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Let's open our eyes to the importance of vaginal microbiota. Correlation between dysbiosis and HPV infection: A review

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Abstract

Infections with the human papillomavirus (HPV) are one of the most common sexually transmitted diseases and are the main cause of precancerous changes and cervical cancer development. However, mere infection does not guarantee the development of disease or carcinogenesis. For this to occur, high-risk types of HPV must integrate into the host cell genome, transitioning into a persistent form of infection.

Following the discovery of risk factors for HPV infection and factors predisposing infection to a persistent form, the number of studies investigating the correlation between vaginal dysbiosis and infection has significantly increased. Numerous studies document a significant association between the state of vaginal bacterial flora and HPV infection, leading to the development of plentiful studies on infection pathogenesis, risk factors, prevention, and treatment methods using bacteria. In this paper, based on recently published studies and current state of science knowledge, we will outline the topic of vaginal microbiome, emphasize the importance of bacteria inhabiting the vagina for human health, and identify the problem of changes in vaginal microflora. We would like to contribute to the dissemination of knowledge about the vaginal microbiome and general knowledge about taking care of its health. We will also summarize available treatment methods based on bacterial environment and discuss those methods for which research is currently underway or should be initiated.

Keywords: Microbiota; Lactobacillus; Dysbiosis; Cervicovaginal microbiome; Human Papillomavirus; HPV; Cervical cancer; Bacteriotherapy;

Introduction

For years, the bacterial flora associated with the human body has been a frequently discussed topic in the scientific world. In recent years, research on the bacterial flora present in female reproductive organs, which accounts for about 9% of the total human microflora, has been increasingly conducted [1]. The vaginal microflora protects the reproductive system from potentially pathogenic microorganisms such as bacteria, fungi, and viruses, and generally from sexually transmitted diseases [2]. But what about diseases that are the result of changes in vaginal microenvironmental conditions?

Purpose

Below, we will outline the topic of vaginal dysbiosis, HPV infection, and their mutually non-trivial influence on each other, as well as present new perspectives on treatment utilizing our knowledge of vaginal bacterial flora.

Vaginal Microflora

Vaginal Microflora is an environment that changes over the course of a lifetime, e.g., during puberty, menstrual cycle [3,4], pregnancy and postpartum [5], menopause [6], contraceptive use [7], and sexual activity [8-11]. Hygienic practices [12], ~~the~~ number of sexual partners, smoking, intrauterine device use, scented soaps, vaginal infection history, and vaginal irrigation also have a significant impact [13-15]. It has been demonstrated that vaginal irrigation, especially after menstruation, significantly increases the risk of vaginal bacterial infection [16], while discontinuing this practice can reduce it [17]. Diet also influences the composition of vaginal microflora, especially the presence of vitamins A, C, E, and D, as well as beta-carotene, folic acid, and calcium [18].

"Normalcy" of Vaginal Microbiome

On a global scale, we cannot define the concept of normalcy of the vaginal microbiome because women in different countries have unique elements in their microbiomes in terms of bacterial species proportion, as confirmed by studies in Canada [19], China [20], Europe [21], and Africa [22]. Ravel et al. [23], examining vaginal samples taken from 396 ethnically

diverse women of reproductive age, demonstrated that the vaginal microbiological profile could be classified into five "community state types" (CST) [24-26]. CST I, II, III, and V are characterized by low species diversity with a dominance of *Lactobacillus crispatus, L. gasseri, L. iners,* and *L. jensenii,* respectively, while CST IV characterizes a heterogeneous group, usually lacking Lactobacillus spp. and enriched with anaerobic species often associated with bacterial vaginosis, e.g., *Gardnerella, Megasphera, Sneathia* and *Prevotella*, but also *Dialister, Prevotella, Atopobium, Gardnerella, Megasphaera, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia,* and *Mobiluncus*. However, sometimes there is a change from CST III to CST IV, which has led to suspicions of differences in providing stability of vaginal microflora by certain bacterial species. Verstraelen et al. [28], based on vaginal microbiome samples from 100 Caucasian women, confirmed that bacterial flora dominated by *L. crispatus* compared to flora dominated by other *Lactobacillus* species is associated with a fivefold decreased risk of vaginal bacterial dysbiosis.

Bacterial Vaginosis

Bacterial vaginosis is caused by a change in vaginal microflora, specifically an increase in facultative and anaerobic bacteria at the expense of *Lactobacillus* species [29-32]. The main "culprits" of this condition are *Gardneralla vaginalis, Mycoplasma hominis, Mobiluncus spp., Bacteroides spp., Prevotela spp., Peptostreptococcus spp., Fusobacterium spp*, *Porphyromonas spp., Megasphera*, and *Sneathia*, corresponding to CST IV [23, 33]. The prevalence rate in 2012 was as high as 29% in the USA [34]. Clinical symptoms include foul-smelling vaginal discharge, burning during urination, and itching in the vaginal and perineal area, although it can also be asymptomatic [35]. There are many risk factors for bacterial vaginosis, including multiple sexual partners, smoking, intrauterine device use, scented soaps, vaginal infection history, vaginal irrigation [13-17], different hygienic practices [12], diet deficiencies (particularly vitamins A, C, E, and D, as well as beta-carotene, folic acid, and calcium) [18].

Bacterial vaginosis is a risk factor for various conditions, such as preterm birth, low birth weight, HIV infection, and increased susceptibility to chlamydia and gonorrhea infections [36-38], and may also contribute to an increased risk of both acquiring and exacerbating HPV infection, which we will further discuss in the later part of the paper.

Human Papillomavirus HPV

Infection with the *Human Papillomavirus* (HPV) is the most common sexually transmitted disease and is the leading cause of precancerous changes and cervical cancer development [39, 40]. It is estimated that over 80% of sexually active women will become infected with or have been infected with this infection at least once in their lifetime, although the vast majority of HPV infections resolve spontaneously [41]. There are over 200 types of HPV, classified into low-risk (6, 11, 40, 42, 43, 44, 54) associated with benign warts, and high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) capable of causing epithelial dysplasia and cervical cancer [42-44].

Despite intensive screening efforts and the increasing frequency of individuals vaccinated against HPV, cervical cancer remains the fourth most commonly diagnosed cancer worldwide among women [45]. Factors associated with prolonged HPV infection and progression to cervical cancer include early onset of sexual activity, multiple sexual partners, coexistence of sexually transmitted diseases, lowered immunity, genetic predisposition, oral contraceptive use, and smoking [46-50].

Increasingly, publications confirm that immune status is significantly correlated with HPV infection. Furthermore, scientific studies and research also confirm that the state of vaginal microflora, which plays a role in regulating the female reproductive tract's immune system, also correlates with infection status [51-52]. There is evidence suggesting a possible relationship between vaginal microflora and the development of cervical intraepithelial neoplasia (CIN), suggesting that an abnormal vaginal environment may play a crucial role in the development and progression of CIN [44, 53-55].

Correlation between dysbiosis and HPV infection

The vaginal microbiome dominated by *Lactobacillus* bacteria protects female genital organs from pathogens [56]. Therefore, vaginal flora with low *Lactobacillus* dominance and increased diversity of pathogenic microorganisms, such as *G. vaginalis, Atopobium, Prevotella, Sneathia, and Megasphaera*, is commonly observed in bacterial vaginosis or dysbiosis [57-61]. During disruptions in vaginal bacterial flora, damage to the mucous structure, cytoskeleton, mucous membrane, and antimicrobial peptide construction may occur, along with increased cell death and promotion of pro-inflammatory cytokine production [62-66].

Anahtar et al. [67], after examining a group of asymptomatic women in South Africa, discovered that the vaginal bacterial flora of most women was characterized by low levels of *Lactobacillus* and high bacterial diversity, including *Sneathia sanguinigens, Sneathia amnii, Mobiluncus mulieris,* and *Prevotella amnii,* which were associated with the presence of pro-inflammatory cytokines such as IL-1x, IL-1ß, and IL-8.

Similar results were obtained by Łaniewski et al. [68] on three-dimensional models of cervical epithelial cells cultured with Lactobacillus as well as with *Gardnerella vaginalis, Atopobium vaginae, Prevotella bivia,* and *Sneathia amnii*. In particular, *Lactobacillus crispatus* increased the protection of the cervical microenvironment, while *Atopobium vaginae* and *Sneathia amnii* induced inducible nitric oxide synthase (iNOS), oxidative stress, and the highest pro-inflammatory cytokines (IL-6, IL-8, TNF-α, etc.). *Gardnerella vaginalis, Prevotella bivia,* and *Sneathia amnii* altered the epithelial barrier by reducing the levels of proteins and metabolites, such as polyamines, sialic acid, and mucins. These changes may result in chronic inflammation, a risk factor for cervical carcinogenesis [69].

Additionally, Fan et al. [70] described the relationship between vaginal bacterial dysbiosis and the proliferation and invasion of cervical cancer cells by studying the fucosylation of the mucous membrane epithelium, whose abnormal course favors the development of cervical cancer.

Lee et al. [71], were the first to use Next Generation Sequencing (NGS) to investigate the influence of HPV on the vaginal microbiome composition. They conducted a cross-sectional cohort study involving 912 women, including 26 monozygotic twins. A clear difference in vaginal flora structure was observed between twins. Women infected with HPV had greater bacterial diversity and significantly fewer *Lactobacillus spp*. compared to their uninfected twin. Furthermore, *Sneathia* was identified as a microbiological marker of HPV infection in this study.

Brotman et al. [72], in their cohort study of 32 sexually active premenopausal North American women, demonstrated that women with CST III and IV had the highest likelihood of HPV infection. Additionally, Brotman and colleagues suggested that CST II, dominated by *L. gasseri*, may be associated with the fastest clearance of acute HPV infection. This observation suggests the potential use of *L. gasseri* as a therapeutic species in maintaining cervical health.

Recent cross-sectional studies have been conducted to characterize vaginal microbiota changes in cervical lesions [73]. It was shown that CIN was associated with decreased

Lactobacillus spp. and increased vaginal microflora diversity. Furthermore, a gradual increase in the frequency of CST IV was observed with increasing disease severity. While in healthy control subjects, CST IV occurred at a frequency of 10%, which is consistent with previous studies involving HPV-uninfected individuals [74].

Di Paola et al. [75], aimed to identify CST associated with persistent HPV by collecting samples from the cervix and vagina of 55 HPV-infected women in Italy and followed up with them after 12 months. They found that over 40% of women with persistent HPV infection had CST IV.

It has also been emphasized that *Gardnerella* species may contribute to maintaining HPV status by secreting sialidase enzyme, important in biofilm formation [75, 76]. Donmez et al. [77], confirmed the association between biofilm formation in the vaginal microenvironment and HPV infection. Utilizing these results, Qingqing et al. [78] identified a high abundance of anaerobes, including *Prevotella, Sphingomonas*, and *Anaerococcus*, associated with persistent HPV and increased presence of Treg, MDSC, IL-6, and TNF-a in cervical secretions.

Lebeau et al. [79], after an 8-year observation of over 6000 patients for HPV infection and vaginal microflora status, found that persistent HPV infection could lead to the inhibition of significant amounts of antimicrobial peptides, several of which are essential for *Lactobacillus* survival, resulting in a significant decrease in *Lactobacillus* concentration. In other words, the presence of HPV in the immune system leads to a microbial imbalance in the vaginal flora of women.

Treatment

Oral treatment

Considering the frequent correlation between vaginal dysbiosis and HPV infection and the significant role of bacteria in the development of this infection and cervical cancer, bacteriotherapy has become a promising form of treatment. Probiotics are the most commonly used representatives of bacteriotherapy. According to WHO, probiotics are live microorganisms that, when administered in the right amount, exert a beneficial effect on the host's health. [80]

The most common types of probiotics in the human diet are *Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus*, and *Enterococcus*, as well as some strains belonging to *Bacillus* and *Saccharomyces* [81]. Recently, there has been rapid development in the use of probiotics for cervical cancer [82-84]. Researchers believed that probiotics could promote apoptosis of

cancer cells and inhibit their proliferation and metastasis [85]. As a result, probiotics can be used as an additional strengthening or modulating agent during the use of other diagnostic or therapeutic methods.

It has been demonstrated that probiotics can affect the presence of HPV and its development in three ways. The first main way is by promoting an immune response [86]. Modulation of the immune system may occur, for example, through *L. gasseri*, which can influence the anti-inflammatory action of HeLa cells by reducing TNF-α and increasing the level of IL-10 cytokine [87]. The strain *Bifidobacterium adolescentis SPM1005-A* has potential antitumor activity by inhibiting the expression of oncogenes E6 and E7 in SiHa cells [84].

The second way is based on increasing the number of protective strains acting on the vaginal microenvironment, which can prevent and limit HPV infections by releasing inhibitory factors such as lactic acid, bacteriocins, biosurfactants, and aggregating molecules, as well as by competing for space or nutrients with bacteria with pro-inflammatory effects. The acidic environment can protect against the invasion and development of pathogens [88].

The third and direct option is the elimination of viruses by secreting specific metabolites [89].

Vaginal Treatment

Research has been conducted on vaginal suppositories containing *Lactobacillus* to prevent vaginal dysbiosis [90, 91]. In a clinical trial by Tomusiak et al. [91], it was shown that vaginal therapy with *Lactobacillus species* is safe and may increase the number of these bacteria and reduce the pH and Nugent score in women with symptomatic bacterial vaginosis after four visits.

Lactoferrin is also considered, a bacteriocin produced by lactic acid bacteria. Lactoferrin can act antibacterially by producing lactic acid and destroying the bacterial membrane. Combination therapy of lactoferrin with the antitumor drug IFN-α2b in the treatment of HPV-infected patients has been studied. Positive results were obtained in terms of restoring the normal vaginal bacterial flora and inhibiting inflammatory factors. [93]

Studies are currently underway to evaluate the effectiveness of combining probiotics with chemotherapy. Previous studies have shown that probiotic supplements may reduce the side effects or toxicity of chemotherapy. Cisplatin is a common treatment method for cervical cancer; however, its toxicity also affects undamaged human cells and tissues. Negi et al. [95] decided to combine cisplatin with pessaries containing probiotics (*Lactobacillus rhamnosus*)

in a mouse vaginal model. They found better outcomes with fewer side effects of cisplatin and reduced tumor volume in the treated group.

Probiotics can help not only with the current disease but also with the remotely appearing accompanying symptoms of cervical cancer treatment. Diarrhea is the most common side effect of radiotherapy in the treatment of cervical cancer [96]. Previous studies have suggested that probiotic supplementation may prevent this gastrointestinal problem. Linn et al. [97], examined the effectiveness of *Lactobacillus acidophilus LA-5* and *Bifidobacterium Animalis subsp. lactis BB-12* in 57 patients with cervical cancer with diarrhea after radiotherapy. The study showed a significant reduction in diarrhea symptoms after three weeks of probiotic use in the mild to moderate group and in the severe diarrhea group.

Vaginal Microbiota Transplantation (VMT) is another treatment option being considered. VMT can improve the imbalance of vaginal bacterial flora by transplanting vaginal secretions from a healthy woman with a high abundance of Lactobacillus [98]. Lev-Sagie et al. [99] described the use of VMT in the treatment of incurable and recurrent bacterial vaginal infections. Out of five patients who underwent therapy, four achieved remission with improved symptoms and no side effects after 5 to 21 months of transplantation. However, we want to emphasize that the number of participants in the study was very small, so the study should be repeated on a larger group for more reliable result.

Conclusions

As presented in the research cited above, the vaginal microbiome plays a huge role in maintaining human health. As emphasized in one of the first paragraphs, we should not speak of a "normal vaginal microbiota" in a global sense, but this concept is permissible regionally. One can also speak of a "normal bacterial flora," which means non-pathogenic microorganisms predominated by *Lactobacillus spp*.

In several paragraphs, one can notice repeated factors that influence the state of vaginal microbiota, the risk of HPV infection, and the development of infection leading ultimately to cervical cancer. The conclusion from these repetitions can be simply summarize: to take care of women's health, it is necessary to raise awareness about the importance of maintaining a healthy vaginal bacterial flora, limiting risk factors for vaginal dysbiosis, systematically observing one's body, and effectively treating emerging dysbiosis or vaginal infections. HPV infection status is undoubtedly associated with cervical-vaginal dysbiosis. One might wonder whether HPV infection causes dysbiosis or dysbiosis causes HPV infection. To protect the

public from both risk in addition to the aforementioned considerations for maintaining a healthy vaginal bacterial flora, measures to promote HPV vaccination are important.

But what about women who did not have the opportunity to get vaccinated before infection? For them, research on the vaginal microbiome are especially important. In just a few years, we have expanded our knowledge to incredible proportions, and there is still much to strive for. Millions of women are waiting for a cure for HPV infection or a drug to halt the progression of infection, and we hope that research will not cease and that the medical-scientific community will strive to solve the problem of HPV infection and its associated consequences.

Author's contribution

Conceptualization, Kostrzewa P; methodology, Przybyla O, Piela K; check, Kostrzewa P, Palmerska A, and Szurma R; resources, Szurma A and Kostrzewa M; writing - rough preparation, Kostrzewa M and Piela A; writing - review and editing, Kostrzewa P and Aniol M; visualization, Pacek S; supervision, Kostrzewa P; project administration, Kostrzewa P; All authors have read and agreed with the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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