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THE ROLE OF THE ENDOMETRIAL MICROBIOME IN INFERTILITY AND REPRODUCTIVE HEALTH: CURRENT EVIDENCE AND FUTURE DIRECTIONS

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ABSTRACT

Infertility affects 10–12% of couples and growing evidence implicates the reproductive tract microbiome in implantation success. This narrative review synthesizes human studies on the vaginal and uterine (endometrial) microbiota in relation to fertility outcomes and mechanistic markers. We searched PubMed/MEDLINE, Embase, and Scopus (2000–30 Oct 2025) for randomized and observational studies reporting implantation, clinical pregnancy, live birth, or relevant biomarkers (e.g., α/β-diversity, inflammatory cytokines, LIF). Data were summarized descriptively due to heterogeneity in sampling, sequencing pipelines, and outcome definitions. Across studies, the uterine cavity is no longer viewed as sterile and typically shows low-biomass, often Lactobacillus-lean communities distinct from the vagina. Dysbiosis—frequently characterized by reduced Lactobacillus dominance and increased anaerobes—has been associated with lower implantation and clinical pregnancy rates and with inflammatory profiles that may suppress LIF. Limited interventional data suggest that targeted therapies (e.g., probiotics or antibiotics followed by probiotics) can restore eubiosis in some patients and may improve implantation, but evidence remains preliminary and at risk of bias. We conclude that microbiome composition is plausibly linked to implantation and early pregnancy outcomes, yet clinical adoption is premature. Standardized sampling, rigorous contamination control, multi-omic profiling, and well-powered randomized trials are needed to define actionable thresholds and therapeutic strategies.

KEYWORDS

Uterine Microbiome, Vaginal Microbiota, Implantation, Infertility

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1. Introduction

The World Health Organization (WHO), defines infertility as a disease of the male or female reproductive system characterized by the inability to achieve a clinical pregnancy after 12 or more months of regular, unprotected sexual intercourse [1,2]. This condition carries not only physical but also significant psychological, emotional, and social consequences [1]. It affects approximately 10–12% of couples worldwide and represents an important public health issue. Infertility not only impacts the well-being of affected individuals but also imposes substantial socioeconomic burdens. Various recommendations have been established to optimize fertility. It is well known that maintaining a balanced diet rich in vegetables, fiber, and adequate protein, along with proper folic acid supplementation and regular, individually tailored physical activity, plays a key role in supporting reproductive health [3].

Despite these well-documented lifestyle recommendations and continuous advances in assisted reproductive technologies (ART), a considerable number of couples still experience infertility, recurrent implantation failure (RIF), or recurrent pregnancy loss (RPL) [4,5]. The most common causes of female infertility include ovulatory dysfunction, uterine abnormalities (such as polyps or fibroids), tubal obstruction, endometriosis, and primary ovarian insufficiency [6]. Although ART—particularly in vitro fertilization (IVF)—offers many couples the possibility of achieving pregnancy, the success rates remain suboptimal. This underscores the need to investigate additional biological and environmental factors that may influence reproductive outcomes [4,5].

The human body is colonized by trillions of microorganisms that inhabit different anatomical niches, forming functional microbial ecosystems essential for health. These microbial communities protect against pathogens, regulate immune responses, and contribute to the proper functioning of metabolic and physiological processes [7]. While the vaginal microbiome has been extensively studied and well characterized, the uterus was long believed to be sterile. Recent research has overturned this view, demonstrating that the uterine cavity indeed contains its own distinct microbiota [8,9]. The development of modern diagnostic tools, especially next-generation sequencing (NGS) technologies, has enabled the detailed study of the endometrial microbiome—

the bacterial community residing within the endometrial cavity [9]. Emerging evidence indicates that variations in the composition of this microbiota can significantly influence embryo implantation and IVF success [10,11]. Typically, a healthy endometrial environment is dominated by Lactobacillus species, such as *L. iners* and *L. crispatus*, whereas dysbiotic profiles, characterized by the presence of *Gardnerella*, *Atopobium*, or *Streptococcus*, have been linked to reduced IVF success rates and increased risk of miscarriage [10–12]. Given the growing evidence connecting endometrial microbiota composition to reproductive outcomes, a comprehensive understanding of its role in fertility is urgently needed.

The aim of this review is to summarize the current evidence regarding the composition and function of the endometrial microbiome and its potential impact on female infertility—particularly in relation to implantation, IVF success, and pregnancy loss. Moreover, this paper discusses methodological challenges, emerging therapeutic approaches, and future perspectives on integrating microbiome analysis into reproductive medicine [1–12].

2.Methodology

We carried out a narrative review on the uterine/vaginal microbiome and fertility. We searched PubMed, Embase, and Scopus for human studies published from 2000 to 30 Oct 2025 using terms like uterine/endometrial microbiome, vaginal microbiota, infertility, implantation, probiotics, LIF, and inflammation. We included RCTs and observational studies that reported fertility outcomes or basic mechanistic markers; we excluded animal studies, case reports with <5 patients, opinion pieces, and abstracts without full text. From each study we noted who was studied, how samples were taken, lab methods (culture, 16S, shotgun), any interventions, and outcomes. Risk of bias was checked with standard tools (RoB 2 for RCTs, Newcastle–Ottawa/AXIS for observational). Because the studies differed a lot, we summarized findings descriptively and did not do a meta-analysis.

3. Results

3.1 Endometrial Microbiome – Basic Concepts

The human microbiome consists of trillions of microorganisms that form a dynamic and complex ecological system. These microbial communities play an essential role in protecting the host against pathogenic bacteria, supporting the immune system, and maintaining homeostasis [7]. Historically, it was believed that microbial colonization was limited to the lower genital tract, particularly the vagina, where the microbiota contributes to protection against infections. For many years, the uterine cavity was thought to be sterile and separated from the vaginal microbiota by the cervix; newer studies dispute this assumption [8]. It is now well established that microorganisms can also be found in the upper reproductive tract, including the endometrium, although in much lower abundance compared with the vagina. The bacterial load of the endometrium is estimated to be approximately 10^2–10^4 times lower than that of the vaginal microbiota, which is why it is often referred to as a "low-biomass microbiota." Despite its low microbial density, the endometrial microbiome is thought to have a significant impact on fertility and pregnancy outcomes [9–11].

3.2 Lactobacillus-Dominant (LD) vs. Non-Lactobacillus-Dominant (NLD) Microbiota

In a landmark study, Moreno et al. classified the endometrial microbiota into two major categories [10]: Lactobacillus-dominant (LD): >90% of bacterial composition consists of *Lactobacillus* species. Non-Lactobacillus-dominant (NLD): <90% *Lactobacillus* with >10% of other bacterial taxa. The presence of an NLD microbiota has been associated with adverse reproductive outcomes, including implantation failure, biochemical pregnancy, and miscarriage [10,11]. *Lactobacillus* species produce lactic acid and short-chain fatty acids (SCFAs) that lower vaginal pH to approximately 4.5, creating an environment that inhibits pathogenic bacteria. However, this mechanism does not appear to apply directly to the endometrial environment, as studies have not shown a correlation between endometrial fluid pH and microbiota composition. It is therefore likely that other biochemical and immunological mechanisms are responsible for maintaining endometrial receptivity and facilitating embryo implantation [10–12].

An NLD microbiota may induce an inflammatory state within the endometrium, potentially impairing implantation. Inflammatory mediators play a crucial role in blastocyst adhesion, and excessive activation of these pathways can be detrimental [11,12]. Moreover, bacterial metabolites and enzymes may directly affect cell signaling pathways in endometrial epithelial and stromal cells. Understanding the molecular dialogue between the endometrial microbiota and the endometrial epithelium represents a rapidly evolving area of research. Approaches based on systems biology—integrating microbiological, immunological, and transcriptomic data—are increasingly being applied to elucidate these complex host–microbe interactions [2,10–12].

3.3 Factors Influencing the Endometrial Microbiota

Research on the endometrial microbiome has produced variable and sometimes conflicting results. Some studies suggest that the endometrial microbiota remains relatively stable despite hormonal fluctuations during the menstrual cycle, while others indicate that both lifestyle and clinical factors may significantly influence its composition [2,3,11]. Among these factors, age at first sexual intercourse, duration and regularity of the menstrual cycle, and reproductive history (such as the number of pregnancies and deliveries) have been identified as potential determinants of microbial diversity [2,3]. Moreover, ethnic and geographical differences appear to play an important role, highlighting the complex interplay between host genetics, immune response, and microbial colonization [9,12]. In addition to host-related factors, various external influences can alter the uterine microbiota. These include the use of antibiotics, hormonal contraceptives, intrauterine devices (IUDs), and assisted reproductive procedures, all of which can modify the local immune and metabolic environment of the endometrium [13,22,23]. A major technical challenge in studying the endometrial microbiome is its low microbial biomass. Because the number of bacteria in endometrial samples is extremely small, there is a high risk of contamination from laboratory air, reagents, or handling equipment. Even minimal contamination can distort sequencing results and lead to misleading conclusions [31]. For this reason, strict laboratory protocols for sample collection, storage, DNA extraction, and sequencing are essential. Negative controls, reagent blanks, and parallel sequencing of control samples should always be included to ensure data reliability [31].

Despite these challenges, the characterization of the endometrial microbiome is crucial for understanding its potential role in female reproductive physiology. The increasing availability of advanced molecular tools—such as next-generation sequencing and quantitative PCR—has made it possible to study this delicate ecosystem with unprecedented precision [9,10,13]. However, the field still lacks standardized methodologies, including consensus on how to classify microbiota profiles (e.g., defining thresholds for *Lactobacillus* dominance) and uniform approaches to data analysis. These inconsistencies contribute to discrepancies across studies and currently limit our ability to draw definitive conclusions about the clinical significance of the endometrial microbiota [10,12,13]. In summary, the composition of the endometrial microbiome is influenced by a combination of biological, environmental, and technical factors. Understanding and controlling these variables is fundamental to accurately determining how microbial communities contribute to fertility and reproductive outcomes [9,10,31].

3.4 Methods for Studying the Endometrial Microbiome – 16S rRNA Sequencing

One of the key analytical methods used to investigate the endometrial microbiome is 16S ribosomal RNA (rRNA) gene sequencing. This molecular technique enables the identification and classification of bacterial species present in a biological sample based on the analysis of conserved and variable regions of the bacterial 16S rRNA gene [9,10,13]. The 16S rRNA gene encodes a structural component of the 30S subunit of the bacterial ribosome and contains both conserved and hypervariable regions (V1–V9). The conserved regions allow for universal amplification of bacterial DNA using polymerase chain reaction (PCR), while the hypervariable regions provide the taxonomic specificity needed to distinguish between bacterial genera and, in some cases, species [31]. In most studies investigating the endometrial microbiome, researchers amplify and sequence selected hypervariable regions of the 16S rRNA gene—most commonly V3–V4 or V4–V5—using next-generation sequencing (NGS) platforms such as Illumina MiSeq or Ion Torrent. The resulting sequences are then compared to reference databases such as SILVA, Greengenes, or the Ribosomal Database Project (RDP), which allow taxonomic classification of bacterial communities, usually at the genus level and occasionally at the species level [31]. The 16S rRNA sequencing method has several advantages that make it particularly suitable for studying low-biomass environments like the endometrium: it is relatively cost-effective and rapid, allowing high-throughput analysis of multiple samples, it can identify non-culturable bacteria, which are often undetectable using traditional culture-based methods, requires small amounts of DNA, making it possible to analyze clinical samples with limited biological material, such as endometrial tissue or fluid aspirates [9,10].

Despite its advantages, the interpretation of 16S rRNA sequencing data involves several limitations and potential biases. Firstly, this method does not differentiate between living and dead bacteria, meaning that DNA from non-viable organisms can still be detected, potentially leading to overestimation of microbial diversity [31].

Secondly, the choice of PCR primers and the region of the 16S gene amplified can significantly affect taxonomic resolution and may yield inconsistent results between studies. For example, using different primer

sets for the V1–V2 or V3–V4 regions may preferentially amplify distinct bacterial taxa, complicating direct comparisons across datasets [31].

Thirdly, and perhaps most importantly, the risk of contamination in low-biomass samples such as the endometrium is extremely high. Contaminant DNA from reagents, laboratory air, or even personnel can easily overshadow the true microbial signal. In some cases, background contamination may represent a substantial portion of the sequencing reads [31]. To minimize these artifacts, it is strongly recommended to implement rigorous contamination control procedures, including: parallel sequencing of negative controls (blank samples), analysis of reagent and environmental blanks, and replication of independent PCR reactions for each sample [31]. These practices help to distinguish genuine microbial DNA from exogenous contaminants and increase the reliability of sequencing results.

Given the inherent difficulties of analyzing low-biomass samples, the establishment of standardized protocols for sample collection, DNA extraction, sequencing, and bioinformatic processing is crucial [31].

The absence of standardized methodologies is one of the main reasons for discrepancies between studies and complicates cross-study comparisons. Differences in sampling methods—whether endometrial biopsy, fluid aspirate, or catheter tip—can also affect bacterial detection and relative abundance results [10,31].

Overall, 16S rRNA sequencing has revolutionized our understanding of the uterine microbial environment. Yet, the technique's sensitivity to contamination and methodological variability requires cautious interpretation. Developing standardized, reproducible protocols and combining 16S rRNA data with complementary metagenomic, transcriptomic, and metabolomic approaches will be essential for obtaining a more accurate picture of the endometrial ecosystem and its implications for female reproductive health [9,10,31].

3.5 Impact of the Endometrial Microbiome on IVF Outcomes

The success of assisted reproductive technologies, particularly in vitro fertilization (IVF), depends largely on proper endometrial receptivity and the ability of the embryo to implant. Recent research suggests that the composition of the endometrial microbiota may have a significant impact on these processes [10,13–15]. In a groundbreaking study, Moreno et al. were the first to demonstrate that women with a Lactobacillus-dominant (LD) endometrial microbiota achieved substantially higher implantation, clinical pregnancy, and live birth rates compared with those harboring a non-Lactobacillus-dominant (NLD) profile [10]. Specifically, implantation and live birth rates reached 60.7% and 58.8%, respectively, in the LD group, versus 23.1% and 6.7% in the NLD group.

These findings have been supported by several subsequent studies confirming that an LD endometrial microbiota correlates with improved reproductive outcomes, including higher clinical and ongoing pregnancy rates following IVF [14–16].

Lactobacillus species—especially *L. crispatus* and *L. iners*—are thought to foster a protective and immunologically balanced environment by inhibiting the growth of opportunistic bacteria and modulating local cytokine expression [13,14,17]. This microbial stability promotes an anti-inflammatory milieu favorable to implantation.

In contrast, NLD microbiota enriched with *Gardnerella*, *Atopobium*, *Prevotella*, or *Streptococcus* species are associated with low-grade chronic inflammation that may impair endometrial receptivity. These bacteria can disrupt epithelial integrity, alter local immune signaling, and interfere with the fine-tuned immune tolerance required for blastocyst adhesion [17,18].

However, the association between microbiota composition and IVF outcomes is not entirely consistent. Several studies have failed to find statistically significant differences in implantation or pregnancy rates between LD and NLD groups [19,20]. Such discrepancies may be attributed to multiple methodological and biological factors, including: differences in study design (prospective vs. retrospective), variability in patient populations, such as age, hormonal profile, or prior ART cycles, divergent hormonal stimulation protocols, which can influence the endometrial immune and microbial environment, technical variability, including DNA extraction methods, sequencing platforms, and data processing pipelines [10,13,14,20].

Furthermore, the definition of Lactobacillus dominance is not standardized across studies. Some researchers define LD as >80% *Lactobacillus*, while others use a stricter threshold of >90%. The type of biological sample analyzed—whether endometrial biopsy, uterine fluid aspirate, or embryo transfer catheter tip—can also affect the microbial composition detected due to potential contamination or sample heterogeneity [21,31].

Despite these inconsistencies, the majority of available data supports the view that a Lactobacillus-rich endometrial microbiota is associated with more favorable IVF outcomes, whereas an NLD profile tends to correlate with poorer reproductive success [10,13–16,18,20].

However, the relationship between microbiota composition and implantation success is clearly multifactorial and cannot be explained solely by the presence or absence of *Lactobacillus*. The interplay between microbial metabolites, immune regulation, and endometrial gene expression likely determines whether implantation will succeed or fail [17,18,20]. Future studies integrating microbiome profiling with host immune and transcriptomic analyses are necessary to identify specific mechanisms linking microbial dysbiosis to impaired implantation. Such integrative approaches could pave the way for the development of targeted therapeutic interventions aimed at modulating the endometrial microbiome to enhance IVF success rates [13,14,16,21].

3.6 Mechanistic Insights: How Non-Lactobacillus-Dominant (NLD) Microbiota Affect Endometrial Function

An endometrial microbiota characterized by a non-Lactobacillus-dominant (NLD) profile has been increasingly associated with implantation failure, early miscarriage, and reduced IVF success rates. Although the uterine cavity was historically considered sterile, molecular studies have revealed that shifts in microbial composition can profoundly affect endometrial receptivity through multiple immunologic, inflammatory, metabolic, and hormonal pathways [17,26].

In a healthy endometrium, immune homeostasis ensures tolerance toward the semi-allogeneic embryo while maintaining protection against pathogens. However, dysbiotic bacteria such as *Gardnerella*, *Atopobium*, and *Prevotella* can activate Toll-like receptors (TLRs) expressed on endometrial epithelial and stromal cells, triggering downstream NF-κB signaling and the production of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor alpha (TNF-α), and IL-8 [27,28].

This state of chronic, low-grade inflammation disrupts key processes involved in implantation, including decidualization and angiogenesis. Elevated levels of IL-6 and TNF-α impair trophoblast invasion and vascular remodeling, while bacterial lipopolysaccharides (LPS) further amplify inflammatory responses and immune cell recruitment [29].

Successful implantation requires a tightly regulated cytokine environment dominated by factors promoting immune tolerance, such as leukemia inhibitory factor (LIF) and transforming growth factor-beta (TGF-β) [30]. In the presence of an NLD microbiota, the overproduction of pro-inflammatory cytokines (IL-1β, IL-6, and interferon-gamma [IFN-γ]) shifts the immune response toward a Th1-dominant profile, which is unfavorable for implantation [30,31]. This inflammatory microenvironment reduces LIF expression and downregulates integrin αvβ3, a key adhesion molecule required for blastocyst attachment and endometrial receptivity [30,31]. Increased concentrations of chemokines such as IL-8 and MCP-1 further attract leukocytes and stimulate extracellular matrix remodeling, thereby worsening the conditions for embryo adhesion and invasion [31].

Lactobacillus species help maintain endometrial stability through the production of lactic acid, which exerts anti-inflammatory effects by suppressing pro-inflammatory gene expression and reinforcing the epithelial barrier.

In contrast, NLD-associated bacteria produce short-chain fatty acids (SCFAs) such as acetate and butyrate, as well as biogenic amines, which can disrupt epithelial tight junctions and alter the epigenetic regulation of endometrial gene expression. These metabolites increase oxidative stress and impair mitochondrial function in endometrial epithelial cells, reducing cellular energy production and the capacity for proper decidualization. Collectively, these changes create a hostile biochemical environment that hinders embryo implantation and may contribute to early pregnancy loss [29].

Dysbiotic bacteria can also interfere with steroid hormone signaling. Certain species produce enzymes such as β-glucuronidase, which alter local estrogen metabolism, leading to an imbalance between estrogen and progesterone.

This imbalance can desynchronize endometrial proliferation and the implantation window, reducing the likelihood of successful embryo attachment. Moreover, inflammatory cytokines such as IL-1β and TNF-α can suppress the expression of progesterone receptor–dependent genes, including insulin-like growth factor-binding protein 1 (IGFBP-1) and prolactin, which are crucial for decidual transformation. Even in the presence of normal systemic hormone levels, this localized inhibition can result in incomplete decidualization and poor endometrial receptivity.

Some NLD-associated bacteria, particularly *Gardnerella* and *Atopobium*, are capable of forming biofilms—structured microbial communities enclosed in a self-produced matrix that adheres to epithelial surfaces. Biofilm formation protects bacteria from immune clearance and antibiotic therapy, enabling chronic infection and persistent dysbiosis.

This mechanism may explain why unfavorable microbial profiles often remain stable despite treatment and continue to compromise implantation potential.

In summary, an NLD endometrial microbiota promotes a pro-inflammatory, metabolically altered, and hormonally dysregulated environment that compromises endometrial receptivity. Through mechanisms involving TLR activation, cytokine imbalance, oxidative stress, and impaired hormonal signaling, dysbiosis disrupts the fine equilibrium necessary for embryo implantation [26–31]. Understanding these molecular interactions is critical for developing microbiome-targeted therapeutic strategies that restore eubiosis and improve reproductive outcomes, particularly in women undergoing IVF [17,26–31].

3.7 Therapeutic Strategies for Modulating the Endometrial Microbiome

Given the potential influence of endometrial dysbiosis on fertility outcomes, several therapeutic strategies have been proposed to restore microbial balance and improve endometrial receptivity before assisted reproduction procedures [10,13,17,22].

3.7.1 Antibiotic Therapy

The use of antibiotics aims to eliminate potentially pathogenic bacteria associated with chronic endometritis or microbial imbalance within the uterus. Several studies have reported partial improvement in implantation and pregnancy rates following antibiotic treatment in women with suspected endometrial dysbiosis or inflammation [22]. Commonly used regimens include broad-spectrum antibiotics such as doxycycline, ciprofloxacin, or metronidazole, administered empirically or after microbial identification.

However, the role of antibiotic therapy remains controversial. While antibiotics can reduce the bacterial load and resolve overt infection, they may also disrupt beneficial *Lactobacillus* populations, leading to secondary dysbiosis or recurrence of imbalance. Furthermore, repeated antibiotic exposure increases the risk of antimicrobial resistance and may alter the vaginal microbiome, indirectly affecting the uterine environment [22,23].

Consequently, antibiotic therapy should be used with caution and preferably guided by microbiological or molecular diagnostic results rather than empirically [22,31].

3.7.2 Probiotic Supplementation

Probiotic therapy represents a more physiological and non-invasive approach to restoring endometrial eubiosis. Preparations containing *Lactobacillus* species, administered orally or vaginally, aim to repopulate the genital tract with beneficial bacteria capable of inhibiting pathogens and modulating the local immune response [23,24]. Studies have shown that supplementation with *L. crispatus* or *L. rhamnosus* can enhance *Lactobacillus* dominance in both the vagina and uterus, reduce local inflammatory cytokine levels, and potentially improve IVF outcomes [23,24]. Some pilot trials have demonstrated higher pregnancy and live birth rates following probiotic use in women with previously dysbiotic endometrial profiles [23,24].

Despite these encouraging results, the evidence remains limited and heterogeneous. Optimal probiotic strains, dosage, route of administration, and duration of treatment have not been standardized [23,24]. Additionally, interindividual variability in host–microbe interactions may explain inconsistent responses across studies. Well-designed, randomized controlled trials are needed to confirm the efficacy and safety of probiotics as adjuncts in fertility treatment [24].

3.7.3 Microbiome Transplantation

An emerging and experimental strategy is microbiome transplantation, inspired by fecal microbiota transplantation (FMT) used for gastrointestinal disorders. In reproductive medicine, vaginal microbiota transplantation (VMT) from healthy donors has been proposed as a means to restore eubiosis in women with recurrent bacterial vaginosis or infertility linked to severe dysbiosis [25]. Early case studies have shown that VMT can successfully re-establish a *Lactobacillus*-dominant microbiota and alleviate recurrent infection symptoms [25]. Translating this approach to the uterine environment could theoretically benefit women with persistent NLD profiles resistant to conventional therapy [25]. However, this technique remains highly experimental and raises important questions regarding donor selection, long-term safety, and ethical considerations [25].

3.7.4 Summary

Collectively, therapeutic modulation of the endometrial microbiome holds great promise but remains in its infancy. Current interventions—antibiotics, probiotics, and microbiome transplantation—have shown potential in restoring microbial balance and improving endometrial receptivity [22–25]. Yet, none of these approaches have been validated through large-scale, randomized trials.

Future research should focus on establishing evidence-based guidelines for diagnosis and treatment, integrating microbiome analysis into personalized fertility care [23–25,31]. Only through rigorous clinical validation can microbiome-targeted therapies become a reliable component of reproductive medicine [10,13,17,22–25].

4. Conclusions

The discovery that the uterus harbors its own distinct microbial ecosystem has transformed our understanding of female reproductive physiology. Once thought to be sterile, the uterine cavity is now recognized as a low-biomass but functionally significant microbiome that may play a crucial role in implantation, embryo development, and the maintenance of pregnancy.

Accumulating evidence suggests that the composition of the endometrial microbiota has a meaningful impact on reproductive outcomes, particularly in women undergoing assisted reproductive technologies (ART) such as in vitro fertilization (IVF). A Lactobacillus-dominant (LD) profile is consistently associated with improved implantation, higher pregnancy rates, and increased likelihood of live birth, whereas a non-Lactobacillus-dominant (NLD) microbiota often correlates with poor reproductive performance, recurrent implantation failure, and early pregnancy loss [13–16,26].

However, this relationship is not absolute. Some women with NLD microbiota still achieve successful pregnancies, suggesting that microbial composition alone does not determine fertility outcomes. Rather, it appears that the interaction between microbial, immunological, hormonal, and genetic factors shapes endometrial receptivity and the likelihood of implantation. From a mechanistic perspective, dysbiosis of the endometrial microbiota disrupts homeostasis through multiple converging pathways. These include the activation of inflammatory cascades via Toll-like receptors (TLR) and NF-κB signaling, cytokine imbalances that favor Th1-type immune responses, and alterations in cellular metabolism caused by bacterial metabolites such as short-chain fatty acids. Dysbiotic bacteria can also impair hormone signaling, hinder decidualization, and reduce the expression of adhesion molecules essential for blastocyst implantation. Together, these mechanisms create a microenvironment that is less receptive to embryo implantation and more prone to inflammatory damage.

Clinically, the recognition of the endometrial microbiome's importance opens new perspectives for the diagnosis, prognosis, and treatment of infertility. Several potential interventions are being explored to restore microbial balance and improve reproductive outcomes: antibiotic therapy, while sometimes effective in treating chronic endometritis or overt infection, carries the risk of disrupting beneficial *Lactobacillus* populations and promoting antimicrobial resistance, probiotic supplementation, using oral or vaginal *Lactobacillus* preparations, represents a more physiological approach. Preliminary studies show promising results, suggesting that probiotic therapy can help restore eubiosis and enhance implantation rates, though larger randomized controlled trials are needed to confirm efficacy. Microbiome transplantation—particularly vaginal microbiota transplantation (VMT)—is an emerging concept that may offer therapeutic potential for refractory dysbiosis, though its clinical use remains experimental and must be carefully evaluated for safety and ethical implications.

Despite growing interest, significant methodological challenges persist. Variability in sample collection, sequencing techniques, and bioinformatic pipelines complicates cross-study comparisons. The absence of standardized definitions of Lactobacillus dominance and differences in sample type (biopsy, aspirate, or catheter tip) further contribute to inconsistencies in reported outcomes. In addition, the low bacterial biomass of the endometrium increases the risk of contamination, necessitating strict laboratory controls and validation procedures. Looking forward, the next phase of research should focus on several key priorities:

1. Standardization of methodologies across laboratories to ensure reproducibility and comparability of results.

2. Integration of multi-omics analyses—combining metagenomic, transcriptomic, proteomic, and metabolomic data—to uncover the functional implications of microbial communities and their interactions with host tissues.

3. Development of diagnostic tools capable of identifying dysbiotic profiles linked to implantation failure or recurrent pregnancy loss.

4. Randomized controlled clinical trials testing microbiome-targeted therapies in well-defined patient populations.

5. Longitudinal studies examining how the endometrial microbiome changes throughout the menstrual cycle, during pregnancy, and postpartum.

Ultimately, while a Lactobacillus-rich endometrial environment appears to favor successful reproduction, the influence of the microbiome should be understood in the broader context of the endometrial immune and endocrine landscape. Microbiome-based interventions are unlikely to serve as universal treatments; instead, they should become part of a personalized medicine framework, tailored to each patient's unique microbial, hormonal, and immunological profile.

The future of reproductive medicine will depend on a truly interdisciplinary approach that integrates microbiology, immunology, endocrinology, and reproductive biology. Through continued research, improved diagnostic precision, and well-designed clinical interventions, the modulation of the endometrial microbiome may soon become a valuable component of fertility treatment, offering new hope to couples struggling with infertility worldwide.

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