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The Role and Clinical Application of Vaginal Microbiota in the Progression of Cervical Diseases

Mingjun Zhang[1*], Yongheng Wang[12], Xiaohong Zhao[1], Manxia Tan[3]

[1]Department of Laboratory Medicine, Chongqing Jiulongpo People's Hospital, Chongqing, China
[2]Key Laboratory of Molecular Biology on Infections Diseases (Ministry of Education), Chongqing Medical University, Chongqing, China
[3]Department of Obstetrics and Gynecology, Chongqing Jiulongpo People's Hospital, Chongqing, China
**Corresponding Author. Email: 610969013@qq.com*

Abstract. Increasing evidence indicates that the vaginal microbiota (VMB) is closely associated with the development and progression of cervical diseases. Alterations in microbial composition have been observed across different stages of human papillomavirus (HPV) infection, cervical intraepithelial neoplasia (CIN), and cervical cancer. In healthy individuals, the VMB is typically dominated by Lactobacillus species, which contribute to the maintenance of an acidic environment and local immune balance. In contrast, vaginal dysbiosis is characterized by a reduction in Lactobacillus and an increased abundance of anaerobic bacteria, accompanied by elevated pH, disruption of epithelial barriers, and persistent inflammatory responses. Clinical and sequencing studies have reported that enrichment of specific bacterial genera, including Sneathia and Fusobacterium, is more frequently detected in high-grade cervical lesions, suggesting a potential association with disease severity. These microbial shifts may facilitate persistent HPV infection and promote lesion progression through multiple biological pathways. In addition, emerging evidence suggests that modulation of the VMB, particularly through probiotic supplementation with Lactobacillus crispatus, may support HPV clearance and improve microbial stability in early disease stages. By integrating findings from recent studies, this review outlines the dynamic changes of key microbial taxa during cervical disease progression and discusses their potential clinical relevance. These observations provide a quantitative reference for future investigations and highlight the possible value of microbiome-based strategies in cervical disease risk assessment and management.

Keywords: Vaginal microbiota, HPV infection, cervical intraepithelial neoplasia, cervical cancer

1. Introduction

Cervical cancer is one of the most common malignant tumors among women worldwide. Persistent infection with high-risk human papillomavirus (HPV) has been established as a necessary etiological factor [1]. However, HPV infection alone is insufficient to cause cervical cancer, as the

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host microenvironment plays a crucial role in its progression [2]. In recent years, the vaginal microbiota (VMB), as a key component of the cervical local environment, has emerged as a focal point in the study of the pathogenesis of cervical diseases [3].

Increasing evidence suggests that variations in microbial composition are associated with different outcomes of HPV infection and with the development of cervical lesions [3]. In healthy women, the VMB is typically characterized by the dominance of Lactobacillus species, which contribute to vaginal acidity and epithelial barrier integrity through the production of lactic acid and other antimicrobial metabolites. In contrast, disruption of this microbial balance is often accompanied by a reduction in Lactobacillus abundance and an expansion of anaerobic bacteria. Such alterations are associated with elevated vaginal pH, increased microbial diversity, and sustained inflammatory responses, conditions that may favor persistent HPV infection and lesion progression [3].

Accumulating studies have examined changes in the vaginal microbial community across the spectrum of cervical disease, ranging from cervicitis and cervical intraepithelial neoplasia (CIN) to invasive cervical cancer. These investigations have reported consistent shifts in the relative abundance of specific bacterial taxa, as well as potential mechanistic links between microbial dysbiosis and epithelial transformation. In this context, the present review synthesizes recent findings on VMB alterations during cervical disease progression and discusses their possible clinical implications, including risk stratification, microbiome-based biomarkers, and microbiota-targeted interventions.

2. The VMB as a key regulator of cervical disease

The VMB plays a central regulatory role in cervical disease. As a dynamic ecosystem integrating microbial communities, endocrine factors, anatomy, and mucosal immunity [4], its transition from health to dysbiosis critically shapes the outcome of HPV infection [5]. Understanding VMB dynamics has therefore become essential for elucidating cervical carcinogenesis, identifying biomarkers, and developing novel interventions.

As shown in Table 1, we summarize the main features of the vaginal microenvironment in both healthy and dysbiotic states. A healthy VMB is characterized by low microbial diversity and dominance of Lactobacillus species, especially Lactobacillus crispatus, Lactobacillus gasseri, and Lactobacillus jensenii [6]. These species maintain a low vaginal pH (3.8–4.5) through lactic acid production and secrete antimicrobial factors such as H_2O_2 and bacteriocins. Among Community State Types (CSTs), CST I (L. crispatus) is considered the most stable and protective because of its efficient D-lactic acid production.

Table 1. Comparison of vaginal microenvironment between healthy and dysbacteriotic states

Feature	Health Status	Transition Status	Dysbiosis Status
Dominant bacterial genus/species	L. crispatus, L. gasseri, L. jensenii	L. iners	Gardnerella, Prevotella, Fannyhessea, Sneathia
Common CSTs	CST I, II, V	CST III	CST IV

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Table 1. (continued)

Typical pH value	<4.5	>4.4	>4.5
Microbial diversity	low	low	high
Key metabolites	D-Lactic acid, hydrogen peroxide, bacteriocin	L-Lactic acid	Amines, sialidase, short chain fatty acids
Mucosal barrier integrity	Complete, thick mucus layer	Poor mucus layer function	Damaged, mucous layer degraded
Immune characteristics	Steady state, local immune tolerance	Relatively high baseline inflammatory state	Pro-inflammatory, elevated cytokine levels (IL-1 β, TNF - α)
Related clinical outcomes	Healthy, resistant to infection	Sub optimal/fragile state, prone to transition to CST IV, increased risk of persistent HPV infection and CIN	Bacterial vaginosis, aerobic vaginitis, increased risk of HPV infection, and increased risk of premature birth, miscarriage, and pelvic inflammatory disease

Dysbiosis is characterized by loss of Lactobacillus dominance and an increase in anaerobic species, forming CST IV. Studies have shown that this microbial configuration commonly includes genera such as Gardnerella, Prevotella, Atopobium, Sneathia, and Fusobacterium [7,8]. The presence of these taxa is associated with elevated vaginal pH and has been reported in conditions such as bacterial vaginosis (BV) and aerobic vaginitis (AV), as well as in women with increased susceptibility to HPV infection, adverse pregnancy outcomes, and pelvic inflammatory disease [9]. Although L. iners (CST III) is classified within the Lactobacillus genus, accumulating evidence suggests that this state represents an unstable transitional microbiota. Compared with other Lactobacillus species, L. iners exhibits limited protective capacity and lacks the ability to produce hydrogen peroxide and several key biosynthetic products [10,11]. VMB communities dominated by L. iners have therefore been frequently observed in association with vaginal dysbiosis, persistent HPV infection, and an increased risk of CIN [3,12]. These findings indicate that species-level resolution may be more informative than genus-level classification when evaluating cervical disease risk. Vaginal dysbiosis should be regarded as an active pathogenic process. CST IV taxa degrade the cervical mucus barrier, form biofilms, and generate inflammatory metabolites [13,14]. These mechanisms highlight the need for therapeutic strategies that not only replenish protective Lactobacillus species but also disrupt pathogenic biofilms [15].

The progression of cervical disease parallels a predictable gradient of microbial deterioration. Cervicitis, often idiopathic, is strongly associated with BV-like dysbiosis. BV-associated bacteria (Gardnerella, Prevotella, Atopobium) correlate with inflammation that may facilitate initial HPV infection. Meta-analyses show dysbiosis increases the risk of acquiring HPV by 33–43% and persistent infection by ~14% [16]. Women with BV have a 1.8–3.4-fold higher risk of persistent high-risk HPV, and Lactobacillus-depleted or L. iners-dominated VMB shows a 2–4-fold greater likelihood of HPV positivity [17,18]. Several anaerobes (Gardnerella, Prevotella, Sneathia, Fusobacterium) serve as potential biomarkers for HPV infection.

As cervical lesions progress from low-grade squamous intraepithelial lesion (LSIL/CIN1) to high-grade squamous intraepithelial lesions (HSIL/CIN2-3), VMB diversity increases while Lactobacillus abundance declines [19]. High-grade lesions are particularly associated with CST IV

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and enrichment of Sneathia, Prevotella, and Gardnerella, which promote inflammation, HPV E6/E7 expression, and viral genome integration, accelerating malignant transformation [20,19]. Even after surgical treatment, dysbiosis often persists, explaining high recurrence rates. In cervical cancer, dysbiosis peaks: alpha diversity markedly increases, Lactobacillus species are depleted, and pathogenic anaerobes such as Fusobacterium, Sneathia, Porphyromonas, and Peptostreptococcus become dominant [21,22]. Certain taxa, including Sneathia sanguinegens and Peptostreptococcus anaerobius, can effectively distinguish HSIL from LSIL [3].

These changes have been repeatedly validated across multiple independent studies. To visually demonstrate this quantitative process, Table 2 integrates data from several investigations, illustrating the trends in the average relative abundance of key microbial taxa across different stages of cervical disease. Although these reference values are not absolute due to variations in study design, populations, and analytical methods, they consistently point toward a similar biological trajectory and highlight the substantial potential of microbiome-based diagnostics. This clear and directional pattern of microbial community succession from health to malignancy strongly suggests a co-evolutionary relationship between microbial communities and host tissues.

Table 2. Key vaginal microenvironment characteristics at different stages of cervical disease development

Microbe	Health (HPV-)	Asymptomatic HR HPV+	LSIL (CIN1)	HSIL (CIN2/3)	Cervical cancer
L. crispatus	50-80	30-60	10-30	< 5	< 1
L. iners	10-30	20-40	20-50	10-30	5-20
Gardnerella vaginalis	< 1	1-10	5-20	10-30	10-25
Prevotella	< 0.5	< 2	2-10	5-15	5-20
Sneathia	< 0.1	< 1	1-5	5-20	8-25
Fusobacterium	< 0.01	< 0.1	< 0.5	1-5	2-10
Atopobium vaginae	< 0.5	< 2	2-8	5-15	5-15
α-diversity (Shannon index)	Low (1.0-1.5)	Low (1.2-1.8)	Middle (1.8-2.5)	High (2.5-3.5)	High (2.8-4.0)
Key metabolite characteristics	Lactic acid dominance	Start transitioning to short chain fatty acids (SCFAs)	SCFAs, Increased biogenic amines	High level SCFAs, altered lipid/amino acid profile	Complex metabolic dysbiosis, significant changes in biogenic amines, lipids, etc

3. Vaginal virome and the microbial continuum

In addition to bacteria, the VMB also harbors a complex community of viruses, collectively referred to as the virome, which is predominantly composed of bacteriophages (phages, viruses that infect bacteria) [23]. Phages serve as key regulators of bacterial communities. Phages specific to Lactobacillus species are associated with Lactobacillus-dominated microbiota and may influence community stability [24]. Moreover, under dysbiotic conditions, certain phages show positive correlations with BV-associated taxa such as Gardnerella, Prevotella, and Atopobium, and these

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cross-domain interactions have been linked to genital tract inflammation [25,26]. This suggests that phages may play a critical role in shaping pathogenic bacterial consortia that drive disease processes. Other viruses, including anelloviruses, are also present in the vagina. Their abundance correlates with genital tract inflammation, further adding complexity to the role of the virome in cervical health [27,28].

Meanwhile, cervical health should not be viewed in isolation, as it forms an integral part of an interconnected reproductive tract ecosystem. Earlier concepts regarded the upper reproductive tract including the uterus and fallopian tubes was considered a sterile environment [29]. With the application of high-throughput sequencing techniques, microbial DNA has now been detected in the endometrium in the proximal region of the reproductive tract. Analyses of these microbial communities indicate that their composition frequently shares characteristics with the cervical and VMB [30]. These observations support the concept of a microbial continuum along the female reproductive tract, in which microorganisms from the lower genital tract may ascend and establish a dynamic ecological gradient. In this framework, alterations of the VMB are not restricted to local cervical effects but may influence the microbial balance of the endometrium. Several studies have reported associations between lower genital tract dysbiosis and endometrial conditions, including chronic endometritis and infertility, and have further suggested possible links to gynecologic malignancies such as endometrial and ovarian cancers [31]. Consistent with this view, inflammatory signatures and bacterial taxa implicated in cervical lesion progression, particularly Gardnerella and Prevotella, have also been identified in endometrial samples from women diagnosed with infertility or endometritis [32]. Rather than remaining confined to the cervix, these microorganisms and the inflammatory responses they promote may extend across anatomical boundaries, thereby influencing disease susceptibility throughout the reproductive tract [33].

The above evidence suggests that interventions aimed at restoring vaginal health may confer profound benefits for overall reproductive health. Conversely, persistent vaginal dysbiosis poses a systemic risk to the entire female reproductive tract.

4. Clinical frontiers: diagnosis, treatment and prevention

4.1. VMB as a predictive biomarker

The VMB is emerging as a valuable clinical tool for improving diagnosis, risk prediction, and treatment of HPV-related cervical disease. Although HPV testing and cytology provide high sensitivity, their limited specificity leads to unnecessary colposcopies and overtreatment [34]. VMB-based biomarkers offer a promising strategy for refined risk stratification. Specific microbial signatures, such as increased Stenotrophomonas, Streptococcus, and Pseudomonas, along with reduced Faecalibacterium and Bifidobacterium, have been proposed as indicators of HSIL [35]. Machine-learning models, including a random forest classifier built on 33 bacterial taxa, highlight L. iners as a major predictor of CIN severity [36]. Additional species combinations, such as Prevotella bivia and Porphyromonas uenonis, show potential in predicting persistent HPV infection or CIN2+ [37]. Ultimately, VMB profiling may enable accurate triage of HPV-positive women by identifying those at genuine risk of progression who require immediate evaluation.

4.2. Therapeutic modulation of the microbiome: probiotics, prebiotics, and synbiotics

Microbiome-modulating therapies represent another frontier for clinical intervention. Several probiotic studies suggest potential benefits for HPV clearance and CIN regression. Daily intake of

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Lactobacillus casei doubled LSIL regression rates compared with controls [38]. Oral L. rhamnosus and L. reuteri reduced abnormal cytology, though without a clear effect on HR-HPV clearance [39]. Intravaginal transplantation of L. crispatus chen-01 showed promising results, including reduced HPV viral load and restoration of healthy VMB composition [40]. A large Bayesian network meta-analysis evaluating eight therapeutic modalities found that combining interferon with Lactobacillus vaginal capsules or with Fuanning produced the strongest HR-HPV clearance effects, outperforming interferon alone [41].

Prebiotics, such as dietary fiber and inulin, have been reported to facilitate the growth of beneficial vaginal bacteria and may contribute to reduced HPV risk. Synbiotics, which integrate probiotics and prebiotics, are likewise under active investigation. Recent consensus recommendations emphasize strain-specific approaches, particularly the use of L. crispatus and L. rhamnosus, tailored to clinical goals such as HPV clearance and CIN regression [42].

5. Conclusion

Accumulating evidence indicates that alterations in the VMB are closely associated with the development and progression of cervical disease. Rather than acting as a static background, the vaginal microbial ecosystem undergoes measurable shifts during HPV infection, cervical intraepithelial neoplasia, and invasive cervical cancer. In health, Lactobacillus-dominated communities help maintain an acidic environment and support local immune equilibrium. Disruption of this microbial structure is commonly accompanied by expansion of anaerobic bacteria, increased vaginal pH, and enhanced inflammatory activity, conditions that have been linked to persistent HPV infection and epithelial transformation. Specific bacterial taxa, including Sneathia and Fusobacterium, have been repeatedly observed at higher abundance in high-grade cervical lesions, suggesting a potential role as indicators of disease progression. These microbial signatures may complement existing screening strategies by providing additional biological context for risk assessment. Beyond diagnosis, insights into vaginal microbiota dynamics also open opportunities for intervention. Approaches aimed at restoring microbial balance, particularly those involving defined Lactobacillus strains such as L. crispatus, represent a promising area of ongoing investigation. Continued longitudinal studies and well-designed clinical trials will be essential to clarify their effectiveness and to determine how microbiome-based strategies can be integrated into cervical disease prevention and management.

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Conflict of interest

There is no conflict of interest.

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