreed with the final, published version of the manuscript.

Acknowledgments

No acknowledgment.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

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

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