INTRICACIES OF VAGINAL MICROBIOME IN HUMAN FEMALE HEALTH: A LITERATURE REVIEW

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ABSTRACT

The vaginal microbiome profoundly impacts women's reproductive health. This review examines its significance, exploring microbial diversity, imbalances, infections, and preventive strategies. Imbalances, triggered by various factors, lead to infections such as bacterial vaginosis, yeast infections, and urinary tract infections. Research into personalized interventions, including probiotics tailored to individual microbial compositions, shows promise. Novel therapeutics targeting dysbiosis and disease prevention strategies, alongside technological advancements in diagnostics, highlight the future of healthcare. Understanding microbiome-associated reproductive outcomes and identifying microbial biomarkers for diseases beyond infections are emerging frontiers. Integrating findings into clinical practice and public education enhances vaginal health practices. This comprehensive overview underscores the need for continued research to develop precise interventions supporting a balanced vaginal microbiome and enhancing women's reproductive well-being. The evolving understanding of the vaginal microbiome holds vast potential to revolutionize healthcare, aiming for personalized, preventive, and effective interventions.

KEYWORDS: Microbiome, Novel Therapeutics, Biomarkers, STDs, Hormones.

INTRODUCTION

A diverse range of bacteria, fungus, and other microorganisms make up the intricate ecology known as the vaginal microbiome. It is essential for preserving the health of the vagina and avoiding infections. Variations in the vaginal microbiota may raise the chance of developing certain illnesses or infections. Microorganisms reside in the cavities and surfaces of the human body that are either exposed to or linked to the outside world. Ecological communities of microbial organisms coexist in mutualistic relationships with their hosts at every bodily site.(1)The types of organisms found differ from location to site because they are largely dependent on the host characteristics and environmental conditions that are in place. Additionally, they change with time and among individuals (2) Many urogenital illnesses, including bacterial vaginosis, yeast infections, STDs, urinary tract infections, and HIV infection (3, 4), appear to be prevented in part by the human vaginal microbiome. According to popular belief, this is caused by lactic acid-producing bacteria that often live in the vagina, specifically Lactobacillus sp. By generating different bacteriostatic and bacteriocidal chemicals, reducing the pH of the surrounding environment through lactic acid production (5), or by competitive exclusion (6), these species are likely to perform important protective roles.

THE VAGINAL MICROBIOME

The complex ecology of bacteria living within the vagina is referred to as the vaginal microbiome. This dynamic community, which is mostly made up of bacteria, is essential to the preservation of vaginal health, the avoidance of infections, and the general reproductive health of women.

- **Normal Microbiota Composition:** A healthy vaginal microbiota is dominated by several species of Lactobacillus, such as L. crispatus, L. jensenii, L. gasseri, and L. iners. Lactic acid, which is produced by these bacteria and helps keep the vagina's pH acidic (usually between 3.5 and 4.5), contributes to a balanced environment. This low pH promotes the vaginal ecosystem's

overall defense mechanism by preventing the proliferation of dangerous infections (7).

- **Microbiome Diversity and Variations:** Although Lactobacillus species are frequently found, individual differences occur in the makeup of the vaginal microbiome. Some women may have a non-Lactobacillus-dominant microbiota, which is characterized by a wide variety of various bacterial species, as well as a diversified microbial community. Hormonal fluctuations, sexual activity, personal hygiene, the use of antibiotics, and heredity all have an impact on this variety. (8)
- **Function and Health of the Vagina:** A healthy vaginal environment is largely dependent on a balanced vaginal flora. In addition to avoiding infections, it also helps in nutrition synthesis, immune response control, and defense against pathogenic microbes. The stability of the microbiome is essential for defense against a variety of illnesses, including yeast infections, bacterial vaginosis (BV), and sexually transmitted infections (STIs). (10, 9)

The balance of the vaginal microbiome is crucial for maintaining optimal vaginal health in women.

- **Protection from Pathogens:** The generation of lactic acid by a balanced vaginal microbiome, which Lactobacillus species prevail most, keeps the environment acidic and prevents the formation of dangerous pathogens. (11) It functions as a barrier, stopping the colonization and proliferation of infections that are sexually transmitted and other potentially dangerous germs including fungus (like Candida species) and bacteria (12).
- **Preservation of Vaginal pH and Homeostasis:** Lactobacilli are essential for maintaining the vagina's acidic pH (3.5–4.5), which makes the environment unsuitable for the growth of pathogenic organisms (11). This pH balance maintains the integrity of the vaginal epithelium and guards against infections by bolstering the natural defensive systems of the epithelium. (13)
- **Regulation of the Immune Response:** The vaginal microbiome interacts with the host immune system, influencing immune responses within the vaginal mucosa. (14) It aids in modulating the immune system to maintain a state of equilibrium, ensuring appropriate responses to pathogens without causing inflammation or adverse reactions.

HEALTHY VAGINAL MICROBIOME

Over the course of a woman's life and her menstrual cycle, the vaginal microbiome is a complex and dynamic microecosystem that is continually changing. Cervicovaginal secretion covers a stratified squamous nonkeratinized epithelium that makes up the vaginal mucosa(15). Because of the restricted blood supply, the vaginal mucosa diffuses in order to obtain from underlying submucosal tissues, glucose, oxygen, and other nutrients (16). As a result, a somewhat anaerobic habitat condition is established. A diverse microbial population that lives in symbiosis with the host is housed in the vagina. Therefore, the complete habitat, often referred to as the vaginal microbiome, is made up of bacteria, their genes, and the natural environment (17).

Better reproductive outcomes, such as a lower risk of preterm delivery, miscarriage, and pregnancy problems, are linked to a healthy vaginal microbiome. (18) Hormone fluctuations are among the physiological factors that produce vaginal microbiota alterations in women of reproductive age. (19). There have been notable reports of variations in the vaginal microbiota between women who are not pregnant and those who are. According to the comparison results, the amount and variation in the vaginal microbiome are much lower in pregnant women. It has also been found that the concentrations of Actinomycetales, Clostridiales, Bacteroidales, and Lactobacillus spp. are higher in pregnant women. Bacteroides, Burkholderiales, Actinobacteria, Prevotella, Streptococcus, Proteobacteria, Bifidobacteriaceae, and Veillonellaceae are reported to be more common in non-pregnant women. (20). Therefore, a single person's vaginal microbiome would alter throughout time. Furthermore, there are significant individual variances in the vaginal microbiota, which can be attributed to a variety of factors such as sexual activity, douching, chronic stress, racial disparities, and other factors (21, 22).

Based on high-throughput sequencing studies, there are five community state types (CSTs) for the vaginal microbiome. Specifically, the study conducted on 396 asymptomatic women from four ethnic groups in North America reveals that one or more Lactobacillus species, which are divided into five CSTs, dominate the majority of vaginal microbiomes. L. crispatus, L. gasseri, L. iners, and L. jensenii are the prevalent species in CSTs I, II, III, and V, respectively. On the other hand, the CST IV indicates a high level of microbial diversity, which is characterized by the presence of anaerobic bacteria. High Nugent scores are generally linked to CST IV, though they can also be

seen in other CSTs. Out of the five groups, 89.7% of Asian and 80.2% of white women have CSTs I, II, III, and V; for black and Hispanic women, the corresponding numbers are 61.9% and 59.6%. There was a discernible shift in ethnic groupings when CST IV predominated (23). Vaginal discharge quantity and composition, ligands on the surface of epithelial cells, immunological system, and host genetic factors may be the primary cause of the variations in vaginal microbiomes across women of different races. The vaginal microbiota of various ethnic groups may be more influenced by host characteristics than by behavioral and cultural differences. (23, 24).

In the anaerobic vaginal environment, Lactobacillus species proliferate and generate a variety of antimicrobial chemicals, including lactic acid, hydrogen peroxide (H2O2), and bacteriocins, which support a robust vaginal microbiota and create a barrier against invasive infections. The primary source of L- and D-lactic acids needed to maintain the habitat's pH below 4.5 is Lactobacillus species (25). In contrast, epithelial cells provide roughly 20% of the L-lactic acid. However, there is still debate over H2O2's function in the vaginal microbiota. Its beneficial effects on preventing the expansion of harmful microorganisms have been shown in certain investigations (26). At healthy levels, H2O2 exhibits the undetectable potential to eradicate pathogenic microorganisms, according to O'Hanlon et al.; yet, at high levels, it demonstrates stronger antimicrobial ability toward Lactobacillus spp. than pathogenic microbes (27). This result suggests that H2O2 is not an essential antibacterial agent for preserving the vaginal microbiome's equilibrium. Additionally, Lactobacillus produces bacteriocins, a class of antimicrobial peptides capable of penetrating non-indigenous germs' microbial cell membranes (28). Moreover, they have the ability to stick to vaginal epithelial cells and fight for binding sites with other microbiological cells (29). This discovery is significant since the pathogen's adherence to epithelial cells is the initial stage and a necessary precondition for infection (30). Notably, the degree of protection provided to the vaginal ecosystem depends on the dominant species of Lactobacillus. For example, low stability and dysbiosis are typically associated with the vaginal microbiota, which is dominated by L. iners. On the other hand, L. crispatus, which produces D- and L-lactic acids, improves the vaginal community's health and high stability (31). Unlike other Lactobacillus species, D-lactic acid-which is more significant than L-lactic acid-cannot be produced by L. iners (32, 33).

IMBALANCES IN THE VAGINAL MICROBIOME LEADING INFECTIONS AND ASSOCIATED COMPLICATIONS

Dysbiosis, which is typified by alterations in the microbial composition, can result from a disturbance in the equilibrium of the vaginal microbiome. The vaginal microbiome can be influenced by a variety of factors, including menstruation, hormone fluctuations, sexual activity, antibiotic usage, douching, and specific medical problems. Vaginal microbiome imbalances can result in infections like bacterial vaginosis (BV), yeast infections (Candididiasis), and an increased susceptibility to sexually transmitted infections (STIs). These imbalances can cause abnormal discharge, itching, and irritation, as well as decreased Lactobacillus species and increased diversity or abundance of other bacteria. If left untreated, these imbalances may cause complications.(34)

BACTERIAL VAGINOSIS (BV) AND BV-ASSOCIATED DISEASES

Due to an imbalance in the vaginal flora, this is one of the most prevalent vaginal infections. It happens when there is an overabundance of other bacteria, such as Gardnerella vaginalis, Atopobium vaginae, and Prevotella species, and a decrease in the amount of advantageous Lactobacillus species. Its development may be aided by variables such as hormone fluctuations, douching, antibiotic use, sexual activity, and specific behaviors or practices.

Worldwide, BV is a very common lower genital tract condition affecting women who are fertile (35). Worldwide, it affects between 23 and 29 percent of women, and the annual cost of treating symptomatic BV is $4.8 billion (36).

Sexually Transmitted Infections: STIs are frequent, severe illnesses. Despite the fact that most STIs are usually not lethal, they cause a significant burden of illness. A number of sexually transmitted infections (STIs), including HIV, HPV, chlamydial, gonococcal, and trichomonal infections, are made more likely by BV. Women who have Nugent scores between 4 and 8 are at intermediate risk of contracting any of the three bacterial STIs (Chlamydia trachomatis, Trichomonas vaginalis, and Neisseria gonorrhoeae) (37). Women who have scores between 9 and 10 are at the highest risk. More recently, a number of studies have discovered a connection between BV and an increased risk of STIs (38,39, 40). Another study on BV-afflicted women discovered that using intravaginal metronidazole and miconazole for a full year lowers the incidence of N. gonorrhoeae, C. trachomatis, or M. genitalium infection (41).

HIV: More than a million women are diagnosed with HIV each year, and BV poses a serious risk for HIV infection (42). For instance, BV has been linked to a higher chance of contracting HIV. (43), and women who have both HIV and BV have higher levels of HIV in their vaginal discharge than do women who just have HIV (44). In a similar vein, one investigation on HIV-positive Indian women revealed a significant incidence of BV among HIV-positive women as well as an increased risk of BV in these women who are also HPV-positive (45). Additionally, diversity of vaginal microbes is crucial for HIV protection. The clinical trial's findings indicate that the vaginal microbiome is necessary for the tenofovir gel microbicide's effectiveness in preventing HIV transmission.

HPV: HPV is the most common STD among young women and is strongly associated with cervical cancer. BV significantly affects the infection of HPV. Persistent HPV is indicated by Atopobium spp. and the sialidase gene of G. vaginalis, and CST IV-BV is a risk factor for this illness (46). The BV prevalence in the high-risk (HR)-HPV clearing group was 5.0%, as opposed to the higher BV prevalence of 11.2% in the HR-HPV persisting group. Furthermore, women with BV at this time reported a lower HPV clearance in comparison to women without BV (47). In a similar vein, BV is purportedly linked to a higher chance of HPV incidence and prevalence as well as a delayed HPV clearance (48). Oncogenic HPV is two times more common in women whose vaginal microbiome has completely lost Lactobacillus (49).

PID or Pelvic Inflammatory Disease: Untreated or repeated infections, which frequently start in the cervix or vagina and progress to the uterus, fallopian tubes, and ovaries, can cause PID. PID can be caused by a variety of bacteria, including those linked to bacterial vaginosis and STDs (such as chlamydia or gonorrhea). Variations in the microbiota of the vagina can affect the likelihood of various infections. PID is an upper genital tract infection-related inflammation. As a risk factor for PID, BV has been linked to unfavorable reproductive outcomes, including ectopic pregnancy, persistent pelvic pain, and infertility (50). Acute endometritis patients are more likely to have BV and less likely to have lactobacilli (51). Infertility and recurrent PID have been associated with A. vaginae, S. amnionii, BVAB1, or S. sanguinegens in relation to PID (52). A recent study of women at high risk of STI found that the presence of BV-associated microbes, such as A. vaginae, Megasphaera spp., Sneathia spp., Prevotella amnii, and Eggerthella-like bacterium, in the vagina can increase the risk of PID development. Furthermore, a larger bacterial load of BV-associated microorganisms was predictive of PID (53). The discovery by PID of bacteria linked to BV indicated a migration from the lower to the upper reproductive tract.

Obstetric Outcomes: A meta-analysis has confirmed that BV is a significant risk factor for late miscarriage and is linked to the incidence of maternal infections and premature birth (54). There is a considerable correlation between the incidence of PTB (hazard ratio 3.3) and high concentrations of BV-associated bacteria, such as A. vaginae and G. vaginalis (55). Mobiluncus curtsii/mulieris, Atopobium, and Sneathia sanguinegens are among the other BV-associated microorganisms that are risk factors for spontaneous PTB (56). Women with PTB have a dramatic reduction in L. crispatus levels and an elevated level of BV-associated bacteria, according to a recent multi-omic investigation of large samples (57).

Yeast Infections (Vaginal Candidiasis): A tiny amount of the fungus Candida albicans is typically found in the vagina. Nonetheless, a yeast infection may result from an overabundance of this yeast. Certain factors can upset the balance and cause an overgrowth of Candida, which can cause symptoms like itching, irritation, and abnormal discharge. These factors include hormonal changes (such as pregnancy or the use of birth control pills), weakened immune systems, antibiotics, uncontrolled diabetes, and wearing tight or damp clothing.(58)

Urinary Tract Infections (UTIs): Variations in the vaginal flora can influence the risk of UTIs, although abnormalities in the vaginal microbiome are not the exclusive cause of UTIs. Escherichia coli and other vaginal bacteria have the ability to ascend into the urinary tract and cause illness. UTIs can result from a variety of circumstances, including vaginal microbiota disruption, hormone fluctuations, anatomical issues, and sexual activity.(59)

Hormonal Changes: The vaginal microbiome may be impacted by fluctuations in hormone levels, which can happen during menstruation, pregnancy, menopause, or while taking hormonal contraceptives. These modifications may foster the growth of specific microbes, which may result in infections and other abnormalities. (60)

By putting these tactics into practice-such as taking probiotics, practicing proper hygiene, and leading a healthy lifestyle-you can lower your risk of infection and encourage a balanced vaginal microbiota.

IMPLICATIONS FOR DIAGNOSTIC AND THERAPEUTIC APPROACHES

Precision Medicine: Understanding a person's unique vaginal microbial composition can help with personalized

medicine by enabling customized treatments for infections and ailments.(61) Diagnostic Biomarkers: A variety of vaginal disorders may have diagnostic biomarkers that can be found by identifying particular microbial signatures linked to health or illness.(62)

Therapeutic Targets: Developing targeted therapeutics, such as probiotics, prebiotics, or microbiome-modulating medications, to maintain or restore vaginal health is made easier with an understanding of the role of the microbiome.(63)

Probiotics and Probiotic Supplements: Lactobacillus Supplementation: A healthy vaginal microbiome may be restored and maintained by probiotic formulations that contain Lactobacillus strains, such as L. crispatus, L. jensenii, or L. rhamnosus. (64)

Application: To encourage the colonization of good bacteria, probiotics can be taken orally or given vaginally as creams, suppositories, or capsules.(65)

PREBIOTIC FOOD PAIRINGS

Prebiotic Intake: Eating foods high in fiber or nutrients that encourage the growth of good bacteria is one way to maintain a healthy vaginal microbiome. (66)

Balanced Diet: The vaginal microbiota can be favorably impacted by a diet low in processed sugars and refined carbs and high in fruits, vegetables, and whole grains. (67)

PREVENTING DOUCHING AND USING HARSH HYGIENE TECHNIQUES

Prevent Douching: Douching throws off the vaginal microbiome's normal equilibrium and makes you more prone to infections.(68)

Gentle Hygiene: Maintaining a healthy vaginal environment without upsetting the microbiota can be achieved by engaging in gentle and light hygiene practices, such as exterior cleansing with mild or unscented soaps. (69)

SAFE SEXUAL BEHAVIOR

Use of Condoms: Using condoms correctly and consistently during sexual activity lowers the risk of contracting STIs and preserves the normal equilibrium of the vaginal flora.(70)

Limitation of Antibiotic Use: Cautious Use of Antibiotics: By eradicating both infections and beneficial bacteria, antibiotics can disturb the vaginal microbiome. Antibiotics should only be prescribed by medical professionals when absolutely essential to prevent disruptions of the microbiota.(71)

Frequent Medical Check-Ups: Routine Exams Frequent gynecological checkups at medical facilities allow for the early identification and treatment of any vaginal health problems, hence enhancing vaginal health in general.(72)

Effect on Reproductive Health: Pregnancy Outcomes: Learning more about the vaginal microbiome's function during pregnancy could help reduce unfavorable pregnancy outcomes, such as preterm birth and miscarriages.(73)

Gynecological disorders and infertility: Studying the impact of the vaginal microbiota on endometriosis and polycystic ovarian syndrome (PCOS) may lead to the development of new therapeutic approaches.(74)

FUTURE RESEARCH DIRECTIONS AND INNOVATIONS

There are great opportunities to improve women's health in the field of vaginal microbiome research and healthcare in the future:

Using Precision Medicine to Treat Microbiomes: Personalized therapies could result from advances in understanding individual variations in vaginal microbial populations. According to research by Nasioudis et al. (2020), treatment efficacy may be increased by customizing probiotics or targeted medicines based on a patient's unique microbial composition. (75)

Innovative Treatments for Dysbiosis: Examining the complex relationships that exist within the vaginal microbiota could lead to the discovery of new therapeutic targets. In order to repair and preserve a balanced microbiome, new research like that of Amabebe and Anumba (2018) investigates the creation of novel therapies like modified probiotics or molecules that modulate the microbiome.(76)

Microbiome-Associated Reproductive Health Outcomes: Additional research on the effects of the vaginal microbiome on gynecological disorders, pregnancy difficulties, and fertility may provide light on reproductive health issues. Studies by Moreno et al. (2021) and Walther-Antonio et al. (2016) explore how changes in the microbiota impact pregnancy outcomes and could direct therapies for better reproductive health.(77, 78)

Disease Prevention and Biomarker Discovery: Identifying the involvement of the microbiome in diseases other than infections, including endometriosis or cervical cancer, can lead to the development of techniques for disease prevention. Potential microbial biomarkers linked to illness risks are investigated in studies by Sharkey et al. (2019) and Hickey et al. (2021), opening the door for early identification and preventive therapies.(79, 80)

Technological and Diagnostic Advancements: As metagenomics and sequencing technologies continue

to progress, they will deepen our knowledge of the vaginal microbiome. Studies by Turovskiy et al. (2011) and MacIntyre et al. (2015) demonstrate how advancements in diagnostic techniques and accessibility can enhance the evaluation and tracking of vaginal health.(81, 82)

Education and Clinical Implementation: It is essential to incorporate research findings into clinical guidelines and public health campaigns. The American College of Obstetricians and Gynecologists (ACOG) guidelines advise that establishing evidence-based procedures can improve healthcare providers' recommendations for better vaginal health practices.

DISCUSSION

The vaginal microbiome represents a complex ecosystem predominantly populated by various bacterial species, notably Lactobacillus, which actively contribute to maintaining a healthy vaginal environment. Lactobacilli species play a pivotal role by producing lactic acid, maintaining an acidic pH, and thwarting the proliferation of harmful pathogens. (83) Imbalances within the vaginal microbiome can occur due to diverse factors such as hormonal fluctuations, antibiotic usage, sexual activity, and specific health conditions. These imbalances can lead to common vaginal infections, including bacterial vaginosis (BV), yeast infections (vaginal candidiasis), and urinary tract infections (UTIs). Bacterial vaginosis involves an overgrowth of diverse bacteria, while yeast infections are primarily caused by Candida species. Furthermore, changes in the vaginal flora, allowing bacteria like Escherichia coli to ascend into the urinary tract, contribute to UTIs.(84)

Research in the realm of vaginal microbiome health has focused on potential applications to support vaginal well-being. Probiotics, particularly those containing specific strains of Lactobacilli, have emerged as a potential intervention to restore and maintain a balanced vaginal microbiome. Moreover, advancements in personalized medicine have led to investigations into microbiome-based therapies tailored to individual microbial compositions.(85) Preventing imbalances and infections in the vaginal microbiome necessitates the adoption of various strategies. These include maintaining good hygiene practices, abstaining from irritants or harsh products in the genital area, practicing safe sex, and embracing a healthy lifestyle. Probiotics, owing to their capacity to promote Lactobacillus dominance, show promise in fostering a balanced vaginal microbiome and reducing infection risks.(86)

Understanding the significance of the vaginal microbiome and its implications for women's health underscores the need for continued research. Investigating its diverse types, imbalances, infections, potential applications, and preventive measures is crucial for advancing interventions that support and sustain a healthy vaginal microbiome.

CONCLUSION

In conclusion, the evolving landscape of vaginal microbiome research offers promising prospects for women's healthcare. Understanding microbial diversity, personalized interventions, novel therapeutics, disease prevention, technological advancements, and education collectively present opportunities to enhance interventions, diagnostics, and practices for sustained vaginal health and improved reproductive outcomes.

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