

The Role of Vaginal Microbiota in Women's Health

Wiktoria Paduch-Jakubczyk, Michalina Dubińska

Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz, Poland

Correspondence: Michalina Dubińska, MD, Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz, dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland, e-mail: dubinska.michalina@gmail.com

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Review article

Abstract

Introduction and Objective: *Lactobacillus* species are essential for maintaining a healthy vaginal microbiome. These bacteria by dominating the vaginal flora, prevent infections, support immune function, and contribute to overall reproductive health. An imbalance in these microbial communities, known as dysbiosis, has been associated with a range of health issues. This review aims to gather insights into the role of vaginal microbiota in the development of diseases affecting the female reproductive system, as well as its potential in preventing and treating these conditions.

Review and Methods: Analysis and summary of accessible studies obtained from Pubmed and Google Scholar.

State of Knowledge: Recent research underscores the significant role of the vaginal microbiome, predominantly composed of *Lactobacillus* species, in female reproductive health. These bacteria help protect the vaginal environment by producing lactic acid, which lowers the pH and inhibits the growth of harmful pathogens. Reduced *Lactobacillus* levels can lead to dysbiosis, associated with complications like bacterial vaginosis, preterm birth, and higher risks of STIs. Additionally, a decrease in *Lactobacillus* and increased vaginal microbiota diversity are linked to a higher risk of HPV infection, cervical lesions, and possibly cervical cancer. Vaginal dysbiosis may also contribute to recurrent implantation failure in IVF treatments.

Conclusions: The current understanding of the vaginal microbiome and its impact on reproductive health has advanced significantly. Research shows that dysbiosis is connected to various gynecological and obstetric issues, with probiotics demonstrating potential in addressing these issues. Ongoing research is essential to develop targeted therapies that can more effectively enhance women's health.

Key words: vaginal microbiota, cervical cancer, probiotics, pregnancy

Introduction

Recent research has expanded beyond the gastrointestinal tract to explore the role of microbiota in other body regions, including the female reproductive system. The vaginal microbiota, which makes up about 9% of the body's total microbial population (1), is predominantly composed of *Lactobacillus* species (e.g., *L. iners*, *L. gasseri*, *L. crispatus*, and *L. jensenii*). These bacteria are essential for maintaining a healthy vaginal ecosystem by preventing pathogenic overgrowth, modulating local immunity, and producing substances that lower vaginal pH.

Vaginal dysbiosis is a condition characterized by an im-

balance in the normal vaginal microbiota, where the natural, protective bacteria (primarily *Lactobacillus* species) are diminished or altered, leading to an overgrowth of potentially harmful microorganisms. These changes in microbial communities can occur due to factors such as puberty, sexual activity, hormonal shifts, and hygiene practices (2). Vaginal dysbiosis has been linked to various health issues, including preterm birth (PTB), miscarriages, recurrent urinary tract infections, sexually transmitted infections (STIs), endometriosis, polycystic ovary syndrome (PCOS), infertility, and gynecological cancers (2-5). Reduced levels of *lactobacilli* have been associated with an increased risk

and worse prognosis for these gynecological disorders and cancers.

Understanding the role of vaginal microbiota in reproductive health is clinically significant because it could revolutionize the prevention and treatment of these conditions. As current studies begin to reveal its impact on vaginal health and infection prevention, the potential to develop more effective, targeted treatments becomes apparent. However, more research is needed to fully understand these interactions and to translate this knowledge into improved clinical practices.

This article aims to explore the influence of vaginal microbiota on various reproductive health conditions and investigate the potential benefits of probiotic use in addressing these issues.

Vaginal Microbiota and Its Influence on Cervical Cancer Development

Cervical cancer (CC) is the most prevalent malignancy in the female reproductive system. While there are many risk factors, such as tobacco smoking or multiple sexual partners, HPV infection is the leading determinant for CC. Despite the broad implementation of HPV vaccination and early screening programs, CC continues to be the fourth leading cause of cancer-related deaths among women (6). Recent research from 2022 has highlighted the potential role of vaginal microbiota (VMB) in development of cervical cancer. Reduction in *Lactobacilli* and increase in VMB diversity, which leads to vaginal dysbiosis, has been linked to both HPV infection and the formation of cervical lesions (3). This reduction may be a factor that promotes a pro-inflammatory environment, enhancing HPV E6 and E7 oncogene expression and subsequent malignant cell proliferation (4). Conversely, there is ongoing debate about whether the association between vaginal dysbiosis and cervical HPV infection is coincidental, considering that both conditions frequently occur in sexually active women.

A study by Cheng Weiye et al. (2020) examined the relationship between VMB composition and HPV infection. The findings revealed that in healthy women, *Lactobacillus* comprised over 80% of the microbiota (6). In contrast, individuals infected with high-risk HPV (HR-HPV) showed increased VMB diversity, characterized by a rise in *Gardnerella* and a decline in *Lactobacillus* (6). Another research from 2021 further supported these findings, demonstrating that the healthy group was predominantly composed of *Lactobacillus* and *Ignatzschineria*, whereas the disease group (HR-HPV positive) was mainly characterized by *Gardnerella* and *Prevotella* (6). The combination of *Gardnerella* and the *Prevotella* was identified as presenting the highest risk for HPV-positive women (7). One potential mechanism linking vaginal dysbiosis to cervical cancer involves the secretion of sialidase by bacteria such as *Gardnerella* and *Prevotella*. These bacteria can produce sialidase, an enzyme that degrades mucosal protective factors and disrupts vaginal epithelial cells, potentially facilitating HPV infection and the development of cervical lesions. However, further studies are needed to confirm the role of sialidase produced by *Gardnerella* and *Prevotella* in promoting HPV-induced cervical lesions (7).

Currently, two primary treatment approaches are being explored to regulate VMB: probiotics and vaginal microbiota transplantation (6). Both strategies aim to support a healthy

VMB to prevent and treat conditions associated with HPV infection and cervical cancer. Study by Verhoeven et al. (8) found that patients infected with this virus receiving probiotics had a higher rate of HPV clearance compared to the control group. While probiotics show some promise in addressing microbiota dysbiosis, their effectiveness has not yet met expectations. There is a need for larger-scale studies that specifically target certain probiotic strains. Similarly, vaginal microbiota transplant is an emerging treatment for dysbiosis but remains in its early stages, requiring further research to establish its efficacy (6).

Impact of Vaginal Microbiome on Pregnancy Complications

The vaginal microbiome is a complex ecosystem where disruptions in *Lactobacillus* dominance can lead to complications in pregnancy. Dysbiosis is linked to conditions like preterm birth, gestational diabetes mellitus, preeclampsia, ectopic pregnancies and miscarriages. Increased diversity and pathogenic bacteria often trigger inflammation, contributing to various pregnancy-related complications.

Premature Rupture of Membranes (PPROM) and Preterm birth (PTB):

Preterm birth is a leading cause of neonatal morbidity and mortality worldwide. One of the significant factors contributing to PTB is Premature Rupture of Membranes, where disruptions in the vaginal microbiome play a critical role. A study on women of Chinese nationality examining the vaginal microbiome's role in PPRM found significant differences in microbial richness, evenness, and diversity between affected and unaffected groups (9). Specifically, *Lactobacillus iners*, *Gardnerella vaginalis*, *Prevotella bivia*, *Ochrobactrum sp.*, *Prevotella timonensis*, and *Ureaplasma parvum* were found at higher relative abundances in the PPRM group, whereas *Lactobacillus crispatus* and *Lactobacillus gasseri* were more prevalent in the control group. *Ochrobactrum sp.*, *Prevotella timonensis*, and *Gardnerella vaginalis* may serve as potential biomarkers for PPRM (9). These findings may provide effective preventative treatments.

Further research highlights that disruptions in the vaginal microbiome, particularly the reduction of protective *Lactobacillus* species, are linked to an increased risk of PTB. However, studies show varying results regarding the relationship between specific microbial communities and this condition. Taxa such as *Gardnerella spp.*, *Mobiluncus curtisii/mulieris*, *Sneathia sanguinegens*, and genera like *Atopobium* and *Megasphaera* have significant associations with PTB (10). These findings underscore the potential role of these bacteria in the etiology of preterm birth, though the precise mechanisms and interactions remain complex and require further research for a clearer understanding.

Gestational diabetes mellitus (GDM): While PTB is directly linked to neonatal outcomes, another critical condition influenced by the vaginal microbiome is gestational diabetes mellitus. It significantly impacts both maternal health and the healthcare system, with a prevalence of 5–20% (11). Its pathophysiology involves decreased insulin sensitivity during pregnancy, leading to glucose intolerance in some cases. Cortez et al. conducted a cross-sectional study exploring the relationship between GDM and the

vaginal microbiome (12). The research involved two groups of pregnant women in their third trimester: 42 glucose-tolerant women (the control group) and 26 women with GDM (the GDM group). There were no significant differences in ethnicity or gestational age at the time of sample collection between the groups. The women with GDM were older and had a significantly higher pre-pregnancy BMI compared to those without this condition. However, binary logistic regression analysis indicated that these differences did not influence the results.

The study showed that the most prevalent phyla in both groups were *Firmicutes*, followed by *Actinobacteria* and *Proteobacteria*. In the GDM group, bacteria from the *Firmicutes* and *Proteobacteria* phyla were more prevalent, whereas the control group exhibited a higher abundance of *Actinobacteria*. Some genera, like *Bifidobacteriaceae* and *Atopobium*, were more abundant in the control group, while *Staphylococcus*, *Megasphaera*, *Shuttleworthia*, *Enterobacter*, and *Enterococcus* were more common in the GDM group. However, these differences were not statistically significant. Important ones were found with the control group showing higher levels of *Varibaculum*, *Prevotella*, *Porphyromonas*, and *Ezakiella*, while the GDM group had more *Bacteroides*, *Veillonella*, *Klebsiella*, *Escherichia-Shigella*, *Enterococcus*, and *Enterobacter*. *Lactobacillus* was the dominant genus in both groups, with a slight increase in the control one. However further research is necessary to clarify all these associations.

Preeclampsia: A 2020 study investigated the impact of vaginal microbiome alterations on severe preeclampsia (SPE) by analyzing bacterial relative abundance in two groups: control and SPE cases, using gene sequencing (13). The research found that while both groups had similar species richness, those with this condition showed greater diversity. In the control group, the five most common phyla were *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Bacteroidetes*, and *Tenericutes*, which together comprised 99% of all detected bacteria. Notably, *Bacteroidetes* was significantly more prevalent in the SPE group.

At the genus level, *Prevotella*, *Atopobium*, and *Aerococcus* were found in higher abundance among SPE cases. At the species level, *Prevotella bivia*, *Atopobium vaginae* were more prevalent, with *Prevotella bivia* being independently linked to this condition. The study highlighted that *Prevotella bivia* and related taxonomic groups were significantly enriched in the vaginal microbiota of SPE cases, suggesting their involvement in the pathogenesis of the condition. However, the research had limitations, such as a small sample size and a specific demographic of participants, which might have affected the generalizability of the findings. Despite these, the study proposed that testing for *Prevotella bivia* colonization during pregnancy could potentially help in predicting and mitigating hypertensive complications associated with pregnancy.

Ectopic pregnancies: Ruptured ectopic pregnancies, particularly tubal pregnancies, contribute to pregnancy-related deaths. Ruan XF et al. study (14) explored the relationship between vaginal microbiome composition and pregnancy location, specifically comparing intrauterine pregnancies (IUP) and tubal pregnancies (TP) in women presenting with pain and/or uterine bleeding. The analysis

used next-generation sequencing (NGS) to assess bacterial diversity and abundance.

It found that women with confirmed ectopic pregnancies had higher diversity in their vaginal microbiome. Increased prevalence of *Gardnerella*, *Prevotella*, *Atopobium*, *Sneathia*, and *Megasphaera* was observed in TP cases. Moreover a threshold of 85% relative abundance of *Lactobacillus* was proposed as a potential biomarker for classifying pregnancy location. A lower abundance of *Lactobacillus* ($\leq 85\%$) was positively associated with TP.

A causal relationship between these microbial alterations and pregnancy location is not fully established.

The study suggests that the relative abundance of *Lactobacillus* in the vaginal microbiota may serve as a potential diagnostic marker. However, it is important to acknowledge that research has limitations, including the small sample size and the specific demographic of participants. Despite these constraints, these results provide a preliminary overview and initial insights into the vaginal microbiota during early pregnancy, setting the stage for further investigation.

Miscarriage: Miscarriage is a frequent concern in obstetrics and is classified by timing: early miscarriages occur before the 12th week, and late ones between the 12th and 22nd weeks. Three or more consecutive miscarriages are termed recurrent miscarriage. Research indicates that women who miscarry often have a vaginal microbiome with increased diversity and richness compared to healthy pregnancies. This variety may result from shifts in bacterial species like *Bacteroides plebeius*, *Bifidobacterium breve*, *Gardnerella vaginalis*, and *Lactobacillus iners*. Miscarriage is also linked to a notable reduction in *Lactobacillus* species and a higher prevalence of certain anaerobes. Interestingly, these changes typically occur before the miscarriage is diagnosed. A prospective study by Sun et al. explored the origins of increased microbial diversity observed in cases of this condition (15). While *Lactobacillus* was the dominant genus in both miscarriage and control groups, its relative abundance was lower in the first one. Additionally, there was a significant reduction in *L. jensenii* and *L. gasseri* in these cases. The study also found that the differences in microbial diversity were linked to higher levels of *Mycoplasma genitalium* and *Ureaplasma* in the miscarriage group compared to the reference group (15). In another research by Chang et al. there was an increased rate of *Ureaplasma species*, particularly *U. parvum*, which has been noted in cases affected by this condition, with a higher frequency of *Lactobacillus iners* (16). Additionally, the largest prospective study on this topic linked second-trimester pregnancy loss to reduced *Lactobacillus* levels early in pregnancy, even after adjusting for confounders (17).

Vaginal Microbiota and Infertility

In vitro fertilization-embryo transfer (IVF-ET) is increasingly being used as a treatment for infertility, offering hope to many couples. However, the persistent challenge of unexplained recurrent implantation failure (RIF) remains a significant barrier to success in numerous cases. One emerging hypothesis suggests that vaginal dysbiosis may be linked to RIF (18).

The composition of the vaginal microbiota within the female reproductive tract plays a crucial role in determining the

success of implantation. Research consistently shows that a *Lactobacillus*-dominant microbiome is strongly correlated with a higher likelihood of successful embryo attachment and subsequent pregnancy. In contrast, a microbiome lacking this dominance tends to create a pro-inflammatory environment that can negatively affect implantation (19).

Women experiencing RIF have been shown to exhibit significantly greater microbial diversity in their vaginal microbiome compared to those in control groups (18). Multiple independent studies have identified a higher prevalence of bacterial genera associated with bacterial vaginosis - including *Gardnerella*, *Prevotella*, *Atopobium*, *Megasphaera*, *Burkholderia*, and *Sneathia* - alongside reduced levels of *Lactobacilli* in the RIF population when compared to controls (19).

A decrease in glycerophospholipids may be a potential cause of recurrent implantation failure in women with vaginal dysbiosis. Glycerophospholipid levels have been found to be significantly positively correlated with the abundance of *Lactobacillus*, a key component of a healthy vaginal microbiota (18). Research indicates that women in the RIF group have glycerophospholipid levels that are reduced by more than fourfold (18). Glycerophospholipids are essential precursors for active biomolecules such as arachidonic acid (AA) and lysobisphosphatidic acid (LPA); AA is further converted into prostaglandin (PG). Both PG and LPA, derived from glycerophospholipids, are critical for embryo implantation. Therefore, maintaining a balanced vaginal microbiota could support proper regulation of glycerophospholipid levels, thereby potentially enhancing the chances of successful embryo implantation.

Future research should prioritize larger-scale studies to gain a more comprehensive understanding of the role of vaginal dysbiosis in infertility and recurrent implantation failure. Expanding the investigation base will help clarify the relationship between vaginal microbiota and reproductive health, paving the way for more effective fertility treatments and improved outcomes for patients facing infertility challenges.

The Role of Probiotics in Reproductive Health

Probiotics are live microorganisms that, when consumed in sufficient quantities, offer health benefits to humans. These beneficial microbes can be found naturally in foods like yogurt and kombucha, as well as in dietary supplements. They work by restoring balance in the gut microbiota, promoting the growth of helpful bacterial colonies, and interacting with immune cells within the gut-associated lymphoid tissue to support overall health (5).

Probiotics have shown effectiveness in treating common vaginal infections, such as bacterial vaginosis (BV), which results from an imbalance in microbiota. Traditionally, BV is treated with antibiotics, but probiotics containing strains like *L. crispatus*, *L. jensenii*, and *L. gasseri* have also been found to be beneficial. A recent meta-analysis of 17 randomized controlled trials demonstrated that probiotics were significantly more effective than a placebo in treating BV (5). Level of the evidence of this research was strong, with RR 15.2 (95% CI 3.87-59.65) (5).

Vaginal candidiasis is another prevalent infection that affects about 75% of women at least once in their lifetime. A recent meta-analysis of 23 randomized controlled trials found that probiotics were effective in preventing recurrent

vaginal candidiasis. The research showed that women who used them were 64% less likely to experience a recurrence of this condition compared to those who did not incorporate beneficial bacteria (5). This study proved less recurrence with RR 0.36 (95% CI 0.21-0.63) (5).

Some research has explored the potential role of probiotics, particularly *L. gasseri*, in treating endometriosis. The findings indicated that the group taking beneficial microorganisms experienced a significant reduction in menstrual pain and dysmenorrhea compared to the placebo group (5). While these results are promising, the study involved a small number of participants, highlighting the need for further research in this area.

Research has shown promising results for using probiotics in treating PCOS. A recent meta-analysis of 17 RCTs found that this supplementation significantly reduced fasting blood glucose, insulin levels, and insulin resistance in women with PCOS. It also led to a notable decrease in total cholesterol, LDL cholesterol, and triglycerides, though HDL cholesterol levels remained unchanged. Additionally, the analysis revealed reductions in luteinizing hormone and testosterone levels, but no changes in follicle-stimulating hormone. Overall, probiotics appear to be a safe and effective option for improving metabolic and hormonal profiles in women with PCOS (5).

Despite their promising potential, probiotics encounter several significant challenges and limitations. The absence of standardization regarding probiotic strains, dosages, and prebiotic formulations complicates the comparison of study results and the identification of optimal therapeutic strategies (20). Ensuring quality control is crucial, yet inconsistencies in manufacturing practices and storage conditions can impact product quality and result in variable clinical outcomes (20). Moreover, it's important to recognize that the effects of probiotics are highly strain-specific, and not every strain offers benefits for reproductive health. While initial findings are encouraging, the evidence base is still constrained by a lack of high-quality, large-scale clinical trials, many of which have small sample sizes and inconsistent methodologies. Focusing on strain-specific research could address these challenges and pave the way for more effective and targeted probiotic therapies.

Conclusion

The vaginal microbiota plays an important role in maintaining reproductive health, with disruptions linked to several pregnancy complications, including preterm birth, gestational diabetes mellitus, preeclampsia, ectopic pregnancies, and miscarriages. Reduced levels of *Lactobacillus* species and increased microbial diversity are consistently associated with negative pregnancy outcomes and gynecological disorders, such as cervical cancer and infertility. Emerging research indicates that probiotics have the potential to significantly aid in the treatment and management of a variety of conditions associated with vaginal dysbiosis and related gynecological issues.

However, there is a need for longitudinal studies to better understand the long-term effects of interventions like probiotics and microbiota transplants. Further investigation is essential to grasp the complex interactions between the vaginal microbiome and reproductive health, ultimately leading to more effective and targeted treatments and interventions.

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