Review Article

Vaginal Microbiome and Pelvic Inflammatory Disease: Integrated Pathophysiological Mechanisms and Clinical Implications

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Abstract

Pelvic inflammatory disease is a complex and multifactorial condition strongly influenced by the composition and function of the vaginal microbiome. In a state of eubiosis, the vaginal environment is predominantly composed of Lactobacillus species, which maintain mucosal integrity and inhibit pathogenic colonization through the production of lactic acid, hydrogen peroxide, and bacteriocins. However, disruption of this balance leads to dysbiosis, characterized by a reduction in Lactobacillus and an overgrowth of anaerobic bacteria such as Gardnerella vaginalis, Atopobium vaginae, and Prevotella species. This altered microbial environment promotes inflammation, biofilm formation, and increased susceptibility to ascending infections. The progression of pelvic inflammatory disease is driven by the interaction between dysbiotic microbiota, sexually transmitted pathogens such as

Chlamydia trachomatis and Neisseria gonorrhoeae, and host immune responses. Disruption of the cervical barrier and alterations in cervical mucus facilitate microbial ascension into the upper genital tract. This process is further amplified by bacterial enzymes and synergistic microbial interactions, leading to persistent infection and chronic inflammation. Activation of innate immunity, cytokine release, immune cell recruitment, and oxidative stress contribute to epithelial injury, fibrosis, and structural damage to the reproductive organs. Clinically, pelvic inflammatory disease presents with a wide spectrum ranging from asymptomatic to severe cases, complicating diagnosis. Persistent dysbiosis is associated with recurrence and adverse outcomes, including chronic pelvic pain, infertility, and ectopic pregnancy. Emerging diagnostic and therapeutic approaches, including microbiome analysis, targeted probiotics, and microbiota transplantation, offer promising strategies for improving disease management. The integration of microbiome research into clinical practice may enhance early detection, risk stratification, and the development of personalized therapeutic interventions.

Key words

Vaginal microbiome, pelvic inflammatory disease, dysbiosis, Lactobacillus, ascending infection, infertility.

Introduction

Pelvic inflammatory disease is defined as an infection of the upper genital tract, involving the uterus, fallopian tubes, and ovaries, and it most commonly arises as a consequence of sexually transmitted infections such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* [1]. From a global perspective, pelvic inflammatory disease continues to represent a significant public health concern. In 2019, the age-standardized prevalence rate reached 53.19 cases per 100,000 population, reflecting a considerable burden despite a declining trend observed since 1990. This condition is also closely associated with adverse reproductive outcomes, particularly ectopic pregnancy, with both entities demonstrating a positive correlation in their global burden, further underscoring the clinical relevance of pelvic inflammatory disease [2].

The vaginal microbiome plays a fundamental role in maintaining reproductive health and preventing infection. Under physiological conditions, a healthy vaginal microbiome is typically dominated by *Lactobacillus* species, which contribute to host defense through the production of lactic acid and other antimicrobial compounds that inhibit pathogenic colonization. However, disruption of this balanced microbial environment leads to a state of dysbiosis characterized by a reduction in *Lactobacillus* populations and a concomitant increase in anaerobic bacteria such as *Gardnerella vaginalis*. This shift is strongly associated with bacterial vaginosis and has been linked to an increased susceptibility to sexually transmitted infections, including those that can ascend and result in pelvic inflammatory disease [3, 4, 6].

The understanding of pelvic inflammatory disease has evolved considerably over time, transitioning from a traditional monomicrobial perspective to a more comprehensive polymicrobial model. This paradigm shift recognizes that the disease is not solely driven by a single pathogen, but rather by complex interactions within diverse microbial communities that contribute to disease initiation and progression [6, 7]. In particular, studies have demonstrated that vaginal microbiomes dominated by non-*Lactobacillus* species, including *Gardnerella*, are associated with an increased susceptibility to pelvic inflammatory disease. Although the precise mechanisms underlying this association remain under investigation, these findings highlight the importance of microbial composition in disease risk [7, 8].

In light of these insights, there is a growing emphasis on understanding the interactions between the vaginal microbiome and the host immune system. These microbiome - host interactions are critical in determining both susceptibility to infection and the progression of pelvic inflammatory disease. Evidence suggests that specific *Lactobacillus* species, such as *L. crispatus*, are capable of modulating the host immune response, thereby reducing inflammation and potentially conferring protection against ascending infections [9, 10]. Consequently, the identification of distinct microbial signatures and their interplay with host immunity represents a promising avenue for advancing diagnostic approaches and developing targeted therapeutic strategies. Such efforts may ultimately improve the prevention and management of pelvic inflammatory disease by addressing both microbial and host-related determinants of disease [6, 8].

The objective of this article is to provide a comprehensive and integrated analysis of the role of the vaginal microbiome in the development and progression of pelvic inflammatory disease, with particular emphasis on the underlying pathophysiological mechanisms, microbiome–host immune interactions, and their clinical implications for diagnosis, risk stratification, and emerging therapeutic strategies.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of the relationship between the vaginal microbiome and pelvic inflammatory disease, with particular emphasis on underlying pathophysiological mechanisms, microbiome–host immune interactions, and their diagnostic and therapeutic implications. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the biological complexity of the vaginal microbiome, the multifactorial nature of pelvic inflammatory disease, and the variability in microbiological, immunological, and clinical approaches across studies, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate microbial, immunological, and reproductive health considerations into a coherent and clinically applicable framework. Special attention was given to microbial dysbiosis, the transition from *Lactobacillus*-dominant states to polymicrobial communities, mechanisms of ascending infection, host inflammatory responses, and the clinical consequences of these alterations in reproductive health. The objective was to provide a structured synthesis capable of supporting a broader understanding of the pathophysiological and clinical relevance of the vaginal microbiome in pelvic inflammatory disease.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2026. The final search was performed in December 2026. This timeframe was selected to capture contemporary advances in microbiome sequencing technologies, molecular characterization of vaginal dysbiosis, host–microbiome interaction studies, and emerging diagnostic and therapeutic strategies related to pelvic inflammatory disease. Foundational studies were incorporated when necessary to contextualize key pathophysiological mechanisms, classical microbial concepts, or the historical evolution of pelvic inflammatory disease models. The search strategy combined MeSH and free-text terms using Boolean operators related to pelvic inflammatory disease, vaginal microbiome, vaginal dysbiosis, bacterial vaginosis, *Lactobacillus*, *Gardnerella vaginalis*, sexually transmitted infections, ascending infection, mucosal immunity, reproductive tract inflammation, and infertility. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 181 records. After removal of duplicates, 122 articles remained for title and abstract screening. Of these, 89 underwent full-text evaluation, and 45 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports, editorials without clinically relevant or mechanistic data, redundant datasets, studies focused exclusively on obstetric or neonatal outcomes without direct relevance to pelvic inflammatory disease, and articles not directly addressing microbiome composition, host response, pathophysiology, diagnosis, or therapeutic implications in the context of pelvic inflammatory disease.

Eligible studies included randomized controlled trials, observational cohorts, case-control studies, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines related to gynecology, infectious diseases, reproductive medicine, and microbiome science. Priority was assigned to studies with robust microbiological characterization, standardized diagnostic definitions, and clinically relevant outcome measures. Extracted variables included study design, population characteristics, microbiome profile, dominant bacterial taxa, presence of dysbiosis or bacterial vaginosis, associated sexually transmitted pathogens, inflammatory or immune markers, clinical manifestations, reproductive outcomes, and diagnostic or therapeutic interventions when applicable. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, reproducibility of microbiome assessment methods, consistency of diagnostic criteria for pelvic inflammatory disease, follow-up duration, and coherence of reported findings. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Structural and Functional Organization of the Vaginal Microbiome

The vaginal microbiome in a state of eubiosis is predominantly composed of *Lactobacillus* species, which play a fundamental role in maintaining a healthy vaginal environment. Although other bacterial genera such as *Gardnerella*, *Vibrio,* and *Atopobium* may also be present, they are typically found in lower abundance within a balanced microbiome. This microbial ecosystem has been systematically classified into five distinct community state types based on the predominance of specific bacterial species [11, 12]. In this classification, community state types I, II, and III are characterized by the dominance of different *Lactobacillus* species, whereas community state type IV is defined by a more diverse microbial composition with reduced *Lactobacillus* abundance and is frequently associated with bacterial vaginosis. In contrast, community state type V is less commonly observed and is characterized by the predominance of other bacterial species [13].

Within this structured microbial environment, *Lactobacillus* species exert multiple protective functions that are essential for maintaining vaginal homeostasis. One of their primary roles is the production of lactic acid, which contributes to the maintenance of a low vaginal pH and creates an environment that inhibits the growth of pathogenic microorganisms. In addition to acidification, these bacteria also produce hydrogen peroxide and bacteriocins, both of which possess antimicrobial properties that further enhance protection against infections. Moreover, *Lactobacillus* species interact closely with the vaginal epithelium, contributing to the preservation of mucosal integrity, a key factor in preventing microbial invasion and maintaining barrier function [11, 14].

Despite this relatively stable protective framework, the composition of the vaginal microbiome is not static and varies according to multiple physiological conditions. Factors such as age, menstrual cycle, pregnancy, and hormonal fluctuations play a significant role in shaping microbial composition. For example, *Lactobacillus crispatus* and *Lactobacillus jensenii* have been shown to be positively associated with estrogen levels and the use of contraceptives, whereas events such as childbirth and breastfeeding are associated with a reduction in their abundance. These dynamic changes in microbial composition are clinically relevant, as they can influence susceptibility to infections and impact broader reproductive health outcomes [15].

Vaginal Dysbiosis and Microbial Shifts Associated with Disease

Dysbiosis refers to an imbalance in the vaginal microbial community, typically characterized by a reduction in Lactobacillus species, which are essential for maintaining vaginal health through the production of lactic acid and other antimicrobial compounds. Among these species, Lactobacillus crispatus has been particularly associated with protective functions, including the production of anti-inflammatory β-carboline compounds that contribute to immune homeostasis and the reduction of local inflammation. The loss of Lactobacillus dominance represents a key feature of dysbiosis and creates a permissive environment for the proliferation of other microorganisms [16, 17].

Bacterial vaginosis represents the prototypical clinical manifestation of vaginal dysbiosis. This condition is characterized by the presence of a polymicrobial community dominated by anaerobic bacteria such as *Gardnerella vaginalis*, *Atopobium vaginae*, and *Prevotella species* [4, 18]. Bacterial vaginosis is frequently recurrent, and standard antibiotic therapies often fail to re-establish a Lactobacillus-dominant microbiota, resulting in persistent dysbiosis. This persistence reflects the complex ecological shifts within the vaginal environment that are not fully reversed by conventional treatments [17, 19].

A central feature of this dysbiotic state is the overgrowth of anaerobic and facultative bacteria, including *Gardnerella vaginalis*, *Atopobium vaginae*, Prevotella species, and Mobiluncus species, which play a significant role in disease pathogenesis. These microorganisms contribute to the formation of biofilms, structured microbial communities that enhance bacterial survival and resistance to antimicrobial therapy. In addition to their role in biofilm formation, these bacteria actively modify the vaginal microenvironment, promoting inflammatory responses and increasing the risk of ascending infections [20].

Biofilm formation is particularly relevant in explaining both the persistence and recurrence of bacterial vaginosis. These biofilms provide a protective niche that shields bacteria from both antibiotic agents and host immune defenses, thereby complicating treatment and facilitating chronic infection [21]. As a result, the presence of biofilms represents a major barrier to achieving sustained restoration of a healthy microbiome and contributes significantly to the difficulty in attaining long-term remission [19].

The development of vaginal dysbiosis is influenced by multiple predisposing factors, including sexual behavior, vaginal douching, antibiotic exposure, and the use of intrauterine devices. These factors disrupt the normal microbial balance, favoring the proliferation of pathogenic bacteria and further destabilizing the vaginal ecosystem [22]. In this altered state, persistent dysbiosis, characterized by reduced Lactobacillus dominance and increased abundance of anaerobic pathogens, is associated with an elevated susceptibility to ascending infections such as pelvic inflammatory disease. The inflammatory responses triggered by these microbial communities not only facilitate infection of the upper genital tract but are also linked to adverse reproductive outcomes, including preterm birth [20].

Mechanisms of Ascending Infection and Microbial Synergy

The integrity of the cervical barrier and the protective function of cervical mucus are closely regulated by the cervicovaginal microbiota, which plays a central role in maintaining epithelial integrity and modulating the local mucosal immune system. Disruptions in this microbial environment can lead to local inflammation and structural damage to the cervical epithelium, thereby increasing susceptibility to sexually transmitted infections and facilitating microbial ascension. In parallel, alterations in cervical mucus, which may result from hormonal changes or microbial dysbiosis, can compromise its protective properties, reducing its ability to act as a physical and immunological barrier and allowing pathogens to migrate into the upper genital tract [6, 23].

In this altered environment, the ascension of microorganisms from the lower to the upper genital tract is primarily driven by the disruption of the cervical barrier in combination with the presence of dysbiotic microbiota. These changes can significantly affect epithelial integrity and local immune responses, creating favorable conditions for infection spread [6, 23]. Among the pathogens most implicated in this process are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, whose ability to ascend is influenced by the composition and stability of the vaginal microbiota [24].

The progression of infection is further amplified by synergistic interactions between these pathogens and the dysbiotic microbial environment. A microbiota characterized by reduced Lactobacillus dominance and increased abundance of anaerobic bacteria not only increases susceptibility to sexually transmitted infections but also impairs the resolution of infection [3, 8]. These interactions between *C. trachomatis*, *N. gonorrhoeae*, and dysbiotic microbial communities enhance inflammatory responses and facilitate the spread of infection to the upper genital tract [23, 24].

In addition to microbial synergy, bacterial enzymes such as proteases and mucinases play a critical role in the invasive process. These enzymes degrade components of the mucosal barrier, thereby facilitating pathogen penetration into deeper tissues and promoting infection dissemination. Through these mechanisms, infection can extend to the endometrium, fallopian tubes, and adnexal structures, contributing to the development of severe reproductive complications [23].

An additional factor that contributes to disease progression is the presence of subclinical infections. Many infections caused by *C. trachomatis* and N. gonorrhoeae are asymptomatic, allowing them to persist undetected and ascend progressively within the genital tract. This silent progression can ultimately lead to chronic complications such as tubal factor infertility and ectopic pregnancy. The ability of these infections to evolve without overt clinical manifestations underscores the importance of early detection and regular screening, as subclinical cases may progress to pelvic inflammatory disease in the absence of timely intervention [23].

Host–Microbiome–Immune Interactions in Pelvic Inflammatory Disease

The activation of innate immunity represents a central component in the pathophysiology of pelvic inflammatory disease, particularly in the context of microbial imbalance and ascending infection. Toll-like receptors, especially TLR2 and TLR4, play a pivotal role in recognizing pathogen-associated molecular patterns and initiating immune responses. TLR2 is primarily associated with physiological inflammatory processes, whereas TLR4 is more closely linked to pathological inflammation, which may result in tissue damage and have detrimental effects on fertility. In this setting, the displacement of protective Lactobacillus species by pathogenic microorganisms can trigger Toll-like receptor activation, leading to the release of pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor alpha, all of which are key mediators of the inflammatory response [26, 27].

As this inflammatory cascade progresses, there is a coordinated recruitment of immune cells, particularly neutrophils and macrophages, to the site of infection. These cells play an essential role in host defense; however, their activity may not always be protective. In certain conditions, such as vulvovaginal candidiasis, neutrophil infiltration has been shown to exacerbate symptoms rather than contribute to pathogen clearance [28]. In the context of pelvic inflammatory disease, the recruitment of these immune cells is largely driven by ascending infections, including those caused by *Chlamydia trachomatis*, which can spread from the lower to the upper genital tract and lead to significant reproductive complications [6].

The presence of dysbiosis further contributes to immune dysregulation and perpetuates the inflammatory process. A vaginal microbiome characterized by reduced Lactobacillus dominance and increased microbial diversity is associated with heightened mucosal inflammation and disruption of epithelial barrier integrity. In addition to these innate immune alterations, dysbiosis also affects adaptive immune responses and mucosal tolerance, which may favor the persistence of inflammation and contribute to ongoing tissue damage [29, 30].

Oxidative stress represents an additional mechanism that amplifies inflammatory injury in this context. The generation of reactive oxygen species promotes further cellular and tissue damage, reinforcing the inflammatory cascade and sustaining a cycle of injury and immune activation. Together, these processes illustrate how innate immune activation, immune cell recruitment, dysregulated host responses, and oxidative stress interact in a coordinated manner to drive the progression and severity of pelvic inflammatory disease [31].

Tissue Damage, Fibrosis, and Reproductive Sequelae

Epithelial injury and inflammation represent central mechanisms in the development of reproductive tract damage associated with pelvic inflammatory disease. Infection with Neisseria gonorrhoeae induces significant inflammatory responses within the fallopian tubes, leading to the loss of ciliated epithelial cells and structural epithelial damage. This process is mediated by cytokines such as interleukin-17C, which promotes the secretion of pro-inflammatory mediators and contributes to tissue injury [32]. Similarly, infection with Chlamydia trachomatis is strongly associated with chronic inflammation and progressive fibrosis in the fallopian tubes, resulting in scarring and increasing the risk of infertility and ectopic pregnancy [33].

As inflammation progresses, the loss of ciliated cells has direct functional consequences on tubal physiology. The impairment of ciliary function disrupts normal tubal motility, which is essential for the transport of the ovum through the fallopian tubes. This dysfunction creates conditions in which a fertilized egg may fail to reach the uterine cavity and instead implant ectopically, thereby increasing the risk of ectopic pregnancy [32]. In parallel, chronic infection and inflammation promote the activation of fibroblasts and the deposition of extracellular matrix components. Infections such as those caused by C. trachomatis induce fibroblast activation through growth factor signaling pathways and epithelial-to-mesenchymal transition, a process by which epithelial cells acquire myofibroblast-like properties and contribute to fibrotic remodeling [33]. This fibrotic response is further exacerbated by the dysregulation of enzymes such as lysyl oxidase-like 2, which enhances collagen cross-linking and stabilizes the extracellular matrix, thereby promoting the persistence and progression of fibrosis [34].

The cumulative effect of these processes leads to the development of fibrosis, adhesions, and structural distortion within the reproductive tract. Chronic inflammation and ongoing tissue remodeling result in the formation of adhesions that can obstruct the fallopian tubes and impair their normal function, ultimately contributing to infertility [35, 36]. In addition, intrauterine adhesions characterized by endometrial fibrosis are associated with interactions between macrophages and stromal cells, as well as transforming growth factor beta signaling, both of which drive fibrotic processes within the endometrium [37]. In more severe cases of pelvic inflammatory disease, these pathological changes may progress to the formation of tubo-ovarian abscesses, which consist of localized collections of pus that further damage surrounding tissues and exacerbate scarring [32].

Together, the combination of epithelial damage, impaired tubal motility, and progressive fibrosis establishes a pathophysiological environment that predisposes to infertility and ectopic pregnancy. Obstruction of the fallopian tubes and disruption of normal tubal function interfere with fertilization and embryo transport, thereby preventing normal implantation within the uterine cavity [6, 32]. Additionally, the cervicovaginal microbiota plays a contributory role in these processes, as the presence of anaerobic bacteria such as Mobiluncus mulieris can amplify inflammation and disrupt extracellular matrix integrity, further worsening reproductive outcomes [20].

Clinical Manifestations and Microbiome-Associated Phenotypes

Pelvic inflammatory disease presents with a wide clinical spectrum, ranging from subclinical forms to mild and severe symptomatic cases. Subclinical pelvic inflammatory disease is particularly relevant, as it often remains undetected and may progress to significant complications if left untreated [8, 24]. In symptomatic cases, the most commonly reported manifestations include pelvic pain, fever, and abnormal vaginal discharge. However, a substantial proportion of affected individuals may not exhibit these classical symptoms, which complicates clinical recognition and delays diagnosis. This variability in presentation highlights the complexity of the disease and underscores the importance of considering both clinical and microbiological factors in its evaluation [24, 38].

Microbial composition has been increasingly associated with disease severity and clinical phenotype. A vaginal microbiome dominated by Lactobacillus species, particularly Lactobacillus crispatus, has been shown to exert a protective effect against pelvic inflammatory disease. In contrast, microbiomes characterized by the predominance of Gardnerella vaginalis and other anaerobic bacteria are associated with increased susceptibility and more adverse clinical outcomes. These findings suggest that microbial profiles not only influence the risk of disease development but also modulate its clinical expression [7, 8].

Dysbiosis plays a central role in the recurrence and persistence of pelvic inflammatory disease. A reduction in beneficial Lactobacillus species, accompanied by an overgrowth of pathogenic bacteria, is strongly associated with an increased likelihood of recurrent or persistent infection [4]. Furthermore, the interaction between the vaginal microbiome and the host immune system is a key determinant of disease trajectory, influencing whether infections are effectively cleared, persist over time, or progress to more severe forms of pelvic inflammatory disease [8, 10].

As the disease progresses, a range of complications may arise, reflecting the cumulative impact of inflammation and tissue damage. Chronic pelvic pain and infertility are among the most significant long-term consequences, resulting from structural and functional damage to the reproductive organs. In more severe cases, pelvic inflammatory disease may lead to the formation of pelvic abscesses, which often require surgical intervention and are associated with increased morbidity [24, 39].

Given the frequency of asymptomatic or atypical presentations, early recognition of pelvic inflammatory disease remains a clinical challenge. Many women do not present with overt symptoms, making it essential to identify subtle or non-specific clinical features in order to initiate timely intervention [38, 39]. In this regard, advances in screening and diagnostic approaches, including the incorporation of microbiome analysis, may improve the identification of individuals at risk and facilitate earlier diagnosis, thereby reducing the likelihood of long-term complications [6, 7].

Diagnostic and Therapeutic Implications of Microbiome Alterations

The diagnosis of pelvic inflammatory disease remains challenging due to the limitations of current clinical and microbiological criteria. Clinical diagnosis is often nonspecific and relies on symptoms that frequently overlap with other gynecological and abdominal conditions, which may lead to misdiagnosis and inappropriate treatment. In addition, traditional microbiological approaches are primarily focused on the detection of specific pathogens such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, despite the fact that these organisms are not identified in all cases of pelvic inflammatory disease, further limiting diagnostic accuracy [39].

In response to these limitations, molecular techniques have emerged as valuable tools for improving the understanding and diagnosis of pelvic inflammatory disease. Among these, 16S ribosomal RNA sequencing enables detailed characterization of the vaginal microbiome by identifying specific bacterial communities associated with increased disease risk [6, 40]. This approach has revealed the presence of species such as *Lactobacillus iners* and other microorganisms that may influence the progression of infections, including those caused by *Chlamydia trachomatis* [6]. Complementary to this, metagenomic techniques provide a broader and more comprehensive analysis of microbial communities, allowing for the identification of previously uncultured species and their potential roles in disease pathogenesis [41]. These methods also facilitate the exploration of microbial interactions and functional characteristics that may contribute to susceptibility and progression of pelvic inflammatory disease [10].

The application of these advanced techniques has enabled the identification of microbiome-based biomarkers with potential clinical utility. Specific microbial signatures, including variations in the abundance of certain *Lactobacillus* species, have been associated with the risk of developing pelvic inflammatory disease and may serve as early indicators of disease susceptibility [3] (Kerry-Barnard et al., 2022). The identification of such biomarkers could support earlier diagnosis and allow for the implementation of preventive strategies in high-risk populations [6].

Despite advances in diagnostic approaches, antibiotic therapy remains the standard treatment for pelvic inflammatory disease. However, these regimens are associated with important limitations, as they can disrupt the vaginal microbiome and contribute to recurrent infections and additional complications [40]. Furthermore, the overuse of antibiotics may promote antimicrobial resistance and does not adequately address the underlying dysbiotic microbial environment that characterizes many cases of pelvic inflammatory disease [42].

In light of these challenges, emerging therapeutic strategies are being explored with the aim of restoring microbial balance and improving clinical outcomes. Targeted probiotic therapies, particularly those containing *Lactobacillus crispatus*, have demonstrated potential in re-establishing a healthy vaginal microbiome and reducing the risk of pelvic inflammatory disease. Clinical trials are currently investigating their efficacy in both prevention and treatment, although results have been variable due to differences in probiotic strains and administration protocols. Another promising approach is vaginal microbiota transplantation, which involves the transfer of vaginal fluid from a healthy donor to restore a protective microbial environment. This strategy has shown potential in the management of recurrent bacterial vaginosis, a condition frequently associated with pelvic inflammatory disease, by re-establishing *Lactobacillus*-dominant communities [6, 42].

The development of personalized microbiome-guided therapies represents an evolving area of interest. These approaches aim to tailor treatment based on the individual's specific microbial profile, thereby optimizing therapeutic effectiveness and addressing underlying microbial imbalances [10]. Such strategies may include customized probiotic formulations or microbiota transplantation protocols designed to reflect the unique composition of each patient's vaginal microbiome [42].

Future Perspectives and Clinical Integration

The development of future research and clinical strategies in pelvic inflammatory disease requires a stronger emphasis on causal models that integrate the vaginal microbiome with host immune responses. The interplay between the cervicovaginal microbiota and host immunity plays a critical role in determining susceptibility to infections such as Chlamydia trachomatis, which may subsequently progress to pelvic inflammatory disease. The construction of causal models that combine microbiome data with immune response patterns may help clarify the mechanisms underlying disease progression and identify key points for intervention [8, 30].

Building on this framework, the development of precision medicine approaches offers a promising direction for improving the management of pelvic inflammatory disease. Individual microbiome profiles may be used to tailor preventive and therapeutic interventions, thereby enhancing clinical effectiveness [43]. In particular, the identification of specific microbial signatures associated with an increased risk of pelvic inflammatory disease could support the design of personalized prevention strategies adapted to individual susceptibility patterns [6].

For these advances to be translated into practice, microbiome analysis must be progressively incorporated into clinical guidelines. The inclusion of microbiome-based approaches has the potential to improve both diagnostic accuracy and treatment efficacy in pelvic inflammatory disease. However, the successful integration of these tools into routine care depends on the standardization of microbiome analysis techniques, which is essential to ensure reproducibility, comparability, and clinical applicability [44].

At the preventive level, modulation of the vaginal microbiome represents an important emerging strategy. Interventions such as probiotics and other microbiome-targeted approaches may help reduce the risk of pelvic inflammatory disease by promoting a more protective vaginal environment. Strategies that favor the maintenance or restoration of a Lactobacillus-dominated microbiome may decrease susceptibility to infections that contribute to the development of pelvic inflammatory disease [5, 7, 8].

At the same time, the advancement of this field depends on the availability of stronger longitudinal evidence. Longitudinal studies are necessary to better understand the temporal dynamics of the vaginal microbiome and its relationship with the onset and progression of pelvic inflammatory disease over time [7]. In parallel, clinical trials evaluating microbiome-targeted interventions are needed to establish their efficacy in the prevention and treatment of the disease [45].

Taken together, these perspectives highlight the broad potential of the vaginal microbiome as a diagnostic, prognostic, and therapeutic tool in pelvic inflammatory disease. Microbiome profiles may be useful for identifying women at increased risk of disease [44]. They may also serve as prognostic indicators of disease progression and response to treatment [6]. Furthermore, therapeutic modulation of the microbiome may complement existing treatment strategies and contribute to improved clinical outcomes [8].

Conclusions

The vaginal microbiome plays a central role in maintaining reproductive tract homeostasis, with *Lactobacillus*-dominant communities providing essential protective functions through antimicrobial activity, immune modulation, and preservation of epithelial integrity, whereas disruption of this balance leads to dysbiosis and increased susceptibility to pelvic inflammatory disease.

Pelvic inflammatory disease is a multifactorial and polymicrobial condition driven by the interaction between dysbiotic microbiota, ascending infections, and host immune responses, resulting in inflammation, tissue damage, fibrosis, and significant reproductive sequelae such as infertility and ectopic pregnancy.

Advances in microbiome characterization have highlighted its diagnostic, prognostic, and therapeutic potential, supporting the development of microbiome-based biomarkers, targeted therapies, and precision medicine approaches, although further standardization, longitudinal research, and clinical integration are required to translate these findings into routine practice.

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