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ENDOMETRIOSIS AND THE MICROBIOME: EMERGING APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN WOMEN'S HEALTH

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ABSTRACT

Introduction: Endometriosis, a chronic and estrogen-dependent inflammatory condition, affects millions worldwide, frequently causing pain, infertility, and a diminished quality of life. Delayed diagnosis remains a major challenge due to the lack of sensitive non-invasive biomarkers. Emerging evidence suggests that alterations in the gut and reproductive tract microbiomes contribute to disease pathophysiology through immune and hormonal dysregulation.
Purpose of the Work: This review aims to synthesize current knowledge on microbiome changes in endometriosis and explore the potential applications of artificial intelligence (AI) and machine learning (ML) for identifying microbiome-derived biomarkers and improving early diagnosis.
Material and Methods: A narrative review of peer-reviewed literature from 2015–2025 was conducted using PubMed, Scopus, and Web of Science. Keywords included "endometriosis," "microbiome," "artificial intelligence," and "machine learning." Studies were assessed for relevance, methodological quality, and contributions to understanding microbiome alterations and AI applications in endometriosis.
Results: Gut dysbiosis appears to influence estrogen metabolism, immune responses, and inflammation, while reproductive tract microbiota contribute to local immune modulation. AI and ML approaches, including Random Forest, Gradient Boosting, and logistic regression, have shown promise in predicting disease and identifying potential microbial biomarkers. Interventions such as probiotics, prebiotics, and fecal microbiota transplantation, coupled with multi-omics analyses, represent potential avenues for personalized treatment.
Conclusion: Integrating microbiome profiling with AI-driven models may enable non-invasive diagnosis, improved disease classification, and precision therapeutic strategies. Further large-scale, multicenter studies are needed to validate these approaches and support their translation into clinical practice.

KEYWORDS
Endometriosis, Gut Microbiota, Reproductive Tract, Artificial Intelligence, Biomarkers, Precision Medicine

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Introduction

Background

Endometriosis is a long-term, estrogen-dependent inflammatory condition estimated to impact around 190 million women and individuals assigned female at birth globally [1]. Endometriosis involves the presence of endometrial glands and stroma outside the uterus, typically affecting the pelvic peritoneum, ovaries, and rectovaginal septum. Its progression is driven by the implantation and growth of these ectopic endometrial cells, which trigger both local and systemic inflammatory responses and contribute to fibrosis [2]. Endometriosis is commonly classified into peritoneal endometriosis, deep infiltrating endometriosis (DIE), or ovarian endometriosis, depending on the type and location of lesions. Although peritoneal endometriosis is the most common form, ovarian endometriosis occurs in 17–44% of patients [3] and is marked by the formation of ovarian endometriomas—cystic lesions containing dark, endometrial fluid. The condition is mainly marked by pain—frequently linked to the menstrual cycle—and can lead to infertility [4]. Endometriosis is primarily characterized by pain, often cyclical and associated with menstruation, which can significantly impair quality of life and may lead to infertility [4]. The chronic and unpredictable nature of symptoms, along with their impact on daily functioning, often contributes to emotional disturbances, including anxiety, irritability, feelings of helplessness, and depression [5]. Beyond the physical and psychological dimensions, individuals with endometriosis also experience social and professional challenges. Many face limited understanding from others, insufficient support, or even minimization of their symptoms by healthcare providers, which can lead to isolation and stigma. Moreover, women with endometriosis often experience strain in interpersonal relationships, especially within intimate or partnership contexts, along with decreased self-esteem related to health issues, including fertility concerns [6,7]. A major factor affecting the diagnosis and management of endometriosis is the absence of reliable non-invasive diagnostic methods. In this context, biomarkers represent a promising approach for non-invasive detection of the disease [8]. Average estimates suggest that the time from the onset of symptoms to a confirmed diagnosis of endometriosis ranges from 7 to 11 years, which may lead to worsening of symptoms and disease progression [9].

The Microbiome–Endometriosis Connection

An increasing number of studies suggest that changes in the microbiome may contribute to the initiation and progression of endometriosis through inflammatory mechanisms. The dysbiosis observed in endometriosis is believed to play a dual role, acting both as a contributing factor and as a result of disease development [10]. Studies have examined the gut, peritoneal fluid, and female reproductive tract microbiota to identify potential microbiome patterns unique to endometriosis. Recent studies are investigating approaches to modulate the microbiome for earlier diagnosis and more effective treatment of endometriosis [10,11]. Understanding these microbiome alterations lays the foundation for applying artificial intelligence and machine learning approaches to identify biomarkers and improve diagnosis in endometriosis.

The Role of Artificial Intelligence in Biomedical Research

Artificial intelligence (AI), including machine learning (ML) techniques, has emerged as a powerful tool in biomedical research, enabling the analysis of complex omics data. Although direct applications of AI in analyzing the microbiome of patients with endometriosis remain limited, AI has been successfully applied in microbiome studies of other chronic conditions to identify microbial signatures, predict disease status, and discover potential biomarkers. For example, machine learning (ML) has enabled the identification of novel microbiota-based biomarkers that differentiate patients with diabetic kidney disease (DKD), diabetes mellitus

(DM), and chronic kidney disease (CKD). In one study, 13 gut microbiota biomarkers identified both by ML algorithms and traditional differential abundance methods demonstrated strong discriminatory power across different patient groups [12]. Similar AI approaches have been applied to the gut microbiome in other chronic conditions, such as hepatitis B-related hepatic fibrosis and chronic fatigue syndrome, highlighting the potential of machine learning to identify microbiome-derived biomarkers for early diagnosis and therapeutic targeting [13,14]. Transvaginal ultrasound is the first-line diagnostic tool for endometriosis, but its accuracy depends on operator skill. AI models have shown performance comparable to expert operators and can assist in automated assessment, highlighting the potential of AI to enhance early diagnosis and clinical decision-making [15].

The application of AI in reproductive health has both technological and societal significance, demonstrating its potential to improve patient care. These findings suggest that AI could be further applied in endometriosis research, particularly for identifying microbiome-derived biomarkers and enabling earlier diagnosis.

Purpose and Significance of the Review

The purpose of this review is to synthesize current knowledge on microbiome alterations in endometriosis and the emerging applications of artificial intelligence (AI) and machine learning (ML) in identifying microbiome-derived biomarkers. Although some studies have explored these areas separately, the number of investigations directly integrating microbiome research with AI-based approaches in endometriosis remains limited. This review is significant because it may highlight novel biomarkers for earlier diagnosis, identify gaps in current research, and inform future studies aimed at improving personalized care and reproductive health outcomes for women with endometriosis.

Material and methods

This review is based on a narrative synthesis of scientific publications investigating microbiome alterations in endometriosis and the application of artificial intelligence (AI) and machine learning (ML) in biomarker discovery. A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, covering the period from 2015 to 2025. Keywords included “endometriosis,” “microbiome,” “machine learning,” and “artificial intelligence.” Original research studies focusing on metagenomic or metabolomic analyses, as well as AI/ML-based approaches for disease prediction or biomarker identification, were included. Only articles published in English and in peer-reviewed journals were considered. Selected studies were assessed for methodological quality, relevance, and contribution to understanding microbiome changes and AI applications in endometriosis. The analysis focused on identifying microbiome alterations associated with endometriosis and evaluating the potential of AI and ML methods to support biomarker discovery and early disease detection.

Current Knowledge

Gut Microbiome in Endometriosis- Pathomechanisms

Microbiota play a crucial role in maintaining human health by protecting against pathogenic microbes, modulating immune responses, and influencing endocrine and cytokine secretion [16]. The pathogenesis of endometriosis remains multifactorial and is not yet fully elucidated, with numerous theories proposed to explain its onset and progression [17]. Recent evidence has increasingly highlighted the role of systemic inflammation and immune modulation, suggesting that the gut microbiome may be a key contributing factor. Studies have shown that alterations in gut microbial composition are linked to various inflammatory disorders including endometriosis[18].

The gut microbiome may influence the pathogenesis of endometriosis through multiple interconnected mechanisms, notably via its impact on estrogen metabolism [19]. Endometriosis is an estrogen-dependent condition, in which elevated estrogen levels stimulate the proliferation of female genital epithelial cells, contributing not only to the development of endometriosis but also to other estrogen-driven disorders such as endometrial cancer and uterine fibroids [20]. Analysis of the gut microbial genome reveals that several bacterial genera, commonly referred to as ‘estrobolomes’, including *Bacteroides*, *Bifidobacterium*, *Escherichia coli*, and *Lactobacillus*, are capable of producing β-glucuronidase, whose activity is influenced by both bacterial population density and diet [16, 21,22]. Importantly, fecal samples from individuals with endometriosis show a marked increase in *Escherichia coli* abundance. These findings support the notion that alterations in the gut microbiota may elevate circulating estrogen levels, creating a high-estrogen environment conducive to endometriosis development [19,23]. Additionally, an imbalance between the *Firmicutes* and *Bacteroidetes* phyla has been observed, which may further contribute to

estrogen dysregulation [24]. Moreover, the gut microbiota can produce estrogen-like compounds from dietary precursors, which may enhance estrogen effects in the body. These molecules can bind to estrogen receptors and imitate the effects of natural estrogens, potentially affecting multiple physiological processes governed by estrogen regulation [16].

Gut dysbiosis can also lead to alterations in the metabolome, resulting in higher concentrations of neuroactive compounds such as serotonin, glutamate, short-chain fatty acids (SCFAs), and gamma-aminobutyric acid. These metabolites can reach the brain and activate neural receptors, including GnRH neurons, ultimately promoting ovarian estrogen production through a cascade of hormonal signaling, thus contributing to disease progression [25].

In addition to hormonal influences, the interaction between the immune system and gut microbiota is fundamental to maintaining immune homeostasis, influencing both local and systemic immune responses that can impact the development and progression of endometriosis. The gut microbiota affects the endometrium primarily by modulating both systemic and local inflammatory processes. Disruptions in microbial balance can lead to chronic low-grade inflammation extending beyond the gut, impacting distant tissues, such as the endometrium. In endometriosis, such dysbiosis may intensify pelvic inflammation and support the growth of ectopic endometrial tissue [16,26]. Patients with endometriosis show increased levels of lipopolysaccharides (LPS) in the gut and serum, which can stimulate innate immune cells and provoke inflammatory responses. This rise is linked to an overrepresentation of Gram-negative bacteria, whose LPS can reshape the immune microenvironment of ectopic lesions, promoting inflammation, disease progression, and associated symptoms [27]. LPS can also activate Toll-like receptor 4 (TLR4) on macrophages and other immune cells, initiating NF-κB–mediated signaling in the peritoneal cavity and triggering a cascade contributing to the immunopathogenesis of endometriosis [22]. Although the theory of retrograde menstruation accounts for the presence of endometrial tissue in the peritoneal cavity, it fails to explain why only some women develop endometriosis. One explanation involves immune dysregulation—women with endometriosis often exhibit an altered peritoneal immune response, potentially influenced by microbiota imbalances, which modulate immune activity and sustain inflammatory processes that favor disease progression [28]. Overall, gut dysbiosis may act as a key driver of immune activation, amplifying and prolonging peritoneal inflammation and contributing to the progression of endometriosis [25].

The composition of the gut microbiota appears to be linked to the proportion of stem cells in the bone marrow, indicating a potential role in regulating stem cell homeostasis [29]. Human endometrial tissue, rich in progenitor stem cells, normally undergoes cyclic regeneration. In endometriosis, stem cell migration to the uterus is disrupted, leading them to ectopic sites via the bloodstream and promoting abnormal growth of endometrial tissue [30].

These findings underscore the multifaceted role of gut microbiota in endometriosis, which will be further explored in the context of gut dysbiosis.

Alterations in the Gut Microbiome

Studies indicate that an imbalance in the intestinal flora plays a key role in the onset and progression of endometriosis [31]. Meta-analyses show gut microbiota dysbiosis in affected women, with higher alpha diversity observed in healthy controls [24]. In animal models, including mice and rhesus monkeys, endometriosis is associated with a predominance of *Firmicutes*, reduced *Bacteroidetes*, lower *Lactobacilli*, and higher Gram-negative bacteria, indicating a disrupted *Firmicutes/Bacteroidetes* ratio [16,32,33]. In humans, fecal microbiota in endometriosis often shows dominance of *Shigella/Escherichia coli, Proteobacteria, Enterobacteriaceae, Streptococcus spp*., and *Gardnerella* [16,22,24,25]. Microbial profiles may also vary according to disease stage, with distinct patterns in early versus advanced endometriosis, and reductions in *L. ruminococcus* have been suggested as potential biomarkers [34]. In patients with endometriosis-associated chronic pelvic pain, rectal *Ruminococcus* abundance was higher [35]. In addition, increased levels of *Clostridia*, capable of producing short-chain fatty acids (SCFAs), may contribute to disease initiation [37,38]. Certain taxa may act as risk or protective factors: *Anaerotruncus* is linked to ovarian endometriosis, *Olsenella* and *Oscillospira* may exacerbate disease via modulation of IL-10, while *Eubacterium ruminantium, Barnesiella*, and *Holdemania* appear protective, particularly in relation to ovarian involvement and infertility [39,40]. These findings highlight the complex interplay between gut microbiota composition, immune modulation, and metabolic pathways in endometriosis.

Reproductive Tract Microbiome in Endometriosis

Recent findings indicate that the gut microbiota may be more effective than the cervical microbiota for the early detection of endometriosis. Alongside the gut, the reproductive tract microbiome—including vaginal and cervical communities—has gained attention as a crucial factor in the pathogenesis of endometriosis, as shifts in microbial composition at these sites can influence local immunity, inflammation, and hormonal regulation, thereby contributing to disease onset and progression. Understanding these alterations is key to the identification of new diagnostic markers and potential therapeutic targets [34]. Disruption of the dominant Lactobacillus population leads to increased vaginal microbial diversity, featuring known pathogens such as *Gardnerella, Prevotella, Ureaplasma, Anaerococci, Alloscardovia*, and *Candida*. Additionally, novel bacterial species, including Parvimonas and Facklamia, as well as a Streptococcus phage (phiARI0746), have been identified in patients with endometriosis. The loss of key *Lactobacillus* species, which are crucial for maintaining a healthy vaginal environment, contributes to dysbiosis and may negatively affect reproductive health [41]. Fusobacterium nucleatum has been shown to modulate the endometrial environment and promote endometriosis; it was detected both in endometrial tissue and vaginal swabs from patients with the condition, while being absent or significantly reduced in control samples [16,42]. A recent review indicated that bacterial vaginosis-associated bacteria and the depletion of Lactobacillus spp. in the cervicovaginal microbiome are often associated with endometriosis and infertility, with higher levels of strictly anaerobic bacteria, such as *Prevotella* and *Anaerococcus*, contributing to vaginal dysbiosis and inflammation [43]. In endometriosis, **t**he abundance of Prevotella jejuni appears to increase with disease progression, while the presence of *Gardnerella vaginalis*, *Prevotella bivia*, and *Porphyromonas* in the endometrium is associated with reduced *Lactobacillus* levels in infertile patients. Other microbes, such as *Alloscardovia*, *Pseudomonas*, *Flavobacterium, Ureaplasma*, *Veillonella*, *Corynebacterium*, *Peptoniphilus*, and *Candida albicans*, have also been implicated in endometriosis [22,25,41]. These findings highlight the complex interplay between vaginal microbiota composition and reproductive tract health, emphasizing its potential as a diagnostic and therapeutic target in endometriosis.

Emerging Microbiome Biomarkers for Endometriosis Diagnosis

Because the onset of endometriosis is often asymptomatic and its definitive diagnosis still relies on invasive procedures such as laparoscopy and histopathological examination, current clinical approaches lack sensitive and specific biomarkers, leading to diagnostic delays and treatment postponement, significantly impairing the quality of life of affected women [44]. Associations between gastrointestinal and reproductive tract microbiota and endometriosis have been increasingly recognized. Metabolomics, the analysis of small-molecule metabolites in tissues or biofluids, can provide insights into the physiological or pathological state of a system, and metabolites produced by the gut microbiota appear particularly promising as diagnostic indicators for the disease. A decrease in alpha-linolenic acid (ALA) levels has been observed in endometriosis. Evidence suggests that ALA may exert anti-inflammatory effects by suppressing the production of nitrite and prostaglandin E2 (PGE2), while also improving the peritoneal inflammatory environment and reducing lipopolysaccharide (LPS) levels in animal models[45]. Short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, are metabolites produced by gut microbiota during dietary fiber fermentation. They support intestinal and systemic health by providing energy to epithelial cells, maintaining the gut barrier, and limiting pathogen invasion. Alterations in SCFA levels have been linked to disease development, and in experimental models of endometriosis, reduced fecal butyrate has been observed. Importantly, butyrate supplementation was shown to inhibit the growth of endometriotic lesions, suggesting that SCFA profiles could serve as potential non-invasive biomarkers for disease detection and progression monitoring [46]. Recent studies indicate that cytokines produced by immune cells, including IL-17A, IL-6, and TNF-α, may serve as immunological biomarkers of dysbiosis. These pro-inflammatory cytokines are elevated in endometriosis and are closely linked to microbial imbalances in both the gut and reproductive tract. For instance, IL-17A correlates strongly with specific microbial taxa, such as *Bacteroides*, and contributes to inflammatory tissue responses [47]. Recent evidence suggests that the diagnostic potential of vaginal microbiota may be lower than that of gut microbiota, highlighting the importance of gastrointestinal microbial markers. Among the microorganisms studied, *Ruminococcus* and *Pseudomonas* have emerged as potential biomarkers detectable in intestinal and peritoneal fluids for endometriosis diagnosis.

A potential host-related factor implicated in the pathogenesis of endometriosis is altered protein glycosylation, which may affect interactions between host molecules and pathogenic microbes. Urinary N-glycome profiling in endometriosis has been reported for the first time, revealing 181 N-glycans and 55 distinct IgG structures. Four novel IgG N-glycans were identified, and differences in urine glycosylation between

patients and controls suggest altered glycoprotein profiles in endometriosis. Interestingly, a specific urine IgG N-glycan and two serum N-glycan profiles were correlated with the presence of *Anaerococcus senegalensis* detected in vaginal samples from women with endometriosis. Although the connection between the glycome and microbiota in endometriosis has not been established previously, host glycans—such as blood group antigens and other glycans present on mucosal surfaces—may act as microbial receptors, influencing infection susceptibility and contributing to autoimmune-related processes [41].

Applications of AI and Machine Learning in Endometriosis Research

Artificial intelligence (AI) encompasses a wide range of computational methods, including machine learning (ML) and neural networks, which often intersect with advanced statistical modeling. These algorithmic systems are designed to mimic human reasoning and decision-making, with ML serving as a subset of AI that enables pattern recognition and performance improvement through data-driven learning without explicit programming [49]. In gynecology, AI shows great promise in enhancing clinical practice by automating routine tasks, reducing physicians 'workload, and allowing greater focus on patient-centered care. Its integration with robotic surgery can enhance anatomical recognition by combining intraoperative assessments with preoperative imaging data, while decision-support systems assist in improving diagnostic accuracy, optimizing treatment selection, and supporting personalized patient management. Furthermore, AI may optimize administrative processes and accelerate research efforts, particularly in complex disorders such as endometriosis and adenomyosis, where it could contribute to earlier diagnosis, tailored therapies, and deeper understanding of disease mechanisms [50].

In a recent study, machine learning algorithms, including Random Forest (RF) and Gradient Boosting (GBM), along with statistical models like Generalized Linear Models (GLM), were used to predict endometriosis based on differentially enriched microbiome bacteria, demonstrating a practical application of AI in microbiome research. The models demonstrated that only the gut microbiome, and not the vaginal microbiome, showed significant taxonomic and functional differences between women with endometriosis and healthy controls, allowing effective discrimination of cases using a Microbial Endometriosis Index (MEI) [51].

A recent study by Huang et al. (2021) applied machine learning, specifically Random Forest (RF), to identify microbial taxa associated with endometriosis and build predictive models. Using RF-selected taxa, the authors demonstrated that gut and peritoneal fluid microbiomes provided the highest predictive accuracy, with AUCs of 0.738 and 0.782, respectively, while cervical microbiome samples performed less effectively (AUC = 0.625). These findings highlight the potential of AI-driven microbiome analysis to support early and non-invasive diagnosis of endometriosis [34].

On the other hand, Perrotta and colleagues (2020) demonstrated that the vaginal microbiome can also provide valuable insights for endometriosis staging. Machine learning, specifically the Random Forest algorithm, was applied to analyze microbial composition during both the follicular and menstrual phases of the menstrual cycle. Their models accurately distinguished early-stage endometriosis (revised American Society for Reproductive Medicine stages 1–2) from advanced-stage disease (stages 3–4), achieving area under the curve values of 0.85 and 0.87, respectively. These results suggest that, although previous studies highlighted the gut microbiome as a more effective and informative source, analysis of the vaginal microbiome using artificial intelligence remains a promising non-invasive approach for evaluating disease severity [52].

A recent study employed three machine learning algorithms—logistic regression, decision trees, and support vector machines—across seven different sample types to detect endometriosis. Logistic regression demonstrated the best performance, achieving an accuracy of 80.1%, a precision of 72.0%, a recall of 81.0%, and an F1 score of 74.8%, highlighting its potential as a reliable, non-invasive diagnostic tool. Interestingly, the authors found that oral microbiome samples contained particularly informative features for predicting disease, suggesting a novel source of surrogate biomarkers. Beyond diagnostic utility, the study emphasizes that AI-driven models could assist clinicians in considering endometriosis as a potential diagnosis while reducing costs and risks associated with traditional endometrial analyses. However, the robustness and generalizability of the findings are restricted by limitations such as the small sample size, particularly in oral samples, and the cross-sectional design. The authors recommend future research with larger cohorts and longitudinal monitoring to validate these models and better understand the temporal dynamics of microbial biomarkers in endometriosis [53].

More research is needed before such AI-driven technologies can be implemented in routine clinical practice, and strict regulatory oversight will be essential prior to their widespread adoption. Meanwhile, it remains the responsibility of clinicians and researchers to expand their understanding in this area, overcoming

skepticism toward machine-based tools and recognizing that such technology may help overcome human limitations, ultimately enhancing diagnostic accuracy, patient care, and disease management. For instance, AI-assisted image analysis can detect subtle endometriotic lesions that may be overlooked during laparoscopic evaluation, while machine learning models integrating clinical, hormonal, and microbiome data can identify hidden diagnostic patterns beyond the capacity of human interpretation [49]. These advancements illustrate how AI can complement clinical expertise, offering a valuable aid in tackling the complexity and heterogeneity of endometriosis.

Future directions

Looking ahead, future research should focus on integrating multi-omics approaches—combining microbiome, genomic, proteomic, and metabolomic data—with artificial intelligence (AI) and machine learning (ML) to unlock novel diagnostic and therapeutic opportunities in endometriosis. Such integration could enable the development of predictive models that identify microbial and metabolic signatures associated with disease onset, progression, and treatment response.

Metabolomic profiling also offers considerable promise as a non-invasive and precise approach for detecting immunometabolic alterations linked to endometriosis. Notable changes include elevated levels of 3-hydroxybutyrate, lactate, succinate, and phosphatidic acids alongside reduced citrate and L-isoleucine levels, reflecting disruptions in lipid and amino acid metabolism as well as heightened inflammatory signaling [54]. This emerging method could be instrumental in monitoring disease progression, stratifying patients, and facilitating personalized therapeutic strategies based on individual metabolomic signatures. Machine learning algorithms achieved strong predictive performance in distinguishing between adenomyosis, endometriosis, and healthy controls, underscoring their potential clinical utility in enhancing disease classification and guiding individualized therapeutic approaches [55].

Promising avenues include microbiome-targeted interventions—such as prebiotic and probiotic supplementation and fecal microbiota transplantation (FMT)—to restore microbial balance (eubiosis) and modulate inflammation-related pathways [34]. When coupled with omics-based analyses of metabolic derivatives, these strategies may facilitate the discovery of microbial biomarkers for early diagnosis and contribute to personalized treatments that alleviate pain and improve clinical outcomes. Exploring underrepresented sample types, such as oral or urinary microbiomes, may reveal additional non-invasive biomarkers and expand diagnostic options.

As a newly emerging area of research, the relationship between microbiota and endometriosis remains largely enigmatic. Inconsistent findings may arise because many existing studies are limited by small sample sizes, a lack of robust randomized controlled trials, and variable microbiome analysis. Moreover, current diagnostic standards and uterine sampling procedures are invasive, restricting the ethical inclusion of asymptomatic healthy populations in research. Future investigations should aim to profile a core female reproductive tract microbiome, identify “keystone” microbial species associated with endometriosis, and clarify their mechanisms of influence, such as dysbiosis-induced immune activation or secretion of microbial metabolites. Understanding the causative links between microbial imbalance, estrogen metabolism, and disease progression, as well as site-specific host-microbiota interactions, will be essential to expand knowledge applicable to other gynecologic or estrogen-mediated disorders [25].

Collectively, these advances highlight a shift toward precision medicine in endometriosis management, though their application remains largely experimental and requires further clinical validation [56]. Developing explainable and interpretable AI models will also be crucial to foster clinical trust and facilitate the adoption of these technologies in routine practice. Future research should prioritize large-scale, multicenter randomized controlled trials with standardized staging systems and clearly defined outcomes to enhance the robustness and generalizability of diagnostic and therapeutic recommendations, thereby supporting the translation of microbiome- and AI-based findings into clinical practice. Finally, interdisciplinary collaboration among clinicians, microbiologists, and data scientists will be key to accelerating the implementation of these approaches and ensuring their global applicability.

Conclusions

In summary, the current body of evidence underscores the significant role of the gut and reproductive tract microbiomes in the pathophysiology of endometriosis. Alterations in microbial composition, particularly in the gut, actively influence estrogen metabolism, immune responses, and inflammatory pathways, thereby contributing to disease onset and progression. Despite promising findings, more extensive research with larger patient cohorts, standardized clinical assessments, and robust methodologies is needed to fully elucidate these relationships.

Integrating microbiome profiling with imaging and clinical evaluation has the potential to serve as a non-invasive screening tool, identifying individuals with chronic pelvic pain and gastrointestinal symptoms who may benefit from referral to a gynecologist specializing in endometriosis. Additionally, coupling microbiome data with machine learning and artificial intelligence algorithms could enhance predictive accuracy, support early diagnosis, and enable personalized therapeutic strategies.

Future investigations should aim to identify core female reproductive tract microbiota, “keystone” microbial species, and their mechanistic roles, including immune modulation and metabolite production, while exploring underrepresented sample types such as oral or urinary microbiomes. Large-scale, multicenter randomized controlled trials with clearly defined outcomes and standardized staging systems will be essential to validate these approaches and bridge translational gaps, ultimately supporting their clinical implementation. Ultimately, the integration of microbiome research with AI-driven predictive models represents a promising avenue for precision medicine, offering the potential to improve diagnosis, optimize treatment, and enhance the overall quality of life for individuals affected by endometriosis.

Disclosure

Conceptualization, U.B., H.P. and O.S.; Methodology, U.B., H.P. and O.S.; Software, U. B, N.K., K.P. and S.S.; Validation, U.B., O.S. and N.K.; Formal Analysis, K.P., S.S. and N.K.; Investigation, U.B., H.P., N.K. and O.S.; Resources,U.B., N.K., S.S.; Data Curation, N.K., S.S. and O.S.; Writing rough preparation, U.B., K.P.and S.S.; Writing – Review & Editing, O.S., K.P. and N.K. and H.P.; Supervision, U. B..; Project Administration, U.B., K.P. and O.S.

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