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Review Article

Uterine microbiota dynamics and new therapeutic opportunities in gynecological diseases

Heyuan Tang, Meng Wu, Siyuan Tan, Cheng Liu, Yulan Cui

Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang, China

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Abstract: Traditional view holds that the uterus is a sterile environment. However, with the increased development of molecular biology technologies, this classical theory has been re-examined. Increasing evidence shows that a low-biomass, uniquely structured microecosystem exists in the healthy uterus. Its composition and dynamic changes are crucial in maintaining endometrial homeostasis, regulating immune responses, and influencing embryo implantation. Uterine microecological imbalance is associated with different gynecological diseases, such as chronic endometritis, endometriosis, and uterine-related tumors. This paper systematically reviews the compositional features of the uterine microecology and the dynamic changes in bacterial communities, as well as summarizes the evidence linking these changes to major gynecological diseases. This work examines current treatment and intervention strategies including antibiotics, probiotics, uterine cavity colonization, and fecal microbiota transplantation, and discusses their potential clinical value and methodological challenges. A deeper investigation of the relationship between uterine microecology and gynecological diseases is expected to provide new biomarkers and therapeutic targets for the precise diagnosis and treatment of gynecological disorders.

Keywords: Uterine microbiota, microbial dynamics, Lactobacillus, gynecological diseases, probiotic therapy

Introduction

Human microecosystems are defined as dynamically balanced microbial communities within the body. They form a complex functional unit together with the host and the environment becoming a focus of life science investigation in recent years [1-3]. Breakthroughs in intestinal microecology have greatly deepened our understanding of the mechanisms underlying metabolic, immune, and neurological diseases, and their roles in gynecological diseases are also being gradually clarified [4-6]. An increasing number of studies have shown that the microbiota not only plays a critical role in maintaining physiological homeostasis but may also exert profound effects on disease onset and progression by modulating host immune responses, metabolic pathways, and endocrine signaling, thereby providing a new theoretical basis for the prevention and treatment of gynecological diseases.

Research on the microecology of the female reproductive system and endometrium, which is closely linked to gynecological diseases, is relatively new and early studies focused on the vaginal microenvironment for a long period [7, 8, 9]. These findings not only challenge the long-standing belief that the endometrium is a sterile environment, but also suggest that the uterine microecology may actively participate in female reproductive physiology by regulating local immunity, influencing endometrial tolerance, affecting embryo implantation, and inducing chronic inflammatory responses, as well as various pathological processes [10, 11]. In addition, the characteristics of the uterine microbiota may serve as important indicators for assessing female fertility, guiding assisted reproductive treatments, and enabling early intervention in gynecological diseases. Earlier studies suggested that bacteria appear in the uterine cavity only during pregnancy or under pathological conditions [12, 13]. Yet more recent evidence demonstrates that the uterus

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harbors an intrinsic, dynamically balanced microbiome even in the absence of disease. In 2015, Caroline et al. performed Quantitative Polymerase Chain Reaction (qPCR) on vaginal and uterine samples from 58 non-pregnant women and found that 95% of participants had detectable bacteria in the endometrium, with *Lactobacillus iners*, *Prevotella*, and *Lactobacillus crispatus* being the most prevalent species. Their results suggested that the endometrium of most women is not entirely sterile and that low-biomass microbial communities can exist without provoking overt inflammation [14]. Similarly, Inmaculada et al. used 16S ribosomal RNA (rRNA) gene sequencing and confirmed that the uterine cavity harbors a microbial community. Two major community types were identified: *Lactobacillus*-dominant and non-*Lactobacillus*-dominant. Notably, the latter was mainly associated with decreased embryo implantation and pregnancy [15].

Increased evidence supports the important role of uterine microecology in women's reproductive health. Uterine microecological imbalance may participate in the occurrence and progression of a gynecological diseases, including chronic endometritis, infertility and endometriosis, by destroying endometrial homeostasis, activating immune-inflammatory pathways or changing hormone receptor signaling [16-18]. Therefore, understanding the dynamic changes of the uterine microbiota not only helps to elucidate the pathogenesis of these diseases but also provides new strategies for clinical diagnosis and treatment. Modulating the endometrial microbiota may improve embryo implantation rates, reduce the recurrence risk of chronic endometritis, and offer personalized intervention approaches for assisted reproductive technologies (ART). Moreover, uterine microbiota characteristics may serve as important biomarkers for early screening, therapeutic evaluation, and prognosis assessment of gynecological diseases, providing scientific guidance for clinical decision-making. With the advancement of high-throughput sequencing, multi-omics analyses, and microbiota-targeted interventions, precision diagnosis and treatment based on the uterine microbiota is expected to become a significant direction in gynecological clinical practice. Therefore, systematically investigating the dynamic patterns of the uterine microbiota and exploring intervention strategies based on microecological regulation have become cutting-edge areas of research in gynecology. A comprehensive understanding of the interactions between the uterine microbiota and the host can reveal the underlying mechanisms of disease and provide a new theoretical foundation and clinical guidance for the early diagnosis, personalized treatment, and reproductive health management of gynecological disorders.

Microbial dynamics: temporal and spatial factors

Uterine microecology is a highly dynamic system, exhibiting significant variations across both temporal and spatial scales. Its stability depends on the fine regulation of the hormone cycle, the integrity of the local anatomical barrier, and the complex interaction network between microorganisms of different sources. Understanding the temporal dynamics of these bacteria and their distribution and movement across different anatomical sites is crucial for revealing the mechanisms that maintain uterine microecological homeostasis (**Table 1**).

Temporal dynamics

The composition of uterine microecology shows significant dynamic changes in different physiological time windows, which is mainly regulated by the hormone cycle and reproductive state. With the cyclical fluctuation of ovarian hormone levels, the endometrium undergoes the proliferation period, secretion period and menstrual shedding period in turn [19], and its local microenvironment, including nutritional availability, glycogen content, immune factor expression and epithelial cell receptors, also changes, thus dynamically shaping the structure and diversity of the microbiota [20, 21]. In the estrogen-dominated proliferation period and progesterone-dominated secretion period, the endometrium thickens and the blood supply is abundant, which provides favorable conditions for the colonization and maintenance of specific bacteria such as *lactobacillus* [22]. In contrast, during menstruation, the shedding of the endometrium, bleeding, and transient opening of the cervical may cause a temporary increase in microbial diversity or the introduction of exogenous microorganisms [23]. In healthy individuals, the uterine microbiota usu-

Table 1. Temporal and spatial dynamics of uterine microecology

Dimension	Influencing Factors	Microecological Features	Biological Significance
Temporal Dynamics	Menstrual cycle	Lactobacillus dominance during proliferation/secretory phases; transient increase in diversity during menstruation	Reflects ecological resilience and the ability to restore homeostasis
	Pregnancy	Low diversity, high stability; ↑ *L. crispat*us	Promotes immune tolerance and ensures pregnancy safety
	Age/Menopause	Decreased estrogen, possible increase in diversity or dysbiosis	Associated with increased inflammation risk and reduced reproductive function
Spatial Heterogeneity	Vagina	High biomass, Lactobacillus as absolute dominant	First defense line, maintains acidic environment
	Cervix	Transitional microbiota, barrier and filtering function	Limits upward microbial migration
	Uterine cavity	Low biomass, hypoxic, specific Lactobacillus dominance	Fine-tunes immune regulation and selective colonization
Microbial Origins	Vaginal ascent	Significant when barrier function is impaired	Directly affects uterine microecology
	Gut-uterus axis	Mediated by immunity and metabolism	Systemically regulates uterine homeostasis
	Oral-reproductive axis	Via inflammatory or circulatory pathways	Suggests distal microbiota influence on the uterus

ally returns to a stable, homeostatic state rapidly at the onset of the next cycle.

Pregnancy represents a distinct period of profound remodeling of the uterine microbiota. To accommodate the fetus, a "semi-allogeneic" graft, the immune system and local uterine environment undergo extensive modulation, resulting in a more stable, low-diversity microbial state [24]. During this phase, the abundance of *Lactobacillus* as *Lactobacillus crispatus* and *L. iners* generally increases [25, 26]. This probiotic-dominant configuration is thought to support an immune-tolerant environment, inhibit the overgrowth of pathogenic bacteria, and thereby ensure a favorable course of pregnancy [27]. If the microecology of the uterus is disturbed or if pathogenic bacteria colonized in early pregnancy, this may be closely related to adverse pregnancy outcomes [28, 29].

Long-term physiological factors such as age and menopause also influence uterine microecology. The marked differences in estrogen levels among women of reproductive age, perimenopausal women, and postmenopausal women may lead to fundamental changes in the endometrial environment, affecting the colonization patterns and diversity of the flora [30]. In addition, individual reproductive experiences such as age at menarche and reproductive history may leave a lasting "biological imprint" on the formation of the uterine microbiota [31].

Spatial heterogeneity and microbial origins

The uterus is not an isolated cavity. Its microecological composition is deeply affected by the microbial community and migration path of adjacent parts, showing obvious spatial heterogeneity. The female reproductive tract is a continuous anatomical system, but the vagina, cervix and endometrium have a unique microenvironment, so the composition of the bacterial community is not only partially overlapping, but also has its own characteristics [32]. Vaginal microecology usually has a high biomass, with *Lactobacillus* as being prominent [33]. As a passage between the vagina and the uterus, the flora of the cervix shows transitional characteristics [34]. The uterine cavity belongs to a low biomass and hypoxia environment. Although the diversity of the flora is lower than that of the vagina, it is still dominated by specific lactobacillus species in a healthy state [35, 36]. This gradient difference suggests that local barriers such as the cervix and its mucus plugs have an important screening and limiting role in the process of ascending flora, and the endometrium itself also exerts strict selective pressure on the colonization of microorganisms.

The sources of uterine flora are characterized by diversity. Vaginal ascent is the most direct potential source. When the cervical barrier function is weakened or the mucus properties change during menstruation or after certain surgical operations, the vaginal flora may rise and affect the microecology of the uterine lining [37]. Moreover, microorganisms in distant areas such as the intestine can indirectly act on the uterus through the mucosal immune system or the circulatory system, which constitutes the so-called "intestinal-uterine axis" [38]. Intestinal flora disorders may change the microenvironment of distal mucosal sites, including the endometrium, through immunoregulation [39]. Oral flora, etc. are also considered to be related to the microecology of the uterus, which can be regarded as a component of the "oral-reproductive axis" [40, 41].

Evidence between the uterine microbiota and major gynecological diseases

Disruption of uterine microbial homeostasis, as a relative decrease in *Lactobacillus* abundance, abnormal increases in microbial diversity, and overgrowth of opportunistic or pathogenic species, *Streptococcus*, and *Escherichia coli*, has been closely associated with the onset of various gynecological diseases. Its underlying molecular mechanisms primarily involve four aspects, inflammatory responses, immune regulation, alterations in estrogen levels, and metabolic abnormalities, as illustrated in **Figure 1**.

Chronic endometritis

Chronic endometriosis (CE) is a mucosal disease driven by persistent intrauterine microecological imbalance and low-grade chronic inflammation. Its main characteristics are abnormal microbial colonization, local immune activation disorders and endometrial microenvironment remodeling and damage [42]. Under normal physiological conditions, endometrial microecology is mainly composed of *lactobacillus*, maintaining a mild acidic environment, bar-

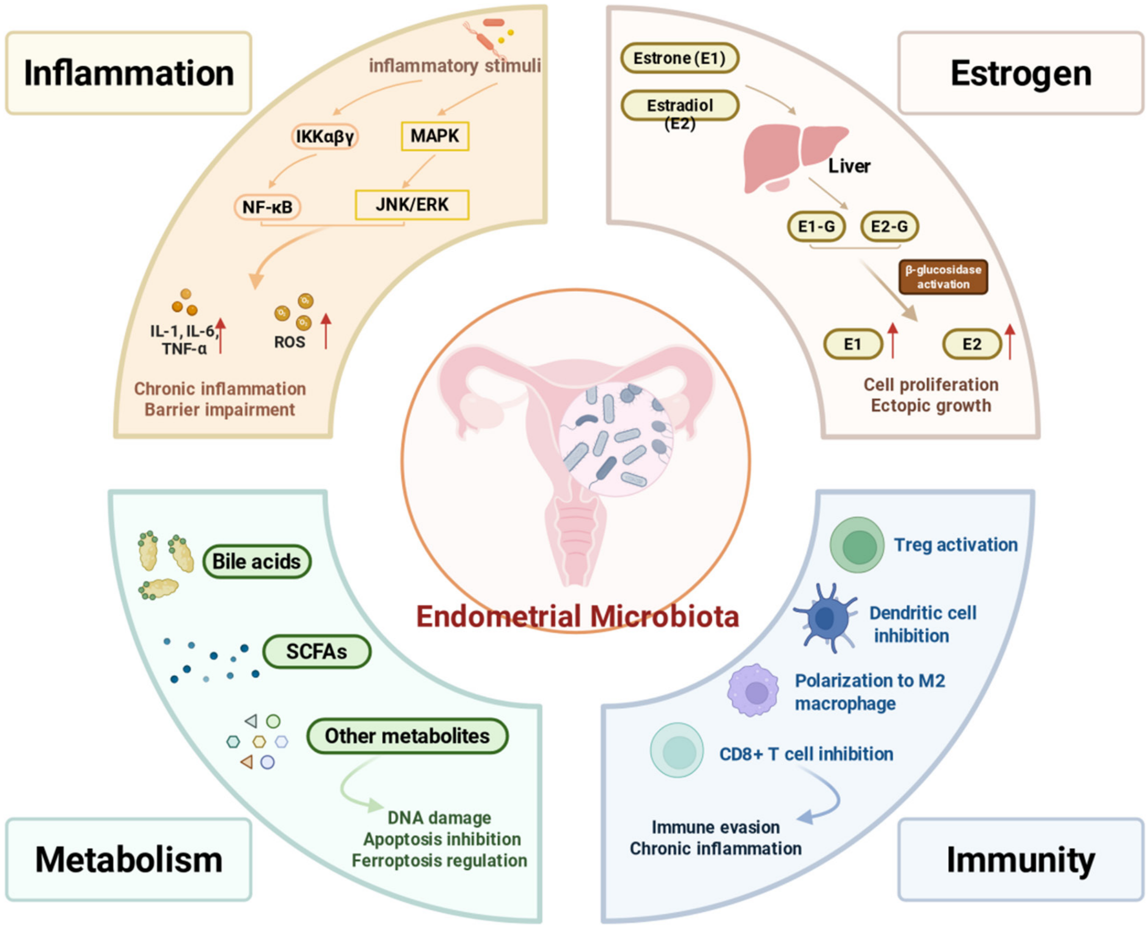

Figure 1. Schematic diagram of endometrial microorganisms regulating female reproductive system diseases. In the inflammatory dimension, microorganisms activate the NF-κB and MAPK signaling pathway to induce the release of pro-inflammatory cytokines and ROS, thus driving chronic inflammation and causing damage to the mucosal barrier. In the hormone dimension, the microbial β-glucosidase mediates estrogen reactivation, forming a local high-estrogen microenvironment, and promoting the growth of ectopic lesions or tumor cell proliferation. In the immune dimension, microbial dysregulation triggers the abnormal activation of Tregs and changes the polarization of macrophages, resulting in immune escape and persistent chronic inflammation. In the metabolic dimension, microbial metabolites are involved in DNA damage, apoptosis regulation and iron death regulation. NF-κB, Nuclear Factor kappa B; MAPK, Mitogen-Activated Protein Kinase; ROS, Reactive Oxygen Species; Tregs, Regulatory T cells.

rier integrity and local immune tolerance. However, in chronic endometriosis, *Lactobacillus* is significantly reduced and replaced by the abnormal enrichment of various conditional pathogens and opportunistic bacteria [43]. This microbiome disorder not only changes the microbial composition in the uterine cavity, but also identifies receptors through the continuous stimulation mode of pathogen-related molecular patterns (PAMPs), resulting in overactivation of downstream signaling pathways, thus maintaining a chronic inflammatory state in the endometrium [44]. Inflammatory reactions further damage the epithelial barrier function, reduce local immune tolerance, promote the continuous release of pro-inflammatory cytokines, and lead to continuous infiltration of immune cells, thus forming a self-continuous inflammatory microenvironment [45]. In addition, the imbalance of microbial metabolites and the accumulation of inflammatory mediators will damage the endometrial repair ability, angiogenesis and endocrine reactivity, ultimately reducing the tolerance of the endometrium and destroying the normal periodic remodeling [46]. In general, these pathophysiological changes reinforce each other, forming a vicious circle, which becomes an important pathogenic basis for repeated implantation failure (RIF) and repeated pregnancy loss (RPL).

CE is widely regarded as a representative disease associated with uterine microbiota disorders [47]. Compared with healthy women, the relative abundance of *Lactobacillus* in patients with CE was significantly reduced, and the level of pathogenic bacteria or opportunistic bacteria increased [48]. Chen et al. systematically compared the endometrial gene expression spectrum and microbiome composition of CE patients and non-CE patients through high-throughput transcriptome sequencing and 16S rRNA analysis, and found that *Phyllobacterium* and *Sphingomonas* were enriched in diseased patients [49]. Fang et al. compared the uterine and vaginal microbiota of healthy women, patients with endometrial polyps (EP) and patients with EP and CE through 16S rRNA sequencing and found that the proportion of thick-walled phyllary in the EP/CE group increased and the proportion of *metamorphic phallus* decreased. At the genus level, *Lactobacillus*, *Gardnerella*, *Bifidobacterium* and *Streptococcus* are enriched, while *Pseudomonas* are reduced. Characteristic changes such as the reduction of *Sphingomonas* and the increase of *Prevotella* were also detected [50]. Retrospective analysis further confirmed that the rate of non-Lactobacillus species in CE patients increased significantly, including Vaginal *Gardnerella*, *Streptococcus* and *Atobacter,* while the abundance of Lactobacillus decreased [51]. This flora disorder not only changes the composition of bacteria, but also triggers a series of chain reactions such as immunity, metabolism and molecular signal transmission [52].

Abnormally colonized microorganisms can continuously activate the local endometrial immune system through a variety of mechanisms. Pathogens are identified through TLRs and NOD-like receptors (NLRs), which can detect PAMPs and activate downstream Nuclear Factor kappa B (NF-κB) and MAPK pathways, leading to excessive secretion of pro-inflammatory cytokines and chemokines [45]. Vito et al. found that Lactobacillus in patients with CE was significantly reduced, while the proportion of opportunistic pathogens such as *Gardnerella* increased, accompanied by and increase in inflammatory markers and reduction of anti-inflammatory or repair factors, which ultimately led to the destruction of the endometrial microenvironment and reduced tolerance [53]. Chronic low-grade inflammation promotes the infiltration and activation of plasma cells, macrophages and dendritic cells, forming persistent inflammatory foci [54]. In addition, microbial metabolites and metabolites of *Clostridium* difficile microorganisms can directly destroy epithelial barrier function and local immune tolerance, further exacerbating the disorder. Zhang et al. found that the microbiota associated with CE is significantly enriched in cofactors, vitamins, secondary metabolites and immune-related pathways, suggesting that the imbalance of the flora may destroy the endometrial immune homeostats through metabolic regulation and local inflammatory activation [55]. This persistent inflammatory state damages the physiological function of the endometrium and provides a pathological basis for RIF and RPL [56, 57].

Endometriosis

Endometriosis (EMs) is a type of chronic inflammation that depends on the hormone estrogen. Its core pathophysiological processes include the ectopic endometrial cell implantation and survival, immune surveillance escape, excessive activation of local estrogen, and persistent inflammation driven by microecological disorders [58]. It is generally believed that the formation of ectopic endomembrane stems from the joint action of many factors, including the theory of menstrual blood reflux, impaired immune clearance, Epithelial-Mesenchymal Transition (EMT), abnormal stem cell migration and changes in the abdominal microenvironment [59]. The latest research further emphasizes that the disorder of the pelvic, uterine and intestinal microbiota has a key amplification effect in the progression of disease [60]. Microecological imbalance can change the local inflammatory threshold of the abdominal cavity and endometrium, leading to abnormal immune cell function and reducing the clearance ability of ectopic endometrial cells [61]. At the same time, PAMPs can activate inflammatory pathways through TLRs, promote the excessive secretion of pro-inflammatory cytokines, and accelerate the adhesion, invasion and angiogenesis of ectopic endomembrane cells [62]. In addition, some microorganisms have β-glucuronidase activity, which can promote estrogen reactivation, thus forming a high estrogen microenvironment in the abdominal cavity that is conducive to the growth of ectopic lesions [63]. The network interaction between inflammation, immunity and hormone regulation forms a positive feedback loop, promoting the gradual expansion of the lesion and leads to chronic pelvic pain, infertility and disease recurrence. Therefore, EMs is an estrogen-dependent disease, with a complex pathological state shaped by microecology-driven immune disorders and persistent inflammation.

A study of 110 women used 16S rRNA sequencing and microbial culture to sample multiple human genital tract sites including cervical canal, uterine cavity, fallopian tube and abdominal fluid. The results demonstrated that the microbiota of the endometrium and ectopic-foci was significantly different from that of the vagina and had higher diversity. Certain microbial taxa were more abundant in adenomyosis or EMs-associated infertility [64]. EMs patients commonly present with reduced *Lactobacillus* and increased pro-inflammatory genera such as *Gardnerella*, *Prevotella*, *Streptococcus*, and *Mycoplasma* [61]. Nicole et al. combined 16S rRNA sequencing with multiplex immune profiling and found that chronic pelvic pain patients with EMs exhibited significant differences in vaginal and rectal microbiota compared to Chronic pelvic pain (CPP)-only patients. Other studies reported dominance of *Lactobacillus*, *Barnesiella*, *Corynebacterium*, and *Pseudomonas* in the uterine cavity of EMs patients, with increased anaerobes and decreased beneficial bacteria, further promoting microbial imbalance [65].

The “microbiota-immune-inflammation” axis is considered a core link connecting microbial dysbiosis and EMs pathogenesis. Dysbiotic microbiota and their endotoxins can chronically activate TLRs on macrophages, dendritic cells, and other immune cells, inducing secretion of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), inducing a chronic inflammatory microenvironment conducive to ectopic endometrial cell adhesion, proliferation, and angiogenesis [66]. Júlia et al. isolated M1/M2 macrophages, NK cells and Tregs from the endometrium of patients with EMs and healthy controls, then combined them with high-throughput RNA sequencing and bioinformatics analysis. They found that M1 macrophages showed pro-inflammatory characteristics, while M2 macrophages abnormally showed pro-inflammatory phenotypes, suggesting abnormal immune polarization in the endometrium [67]. Chandni et al. identified fecal microbial metabolites associated with EMs, including reduced 4-hydroxyindole levels, which can regulate inflammation and pain sensitivity and affect the proliferation of ectopic endometrial cells [68]. Some bacteria can activate estrogen through β-glucuronidase activity, thus increasing local estrogen levels and promoting the growth of ectopic inner membranes, which supports the “estrogen-microbial hypothesis” [69, 70]. However, Inmaculada et al. conducted metagenomic sequencing of gut microbiota from 136 EMs patients and 864 controls, assessing species composition, functional pathways, and estrogen-metabolizing enzyme abundance. No significant differences were observed, showing that gut microbiota may not be a primary driver of EMs [71]. Nonetheless, large-scale metagenomic studies on the uterine microbiota are lacking. Immune dysfunction, including altered regulatory T cell numbers or activity and reduced NK cell cytotoxicity, allows ectopic endometrial tissue to persist. Microbiota dysbiosis may contribute to this immune dysfunction, although causality remains to be established [61]. Despite most evidence coming from cross-sectional and small-cohort studies, abnormal uterine microbiota appears to be a significant facilitator of EMs, making microbiota-targeted diagnostics and interventions a research hotspot.

Endometrial cancer

Endometrial cancer (EC) is a typical hormone-dependent cancer. Its occurrence and progression are driven by different factors, including genetic changes, chronic inflammation, hormonal imbalance and uterine microecological disorders [72]. The latest metagenomic studies show that there is a characteristic “cancerous microbiome spectrum” in EC patients, manifested as a significant Lactobacillus decrease and anaerobic bacteria increase [73]. Microecological disorders may promote tumor development through a variety of mechanisms, including maintaining low-grade chronic inflammation, producing gene-toxic metabolites, changing estrogen reactivation through bacterial β-glucuronidase activity, and weakening immune surveillance [74]. The accumulation of reactive oxygen species (ROS)/reactive nitrogen species (RNS), the continuous activation of NF-κB signals and the excessive cytokines caused by flora disorders will not only lead to epithelial DNA damage, but also enhance abnormal proliferation, angiogenesis and immune escape. On the other hand, tumor-related microorganisms can also regulate metabolic pathways and iron death sensitivity and may affect hormone reactivity and therapeutic effect [75]. Although the causal relationship needs to be further verified, existing evidence shows that microecological disorders play a crucial amplification role in EC by synergizing inflammation, metabolism and immune microenvironment.

Emerging metagenomic studies reveal the potential role of intrauterine microbiota in EC. Compared with benign endometrium, EC patients show a characteristic distribution of "carcinogenic microorganisms", among which *lactobacillus* is reduced, while *Prevo*, Bacillus, Atopobium and Clostridium are more abundant [76, 77]. Bartłomiej and others analyzed the vaginal vault and cervical canal samples of benign uterine diseases, precancerous lesions and EC patients, and found that the benign cases mainly had *Lactobacillus iners,* while *Dialister pneumosintes* and *Mobiluncus curtisii* in EC is more common and may have a synergistic carcinogenic effect [78]. Xiong et al. used two-sample Mendelian randomization (MR) to detect the relationship between intestinal flora and gynecological tumors and found that the abundance of *Lachnospiraceae* changes are related to tumor risk, which may be activated through the regulation of immune inflammatory response, short-chain fatty acid metabolism and estrogen pathway [79]. In addition, EC patients also showed uterine microbial structure disorders, increased α diversity, and significant changes in fungal groups, such as increased *Penicillium* and decreased *Sarocladium* [80]. These specific microorganisms may participate in the formation of carcinogenic microenvironments through mechanisms such as chronic inflammation, metabolite toxicity, interference with hormone metabolism and induction of immunosuppression [11].

Microbial disorders can trigger persistent chronic inflammation of the endometrium, producing a large amount of ROS and RNS, leading to DNA damage, thus increasing the mutations and tumors [81]. Under the condition of increased vaginal pH, carcinogens such as Porphyromonas can stimulate the pro-inflammatory cytokines, further activate NF-κB signals, promote endometrial cell proliferation and inhibit apoptosis and induce angiogenesis and adhesion molecular expression, thus forming an environment conducive to tumor development [82]. Lu et al. reported that the IL-6 protein and mRNA levels in EC patients were significantly increased, and the abundance of Micrococcus was mainly correlated with IL-6 mRNA, suggesting that in the uterus membrane flora disorder may participate in the occurrence of EC through pro-inflammatory pathways, especially cytokine upregulation mediated by Micrococcus [83]. In another study, Anita et al. found that L. crispatus can inhibit endometrial organ proliferation in EC patients, but has limited effect on inflammatory factors, indicating that flora dysregulation may participate in EC by regulating the inner membrane microenvironment, affecting cell proliferation and inflammatory response [84].

Anaerobic bacteria such as *Prevotella* and *Porphyromonas* can produce secondary metabolites, which can be directly genetically toxic or act as ligands to activate the host cancer-promoting signaling pathway. These metabolites can also change epithelial cell autophagy, cell cycle regulation and apoptosis signals, making cells more susceptible to malignancy [85]. Chen et al. identified more than 5,000 active microorganisms in the endometrium of EC, and their composition was significantly different from that of healthy controls. These microorganisms participate in the metabolism of 6-sulfuric acid saliva Lewis X epitope and N-acetyl-β-glucosamine, and interact with the host through Apelin signals and tumor migration-related pathways [86]. However, Xue et al. systematically evaluated the relationship between intestinal specific flora and cyclic metabolites and EC risk, and found that there was no significant causal relationship, suggesting that changes in intestinal flora and systemic metabolites may reflect the disease status, rather than directly driving the occurrence of EC [87].

The endometrial microbiota is also involved in local estrogen metabolism and enterohepatic circulation. Bacterial β-glucuronidase acid glycoside enzyme can de-bond the bound estrogen, thus improving its local concentration and forming an environment conducive to the progression of hormone-dependent tumors. The reduction of *lactobacillus* and the decline of glycogen availability, especially after menopause, can further increase the pH and promote the colonization of carcinogenic bacteria [88]. In addition, Li et al. found that butyric acid-producing bacteria in tumors in progesterone-sensitive patients increased, accompanied by an increase in butyric acid levels. Butyric acid can inhibit tumor cell proliferation, upregulate progesterone receptors, and promote iron death by downregulating CDGSH iron sulfur domain 1 (CISD1), thus enhancing the therapeutic effect of progesterone. This suggests that microorganisms in tumors and their metabolites may participate in the development of EC by iron death, inflammation and hormone signaling pathways [75].

Microbial dysregulation can also induce an immunosuppressive microenvironment, manifested as enhanced regulatory T cell activity and reduced NK cytotoxicity, so that endometrial cells escape immune clearance. The increase of Micrococcus is positively correlated with IL-6 and interleukin-17 (IL-17), suggesting that it can maintain local chronic inflammation through pro-inflammatory factors while inhibiting effective anti-tumor immune response [89]. Samia et al. combined the Cancer Genome Atlas (TCGA) data with microbiome analysis and found that a variety of bacteria and viruses related to the abnormal distribution of immune cells, suggesting that flora dysregulation is regulated by peptidoglycan recognition protein 2 (PGLYRP2), olfactomedin 4 (OLFM4), and toll-like receptor 5 (TLR5). The host genes change the immune surveillance in the tumor microenvironment, thus promoting the occurrence and progression of EC [90]. Other studies have shown that dominant changes in the internal microbiome of tumors in EC patients, and the low endometrial resident flora score is associated with an increase in immune cell infiltration, suggesting that flora dysregulation may promote tumor development by regulating the immune microenvironment. In addition, the endometrial resident flora score is related to chemotherapy sensitivity, indicating that the microbiota not only participates in the onset of EC, but also may affect the treatment response [91].

Ovarian cancer

Ovarian cancer (OC) is a type of cancer with the highest mortality rate in females. About 70% of patients are diagnosed in the late stage, with more than 300,000 new cases worldwide, making it the leading cause of death from gynecological tumors [92, 93]. The occurrence of OC is jointly driven by genetic changes, chronic inflammation, hormonal disorders and imbalance of the reproductive microbiota [94]. In healthy women, the reproductive tract is usually dominated by lactobacillus, which protect the ovaries and reproductive system by maintaining an acidic environment, producing antibacterial factors, and regulating the mucosal immune homeostasis [11]. Pathogenic bacteria can release endotoxins and pro-inflammatory mediators, then activate inflammatory pathways, causing chronic inflammation, DNA damage, apoptosis inhibition and angiogenesis enhancement, creating a favorable environment for tumor growth [95]. Some pathogenic bacteria can also interfere with estrogen metabolism, increase free estrogen levels, and stimulate abnormal proliferation of ovarian epithelial cells. Mucosal barrier damage and regulatory T cell amplification further weaken antitumor immune surveillance, allowing abnormal cells to escape immune clearance [96]. Recent studies have also shown that the microbial-metabolite axis has a potential role in the pathogenesis of OC. The microecological imbalance of the reproductive tract promotes the occurrence and development of OC through mechanisms such as chronic inflammation, hormone metabolism disorders, immune escape and metabolic reprogramming, suggesting that future intervention strategies for microbiota have potential application value [97].

Among healthy women, the reproductive tract is mainly abundant in *lactobacillus*. These probiotics protect the ovaries and reproductive health by maintaining an acidic vaginal environment, producing hydrogen peroxide and bacteriocins, and regulating local immune homeostasis [98]. However, when the abundance of Lactobacillus decreases and pathogenic bacteria (*Gardnerella*, *Escherichia coli*) or opportunistic pathogens *Mycoplasma* grow excessively, microbial imbalance can promote ovarian cancer through a variety of mechanisms [11].

On the one hand, pathogenic bacteria release endotoxins and pro-inflammatory factors (such as IL-6, TNF-α), continuously activate inflammatory pathways including NF-κB, causing chronic inflammation, DNA damage, apoptosis inhibition and angiogenesis, thus creating a favorable microenvironment for tumor growth [99]. On the other hand, some pathogenic bacteria can interfere with estrogen metabolism, increase free estrogen levels, and stimulate abnormal proliferation of ovarian epithelial cells [100]. Microecological imbalance can also destroy the mucosal barrier function, over-activate Tregs and inhibit the anti-tumor response, and weaken the body's ability to remove abnormal cells [101].

Chen et al. evaluated the relationship between intestinal microbiota, related circulatory metabolites and OC through two-sample MR and reverse MR analysis systems, and found that the abundance of a variety of pathogenic groups in OC patients increased, including *Euryarchaeota*, *Escherichia-Shigella*, *Prevotella9*, and *FamilyXIIIAD3011*; and found that *Christensenellaceae* R.7 group, *Tyzzerella3*, and *Victivallaceae* may have a protective effect. This microbiota may promote abnormal proliferation of ovarian epithelial cells and change the tumor microenvironment by regulating inflammation and metabolic pathways. In addition, circulating metabolites such as cytidine are considered to be potential intermediaries between microorganisms and OC, suggesting that the microbiological-metabolite axis may be involved in the pathogenesis of OC [102]. Li et al. observed that in the ovarian cancer model, the vaginal microbiome was out of order, accompanied by changes in the metabolism of amino acids and hemolytic phospholipids, suggesting that microbial imbalance may promote tumor development through metabolic pathways [103]. In general, microbial imbalance in the reproductive tract can drive OC progression through chronic inflammation, estrogen metabolism disorders and impaired mucosal immune barrier. These findings suggest that microbial regulation may become a potential strategy for the prevention and intervention of ovarian cancer.

Existing studies on the reproductive tract microbiota and gynecological diseases have revealed correlations between microbial dysbiosis and conditions such as chronic endometritis, endometriosis, and gynecological tumors, and have preliminarily explored the potential mechanisms by which the "microbiota-immune-inflammation" axis influences disease onset and progression (**Table 2**). However, significant limitations remain. Most studies have small-samples, and cross-sectional observations, making it difficult to establish causal relationships; heterogeneity in sampling sites, sequencing methods, and analytical workflows affect the comparability and integration of results; confounding factors are insufficiently controlled, and mechanistic investigations often rely on indirect evidence. Future research should focus on large-sample, prospective cohort and interventional studies, employing multi-omics approaches to dynamically elucidate microbial functional metabolism and host interactions, thereby advancing the development of precision diagnostics and microbiota-targeted therapeutic strategies.

Therapeutic and interventional strategies

A deep understanding of the dynamics of uterine microbiota is promoting changes in the prevention and management of gynecological diseases. The treatment concept is shifting from the traditional "anti-infection" method to the innovative "microbial regulation" strategy, which aims to restore microbial homeostasis by accurately regulating the microbiota composition and function. This method not only provides a new way to improve the efficacy of chronic endometritis and enhance the success rate of assisted reproduction but also shows great potential in preventing major diseases such as endometrial cancer. The current intervention strategy covers a variety of methods from traditional antibiotics to advanced methods, including microbial transplantation and metabolic regulation (**Table 3**).

Antibiotic therapy: the "old-fashioned" approach to pathogen clearance

Antibiotics are still the first line and basic treatment methods for clarifying the pathological conditions driven by bacterial infection. Oral or uterine injection can effectively remove overgrown pathogens, *Streptococcus*, *Escherichia coli*, and *Prevotella*, quickly relieve endometrial inflammation and improve histopathological characteristics [104]. However, antibiotics are a non-selective "removement" strategy. Long-

Table 2. Microbial alterations and pathophysiological mechanisms in gynecological disorders

Disease	Pathological Features	Microbial Changes	Mechanism	Clinical Relevance
Chronic Endometritis (CE)	Intrauterine microecological imbalance, low-grade chronic inflammation	*Lactobacillus*↓, pathogenic/opportunistic bacteria↑	Dysbiosis activates TLRs/NLRs → pro-inflammatory cytokines↑, metabolic disruption impairs endometrial repair and angiogenesis	Recurrent implantation failure, recurrent pregnancy loss
Endometriosis (EMs)	Estrogen-dependent chronic inflammation, ectopic endometrial survival	*Lactobacillus*↓, *pro-inflammatory genera*↑	Dysbiosis triggers inflammatory pathways, immune polarization, and β-glucuronidase-mediated local estrogen reactivation	Chronic pelvic pain, infertility, lesion recurrence
Endometrial Cancer (EC)	Hormone-dependent tumor	*Lactobacillus*↓, *oncogenic bacteria*↑, fungal changes	Dysbiosis induces chronic inflammation, immune suppression, and estrogen metabolism alterations → promotes cell proliferation and ferroptosis	DNA damage, abnormal proliferation → tumor development and progression
Ovarian Cancer (OC)	High mortality, often diagnosed at late stage	*Lactobacillus*↓, *pathogenic bacteria*↑	Endotoxins/pro-inflammatory factors activate inflammation and immune suppression, disrupt hormone metabolism, and alter metabolic environment	Abnormal proliferation → tumor progression, impaired immune surveillance

Table 3. Therapeutic and intervention strategies targeting the uterine microbiota

Strategy	Advantages	Limitations/Challenges
Antibiotics	Rapid clearance of pathogens; reduces acute inflammation; widely available	Non-selective; may cause resistance and secondary dysbiosis; may not restore beneficial bacteria; limited effect on reproductive outcomes
Probiotics	Restore beneficial bacteria; modulate immunity; enhance epithelial barrier; inhibit pathogens; safe and generally well-tolerated	Strain-specific effects; optimal dose, route, and duration unclear; efficacy may vary among individuals; long-term colonization not guaranteed
Prebiotics	Selectively nourish beneficial bacteria; promote SCFA production; maintain acidic pH; support immune function	Strain- and substrate-specific; may have limited effect in severely dysbiotic microbiota; clinical evidence still limited
Postbiotics	Stable, safe; provide bioactive metabolites without live bacteria; modulate immunity and inhibit pathogens; suitable for immunocompromised	Mechanisms less well-characterized; may not fully replicate live microbiota functions; dosage and formulation require optimization
Microbiota Transplantation (Vaginal/Uterine)	Rapid restoration of microbial ecosystem; competitive pathogen exclusion; re-establish immune homeostasis; can improve reproductive outcomes	Technical and ethical challenges; donor selection critical; risk of pathogen transfer; uterine transplantation still experimental
Combined Interventions	Synergistic effects (e.g., antibiotic "reset" + probiotics/prebiotics); improved microbial balance and reproductive outcomes	Complex protocols: optimal timing, combinations, and long-term effects need validation; personalized approaches required
Diagnostics/Risk Assessment	Enables personalized treatment; identifies high-risk patients; guides intervention strategies	Requires standardized sampling and analysis; dynamic microbiota fluctuations may affect accuracy; clinical translation still in early stages

term or broad-spectrum use may lead to bacterial drug resistance, secondary disorders of vaginal and intestinal flora, and even excessive growth of fungi [105]. More importantly, in the state of non-specific "non-*lactobacillus* advantage", antibiotic treatment does not always improve reproductive outcomes, which suggests that simple removal of pathogenic bacteria may not be enough to actively promote the establishment of healthy microbiota [106].

Therefore, from the perspective of modern microbiology, antibiotics should be regarded as a short-term "reset" tool for the subsequent colonization of probiotics to remove obstacles, rather than a long-term maintenance means. Its use should be more accurate. Ideally, it should be guided by microbial culture, antibiotic sensitivity test or specific molecular markers.

Probiotic intervention: directly "building" beneficial microbiota

As an active microbial preparation, probiotics can improve the microbial balance of the endometrium and vagina through a variety of mechanisms. Commonly used strains include *Ligilactobacillus BPL005*, *Lactobacillus rhamnosus* RC-14, and GR-1 [30, 107]. Probiotics can improve the host microecology by competitively repelling pathogenic bacteria, maintaining an acidic environment, regulating immune responses, regulating microbial metabolites, and enhancing epithelial barrier function [108, 109].

Specifically, *Lactobacillus* occupies an ecological position and competes with nutrients, thus limiting the colonization of pathogenic bacteria. They release lactic acid to reduce the pH value, inhibit pathogenic bacteria growth, and promote local immune tolerance and mucosal barrier integrity by regulating Tregs and anti-inflammatory cytokines [110, 111]. *Ligilactobacillus BPL005* can reduce the level of endometrial propionic acid and improve the organic acid spectrum. Empar et al. showed in vitro experiments that co-culture with BPL005 can significantly reduce the abundance of *P. acnes* and *S. agalactiae* while lactic acid production reduces pH and inhibits the growth of pathogenic bacteria. BPL005 colonization can also reduce the levels of IL-6, interleukin-8 (IL-8) and Monocyte Chemoattractant Protein-1 (MCP-1), while increasing interleukin-1 receptor antagonist (IL-1RA) and IL-1β, thus regulating local immunity and improving the endometrial microenvironment [112].

Lactobacillus rhamnosus RC-14 and GR-1 can strengthen the uterine epithelial barrier and resist the invasion of viruses and pathogens. Chen et al. found that RC-14 can restore microbial balance through elevating the beneficial Lactobacillus abundance under microecological disorders, providing an effective tool for targeted and personalized microbial intervention [113]. Ameda and others reported that the Ld45E strain grows well in the acidic vaginal environment, showing strong adhesion and self-agglomeration, which can inhibit *Group B Streptococcus*, *E. coli*, and *Klebsiella*, and significantly reduce the expression of IL-17 induced by pathogenic bacteria. At the same time, it has no hemolytic activity and is sensitive to common antibiotics. Ld45E inhibits the colonization of pathogenic bacteria through adhesion, copolymerization and competitive rejection, and regulates local inflammation to maintain vaginal microbial balance [114].

Clinical studies further support the benefits of probiotic interventions. In a multicenter and placebo-controlled trial, Zohar et al. administered oral probiotics to pregnant women after vulvovaginal infection (VVIs) clearance. While recurrence rates, time to first infection, and pregnancy outcomes were not significantly different, the probiotic group showed potential advantages in maintaining vaginal microbial balance and increasing *Lactobacillus* abundance, with no safety concerns [115]. Other studies have also shown that vaginal or oral supplementation with *L. crispatus*, *L. jensenii*, *L. delbrueckii*, as well as GR-1 and RC-14 strains, can effectively increase *Lactobacillus* abundance, reduce the proportion of Bacterial Vaginosis (BV)- or Vulvovaginal Candidiasis (VVC)-associated pathogens, alleviate symptoms such as discharge odor and itching, improve Nugent scores, and significantly lower recurrence rates [116]. As a randomized, double-blind, placebo-controlled crossover study, the Pro II mixed-strain group significantly reduced the Nugent score and *Gardnerella vaginalis* abundance, while the Pro I group showed a decrease in total vaginal bacterial count. These findings indicate that oral administration of specific probiotics can safely and effectively restore vaginal microbial balance and inhibit pathogen colonization [117]. Yang et al. conducted a double-blind, placebo-controlled, randomized study to evaluate the oral *Ligilactobacillus GR-1* and *L. rhamnosus RC-14* on vaginal microbiota, cytokines, and pregnancy outcomes in pregnant women with low risk. The results showed that there was no significant difference between the two groups in terms of Nugent score recovery, Shannon diversity index and pregnancy outcome. However, probiotics show potential advantages in maintaining the stability of vaginal *Lactobacillu* abundance, supporting immune homeosis and ensuring safety, and no adverse reactions have been reported [118]. In addition, a randomized and controlled trial evaluated the effect of *Lactobacillus* probiotics on the vaginal and intestinal microbiota of pregnant women with VC infection. The study found that in the placebo group, the abundance of vaginal *Lactobacillus* decreased, while the abundance of harmful bacteria such as P *Prevotella* and *Atopobium* increased. In contrast, the probiotic group maintained a stable microbial composition [119]. These results further show that Lactobacillus probiotics can effectively maintain and restore the balance of vaginal microorganisms, inhibit the harmful bacteria and improve the local microenvironment.

In summary, probiotics can promote the colonization of probiotics and inhibit the proliferation of pathogenic bacteria through a variety of mechanisms, including direct competition, environmental regulation, biofilm formation and metabolite regulation, so as to effectively balance the uterine and vaginal microbiota [120, 121]. Probiotics are highly safe and targeted, especially in restoring the host microbiota after antibacterial treatment. However, the therapeutic effect of probiotics has strain specificity, and the optimal strain combination, route of administration, dose and treatment cycle still need to be verified by large-scale, multi-center randomized controlled trials.

Application of prebiotics: "energizing" beneficial bacteria

Prebiotics refer to substances that cannot be digested by the host but can promote the probiotics growth and activity, including oligosaccharides (FOS), inulin, β-glucan and galact-oligosaccharide (GOS) [110]. By providing nutrition for probiotics in the vaginal microbiome, especially Lactobacillus, probiotics can promote the proliferation and activity of healthy microbiota and play a key role in protecting the vaginal microenvironment, maintaining acidic pH, and inhibiting the colonization of pathogenic bacteria [122]. Lactobacillus can ferment prebiotics to produce short-chain fatty acids (SCFAs), construct an acidic environment inhibiting the growth of pathogenic bacteria, and stimulate local immune responses, including the secretion of cytokines and antibacterial peptides, thus enhancing the vaginal defense mechanism [123]. Studies show that the SCFAs produced by the vaginal microbiota not only have antibacterial activity but also may have antitumor and immunomodulatory effects. However, the ability to use prebiotics has strain and substrate specificity, so the safety and effectiveness of the selected probiotics need to be verified. Locally applied prebiotics should tolerate vaginal acid pH, maintain structural integrity and functional characteristics, and have appropriate solubility to ensure effective distribution and absorption in the vaginal environment, without irritation or allergic reaction to the fragile vaginal mucosa [124, 125].

Existing studies have evaluated the effects of FOS and GOS on *L. crispatus*, *L. jensenii*, and *L. vaginalis*, showing that these *Lactobacillus* species can efficiently utilize these prebiotics, whereas pathogens such as *Gardnerella*, *E. coli*, and *Candida albicans* cannot metabolize them [126]. Federica et al. analyzed multicenter case-control data to assess the relationship between dietary intake of fiber-type prebiotics and hormone-related female cancer risk. They found a marginal positive association between nystose intake and breast, ovarian, and endometrial cancer risk, whereas high-dose 1F-β-fructofuranosyl nystose intake was negatively associated with ovarian cancer risk. Other prebiotics, such as inulin, kestose, raffinose, and stachyose, showed no significant association [127]. Angela et al. developed a hydrogel using chitosan (CS), non-dried bacterial nanocellulose (NDBNC), and Poloxamer 407 (PX), embedding water-soluble active components in the hydrophilic portion and hydrophobic components in the hydrophobic core. The probiotic hydrogel supports cell proliferation, significantly promotes the growth of probiotics such as Lactobacillus, and inhibits the formation of pathogenic bacteria and biofilms. It provides stable nutritional support in the vaginal environment, maintains the advantages of probiotics, inhibits the growth of pathogens, and improves the microecological balance [128]. Another study recruited 32 women who had failed in vitro fertilization (IVF) in the past and were given oral probiotic formulas (including vaginal-specific *Lactobacillus* combined probiotics, Personal Flora 2®) to regulate the vaginal microbiota. Probiotic intervention significantly reduces species diversity, promotes the advantages of *Lactobacillus* and *Bifidobacterium*, and reduces the proportion of *Atopobium*, *Gardnerella*, and *Prevotella*. *Lactobacillus*, improve the microbial structure of the vagina, inhibit the growth of pathogens, maintain a healthy vaginal ecosystem, and may improve the success rate of ART pregnancy, showing the significant advantages of prebiotics in regulating vaginal microecology [129].

Postbiotics are inactive components or metabolites of probiotics, including SCFAs, extracellular polysaccharides (EPS), cell lysates, cell wall components and bacterins [130]. The product prebiotics have immunomodulation and antibacterial characteristics, high stability and safety, and are especially suitable for people with low immune function [131]. They can acidify the vaginal environment, inhibit the metabolism of pathogenic bacteria, and block the formation of biofilms, to prevent and treat VVC infection and other vaginal infections [132]. The use of probiotics can significantly reduce the abundance of pathogenic bacteria, enhance the colonization of healthy *lactobacillus*, restore the microecological balance, and avoid the potential risks that may be brought by live bacteria [133]. Barbara et al. found that BC17 product prebiotics can safely and effectively promote the growth of probiotics, inhibit the formation of pathogenic bacteria and biofilms, provide a reliable strategy for regulating the infant's intestinal microbiota in the absence of live bacteria, highlighting the advantages of product prebiotic therapy: being safe, stable, controllable with dual adjustment and joint action [134]. Another research report points out that Lactobacillus cell-free supernatant (CFS) significantly inhibits the proliferation, viability and metabolic activity of *C. parapsilosis*, and enhances the epithelium's resistance to fungi. It is worth noting that the effect still partially persists after the removal of CFS, indicating that CFS has stable activity similar to that of prebiotics [135].

Microbiota transplantation (VMT/UMT): reconstructing the microecology

Microbial transplantation aims to directly and quickly reconstruct the healthy microenvironment by transferring the entire microbiota of the healthy donor and its ecological network to the receptor body [136]. In the field of obstetrics and gynecology, this strategy mainly includes vaginal microbial transplantation (VMT) and exploratory uterine microbial transplantation (UMT).

VMT involves the transplantation of cervical and vaginal secretions from strictly screened healthy donors or isolated and cultured lactobacillus strains into the recipient's vaginal vault [137]. Its fundamental goal is to use the overall function of healthy microbiota to competitively repel pathogenic bacteria, return to a normal acidic environment, and rebuild local immune homeostats. A randomized controlled trial conducted by Liu et al. provided strong evidence for the effectiveness of this strategy. In this study, 100 high-risk HPV-infected women were randomly assigned to receive VMT or placebo treatment with Lactobacillus *Lactobacillus crispatus* CP-1 isolated from healthy donors. Compared with the placebo group, VMT significantly reduced the HPV viral load and significantly improved the complete clearance rate of HPV. In addition, VMT effectively alleviated local inflammation without serious adverse events. 16S rRNA sequencing analysis confirmed the successful colonization of transplanted microorganisms and restored the dominant community of *Lactobacillus crispatus* [138]. The study shows that VMT is not only a bacterial replacement, but also introduces a fully functional probiotic ecosystem, reshapes vaginal microecology, enhances the advantages of probiotics, and regulates the immune microenvironment - ultimately enhancing the host's defense against pathogens. In another case report, Tine et al. transplanted *Lactobacillus*-dominated cervical vaginal secretions from healthy donors into a patient with severe vaginal microecological imbalance and recurrent abortion. Before transplantation, the patient's vaginal microbiota was mainly *Gardnerella* (90%). After a single VMT, the microbiota returned to a healthy structure, mainly *L. crispatus* (81.2%) and *L. jensenii* (9%), and vaginal irritation and abnormal secretions completely disappeared. It is worth noting that VMT has achieved effective recovery of vaginal microecology, local inflammation improvement and reproductive health recovery without the need for antibiotic pretreatment [139]. These findings show that VMT has the potential to be a safe, lasting and fertile treatment option.

Inspired by the successful experience of VMT, UMT was born as a cutting-edge concept. UMT aims to deliver healthy microbiota directly to the uterine cavity through uterine perfusion to correct endometrial microbiota disorder [140, 141]. In reproductive medicine, transplanting a *Lactobacillus*-based microbial community can enhance endometrial tolerance, create a benefit environment for embryo implantation, and bring hope for patients with recurrent embryo implantation failure. In terms of tumor prevention, in view of the established association between specific microbial spectrum and endometrial cancer, early UMT-based intervention may help rebuild uterine microbial homeostasis and interrupt the pathological "chronic inflammation-cancer" cascading process. However, UMT is still in the conceptual and early experimental stage, and its technical and ethical challenges are far greater than VMT.

Combined intervention strategies: a multimodal synergistic approach

For patients with chronic endometritis or recurrent embryo implantation failure, the "probiotics/probiotic consolidation after short-term antibiotic treatment" has become a promising clinical path. The strategy first removes pathogenic bacteria, and then supplements probiotic microorganisms and provides growth support, to achieve a longer-lasting recovery of microbial balance. Preliminary studies have shown that such combined interventions can significantly improve reproductive outcomes. Russo et al. conducted a double-blind randomized clinical trial, including 48 women with recurrent bacterial vaginosis (BV). All participants received standard metronidazole treatment (500 mg per day, twice, for 7 days) and randomly assigned probiotics combined with bovine lactoferrin or placebo for follow-up for 6 months. The probiotic plus lactoferrin group was significantly better than the placebo group in terms of symptom relief, normalization of Nugent score and reduced recurrence rate. Research shows that probiotics have good treatment tolerance and can be used as an effective auxiliary for antibiotics by rebuilding the advantages of healthy microorganisms, enhancing the vaginal barrier and maintaining long-term microbial homeostasis [142]. Similarly, Qi and others conducted a parallel control study, including 67 Chinese BV patients. The participants were randomly divided into the control group and the probiotic group (metronidazole plus oral *Lactobacillus rhamnosus* TM13 and *Lactobacillus delbrueckii* LG55, lasting for 30 days). Although the cure rate of the two groups was comparable, the vaginal health recovery of the probiotic group was better, and the proportion of patients with a Nugent score of <4 was significantly higher, showing the advantage of Lactobacillus and the successful reconstruction of microbial balance [143].

With the integration of macro genomics and metabolomics, therapeutic targets are expanding from microbial composition to their functional products. Future interventions may include direct supplementation of prebiotic microbial metabolites (such as butyric acid) [144], or pharmacological neutralization of harmful metabolites (such as secondary bile acid), to regulate endometrial inflammation and immunity under a more refined framework of "microbial-host interaction". Zhu et al. found that oleic acid (OA) and similar long-chain fatty acids can selectively inhibit the growth of *L. iners* and promote the proliferation of *L. crispatus* - this process depends on OA-inducible genes, such as *oleate hydratase* (*ohyA*) and *atty acid efflux pump* (*farE*), these genes are highly conservative in the probiotic Lactobacillus [145].

In addition, Lu et al. studied a variety of interventions in the mouse model of EMs, including vaginal broad-spectrum antibiotics, abdominal NF-κB inhibitors, VMT or subcutaneous gonadotropin-releasing hormone agonists (GnRH-a). All treatments significantly inhibited the development of ectopic lesions, reduced the level of pro-inflammatory cytokines in the abdominal cavity, and reduced the expression of Ki-67 and Iba-1 in the foci. Local vaginal antibiotics or VMT drugs, especially when combined with GnRH-a, effectively improved EMs pathology and inflammation [146]. The study highlights the potential of microbiome-based interventions as safe, targeted and can be combined to treat endometriosis and other uterine microecological diseases.

In addition to microbial-based interventions, certain traditional or plant-derived agents with anti-inflammatory, hemostatic, and tissue-repairing properties may also hold potential in modulating the endometrial microenvironment. For instance, a systematic review and meta-analysis of randomized controlled trials suggested that Yunnan Baiyao, a traditional Chinese herbal formula, exhibits efficacy in hemostasis and anti-ulcer effects, possibly through mechanisms involving inflammation modulation and microcirculation improvement [147]. Although direct evidence in uterine disorders is limited, such agents could be explored as adjunctive options in managing inflammation-associated gynecological conditions such as chronic endometritis or endometrial bleeding disorders.

Microecology as a diagnostic and risk assessment tool

The value of uterine microecology lies not only in its therapeutic potential, but also in its prospects as a source of new biomarkers. Specific “microbial characteristics”, such as the advantage of Lactobacillus less than 90% or the abundance of Prevotella and *Gingival* Porphyromonas, can be used as indicators to assess the risk of embryo implantation failure, and can also be used for early screening and risk of endometrial cancer.

Tang et al. found that the level of basal epithelial cells, white blood cells and small bacteria increased significantly in the vaginal microenvironment of patients with premature rupture of the membranes (PPROM). While, the abundance of pathogenic bacteria increased significantly, women who gave birth at full dormancy maintained predominant Lactobacillus strains (*L. jensenii*, *L. crispatus*), showing the stability of the ecosystem. These findings show that microbiota-based diagnosis can accurately identify pathogenic bacteria and disordered subtypes, thus guiding individualized antibacterial or probiotic interventions, restoring vaginal microecology and reducing the risk of PPROM [148]. Similarly, Anita et al. observed that the microbial load of the cervix, vagina and rectum in patients with EC was significantly reduced, the types of *Lactobacillus* were significantly reduced, and anaerobic bacteria were enriched, accompanied by increased microbial diversity [84]. These changes are closely related to EC, suggesting that uterine microecological imbalance plays a key role in the process of carcinogenesis. These patient-specific microbial spectra can be used as valuable biomarkers for early diagnosis, risk assessment and individualized prevention, providing new ideas for the development of screening and treatment strategies based on microbiota. In addition, another research report pointed out that the microbial diversity of patients with endometriosis increased significantly, and there were obvious changes in microbial communities, especially the abundance of Faecalibacterium prausnitzii [149]. These characteristic changes in the endometrial microbiota may serve as potential diagnostic and prognostic indicators of endometriosis, providing a basis for the formulation of early screening and individualized treatment strategies.

Although existing studies on microbiota-targeted strategies for gynecological disorders have demonstrated the potential applications of probiotics, prebiotics, postbiotics, and microbiota transplantation, the level of clinical evidence remains limited. Most studies are constrained by small sample sizes and high heterogeneity in study design, making it difficult to draw generalizable conclusions. Mechanistic research largely relies on in vitro or animal models, and the precise regulatory pathways in the complex human environment remain unclear. Personalized intervention strategies are lacking, and cutting-edge approaches such as microbiota transplantation face significant challenges in safety and standardization. Future efforts should focus on advancing “precision microbiome medicine” by matching targeted therapies to patients’ microbial functional phenotypes, deepening mechanistic studies using organoids and multi-omics technologies to elucidate interaction networks and develop predictive biomarkers, establishing standardized safety assessment frameworks, exploring intelligent delivery and combination therapy strategies, and expanding patient-centered, multi-dimensional outcome evaluation systems, ultimately translating microbiome research into safe and effective clinical practice.

Conclusions and perspectives

In recent years, with the rapid advancement of high-throughput sequencing, single-cell sequencing, and spatial transcriptomics, research on uterine microecology has shifted from focusing on "whether it exists" to "how it functions". Substantial evidence now indicates that the uterus is not a sterile cavity but rather a low biomass yet highly specialized microecosystem, hosting a complex microbial community. This system plays a crucial role in maintaining endometrial homeostasis, regulating local immune responses, modulating hormone sensitivity, and influencing reproductive health. In a range of gynecological disorders, including chronic endometritis, endometriosis, endometrial cancer, and ovarian cancer, microbial dysbiosis is closely associated with local chronic inflammation, hormonal imbalance, and disruption of the immune barrier. These findings provide a novel microecological perspective on disease pathogenesis and suggest that the microbiome could serve as an important target for early diagnosis and therapeutic intervention.

Current studies have preliminarily established a core pathological axis of "microbial dysbiosis-chronic inflammation-immune-metabolic dysfunction- disease onset". While different gynecological conditions may share common microecological features, such as reduced Lactobacillus abundance and enrichment of specific opportunistic pathogens, each disease also exhibits distinct microbial and metabolic signatures. This duality suggests that the uterine microbiome may simultaneously serve as a "shared pathological foundation" and a "disease-specific regulatory factor", providing a theoretical basis for precise diagnosis and individualized intervention. Accordingly, the paradigm of disease prevention and treatment is shifting from the traditional "anti-infection" approach toward modern "microbial regulation", with therapeutic goals extending beyond pathogen clearance to the restoration of a healthy microecosystem and endometrial immune and functional balance.

In terms of interventions, diverse strategies have been explored to restore microecological homeostasis. Antibiotics remain useful as a "reset tool" for acute pathogen clearance, rapidly suppressing overgrown pathogenic bacteria and creating ecological niches for probiotic colonization. Probiotics, prebiotics, and postbiotics exert therapeutic effects by directly supplementing beneficial microbes, providing selective nutritional support, and modulating local immune responses, thereby improving the endometrial and vaginal microenvironment. Vaginal microbiota transplantation, as a more direct ecological reconstruction approach, has achieved breakthroughs in treating recurrent vaginal infections and HPV-related lesions. Clinical studies indicate that sequential interventions combining "antibiotic clearance followed by probiotic consolidation" can significantly improve reproductive outcomes in patients with chronic endometritis, highlighting the clinical feasibility and therapeutic potential of microbiota-targeted strategies in reproductive medicine.

Nevertheless, uterine microecological interventions face multiple challenges and limitations. Current studies are characterized by high heterogeneity, small sample sizes, and short follow-up durations, resulting in limited evidence levels. Mechanistic understanding remains largely associative, with causal pathways and molecular mechanisms yet to be fully elucidated. Individualized treatment strategies have not been established, preventing precise, patient-specific microbial modulation. Emerging approaches, such as uterine microbiota transplantation, also require systematic evaluation of safety, ethical standards, and long-term outcomes. These challenges underscore the need for standardized protocols, multi-center data integration, and rigorous regulatory frameworks before broad clinical implementation.

Looking forward, research on uterine microecology is expected to advance synergistically in mechanistic elucidation and clinical translation. Establishing standardized workflows for sample collection, storage, sequencing, and data analysis, combined with integrated multiomics approaches, including metagenomics, meta transcriptomics, metabolomics, single-cell, and spatial omics, will enable dynamic characterization of microbial functions and their interactions with host immune, endocrine, and metabolic systems. Attention to microbial metabolites, such as short-chain fatty acids, indole derivatives, and secondary bile acids, will clarify their roles in regulating endometrial immune tolerance, hormonal responsiveness, and cellular fate. The integration of artificial intelligence and personalized medicine models promises to enable precise, patient-specific microbial interventions, shifting from one-size-fits-all approaches to customized, predictive, and efficient regulation. Over the next decade, through technological innovation, interdisciplinary collaboration, standardization, and large-scale clinical validation, it is anticipated that uterine microecology can be accurately assessed and effectively modulated, providing new strategies for the prevention, diagnosis, and treatment of gynecological inflammatory diseases, infertility, and gynecological tumors, ultimately improving reproductive health outcomes across the female lifespan and offering a paradigm for understanding the interplay between the microbiome and human health.

Disclosure of conflict of interest

None.

Address correspondence to: Yulan Cui, Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Harbin Medical University, No. 246 Xuefu Road, Nangang District, Harbin 150-086, Heilongjiang, China. Tel: +86-0451-86605175; E-mail: 823753@hrbmu.edu.cn

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