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CERVICOVAGINAL MICROBIOTA

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Abstract

As known, vaginal microbiota is crucial for women's health. Host–microbiome interaction is critical for numerous essential host functions. The composition of the vaginal microbiota changes throughout a woman's lifetime from birth, through puberty, reproductive age and menopause.

The vagina contains a number of immune-related cells and receptors to help sense the microbial environment. Vaginal microbiota differs within individuals and between human populations. More than 50 microbial species have been described in the vaginal tract, dominated by Lactobacillus species (70% of the total). Daily fluctuations in the composition of the vaginal microbiota have been previously documented by microscopy and cultivation studies.

The vaginal microbiota is unique in that in many women it is most often dominated by Lactobacillus species. Therefore, vaginal bacteria, including species of Lactobacillus, can reduce or increase susceptibility to infectious agents.

The vaginal microbiota in combination with other factors is associated with adverse reproductive and obstetric outcomes. Therefore, the purpose of the current study was to assess the interactions between the cervicovaginal microbiota, genital immunology.

Keywords:

cervicovaginal microbiome, lactobacillus, mucosal immunology, probiotics

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While the vaginal microbiota is well described, the uterine microbiota is underexplored. Vaginal microbiota differs within individuals and between human populations. Bacterial vaginosis (BV) is a relatively undefined polymicrobial disorder characterized by mix of aerobic and anaerobic vaginal microbiota.

The lower reproductive tract (the vagina and cervix) exhibits low bacterial diversity and is dominated by Lactobacillus bacteria.

The vaginal microbiome is a specific compartment of the human microbiome. Interestingly, the researchers found correlation between differences in these microbes and the different phases of the menstrual cycle (1-6), (Fig,1).

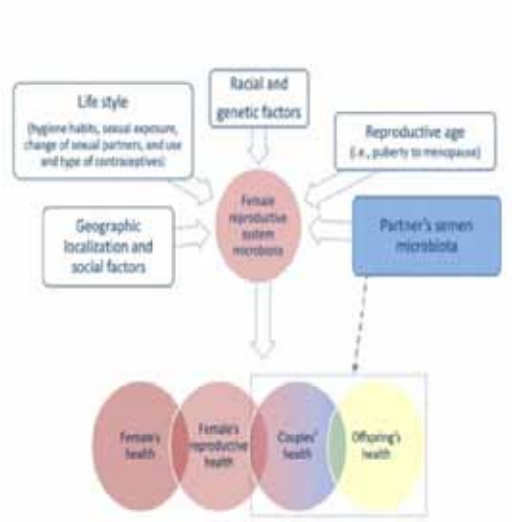

Fig. 1 Individual variability factors affecting female reproductive system microbiota composition processes in which it has been suggested to play a role (3).

Daily fluctuations in the composition of the vaginal microbiota have been previously documented by microscopy and cultivation studies (2, 7, 9, 10), (Fig,2).

The microbiome consists of microorganisms from various kingdoms with numerous physical and chemical properties Lactobacillus species constitute the highest percentage of healthy cervical and vaginal microbiota (11), (Fig,3).

Dysbiosis may cause adverse outcomes, e.g., bacterial vaginosis, pelvic inflammatory disease and pregnancy complications (12).

Vaginal microbiota differs within individuals and between human populations. The interaction between the human host and the vaginal microbiota is highly dynamic (7).

The potential role of commensal cervicovaginal bacteria in modulating immune responses is largely unknown at the present time (13, 14).

Cervicovaginal microbiota plays a critical role in women's health and reproductive outcomes.

Major changes in the vaginal physiology and microbiota over a woman's lifetime are largely shaped by transitional periods such as puberty, menopause and pregnancy, while daily fluctuations in microbial composition observed through culture-independent studies are more likely to be the results of daily life activities and behaviours (15, 16).

Cervicovaginal microbiota were investigated using PCR on extracted genomic DNA with universal 16S rRNA gene (rDNA) bacterial primers for the V3/4 region followed by MiSeq sequencing.

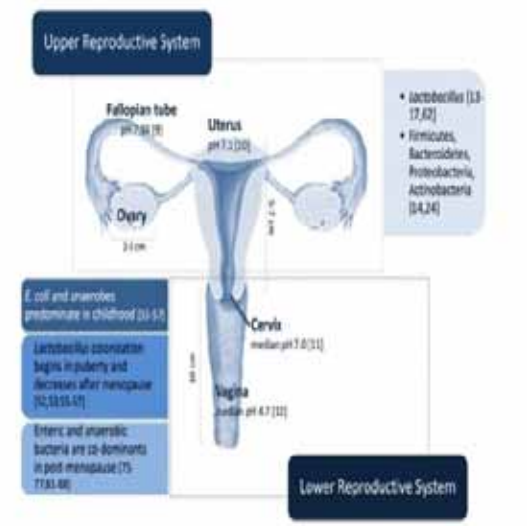

Fig. 2 The female reproductive system microbiome in physiological conditions is not sterile but hosts a specific microbiota. In particular, the female upper reproductive system, which also includes the uterus and Fallopian tubes, hosts 10,000 times less bacteria than the vagina (4).

In the vagina, microbes exist in a finely tuned mutualistic relationship with the host and provide the first line of defence against the colonization by opportunistic pathogens.

While the role of the intestinal microbiota in human health and disease has been well described, the function of cervicovaginal bacteria, which number approx10^8 per gram of vaginal fluid, is less well understood.

Healthy vaginal flora has long been characterized as lactobacillus dominant with low bacterial diversity and an accompanying low pH. (17).

Sexual activity is associated with BV and decreased vaginal colonization with lactobacilli.

Condom use is associated with a higher likelihood of a Lactobacillus-dominant vaginal microbiota.

While male circumcision decreased the rate of BV in female partners by 40%, antibiotic treatment of male sexual partners has not successfully decreased risks for recurrent bacterial vaginosis.

The most common type of cervicovaginal dysbiosis (defined as a cervicovaginal microbiome not dominated by Lactobacilli) is bacterial vaginosis.

Bacterial vaginosis is characterized by a persistent decrease in Lactobacilli and an increase in fastidious anaerobes.

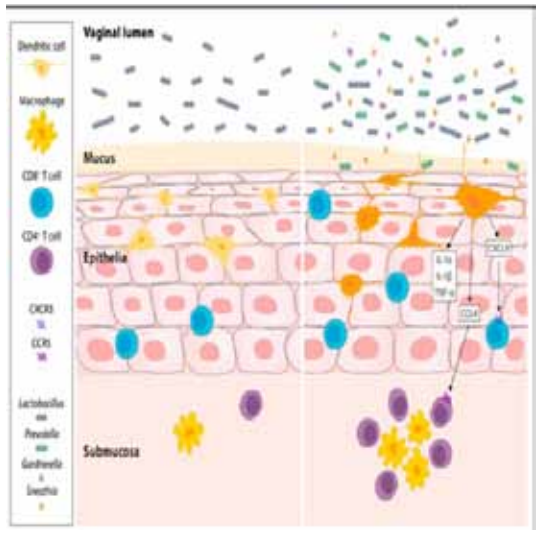

Fig. 3 Vaginal microbial composition influences inflammation and T cell abundance (10)

Limited studies of women with cervical cancer have found the cervicovaginal microbiota to have increased overall bacterial diversity, increased predominance of Fusobacterium species, and decreased abundance of Lactobacillus species (18).

The production of lactic acid has been associated with contributing to the overall health of the vagina due to its direct and indirect effects on pathogens and host defence.

High vaginal pH (an indicator of vaginal dysbiosis) was also significantly associated with endometrial cancer.

Thus, any firm relationships between microbiome composition, pH, and cancer remain unclear and require further investigation. Interestingly, increased vaginal pH has also been shown to be associated with endometriosis, which may suggest a relationship between the vaginal microenvironment on proliferative uterine diseases driven by hormones or vice versa.

The presence of bacteria in the uterus has been associated as causative agents in adverse conditions such as recurrent abortion and preterm labor (19).

Conversely, "unhealthy" flora is often characterized by high diversity bacterial populations with increased anaerobic bacteria and lactobacilli present at reduced levels.

The early childhood vaginal microbiota comprise a variety of anaerobes, diphtheroids, coagulase-negative staphylococci, and E. coli, whereas postmenopausal women often experience a loss of Lactobacillus spp. associated with the decrease in estrogen controlling vaginal epithelial proliferation, maturation, and accumulation of glycogen, which is directly or indirectly nutritionally necessary for the maintenance of Lactobacillus spp. Less Lactobacillus and higher diversity of microbiota were associated with more severe pathological status. Surprisingly, even in Lactobacillus spp. dominated cervicovaginal microbiota, low β-defensin-2 was associated with increased risk of spontaneous preterm birth.

Historically, Lactobacillus-dominated vaginal microbial communities have been associated with healthy reproductive-aged women and are characterized by the production of copious amounts of lactic acid and thus a pH < 4.5.

Maintaining acidity alone is not sufficient to promote a healthy vaginal microbiota. This acidic environment is thought to be highly protective against infections or colonization of the vagina by pathogens and non-indigenous microbes.

Interestingly, Lactobacillus spp. was originally thought to directly ferment glycogen in the vagina. However, this idea was gradually refuted and recent evidence suggests that human α-amylase catabolizes glycogen into smaller polymers, namely maltose and maltotriose, which can then be used by Lactobacillus spp. for metabolism. However, in some women it lacks Lactobacillus spp. and is comprised of a wide array of strict and facultative anaerobes, a state that broadly correlates with increased risk for infection, disease, and poor reproductive and obstetric outcomes.

Indeed, estrogen levels peak during reproductive age and contribute to shaping the composition of the vaginal microbiota. In menopause, vaginal application of estrogen cream is associated with vaginal epithelial maturation, the accumulation of glycogen

and acidic pH (<4.0), the latter indicative of the presence of high number of Lactobacillus spp.

Only a minority (37%) had a lactobacillus-dominant vaginal microbiota. Cervicotype 1 (CT1) is dominated by Lactobacillus crispatus; CT2 dominated by L. iners; CT3, Gardnerella; and CT4 consisting of a complex mixture of bacteria including Prevotella. What determines the diverse nature of the vaginal microbiota.

In the case of gastrointestinal microbiota, non-Western diets have been linked to specific microbial profiles, but it is unclear whether similar links exist for the vaginal microbiota.

Therapeutic strategies could include immune modulators and microbiome-based therapeutics to reduce this significant health burden.

Hormonal therapy offers another potential approach to altering the cervicovaginal microbiota. Sexual activity is associated with bacterial vaginosis and decreased vaginal colonization with lactobacilli.

Large cross-sectional studies have demonstrated that pregnant women with BV in the second or third trimester have a 40%–84% higher risk of giving birth to a premature infant relative to women without BV.

Bacterial vaginosis, characterized by increased bacterial diversity, an overabundance of anaerobes, and a paucity of Lactobacillus spp.

Therapeutic strategies could include immune modulators and microbiome-based therapeutics to reduce this significant health burden.

Oral and vaginal probiotics studied for the promotion of vaginal health include various combinations of L. acidophilus, L. rhamnosus, L. reuteri, L. plantarum, L. gasseri, and L. crispatus; only the latter two species are commonly found at high prevalence in cervicovaginal microbial communities.

Two small studies of probiotic yogurts showed no alteration of vaginal microbiota, even after a month of treatment.

In post-menopausal women, treatment with oral estradiol hormone replacement therapy was associated with increased vaginal Lactobacillus colonization.

Additional factors contributing to vaginal defence include mannose binding lectin, vaginal antimicrobial peptides and immunoglobulin A and G (IgA, IgG).

IgA and IgG may help to prevent vaginal epithelial cell adherence and uptake, as well as contribute to the neutralization and clearance of infectious microbes from the vagina.

Lactic acid is produced mainly by vaginal microbes and helps maintain healthy host physiological functions.

Interestingly, lactic acid isomers may also play a role in determining host response and the subsequent host-microbiota relationship.

Lactic acid exists in the vagina in both D-(-)- and L-(+)-isomers, with the host contributing only about 4-30% of the total lactate, suggesting a large reliance on microbes to supply the majority of lactic acid for protection.

Moreover, women with BV were found to be deficient in both isomers, while those with vulvovaginal candidiasis have elevated L-(+)-lactic acid. the ability of vaginal microbes to produce D-(-)-lactic acid, may help to inhibit pathogens and inflammatory responses while also favouring Lactobacillus spp. survival by using host cells resources for carbon sources (21).

High levels of proinflammatory cytokines were associated with the presence of anaerobic bacteria and inversely correlated with the presence of Lactobacillus(22).

High levels of multiple proinflammatory cytokines were strongly associated with highly diverse bacterial communities in patients, suggesting that specific genital bacteria induced a robust local immune response.

Pre- or post-menopausal status is a critical factor influencing diversity of the cervicomicrobiome.

Young healthy women had dominant L. crispatus or L. iners communities, whereas postmenopausal women had a paucity of Lactobacillus and dominant Streptococcus, Prevotella and Atopobium. Cervical mucus is more abundant in young women.

Tobacco smoking is a risk factor for bacterial vaginosis, and Peptostreptococcus and Veillonella are associated with smoking.

Smoking is associated with a lower proportion of Lactobacillus than observed in non-smokers.

Cervicovaginal dysbiotic states lead to an altered metabolic profile and reduced cervicovaginal barrier function.

Lactobacillus-deficient cervicovaginal bacterial communities are associated not only with dramatically higher genital proinflammatory cytokine levels, but also with increased genital antigen-presenting cell activation.

The diagnosis and impact of the cervicovaginal microbiome on gynecologic neoplastic changes are a new field under investigation.

Therapeutic strategies could include immune modulators and microbiome-based therapeutics to reduce this significant health burden.

Probiotics, which involve the direct application of viable microbes to the targeted environment, are strong candidates to promote specific cervicovaginal bacteria.

Hormonal therapy offers another potential approach to altering the cervicovaginal microbiota.

In post-menopausal women, treatment with oral estradiol hormone replacement therapy was associated with increased vaginal Lactobacillus colonization.

Behavioral changes, such as douching cessation and changing vaginal cleansing practices, may also promote a healthy vaginal microbial community, but are hard to implement successfully.

Further studies are needed to better understand the functional underpinnings of how the vaginal microbiota affect host physiology but also how host physiology affects the vaginal microbiota.

In the future, the cervical microbiota needs to be further analyzed by metagenomics, single-cell sequencing.

Conclusion

Lactobacilli and other fermentative bacteria together with vaginal epithelial cells produce lactic acid and are responsible for acidifying vaginal milieu.

Throughout a woman's lifespan, the vaginal microbiota undergoes major changes associated with transitional reproductive periods such as puberty and menopause.

This microbiota is manifested by a low degree of diversity and by the high dynamics of changes of its composition under the influence of various exogenous and endogenous factors.

Increase in diversity can be paradoxically associated with a dysbiosis such as bacterial vaginosis.

The composition and function of the vaginal microbiota appear to play an important role in pregnancy and fertility treatment outcomes.

Dysbiosis, which is an imbalance between the species of microorganisms, may contribute to the development of numerous adverse outcomes.

However, it is not known whether dysbiosis induces persistence of the infection or vice versa. Cervicovaginal microbiota play a critical role in women's health and reproductive outcomes.

Further studies are required to challenge this finding and develop potential strategies to induce the formation of a healthy seminal microbiota.

Conflict of interest

The author declare no conflict of interest

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