AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-3| 2026 Published: |30-03-2026

THE ROLE OF CERVICOVAGINAL MICROBIOME HOMEOSTASIS IN THE EARLY DIAGNOSIS AND MANAGEMENT OF PELVIC INFLAMMATORY DISEASE

https://doi.org/10.5281/zenodo.19277399

Ismoilova Shokhista

Assistant of the Department of Obstetrics and gynecology, reproductology, Tashkent state medical university, Tashkent, Uzbekistan; E-mail: applebirodarx289@icloud.com

Abstract

Pelvic inflammatory disease (PID) is a major cause of reproductive morbidity and is traditionally linked to sexually transmitted pathogens, particularly *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. However, growing evidence indicates that disruption of cervicovaginal microbiome homeostasis also plays a central role in the pathogenesis, progression, and persistence of PID. Objective: To review current evidence on the role of cervicovaginal microbiome homeostasis in the early diagnosis and management of PID, with emphasis on mechanisms of dysbiosis, microbiome-based diagnostic markers, and emerging restoration-focused therapeutic strategies. Methods: This narrative review synthesizes recent literature addressing cervicovaginal microbiome composition, vaginal eubiosis and dysbiosis, bacterial vaginosis-associated microbial shifts, microbial predictors of upper genital tract spread, and microbiome-informed interventions relevant to PID. Results: Available evidence indicates that a stable cervicovaginal microbiome, typically characterized by *Lactobacillus* dominance, supports mucosal barrier integrity, acidic vaginal pH, and colonization resistance. In contrast, dysbiosis is associated with anaerobic overgrowth, biofilm formation, inflammatory activation, and increased risk of ascending infection. Reduced abundance of protective taxa, particularly *Lactobacillus crispatus*, and specific microbial signatures have emerged as promising biomarkers for early PID risk stratification and detection of subclinical disease. In parallel, microbiome-informed management strategies, including probiotics, ecological restoration approaches, and dietary modulation through the gut-vagina axis, have shown potential as adjuncts to conventional antimicrobial therapy. Nevertheless, current evidence remains heterogeneous, and clinical application is limited by variation in study design, sampling methods, and biomarker validation. Conclusion: Cervicovaginal microbiome homeostasis is increasingly recognized as a key determinant of susceptibility to PID and a promising target for earlier diagnosis and improved management.

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Keywords

Pelvic inflammatory disease; cervicovaginal microbiome; vaginal dysbiosis; *Lactobacillus crispatus*; bacterial vaginosis; early diagnosis; microbial biomarkers; probiotic therapy.

Introduction. 1. Pelvic inflammatory disease (PID). Pelvic inflammatory disease (PID) is increasingly understood not only as an infection-driven disorder, but also as a condition shaped by ecological disruption within the female reproductive tract. Recent evidence demonstrates that cervicovaginal microbiome composition and absolute bacterial quantity are associated with PID, suggesting that microbial imbalance may influence both susceptibility and disease expression [1]. This concept is supported by broader narrative work on vaginal and endometrial microbiota in gynecologic and obstetric disorders, which places microbial homeostasis at the center of reproductive tract health [2]. From a clinical perspective, PID remains a major cause of reproductive morbidity, with recognized links to infertility, pelvic pain, and other adverse sequelae in women attending sexual and reproductive health services [3]. At the same time, disturbed cervicovaginal microbiota appears to modify the course of *Chlamydia trachomatis* infection and its associated reproductive outcomes, further strengthening the connection between lower genital tract ecology and upper tract disease [4]. These observations fit well with current models of vaginal microbiome stability, which define homeostasis as a dynamic balance between host factors, microbial interactions, and environmental pressures [5].

The healthy cervicovaginal environment is not merely a passive microbial habitat. It is an actively regulated mucosal ecosystem in which microbial metabolites, epithelial integrity, host immunity, and hormonal signals work together to suppress pathogen overgrowth and ascending infection. Disruption of this system may precede overt PID, help explain subclinical disease, and provide opportunities for earlier diagnosis and more rational therapy. Accordingly, this review examines the role of cervicovaginal microbiome homeostasis in PID pathogenesis, discusses its emerging value in early diagnosis, and evaluates how microbiome-informed management may complement conventional treatment.

2. Biological Basis of Cervicovaginal Homeostasis. The protective function of the cervicovaginal microbiome depends heavily on metabolites produced by beneficial bacteria. Lactic acid and short-chain fatty acids generated during eubiosis exert both antimicrobial and immune-modulatory effects, helping to maintain a low vaginal pH and an anti-pathogenic mucosal environment [6]. This biochemical protection is clinically relevant because microbial features in the lower tract may

predict whether *C. trachomatis* remains localized or spreads to the upper genital tract, making the vaginal ecosystem an early determinant of disease extension [7]. By contrast, bacterial vaginosis (BV) represents one of the clearest examples of microbiome collapse, and current reviews continue to identify BV as a major setting in which loss of protective organisms, persistence of mixed anaerobes, and recurrence intersect with ascending infection risk [8]. Recent work has further refined this view by showing that BV reflects not just compositional change, but also functional dysbiosis, altered biofilm behavior, and disturbed mucosal defense [9]. In line with this, women with PID exhibit distinct vaginal microbial profiles compared with controls, supporting the idea that microbial community structure is clinically meaningful in this disorder [10].

The concept of restoring homeostasis is therefore gaining momentum. In silico frameworks have been proposed to rationally design vaginal probiotic therapies that match ecological compatibility and improve colonization potential [11]. At the same time, microbiota-centered therapeutic thinking has expanded beyond BV to other vaginal disorders, including vulvovaginal candidiasis, underscoring the broader translational value of ecosystem restoration [12]. Epidemiologic work has also linked higher dietary fiber intake to lower PID risk [13], while dietary indices favorable to gut microbial health have likewise been associated with reduced PID risk, suggesting that reproductive tract homeostasis may be influenced by the gut-vagina axis and systemic inflammatory tone [14]. These findings widen the scope of PID research from local infection to broader host-microbiome regulation.

The homeostatic model is especially relevant in STI biology. Longitudinal evidence indicates that the cervicovaginal microbiome influences the natural history of *C. trachomatis* infection in adolescents and young women [15]. More broadly, the vaginal microbiome and sexually transmitted infections are now recognized as deeply interlinked, with consequences for both treatment and prevention [16]. Earlier pilot work demonstrated altered cervical microbial diversity in asymptomatic *C. trachomatis* infection [17], and immunomicrobial studies further showed that selected immune mediators shift alongside cervical microbial signatures during infection [18]. Together, these studies support a model in which microbial homeostasis is a biologically active defense system, not simply an associated marker.

3. Vaginal Eubiosis, Dysbiosis, and the Transition Toward PID. The healthy vaginal microbiome in reproductive-age women is typically characterized by low diversity and relative dominance of lactobacilli, whereas dysbiosis is marked by depletion of these protective organisms and expansion of anaerobic communities [19]. Importantly, similar microbial alterations have been described in women with

infertility and *C. trachomatis* infection, suggesting that dysbiosis may signal broader reproductive tract vulnerability rather than a purely local disturbance [20]. This shift is central to modern thinking about BV, in which the vaginal microbiome becomes more heterogeneous, metabolically disruptive, and inflammatory [21].

The consequences of dysbiosis may extend beyond the vagina. Methodological advances now make assessment of fallopian tube microbiota increasingly feasible, raising important questions about upper tract microbial signatures in infertility and inflammatory disease [22]. The uterine cervix, long viewed mainly as a physical barrier, is also being reconsidered as a biologically active regulator of reproductive tract pathology, potentially mediating the transition from lower tract disruption to upper tract disease [23]. This reframing is important for PID, because ascending infection is unlikely to depend on pathogen presence alone; rather, it may reflect failure of a multilayered ecological barrier involving mucus integrity, pH, innate immunity, and cervical gatekeeping.

Supportive management strategies have therefore expanded to include dietary and probiotic measures. Reviews addressing BV and vulvovaginal candidiasis suggest that diet and probiotics may help restore microbial balance and reduce recurrence [24]. Mechanistic perspectives on PID and endometriosis likewise point to shared inflammatory pathways in which chronic microbial disturbance could play a reinforcing role [25]. Experimental and clinical work on probiotic lactobacilli further supports their potential usefulness in the treatment of vaginal infections and in re-establishing a more protective environment after dysbiosis [26]. In parallel, prospective community data show that vaginal microbiota differ between women who later do and do not develop PID, indicating that microbial profiling may have predictive value even before clinically apparent disease [27].

This diagnostic promise is strengthened by methodological developments. Multiplex detection systems can distinguish bacteria associated with normal vaginal microbiota from those linked to BV [28], and dynamic studies of recurrence-related flora suggest that microbial composition may help predict which dysbiotic states are likely to persist or recur [29]. More broadly, reviews of vaginal microbiota composition continue to emphasize the combined role of nutrition and probiotics in maintaining eubiosis [30]. Host immunity must also be considered, since chronic endometrial inflammation with persistent infectious agents is associated with altered immune functioning and reproductive disorders [31]. Thus, PID should not be conceptualized only as a short-lived infectious event, but as a potential consequence of interacting microbial, epithelial, and immune failures.

4. Mechanistic Links Between Cervicovaginal Dysbiosis and Ascending Infection. A major strength of the microbiome framework is that it offers

mechanisms, not just associations. In a eubiotic state, lactobacilli help maintain acidity, compete for epithelial adherence sites, and generate metabolites that suppress inflammation and pathogen survival [6,19,30]. When this balance collapses, anaerobic bacteria can proliferate, biofilms may form, and cervical mucus defenses may weaken. This altered state may permit STI pathogens and pathobionts to persist longer, ascend more efficiently, and trigger inflammatory responses that damage the endometrium and fallopian tubes [4,7,16,21].

Subclinical PID fits especially well within this model. Some women may not present with dramatic symptoms yet still experience ongoing inflammation and reproductive damage. In such cases, microbial depletion of protective taxa, enrichment of pathobionts, and altered immune signaling could precede overt clinical diagnosis [1,10,27]. This may also explain why some patients respond incompletely to standard antimicrobial therapy: eradication of recognized pathogens does not necessarily restore ecological balance. A microbiome-based interpretation therefore helps bridge several clinical puzzles, including recurrence, low-grade inflammation, discordance between symptoms and tissue injury, and variable reproductive outcomes following infection.

Another important issue is the distinction between relative abundance and absolute quantity. Traditional sequencing often emphasizes proportions, but a reduction in absolute abundance of key protective organisms may be more clinically informative than proportional shifts alone [1]. This point is particularly relevant for *Lactobacillus crispatus* depletion, which may represent a meaningful loss of functional protection even when relative abundance metrics appear less dramatic. For early diagnosis, such quantitative approaches could improve risk stratification in women with mild symptoms, recurrent cervicitis, persistent STI, or unexplained pelvic pain.

5. Early Diagnosis: Toward Microbiome-Informed Risk Stratification. The diagnosis of PID remains difficult because symptoms are often nonspecific, clinical thresholds vary, and subclinical disease is common. In this context, microbiome-informed markers could strengthen early recognition. Current evidence suggests several candidate approaches: absolute quantification of protective taxa, identification of dysbiotic signatures associated with upper tract spread, and combined microbial-immune profiling [1,7,18]. Such strategies may be particularly useful in young women with *C. trachomatis*, recurrent BV, or ongoing pelvic symptoms despite negative routine workup [4,8,15].

Microbiome profiling may also help identify women whose vaginal environment is permissive for persistence or ascent of infection. The sequential evidence from STI-linked microbiome studies suggests that the transition from

eubiosis to dysbiosis is not random; rather, it reflects a reproducible pattern involving ecological instability, altered diversity, and reduced colonization resistance [15-18]. This opens the possibility that microbiome testing could be integrated as an adjunct to conventional STI diagnostics, especially in high-risk populations or patients with recurrent disease.

That said, implementation challenges remain substantial. Microbiome assays differ in sampling site, sequencing platform, detection thresholds, and data analysis methods. Some studies focus on relative composition, whereas others emphasize total bacterial load or selected taxon abundance [1,10,28]. Clinical translation will therefore require standardization, external validation, and evidence that microbiome-informed decisions improve outcomes beyond existing diagnostic pathways.

6. Management: From Eradication to Ecological Restoration. Standard PID treatment remains essential, especially because delay in therapy can worsen reproductive outcomes. However, the microbiome literature strongly suggests that antibiotics alone may not be enough in all patients. If dysbiosis persists after pathogen suppression, the vaginal ecosystem may remain vulnerable to recurrence, reinfection, or continued inflammatory signaling [8,9,21]. This has motivated growing interest in therapies aimed at ecological restoration.

Probiotics are the most immediate example. Rational design models propose that future probiotic therapy could be individualized according to microbial compatibility rather than selected empirically [11]. Broader reviews of vaginal infections also support microbiota-targeted approaches as part of a prevention-and-restoration strategy [12,24,26]. Nutritional interventions may reinforce this by modulating gut microbiota, inflammatory tone, and estrogen-related microbial pathways [13,14,30]. Although such measures should not replace standard PID therapy, they may become useful adjuncts, particularly in women with recurrent BV, recurrent STI-associated dysbiosis, or persistent ecological instability after treatment.

A second therapeutic implication is the need to think beyond the vagina alone. If upper tract inflammation, cervical gatekeeping, and host immune dysfunction are involved, then management should consider persistent endometrial inflammation and broader reproductive tract ecology [22,23,31]. This does not mean every patient requires invasive testing, but it does suggest that recurrent or unresolved cases may warrant a more integrated biological assessment.

7. Broader Pelvic and Gynecologic Context. Studies of peritoneal microbial features and tumor markers in ovarian cancer suggest that pelvic microbial environments may contain diagnostically relevant information [32]. Reviews of

ovarian cancer and the microbiome further argue that altered microbial patterns may eventually support earlier diagnosis or therapeutic innovation [33]. Similar work in endometrial cancer has identified microbial signatures along a continuum from benign to malignant states [34].

The stronger clinically relevant overlap, however, is with endometriosis rather than cancer. Large cohort data indicate that PID is associated with an increased later risk of endometriosis [35], and systematic review evidence shows that the vaginal microbiota is also linked with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and HPV infection, placing PID within a broader microbial susceptibility landscape [36]. Meta-analytic work on vaginal pathobionts further refines this picture by identifying organisms that destabilize otherwise protective microbial communities [37]. Population data additionally show that BV risk is shaped by host and contextual factors, including HIV status and associated exposures [38]. Common intimate hygiene practices may also modify the vaginal microbiome and thereby influence the stability of homeostasis [39]. For completeness, systematic evidence has also explored the relationship between genital microbiota and ovarian cancer, although this remains peripheral to the main clinical focus of PID [40].

8. Limitations and Future Directions. Despite the growing literature, several limitations should be acknowledged. First, much of the available evidence remains associative. Dysbiosis may contribute to PID, but PID-related inflammation may also reshape the microbiome, producing bidirectional effects that are difficult to disentangle. Second, studies vary in case definitions, analytical pipelines, and sampling approaches, which limits direct comparison. Third, many restorative approaches are promising in concept but still lack PID-specific randomized evidence. Finally, while broader gynecologic microbiome research is useful for context, a PID-focused review should resist overextending into areas where direct clinical applicability remains limited.

Future work should prioritize longitudinal studies that define the sequence of microbial disruption before clinical PID, standardized quantitative biomarkers that can be implemented in practice, and trials testing whether microbiome restoration improves reproductive outcomes when added to standard therapy. A particularly valuable direction would be combining microbial profiling with host inflammatory markers to identify women at highest risk of silent upper tract injury.

Conclusion. Cervicovaginal microbiome homeostasis is emerging as a central determinant of protection against ascending genital tract infection and pelvic inflammatory disease. A stable, protective ecosystem supports mucosal defense, limits pathogen persistence, and may reduce the probability of upper tract spread.

By contrast, dysbiosis weakens these defenses, promotes inflammatory instability, and may help explain why some women develop overt or subclinical PID despite apparently similar infectious exposures. The most clinically meaningful advances are likely to come from microbiome-informed risk stratification, early diagnosis based on quantitative and functional microbial markers, and management strategies that combine antimicrobial therapy with restoration of ecological balance. In that sense, the microbiome should not be viewed as a secondary bystander in PID, but as a biologically relevant target for prevention, diagnosis, and long-term reproductive health management.

Funding. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability. The data supporting the findings of this study were obtained from previously published articles and publicly accessible scientific databases. Further details are available from the corresponding author upon reasonable request.

Ethics Declaration. Ethical approval was not required for this study because it is a narrative review based exclusively on previously published data.

Competing Interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements. The authors would like to acknowledge the contributions of all researchers whose published studies were included in this review. The authors also thank their respective institutions for academic support during the preparation of this manuscript.

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