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Vaginal microbiome: modern approaches for correction and/or restoration

V. V. Artyomenko[1,2], L. V. Mnikh[1], N. V. Domakova[1,3], Ioan Dumitru Suciu[4]
[1]Odessa National Medical University
[2]MNE «Odesa Maternity Hospital No. 5» of Odesa City Council
[3]CNE «Bilyaiv Multidisciplinary Hospital» of the Bilyaiv City Council
[4]Polizu Clinical Hospital, Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest, Romania

Today, women's health is a separate issue for doctors of many specialties, including obstetricians and gynecologists, family doctors, etc. There is a wide range of treatment options for managing diseases of the reproductive system in women. But despite this, many of these strategies do not work for our patients. Therefore, we need the latest personalized approaches to therapy.
One of the newest trends in women's health is the correction or restoration of the vaginal microbiome. In our previous publications, we have covered the issue of the normal composition of the vaginal microbiome and its changes in various pathological conditions. Modification of the vaginal microbiome can be a useful strategy in the treatment of sexually transmitted infections, bacterial vaginosis, candidiasis, benign, precancerous and even malignant diseases of the female reproductive system, miscarriage, preterm birth and other pregnancy complications.
The concept of using exogenous microorganisms as a treatment has been known for centuries. Possible mechanisms by which exogenous strains of lactobacilli can affect vaginal microbiome include vaginal recolonization, increased production or release of lactic acid and other antimicrobial compounds, and modulation of the local mucosal immune response.
From a microbiome perspective, "prebiotics" are nutraceutical compounds that induce bacterial growth or the activity of probiotics or beneficial endogenous microorganisms. One of the limitations of prebiotics is their dependence on the presence of lactobacilli, which are absent or almost absent in dysbiosis. Symbiotics are combinations of prebiotics and probiotics based on the concept that the first nutraceutical can improve the bacterial growth and function of the other.
This review highlights the latest views on correction and/or restoration of the vaginal microbiome using not only probiotics, prebiotics, and symbiotic, but also phage-altering agents, phage therapy, vaginal microbiome transplantation, etc. Such methods of correction and/or restoration are currently relevant in the reproductive medicine, gynecology and obstetrics all over the world. Despite the fact that these are the newest methods of correction and/or restoration, they are developing every day and require more detailed coverage of this issue.
Keywords: *vaginal microbiome, probiotics, prebiotics, symbiotics, transplantation of the vaginal microbiome, personalized medicine.*

Вагінальний мікробіом: сучасні підходи до корекції та/або відновлення

В. В. Артьоменко, Л. В. Мніх, Н. В. Домакова, Ioan Dumitru Suciu

Здоров'я жінки сьогодні – це окрема тема для лікарів багатьох спеціальностей, у тому числі акушерів-гінекологів, сімейних лікарів тощо. Існує широкий вибір засобів для лікування захворювань репродуктивної системи у жінок. Але незважаючи на це, багато з цих стратегій не працюють. Тому потрібні новітні персоналізовані підходи до терапії.
Однією з новітніх тенденцій є корекція або відновлення мікробіому піхви. У наших попередніх публікаціях висвітлено питання нормального складу мікробіому піхви та його змін за різних патологічних станів. Модифікація вагінального мікробіому може бути корисною стратегією у лікуванні інфекцій, що передаються статевим шляхом, бактеріального вагінозу, кандидозу, доброякісних, передракових і навіть злоякісних захворювань жіночої репродуктивної системи, викидня, передчасних пологів та інших ускладнень вагітності.
Концепція використання екзогенних мікроорганізмів як лікування відома людству протягом століть. Можливі механізми, за допомогою яких екзогенні штами лактобактерій можуть впливати на вагінальний мікробіом, включають реколонізацію піхви, збільшення виробництва або вивільнення молочної кислоти та інших антимікробних сполук, а також модуляцію місцевої імунної відповіді слизової оболонки.
З погляду мікробіому, «пребіотики» – це нутрицевтики, які індукують ріст бактерій, або активність пробіотиків, або корисних ендогенних мікроорганізмів. Одним з обмежень пребіотиків є їхня залежність від наявності лактобактерій, які відсутні або майже відсутні при дисбактеріозі. Симбіотики – це комбінації пребіотиків і пробіотиків, засновані на концепції, що перший нутрицевтик може покращити ріст бактерій і функцію іншого.
У цьому огляді висвітлюються останні погляди на корекцію та/або відновлення вагінального мікробіому за допомогою не лише пробіотиків, пребіотиків і симбіотиків, а й фагозмінних агентів, фаготерапії, трансплантації вагінального мікробіому тощо. Такі методи корекції та/або відновлення на сьогодні є актуальними у світовій репродуктології, гінекології та акушерстві. Незважаючи на те, що це новітні методи корекції та/або реставрації, вони розвиваються з кожним днем і вимагають більш детального висвітлення.
Ключові слова: *вагінальний мікробіом, пробіотики, пребіотики, симбіотики, трансплантація вагінального мікробіому, персоналізована медицина.*

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Over the past decade, technological advances have increased the number and quality of studies of the human microbiome. One of the areas of this research is the vaginal microbiome (VMB), which helps to better understand the changes in the VMB in different conditions and the interaction between microbes and the host. Despite a number of publications on VMB, no significant progress has been made to date correction and/or restoration VMB.

Standard approaches based on the use of antibiotics or antifungal agents are usually effective in acute episodes, but often insufficient in recurrent conditions. A current issue is progressive antibiotic resistance, which is a predictor that such therapeutic strategies are not acceptable for some patients. At the same time, it is known that VMB undergo changes in various pathological conditions, such as viral, bacterial and fungal infections, polycystic ovary syndrome, physiological and complicated pregnancy, etc., and these conditions require a holistic and personalized approach to the treatment of such women.

In our previous publications, we have covered the issue of the normal composition of the VMB and its changes in various pathological conditions [1, 2]. Thus, it is known that the microbiome of the VMB mainly consists of anaerobic and facultative anaerobic flora. Normally, the dominant bacteria in the vagina are lactobacilli. In addition, the VMB is homeostatic and regulated by estrogen levels. The vaginal microbiome undergoes changes during pregnancy, menstruation, menopause, hormone use, and age-related changes in women (Fig. 1).

A thorough characterization of the optimal/healthy bacterial community is a fundamental issue in vaginal microbiome research. Initially, the vaginal microbiome was thought to be simply composed of Lactobacillus. With the introduction of high-throughput sequencing methods, it is now well-established that the vaginal microbiome is more diverse than previously thought [4–6].

It is important that the composition of the vaginal microbiome changes dynamically in response to various internal and external factors [7]. Many scientists have tried to determine the optimal microbial composition of the vagina, despite the enormous difficulties due to the dynamic nature of the vaginal microbiome [2].

Modification of the VMB can be a useful strategy in the treatment of sexually transmitted infections (STIs), bacterial vaginosis (BV), candidasis, benign, precancerous and even malignant diseases of the female reproductive system, miscarriage, preterm birth and other pregnancy complications [8]. As mentioned above, antibacterial and antifungal drugs can be one of the treatment strategies, but the insufficient level of therapeutic response and high relapse rate are pushing scientists to find new treatment tactics [9].

To date, there are various approaches aimed at therapeutic «manipulation» of existing VMBs, such as probiotics, prebiotics, symbiotics, acidifiers, activated charcoal, phage therapy and VMB transplantation. So, in this publication, we would like to cover these strategies in more detail.

Peculiarities of prescribing drugs for Correction and/or Restoration of the vaginal microbiome

The method of administration is a key factor affecting the effectiveness of the drug, especially a probiotic. Vaginal use is more acceptable because of the direct delivery of

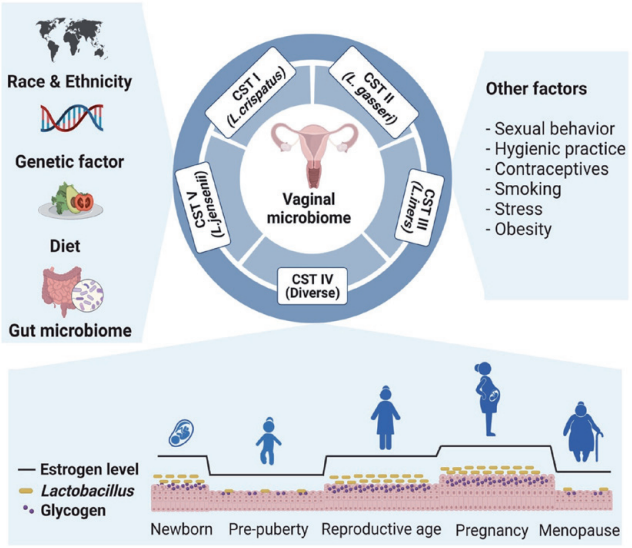

Fig. 1. Various internal and external factors affecting the vaginal microbiome [3]

drugs from the microorganism. Thus, we get a high concentration in the place where their activity is needed. Nevertheless, oral administration is chosen by most women as more acceptable and compliant. Oral administration may be preferred to topical application during menstruation. Oral administration also involves the gut microbiome in the mechanism of action of pro-, pre- and symbiotics. Since there is a direct link between food, the gut and the vagina, the fecal microbiome is a potential source of VMB [10–12].

The gut is a key environment for the interaction between the microbiome and the immune system, affecting: T cell populations, such as regulatory T cells; short-chain fatty acids, etc. Thus, microbes in the gut can also indirectly affect diseases not related to the gut itself, but be one of the links in the pathogenetic mechanism (Fig. 2) [13].

Probiotics

The concept of using exogenous microorganisms as a treatment has been known to mankind for centuries. Possible mechanisms by which exogenous strains of lactobacilli can affect VMB include vaginal recolonization, increased production or release of lactic acid and other antimicrobial compounds, and modulation of the local mucosal immune response [9].

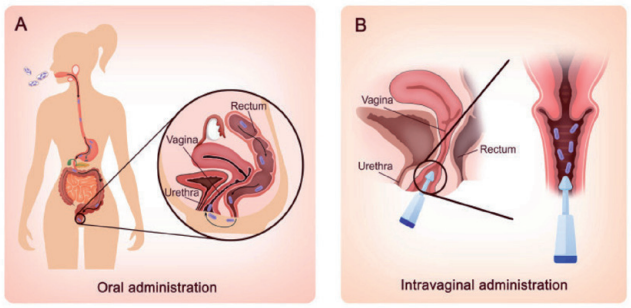

Fig. 2. (A) Oral administration. (B) Intravaginal administration [14]

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Probiotics are living microorganisms that provide health benefits when consumed in adequate amounts [11]. Probiotics are commonly used to treat or prevent vaginal conditions, either alone or as part of a holistic treatment regimen. Probiotics are generally considered safe, but side effects and complications can vary and include gastrointestinal changes and even serious ones such as sepsis and the transfer of antibiotic-resistance genes to host bacteria.

There are several problems in interpreting the study. First, different probiotic products contain a wide range of lactobacilli and other bacteria. Second, there is little evidence to date that probiotic use leads to vaginal colonization with these strains, and most studies do not distinguish between endogenous lactobacilli and probiotic strains. Thirdly, there is a lack of quality control in the production of probiotic products, which means that the purity and efficacy of the products may be variable [15–17].

To date, it has been established that probiotics containing lactobacilli and administered vaginally may be promising for the treatment and prevention of bacterial vaginitis, but their effectiveness against fungal flora has not yet been proven. Long-term antibiotic use has also been found to be more effective in reducing the recurrence of bacterial vaginitis than the use of probiotics [18–20]. In addition, studies have found that the detection of probiotic strains in the vagina after a period of treatment does not last long, suggesting that none of the probiotic strains evaluated have sufficiently colonized the vagina [9].

In VMB, L. crispatus is associated with the lowest vaginal pH, lowest levels of pro-inflammatory cytokines, and lowest risk of gynaecological and obstetric complications, and is therefore considered the dominant species associated with vaginal health. Most probiotic studies have not evaluated L. crispatus strains and have used strains derived from the gut or from traditional fermented foods.

In our opinion, the use of probiotics based on lactobacilli in women with lactose intolerance is logically questionary. The latest data suggest that the use of probiotics containing lactobacilli (Lactobacillus reuteri DSM 17938 and Lactobacillus acidophilus DDS-1, etc.) has a positive effect on the course of lactase deficiency and lactose intolerance in patients [21, 22].

L. crispatus CTV-05 was isolated more than 26 years ago from the vagina of a healthy woman [23, 24]. A series of studies were conducted on its basis to assess its colonization potential [23], to develop a fingerprinting method to distinguish the probiotic strain from endogenous lactobacilli [24]. These studies demonstrated that CTV-05 did not colonies effectively in women who already had L. crispatus in their breast milk, unprotected sex reduced the likelihood of successful colonization, and there was no overall benefit in preventing the recurrence of BV [23].

Currently, the Lactobacillus crispatus CTV-05, is a live biopharmaceutical containing a strain of Lactobacillus crispatus that is being developed for the treatment of urinary tract infections (UTIs) and BV in women [9, 10]. The Food and Drug Administration has approved the use of this drug as an adjunctive therapy to prevent recurrence of BV and recurrent urinary tract infections after antimicrobial treatment [25].

A recently published, randomized, double-blind, placebo-controlled study evaluated the ability of CTV-05 to prevent recurrence of BV after a course of vaginal metronidazole [26]. By week 12, 30% of the CTV-05 group and 45% of the placebo group had recurrent BV by this time. Lactobacillus crispatus CTV-05 was detected in 79% of participants in the CTV-05 group at 12 weeks after treatment completion and only 48% of participants at 24 weeks.

Overall, these studies demonstrate that while this intervention has a significant effect, the attenuation of the effect at week 24 suggests that continued use may be required to maintain this effect, and the lack of colonization among women who have unprotected sex may be a serious limitation to the use of this probiotic [23].

The theoretical potential of probiotics to favorably modulate the dysbiosis environment of the female genital tract has been tested as a possibility to reduce the risk of preterm birth. A meta-analysis found no evidence that taking probiotics during pregnancy increases or decreases the risk of preterm birth or other adverse pregnancy outcomes for either the baby or the mother [27].

The studies observed at the role of probiotics in the regression of human papillomavirus infection after 6 months: one found no differences between the groups, and the other showed a higher rate of regression with treatment [28, 29].

Despite the high consumer demand for probiotics to improve vaginal health, most probiotics are marketed without specific indications for use, which is a result of the significantly low level and quality of evidence supporting the effectiveness of these products. Therefore, further research is needed to either confirm or refute an opinion that probiotics are beneficial in BV.

One study investigated the effects of an oral yeast probiotic and menstruation on specific taxa of potential pathogens or pathobionts, such as members of the genera Gardnerella, Prevotella and Streptococcus (Fig. 3).

As can be seen from the figure 3, the number of Prevotella spp. remained more stable in the probiotic group, although this did not lead to a significant difference between the probiotic and placebo groups. For the genera Gardnerella and Streptococcus, no significant differences were observed between the probiotic and placebo groups, but both showed a specific temporal trend [30].

Prebiotics

From a microbiome perspective, “prebiotics” are nutraceutical compounds that induce bacterial growth or the activity of probiotics or beneficial endogenous microorganisms.

Since prebiotic consumption is a very effective approach to improving gut health, it was assessed whether these substances could affect vaginal lactobacilli [30]. Monocultures of L. crispatus, L. vaginalis, L. gasseri, L. johnsonii, L. jensenii and L. iners and Candida albicans were tested in vitro for their ability to interact with prebiotics that included lactitol, lactulose, raffinose and oligofructose. The lactulose disaccharide was found to stimulate vaginal lactobacilli, including L. crispatus, but not C. albicans [31, 32].

Lactoferrin, an iron-binding glycoprotein, is being used as a possible treatment for BV and to reduce the number of preterm births [33, 34]. Proposed mechanisms

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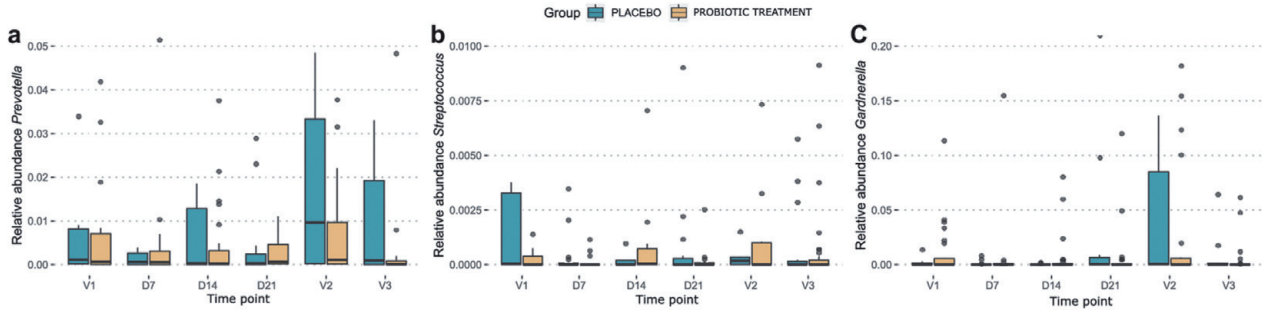

Fig. 3. Relative numbers of Prevotella (a), Gardnerella (b) and Streptococcus (c) during the study, separated for the probiotic (blue) and placebo (yellow) groups [29]

of action include anti-inflammatory and anti-infective effects, as well as sequestration of iron, making it unavailable for bacterial metabolism [35]. It has been found that vaginal dysbiosis has a marked increase in lactoferrin levels; this may represent a protective response by reducing available iron [35]. The problem with using lactoferrin in dysbiosis is that the metabolism of most lactobacillus species also depends on iron [36–38].

The route of delivery of prebiotics is still a matter of debate; vaginal use, including pessaries, creams and douching, is currently the most commonly used. Prebiotics are generally considered safe; their adverse effects (diarrhea, bloating, flatulence) are attributed to their osmotic effect on gut function [39, 40].

Symbiotics

One of the limitations of prebiotics is their dependence on the presence of lactobacilli, which are absent or almost absent in dysbiosis. Symbiotics are combinations of prebiotics and probiotics based on the concept that the former nutraceutical can improve the improve bacterial growth and function [40]. In a randomized controlled trial in patients with recurrent BV, a combination of probiotics (Lactobacillus acidophilus GLA-14 and Lactobacillus rhamnosus HN001) and bovine lactoferrin as an adjuvant to metronidazole was shown to improve relapse [41, 42].

One recent study investigated the impact of prebiotics, probiotics and symbiotic on the prevention and treatment of cervical cancer (Fig. 4).

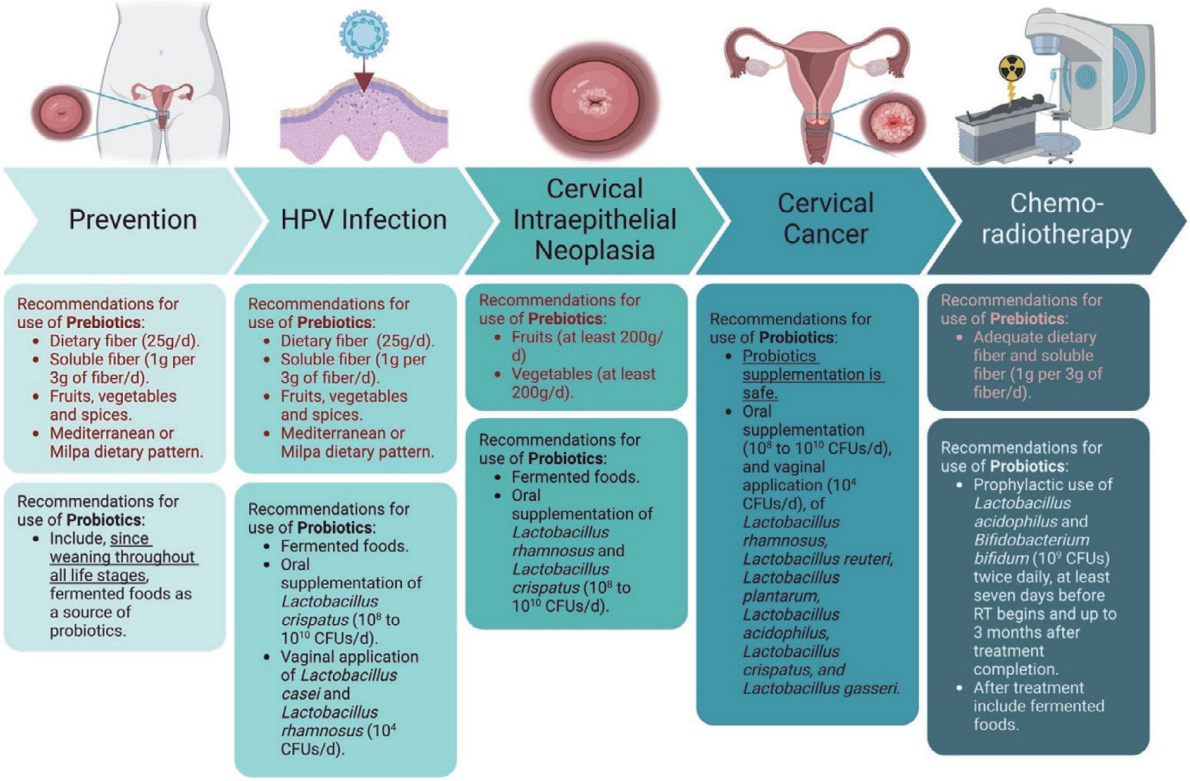

Fig. 4. Recommendations for the use of prebiotics and probiotics according to the natural progression of cervical cancer, from prevention of HPV infection to treatment of patients with locally advanced cervical cancer [43]

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Researchers have found that higher dietary fibre intake is associated with a reduced risk of human papillomavirus (HPV) infection (Fig. 4). Certain probiotics have shown promising results in the prevention and comprehensive treatment of HPV. In addition, certain strains of prebiotics such as inulin and fructo-oligosaccharides and symbiotic reduce the incidence of gastrointestinal side effects in patients with cervical cancer. These agents achieve their goal by modulating key metabolic pathways, including reducing inflammation and oxidative stress, promoting apoptosis, inhibition of cell proliferation and suppression of oncogenic activity, thus attenuating tumorigenesis [43].

Substances that change the pH

Lactic acid, a metabolite of lactobacillus activity, is believed to be involved in the regulation of bacterial growth. Given that lactobacilli thrive in a low pH environment, while the growth of potentially pathogenic bacteria in this environment is limited, acidifiers have been proposed to restore normal VMB. A recent systematic review described the effect of intravaginal products containing lactic acid on the treatment of BV and their impact on VMB composition [44]. The results of several publications were contradictory regarding the efficacy of vaginal pH-altering agents and the authors concluded that there is a lack of high-quality evidence to support the use of lactic acid products to modify VMB.

Phage therapy

More than a century ago, and almost a decade before the discovery of penicillin, the practice of phage therapy was developed to treat bacterial infections such as Shigella dysenteriae [45]. The development of antibiotic therapy has led to a decline in the use of phage therapy; however, the emergence of antibiotic resistance has increased attention to the therapeutic potential of phages in the treatment of bacterial infections.

Phages are bacteria-specific agents that depend on their host bacteria for survival and play a crucial role in the regulation of bacterial populations. Typically, bacteriophages bind to specific receptors on the surface of a bacterial cell and incorporate their genetic material into the host cell. The phage mechanically acts through 1 of 2 pathways. "Moderate" phages integrate genetic material into the bacterial genome and reproduce vertically. "Lytic" phages take over the bacterial replication mechanism to produce the next generation of phage progeny and thus lysate the cell (Fig. 5).

Once a critical mass of phage progeny is reached, lytic proteins become active and hydrolyze cell wall peptidoglycan, releasing the phages to restart the lytic cycle [46]. Most phages are virulent only to bacteria that carry their respective receptor, which in turn determines the range of phage hosts [47]. As a therapeutic agent, phages have several important advantages over antibiotics, such as host specificity, self-amplification, biofilm degradation, and low human toxicity [48, 49].

The phage genome can be manipulated using biotechnological approaches to better deliver and treat bacterial infections. Two phage therapy strategies are used: natural phage therapy and artificial/synthetic phage therapy.

Correction of VMB with phages may be relevant in dysbiotic conditions, although little is known about this

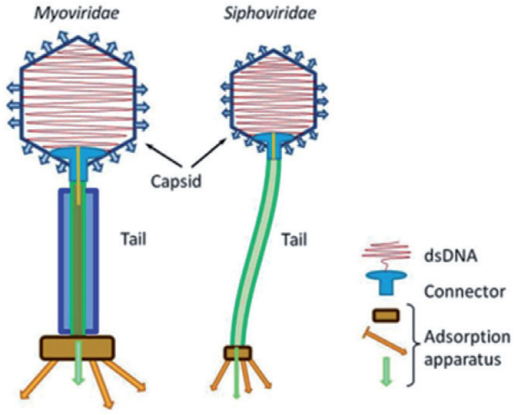

Fig. 5. Structure of a phage virus [46]

effect. A recent study showed that vaginal agents is clearly related to the structure of the bacterial community [50]. One theory regarding the etiology of BV involves sexually transmitted phages that specifically target lactobacilli and promote the proliferation of anaerobic bacteria [51, 52]. Evidence suggests that lytic phages may target lactobacilli, thus contributing to the change in VMB [53–55].

The same concept could be used in the future to treat dysbiosis by producing specific phages that target the microorganisms that cause this imbalance. To date, several researchers are developing phage-based therapies to correct VMB by selectively targeting Gardnerella vaginalis [55].

Substances that destroy biofilms

Another promising treatment for VMB is a new boric acid-based vaginal antiinfective agent enhanced with ethylenediaminetetraacetic acid with antibiotic film activity (TOL-463) [56]. Clinical studies have demonstrated that TOL-463 treatment is safe and well tolerated, resulting in 59% and 50% clinical cure rates for tampons and gel, respectively, at 9 and 12 days. Ethylenediaminetetraacetic acid has been shown to enhance the antimicrobial activity of boric acid and provide enhanced antibiotic film action against G. vaginalis and Candida, while preserving lactobacilli [56].

Transplantation of the vaginal microbiome

The success of microbiota transplantation in the treatment of infection has sparked interest in the potential of using transplanted human material to treat a wide range of conditions associated with vaginal dysbiosis or vaginal infection (Fig. 6).

In the present study, the aim was to restore the harmonious balance of the vaginal microbiota, which is often disrupted in BV (Fig.6). This method represents an encouraging way to address this common disease by harnessing the potential of beneficial microorganisms to fight off harmful ones: H_2O_2 has been enhanced; competition for food has increased. In addition, there has been an improvement in the adhesion ability of epithelial cells, and the presence of Lactobacillus in large numbers. The pH level is low, creating a functional and protective barrier [57, 58].

Future studies with larger cohorts and a randomized, placebo-controlled design are needed to determine the ef-

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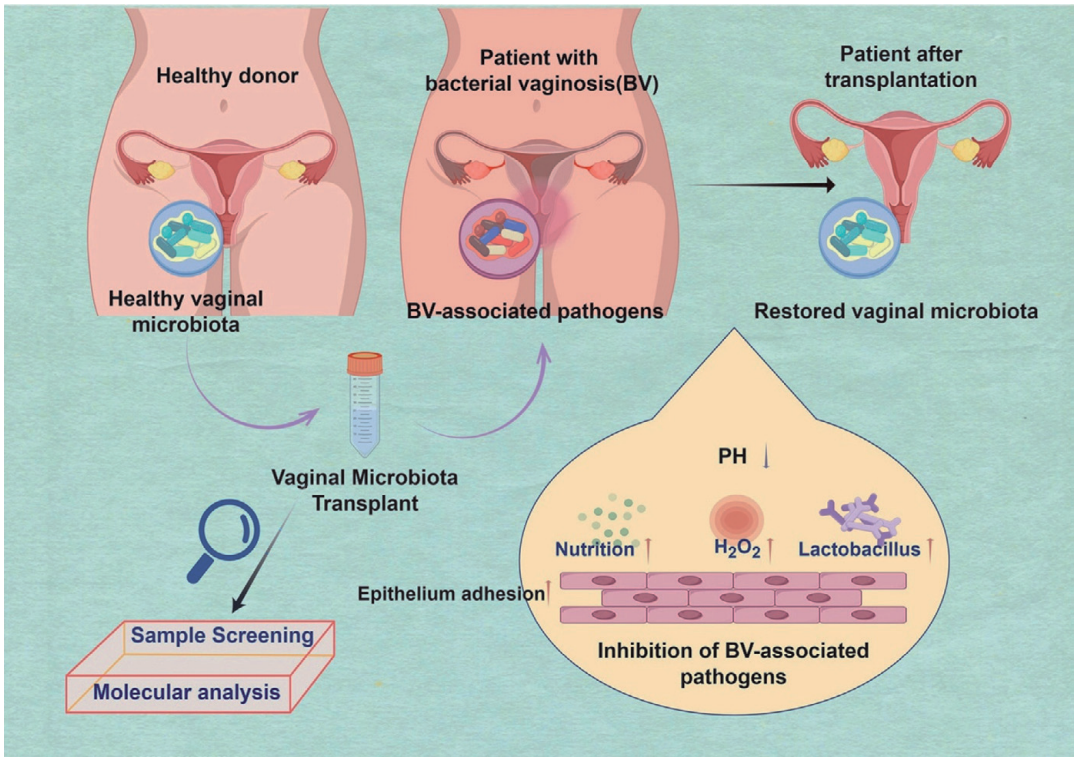

Fig. 6. Use of beneficial vaginal microbiota transplantation (VMT) to restore the vaginal microbiota [57]

ficacy and safety of VMB transplantation. Given the risk of human-to-human transmission of pathogens, future trials will presumably identify specific mixtures of bacterial strains that will provide health benefits, with the goal of producing «purified» versions of these microbial cocktails for clinical use. Another theoretical treatment option in microbiome transplantation could involve manipulating and bioengineering microorganisms to give them specific characteristics that provide health benefits, including specific drug production capabilities [59–64].

CONCLUSIONS

Studies reveal variations in the composition of the microbiota after the introduction of probiotics, which led to subsequent changes in metabolic activity. This confirms that probiotics, by modulating the microbiome and related metabolic pathways, can potentially have positive effects on women's health. The vaginal microbiome plays a critical role in maintaining reproductive health through the production of various metabolites such as lactic acid, short-chain fatty acids, and bacteriocins.

By modulating hormonal levels, these bacteria significantly affect the vaginal environment and reproductive processes. These metabolites modulate local immune responses, influencing inflammation and susceptibility to infection—factors critical to reproductive success. In addition, the vaginal microbiome can increase the bioavailability and absorption of essential nutrients, influencing the overall metabolic state.

Probiotics are widely used as an alternative or as an adjunct to antibiotics and antifungals, despite a lack of quality evidence to support this. The idea that lactobacilli cannot thrive in an already unfavorable environment led to the idea of using prebiotics and symbiotics in an attempt to promote colonization by lactobacilli. However, even this approach appears to be insufficient, and for this reason more sophisticated approaches may be needed, as vaginal microbiome transplantation is one of the most promising areas of research in this field.

Information about the authors

Artyomenko Volodymyr V. – MD, PhD, DSc, Professor, Department of Obstetrics and Gynecology, Odessa National Medical University. *E-mail: vartyomenko2017@gmail.com*
ORCID: 0000-0003-2490-375X
Mnikh Liudmyla V. – MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Odessa National Medical University
ORCID: 0000-0002-2159-6814
Domakova Nataliia V. – MD, PhD, Odessa National Medical University
ORCID: 0009-0009-1523-1710
Ioan Dumitru Suciu – MD, PhD, Department of Obstetrics and Gynecology, Polizu Clinical Hospital, Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest, Romania
ORCID: 0009-0000-9074-2048

Відомості про авторів

Артьоменко Володимир Вікторович – д-р мед. наук, проф., кафедра акушерства та гінекології, Одеський національний медичний університет. *E-mail: vartyomenko2017@gmail.com*
ORCID: 0000-0003-2490-375X
Мніх Людмила Василівна – канд. мед. наук, доц., кафедра акушерства та гінекології, Одеський національний медичний університет
ORCID: 0000-0002-2159-6814
Домакова Наталія Василівна – канд. мед. наук, Одеський національний медичний університет
ORCID: 0009-0009-1523-1710
Ioan Dumitru Suciu – канд. мед. наук, відділення акушерства та гінекології, клінічна лікарня Полізу, Національний інститут здоров'я матері та дитини Алессандреску-Русеску, м. Бухарест, Румунія
ORCID: 0009-0000-9074-2048

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