

ORCID кожного автора та його внесок до статті:

Sherstyuk S. O.: <https://orcid.org/0000-0001-6062-7962>^{AEF}
Nakonechna S. A.: <https://orcid.org/0000-0002-4718-1465>^{BD}
Zotova A. B.: <https://orcid.org/0000-0001-6215-0846>^{BD}
Khranova T. O.: <https://orcid.org/0000-0002-7445-6786>^{BE}
Fedorchenko M. O.: <https://orcid.org/0000-0002-0873-8590>^{BE}

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Наконечна Світлана Анатоліївна
Харківський національний університет імені В.Н. Каразіна
Україна, 61022, м. Харків, м-н Свободи 6
Тел.: +380669061201
E-mail: s.nakonechna@karazin.ua

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Shuba S. S., Sidashenko O. I.

COMPOSITION OF THE VAGINAL MICROBIOME AND ITS EFFECT ON REPRODUCTIVE FUNCTION IN WOMEN

Dnipro University of Technology (Dnipro, Ukraine)

microb.sidashenko@gmail.com

The vaginal microbiome is an important component of the microbiocenosis of the female reproductive tract and participates in maintaining local homeostasis. In women of reproductive age, its structure is mainly characterized by the dominance of representatives of the Lactobacillus, which contribute to maintaining the acidic environment of the vagina and limit colonization by pathogenic and opportunistic microorganisms. Disruption of the microbial balance may be accompanied by dysbiotic changes and be associated with adverse reproductive consequences. The work summarizes the results of modern studies devoted to the structure and functional properties of the vaginal microbiome. It was established that the most common representatives of the vaginal microbiota of women of reproductive age are Lactobacillus crispatus, L. gasseri, L. iners and L. jensenii, and the dominance of L. crispatus is more often associated with a physiological acidic pH. It is shown that the composition of the microbiome depends on age, hormonal status, phase of the menstrual cycle, pregnancy, contraception, medication and other biological and external factors. Dysbiotic changes, characterized by a decrease in the number of lactobacilli and an increase in the titer of various anaerobic microorganisms, may be associated with infertility, early pregnancy loss, preterm birth and certain adverse outcomes of assisted reproductive technologies (ART). The vaginal microbiome is a dynamic ecosystem, the state of which indirectly affects the reproductive health of women. Further study of its composition and functional activity will contribute to the clarification of the mechanisms of interaction of the microbiome with the reproductive system and the assessment of the possibilities of using microbiome indicators to predict reproductive outcomes.

Key words: vaginal microbiome, Lactobacillus, endometrial microbiome, dysbiosis, reproductive health.

Connection of the publication with planned research work.

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Introduction.

A woman's reproductive health is determined by the complex interaction of the endocrine, immune, nervous and reproductive systems. One of the current directions of modern reproductive biology is the study of microbial associations of the female reproductive tract and their possible impact on fertility and the course of pregnancy.

The microbiome is the totality of the genetic material of microorganisms inhabiting a certain ecological niche, together with the functional potential of the microbial community formed by them and its interaction with the host organism and the environment. The human microbiome includes bacteria, archaea, fungi and viruses, which form complex dynamic microbial ecosystems [1]. In the female reproductive tract, microbial associations that form biofilms are localized, in particular, in the vagina and cervix, and their composition and functional activity can be associated with the state of the mucous membranes, local immune response and reproductive processes [2, 3].

The development of high-throughput sequencing, 16S rRNA analysis and metagenomic methods has significantly expanded the understanding of the composition and functional properties of the vaginal microbiome [4, 5].

The vaginal microbiome in women of reproductive age is mainly characterized by the dominance of representatives of the genus *Lactobacillus*, among which *Lactobacillus crispatus*, *L. gasseri*, *L. iners* and *L. jensenii* are most often found. Lactobacilli provide an acidic environment in the vagina, inhibit the development of pathogenic and opportunistic microorganisms, interact with the vaginal epithelium and the local immune system [4–6]. At the same time, the structure of the vaginal microbiome is dynamic and depends on many external and internal factors [7, 8].

Disturbances of microbial balance, accompanied by a decrease in the number of lactobacilli and an increase in the number of various anaerobic bacteria, are considered vaginal dysbiosis. Microorganisms associated with such changes include representatives of the *Gardnerella*, *Prevotella*, *Atopobium*, *Sneathia*, *Megasphaera*, *Mobiluncus* and other genera [9, 10]. *L. iners* is of particular interest, as it is found both in a relatively stable vaginal microbiome and in conditions of dysbiotic changes, which highlights the complexity of its biological role [6].

Data obtained in recent years indicate a possible connection of the vaginal microbiome with female reproductive function. A systematic review by de Souza et al. [11], which included 18 studies involving 2,011 women, found that women of reproductive age had a more frequent *Lactobacillus*-dominant vaginal microbiome profile, while women with infertility showed dysbiotic changes.

The vaginal microbiome has also been investigated in the context of assisted reproductive technologies. In particular, vaginal dysbiosis has been associated with lower clinical pregnancy rates and an increased risk of early pregnancy loss. *L. crispatus* dominance has been associated with more favorable reproductive outcomes in some studies [12–14].

Changes in the vaginal microbiome also have potential implications for pregnancy outcomes. Decreased Lactobacilli and increased microbial diversity are associated with an increased risk of preterm birth. At the same time, most modern studies demonstrate mainly associative relationships, and the heterogeneity of research methods and criteria for assessing the microbiome complicates direct comparison of the results obtained [13, 15, 16].

Thus, the relevance of research on the vaginal microbiome is due to the need to study its role in maintaining female reproductive function, the course of pregnancy and the effectiveness of assisted reproductive technologies. The lack of certainty of the causal mechanisms of interaction of the microbiome with the female body and the possibilities of using microbiome characteristics as prognostic markers necessitates further systematic analysis of modern scientific data.

The aim of the study.

To analyze and summarize modern literature data on the taxonomic and functional composition of the vaginal microbiome and determine its potential impact on women's reproductive function.

Object and research methods.

The object of the study was current scientific evidence on the composition, functional properties, and determinants of the vaginal microbiome, as well as its potential impact on women's reproductive health. The study involved the analysis and synthesis of scientific literature addressing the taxonomic composition of the vaginal microbiota, mechanisms underlying dysbiotic alterations, and factors influencing the structure of microbial communities within the female reproductive tract. Particular attention was paid to representatives of the genus *Lactobacillus*, vaginal dysbiosis, female reproductive function, in vitro fertilization (IVF) outcomes, and the course of pregnancy, including the potential associations of the vaginal and endometrial microbiomes with fertility and reproductive complications. General scientific methods of analysis, comparison, systematization, and synthesis of data from contemporary scientific publications were applied.

Main part.

Composition of the vaginal microbiome. The vaginal microbiome is a complex, dynamic, multicomponent ecosystem that includes bacteria, fungi, archaea, and viruses [4, 17]. The most thoroughly studied component of it is the bacterial community, the possibilities of studying which have significantly expanded after the introduction of modern molecular genetic methods, in particular, 16S rRNA gene sequencing and shotgun metagenomic sequencing. The use of these technologies made it possible to detect a much wider spectrum of microorganisms than when using traditional culture methods, as well as to study the patterns of their coexistence and potential functional interaction with the host organism [4, 5].

In women of reproductive age, the vaginal bacterial community is mainly characterized by the dominance of representatives of the *Lactobacillus*. *Lactobacillus crispatus*, *L. gasseri*, *L. iners* and *L. jensenii* are most often found among them [4, 6]. At the same time, the predominance of lactobacilli does not always indicate a normal state, since different species have different metabolic properties and may be differently associated with the stability of the vaginal microbial ecosystem [6, 8]. The most favorable profile is considered to be a microbiome with a predominance of *L. crispatus*, this species creates conditions unfavorable for the overgrowth of many pathogenic and opportunistic microorganisms [4, 15], such as *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella spp.*, *Mobiluncus spp.*, and *Escherichia coli*.

Similar protective properties may be inherent in *L. gasseri* and *L. jensenii*, which are also involved in the production of lactic acid and the maintenance of colo-

nization resistance. However, the relationship of these species with individual reproductive outcomes is less clearly understood, so it is advisable to assess the state of the vaginal microbiome taking into account not only the total abundance of lactobacilli, but also the species composition of the microbial community [4, 8]. *L. iners* attracts special attention, since its biological role is more complex compared to other common members of the *Lactobacillus*. This species can be dominant both in a relatively stable vaginal microbiome and in conditions of dysbiotic changes, in particular during the transition to conditions associated with bacterial vaginosis. A systematic review by Zheng et al. [6] showed that *L. iners* is one of the most common components of the vaginal microbiome and can be detected in different microbial conditions. This feature indicates that the assessment of the total number of lactobacilli alone does not always allow to reliably determine the functional state of the vaginal ecosystem. A more informative approach is to establish the species composition of the microbiota and, if possible, the characteristics of individual strains.

The functional properties of vaginal lactobacilli are largely determined by their metabolic activity [4, 6]. In addition to lactic acid, individual representatives of *Lactobacillus* can also synthesize bacteriocins, hydrogen peroxide and other metabolites that can affect the viability and colonization of competing microorganisms [6]. An important defense mechanism is also the ability of lactobacilli to adhere to vaginal epithelial cells, compete with other microorganisms for colonization sites and interact with components of the local innate immune response [4–6].

Vaginal microbial profiles and features of the endometrial microbiome. In women of reproductive age, the vaginal microbiome is often characterized by relatively low microbial diversity and a predominance of representatives of *Lactobacillus*, among which *L. crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii* are most commonly found [6, 8]. Based on the dominant bacterial taxa, vaginal microbial communities are divided into five main community state types (CST). CST I is characterized by a predominance of *L. crispatus*, CST II by *L. gasseri*, CST III by *L. iners*, and CST V by *L. jensenii*. CST IV, in contrast to the other types, is characterized by the absence of a pronounced dominance of one species of *Lactobacillus* and a higher bacterial diversity with an increased representation of anaerobic microorganisms [8, 15].

Microbial taxa that may be present in CST IV include *Gardnerella*, *Prevotella*, *Fannyhessea*, *Sneathia*, *Megasphaera*, *Dialister*, *Mobiluncus*, *Peptoniphilus*, and other anaerobic bacteria [9, 15]. An increase in their relative count is often accompanied by a decrease in the number of lactobacilli and an increase in vaginal pH, which is characteristic of microbial profiles associated with bacterial vaginosis [9, 10, 15]. However, the presence of individual representatives of these microorganisms does not necessarily indicate a pathological condition, since the vaginal microbiota is a dynamic ecosystem, and its composition can vary significantly between women without clinical manifestations of the disease [6, 8]. Of particular importance among vaginal lactobacilli is *L. crispatus*, the dominance of which is usually associated with a more stable and favorable microbial profile. In a systematic review based on a meta-analysis by Gudnadottir et al. [15], women with a microbial profile with

a low representation of lactobacilli had a higher risk of preterm birth compared with women with a dominant *L. crispatus* (OR 1.69; 95% CI 1.15–2.49). Therefore, the dominance of *L. crispatus* can be considered as a marker of a microbial profile associated with a lower risk of certain adverse pregnancy outcomes, but not as a universal prognostic indicator.

L. gasseri and *L. jensenii* are also capable of producing lactic acid and are involved in the maintenance of colonization resistance. In contrast, *L. iners* has some different biological properties and is often found in both relatively stable and transient microbial states, in particular during the transition between a lactobacilli-dominant profile and dysbiosis [6].

The uterine endometrium has long been considered a sterile environment. However, with the development of molecular genetic methods, data have emerged on the possible presence of microbial signals in the upper parts of the female reproductive tract [18, 19]. At the same time, the endometrium belongs to low-biome environments, which significantly complicates the study of its microbiome. The results may depend on the method of material collection, DNA extraction protocols, sequencing methods and control of contamination from the lower parts of the reproductive tract or laboratory reagents, so the question of the existence, stability and exact composition of the endometrial microbiome remains a subject of scientific debate [18–21]. According to a number of studies, representatives of the *Lactobacillus*, *Gardnerella*, *Prevotella*, *Streptococcus*, *Staphylococcus*, *Corynebacterium* and other bacteria can be detected in endometrial samples [18, 19]. At the same time, the results of various studies on the prevalence of certain taxa are not unambiguous. Some studies have reported a higher abundance of *Lactobacillus* in endometrial samples from women with more favorable reproductive outcomes, while other studies have not confirmed the existence of a stable *Lactobacillus*-dominant profile [18, 20, 21]. This discrepancy may be due to both biological variability and methodological features of the study of low-biome samples [18, 21].

Of particular interest is the possible association of the endometrial microbiome with implantation processes and early stages of pregnancy. It is assumed that microbial components can interact with endometrial cells and potentially influence the local immune response, inflammatory processes, and other characteristics of the endometrial microenvironment. At the same time, current studies do not provide sufficient grounds for an unambiguous conclusion about the direct causal effect of a certain composition of the endometrial microbiome on the success of implantation or pregnancy [18–21].

Consequently, compared with the relatively well-studied vaginal microbiota, the endometrial microbiome requires further investigation using standardised sampling methods, strict control of contamination and modern metagenomic approaches [18, 21]. This is important for establishing the real contribution of microorganisms of the upper reproductive tract to the processes of fertility, implantation and early pregnancy development.

Functioning of the vaginal microbiome and factors determining its structure. The functional state of the vaginal microbiome largely depends on the hormonal status of a woman. Estrogens stimulate the proliferation

of the vaginal epithelium and the accumulation of glycogen in it, the metabolism of which creates conditions for maintaining lactobacilli populations. Disruption of this balance may be accompanied by a restructuring of the microbial community and the development of dysbacteriosis [7, 8]. Vaginal dysbiosis is a condition characterized by changes in the qualitative and quantitative composition of the microbial community of the urogenital tract, in particular, a decrease in the number of *Lactobacillus* and a simultaneous increase in the proportion of anaerobic and facultative anaerobic microorganisms. Among the genera that are often detected under such conditions are *Gardnerella*, *Prevotella*, *Fannyhessea*, *Sneathia*, *Megasphaera*, *Mobiluncus* and other bacteria [9, 10, 15]. One of the most common clinical conditions associated with a bacterial vaginosis. This is a polymicrobial condition in which a complex bacterial biofilm can form, which contributes to the stabilization of the dysbiotic community and may be one of the factors for disease recurrence [9, 10]. At the same time, the detection of a certain taxon, in particular *Gardnerella vaginalis*, cannot be considered by itself as a sufficient sign of a pathological condition, since representatives of this genus can also be detected in women without clinical manifestations of bacterial vaginosis [9]. The formation of a dysbiotic microbial community can potentially affect the state of the female reproductive tract through several interrelated mechanisms. These include changes in the epithelial barrier, impaired vaginal acidity, changes in the local immune response, and possible ascending spread of microorganisms to the upper reproductive tract [10, 15, 16]. That is why it is advisable to consider the vaginal microbiome not only as a characteristic of the local state of the vagina, but also as a potential component of general reproductive health. The structure of the vaginal microbial community is formed under the influence of numerous endogenous and exogenous factors. One of the key regulators is the level of sex steroids. In the reproductive age, estrogen stimulation contributes to maintaining conditions favorable for the dominance of lactobacilli, while a decrease in estrogen levels, particularly in postmenopause, may be accompanied by a decrease in their representation and an increase in vaginal pH [7, 8]. The menstrual cycle plays an equally important role. A study by Krog et al. [7] found that during menstruation, microbial diversity increases and the quantitative composition of lactobacilli decreases, after which a tendency to restore a lactobacilli-dominant profile is observed in the subsequent phases of the cycle [7]. Such dynamics demonstrate that the vaginal microbiome is a structure that is constantly adapting to physiological changes in the body. The composition of the vaginal microbiome can be influenced by other factors, including sexual activity, the use of antibacterial drugs, hormone therapy, pregnancy, the use of contraceptives, features of intimate hygiene and other biological and external factors [8, 10]. Sexual activity and the number of sexual partners can affect the state of the vaginal microbiome due to the translocation of microorganisms between partners, a temporary shift in pH, as well as the risk of infection with pathogens of sexually transmitted infections (STIs) [8, 10]. A review by Dubé-Zinatelli et al. [8] shows that the structure of the vaginal microbiome is shaped by a complex of interrelated biological, hormonal, environmental, and behavioral

factors. This is characteristics cannot be reduced to the action of only one factor [8].

The influence of the vaginal microenvironment on the realization of reproductive potential. The revealed patterns have caused considerable interest in the possible connection of the vaginal microbiome with the realization of reproductive function. The reproductive ability of a woman is a multifactorial characteristic that depends on ovulatory function, oocyte quality, patency of the fallopian tubes, endometrial condition, hormonal and genetic status, as well as many other factors. Under such conditions, the vaginal microbiome should be considered as one of the potential modulating factors that can influence the reproductive microenvironment by maintaining a local protective barrier and limiting infectious and inflammatory processes [11, 17]. A systematic review by de Souza et al. [11], which included 18 studies involving 2,011 women, showed that *Lactobacillus* dominance was more common in fertile women, while dysbiotic microbial profiles were more common in infertile women [11]. However, these results cannot be interpreted as evidence of a direct causal effect of dysbiosis on infertility. Reproductive disorders can be accompanied by hormonal, metabolic and inflammatory changes, which, in turn, can change the composition of the vaginal microbiota. In this regard, Tomaiuolo et al. [17] shows the need to clearly distinguish between correlation and cause-and-effect relationships when analyzing the role of the female reproductive tract microbiota in the formation of infertility [11, 17]. A separate aspect of this interaction is the possible influence of the vaginal microbiota on spermatozoa. After ejaculation, spermatozoa come into contact with the vaginal microenvironment, so the properties of the microbial community can potentially affect their viability, motility and agglutination. Zhang, Dai and Chen [22] have reviewed possible mechanisms of interaction between lactobacilli and other bacteria and sperm, including the potential impact of bacterial adhesion on agglutination and motility of male gametes. However, many of the proposed mechanisms require further experimental validation, and the available data do not allow us to conclude that there is a direct negative or positive regulation of female fertility based solely on the number of vaginal lactobacilli.

The influence of the vaginal microbiome on reproductive technologies. The issue of the relationship between the microbiome and reproductive function in the field of assisted reproductive technologies (ART) is of particular importance. During in vitro fertilization, the outcome of treatment depends on a number of sequential stages, including oocyte maturation, fertilization, embryo development, its transfer and implantation, therefore, changes in the reproductive microenvironment can potentially be associated with the results of individual stages of infertility treatment.

In a systematic review by Rajani Dube and Subhranshu Sekhar Kar [14], data on the relationship between the state of the urogenital microbiome and the results of ART were analyzed. The authors note that the results of individual studies are contradictory, and the conclusions depend on the methods of assessing the microbiome and the characteristics of the studied populations. At the same time, the accumulated data indicate a possible relationship between the characteristics of endometrial

microbial communities and the effectiveness of infertility treatment.

A larger systematic review and meta-analysis by Maksimovic Celicanin et al. [12] included 25 studies including 6835 patients undergoing in vitro fertilization (IVF). The prevalence of vaginal dysbiosis among the participants was 19%. The presence of dysbiosis was associated with an increased risk of early pregnancy loss (RR 1.49; 95% CI 1.15–1.94) and a lower clinical pregnancy rate (RR 0.82; 95% CI 0.70–0.95). However, there was no statistically significant effect on the rate of successful pregnancy. Thus, vaginal dysbiosis may be associated with certain IVF outcomes, but its prognostic value for the final outcome of treatment remains poorly defined.

Similar findings were reported in a systematic review and meta-analysis by Samama et al. [13] on the relationship between the vaginal microbiome and the outcomes of assisted reproduction (ART). The authors demonstrated an association between a more favorable microbial profile and higher pregnancy and live birth rates, with a significant presence of *L. crispatus* associated with more favorable reproductive outcomes. However, the results should be interpreted with consideration of the heterogeneity of studies, differences in microbiome analysis methods, and the risk of bias. Therefore, the data obtained confirm the promising potential of microbiome profiling in reproductive medicine, but do not yet justify its independent use for predicting ART outcomes [13, 14].

Vaginal microbiome and risk of gestational complications. Of particular interest is the possible association of the vaginal microbiome with early pregnancy loss. In a prospective study by Shahid et al. [23] of 24 pregnant women, differences in the composition of the vaginal microbiota were found between participants with adverse and favorable pregnancy outcomes. Women whose pregnancies ended in miscarriage were more likely to have microbial profiles associated with *L. iners*, whereas women without an adverse outcome were more likely to have a dominance of *L. crispatus*. However, the small sample size significantly limits the possibility of extrapolating these results to the general population and does not allow us to consider the differences found as evidence for a causal effect of the microbiome on miscarriage.

Review by Gerede et al. [16], which included 44 studies, demonstrated an association between a decrease in the number of lactobacilli, an increase in microbial diversity and a number of pregnancy complications, including pregnancy loss. The authors also draw attention to the potentially protective role of *L. crispatus* and the possible association of individual dysbiotic taxa with adverse pregnancy outcomes. However, heterogeneity of studies and differences in the definition of microbial profiles limit the possibility of formulating universal prognostic criteria. The relationship of the vaginal microbiome to preterm birth is still being actively investigated. Meta-analysis by Gudnadottir et al. [15], women with a low representation of lactobacilli had an increased risk of preterm birth compared with women with a dominance of *L. crispatus*. Potential mechanisms may be the ascending spread of microorganisms and the activation of local inflammatory reactions. Bacteria characteristic of dysbiotic microbial profiles may interact with epithelial cells and components of the innate immune system,

potentially contributing to the formation of a pro-inflammatory microenvironment [15, 16]. However, preterm birth has a multifactorial etiology, so the presence of a dysbiotic profile does not mean that the development of this complication is inevitable.

The relationship between the vaginal microbiome and sexually transmitted infections. Another important pathway through which the microbiome may indirectly influence reproductive function is its interaction with sexually transmitted infections (STIs), including infections caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, and human papillomavirus. A lactobacillus-dominant microbiota may create unfavorable conditions for the colonization and proliferation of a number of potentially pathogenic microorganisms, while dysbiotic profiles may be associated with increased susceptibility to certain infections [4, 6, 9, 10, 15].

The interaction between the vaginal microbiota and STIs is bidirectional: the infectious process may alter the local microbial environment, and features of the microbial community may potentially modulate the conditions for colonization and the course of infection [4, 24]. The consequence of infectious and inflammatory processes can be damage to the pelvic organs, and in some cases, damage to the fallopian tubes and other changes that can negatively affect reproductive potential. Therefore, the vaginal microbiome can be considered as one of the components of a complex system of factors that modulate the risk of infections and related reproductive disorders.

New ways of studying the reproductive tract microbiome. Traditional culture methods allow the identification of only a part of microorganisms and have limitations in assessing complex polymicrobial communities. In contrast, sequencing of the 16S rRNA gene allows determining the bacterial composition of the sample and assessing the relative representation of individual taxa [4, 5]. Shotgun metagenomic sequencing has broader capabilities, as it allows studying not only the taxonomic structure, but also the potential functional genetic potential of the microbial community [4, 5]. Further combination of metagenomics with metatranscriptomics and metabolomics opens up the possibility of assessing the functional activity of microorganisms and the composition of their metabolic products.

However, the results of microbiome studies may significantly depend on the method of sampling biological material, the phase of the menstrual cycle, the method of storing samples, the DNA extraction protocol, and the features of bioinformatic analysis [7, 24]. Contamination control is particularly important when studying low-biome samples, particularly endometrial material [18, 21]. Therefore, comparison of results from different studies requires caution, and standardization of methodological approaches is a necessary prerequisite for the widespread implementation of microbiome profiling in clinical practice.

The accumulation of data on the relationship between microbial composition and reproductive outcomes creates the prerequisites for considering the vaginal microbiome as a potential biomarker of reproductive health. A particularly promising characteristic is the dominance of *L. crispatus*, which has been associated with more favorable reproductive outcomes in a number

of studies [12, 15]. At the same time, the characterization of the microbiome by a single species is insufficient. A potential prognostic test should take into account the taxonomic composition of the community, the relative representation of individual microorganisms, their functional properties, and the stability of the microbial profile over time.

The dynamics of the vaginal microbiota are also supported by the results of a randomized study by Jepsen et al. [25]. In it, spontaneous improvement of the unfavorable microbial profile was observed in 34.2% of participants within one to three months.

Conclusions.

Consequently, current evidence suggests that the vaginal microbiome is a dynamic ecosystem, the state of which depends on the species composition of microorganisms, hormonal status and a number of external and internal factors, and the dominance of certain *Lactobacillus* representatives, in particular *L. crispatus*, is associated with a more stable microenvironment and a lower risk of certain reproductive complications. The identified relationships between dysbiotic changes and infertility, early pregnancy loss, preterm birth and the results of as-

sisted reproductive technologies indicate the prospects for using the characteristics of the vaginal microbiome to assess reproductive health and predict certain adverse outcomes. At the same time, the available data mainly demonstrate associative relationships, and the causal nature of these interactions, the optimal criteria for microbiome profiling, and the clinical effectiveness of microbiome-oriented interventions require further confirmation in standardized prospective and randomized studies.

Prospects for further research.

Prospects for further research consist in an in-depth study of the relationships between the species composition and functional activity of the vaginal microbiome and indicators of women's reproductive health, in particular fertility, pregnancy outcome, and the results of assisted reproductive technologies. It is planned to study the peculiarities of the dynamics of the vaginal microbiome depending on hormonal status, menstrual cycle, and other factors, as well as to assess the prospects for using microbiome markers to predict reproductive outcomes and develop personalized approaches to correct dysbiotic conditions.

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СКЛАД ВАГІНАЛЬНОГО МІКРОБІОМУ ТА ЙОГО ВПЛИВ НА РЕПРОДУКТИВНУ ФУНКЦІЮ У ЖІНОК

Шуба С. С., Сідашенко О. І.

Резюме. Вагінальний мікробіом є складною та динамічною мікробною екосистемою жіночого репродуктивного тракту, яка відіграє важливу роль у підтриманні локального гомеостазу, захисті слизових оболонок від колонізації потенційно патогенними мікроорганізмами та формуванні сприятливого середовища для репродуктивних процесів. У жінок репродуктивного віку вагінальна мікробна спільнота переважно характеризується домінуванням представників роду *Lactobacillus*, серед яких особливе значення мають *Lactobacillus crispatus*, *L. gasseri*, *L. iners* та *L. jensenii*. Порухення стабільності мікробного складу, що супроводжується зниженням представленості лактобацил і збільшенням частки анаеробних мікроорганізмів, розглядається як вагінальний дисбіоз та може бути пов'язане з низкою несприятливих наслідків для репродуктивного здоров'я.

У статті узагальнено результати сучасних досліджень, присвячених взаємодії вагінальної мікробіоти з репродуктивною системою. Встановлено, що переважання *L. crispatus* частіше асоціюється зі стабільним кислим мікросередовищем та сприятливішими умовами для підтримання мікробного гомеостазу, тоді як дисбіотичні профілі характеризуються підвищеною представленістю *Gardnerella*, *Atopobium*, *Prevotella*, *Sneathia*, *Megasphaera* та інших анаеробних мікроорганізмів. Показано, що структура вагінального мікробіому може змінюватися залежно від гормонального статусу, фази менструального циклу, вагітності, використання контрацептивів, антибактеріальної терапії та інших біологічних і зовнішніх чинників. Узагальнення результатів досліджень свідчить про асоціацію дисбіотичних змін із жіночим безпліддям, ранньою втратою вагітності, передчасними пологами та окремими несприятливими результатами допоміжних репродуктивних технологій. Водночас роль окремих мікроорганізмів, зокрема *L. iners*, залишається неоднозначною, а наявні дані переважно демонструють асоціативні взаємозв'язки та не дають змоги однозначно встановити причинно-наслідкові механізми. Перспективним напрямом є використання характеристик вагінального мікробіому як потенційних біомаркерів репродуктивного здоров'я та прогнозування результатів репродуктивного лікування. Отримані дані свідчать про важливе значення вагінального мікробіому для підтримання репродуктивного гомеостазу та обґрунтовують необхідність подальших проспективних і рандомізованих досліджень для уточнення причинно-наслідкових механізмів, визначення найбільш інформативних мікробіомних маркерів та розроблення персоналізованих підходів до корекції дисбіотичних порушень.

Ключові слова: вагінальний мікробіом, *Lactobacillus*, мікробіом ендометрію, дисбіоз, репродуктивне здоров'я жінок.

COMPOSITION OF THE VAGINAL MICROBIOME AND ITS EFFECT ON REPRODUCTIVE FUNCTION IN WOMEN

Shuba S. S., Sidashenko O. I.

Abstract. The vaginal microbiome is a complex and dynamic microbial ecosystem of the female reproductive tract, which plays an important role in maintaining local homeostasis, protecting the mucous membranes from colonization by potentially pathogenic microorganisms, and forming a favorable environment for reproductive processes. In women of reproductive age, the vaginal microbial community is mainly characterized by the dominance of representatives of the genus *Lactobacillus*, among which *Lactobacillus crispatus*, *L. gasseri*, *L. iners* and *L. jensenii* are of particular importance. Disruption of the stability of the microbial composition, accompanied by a decrease in the representation of lactobacilli and an increase in the proportion of anaerobic microorganisms, is considered as vaginal dysbiosis and may be associated with a number of adverse consequences for reproductive health.

The article summarizes the results of modern studies on the interaction of the vaginal microbiota with the reproductive system. It was found that the predominance of *L. crispatus* is more often associated with a stable acidic microenvironment and more favorable conditions for maintaining microbial homeostasis, while dysbiotic profiles are characterized by an increased representation of *Gardnerella*, *Atopobium*, *Prevotella*, *Sneathia*, *Megasphaera* and other anaerobic microorganisms. It was shown that the structure of the vaginal microbiome can change depending on hormonal status, phase of the menstrual cycle, pregnancy, use of contraceptives, antibacterial therapy and other biological and external factors. The generalization of the research results indicates an association of dysbiotic changes with female infertility, early pregnancy loss, preterm birth and some adverse outcomes of assisted reproductive technologies. At the same time, the role of individual microorganisms, in particular *L. iners*, remains ambiguous, and the available data mainly demonstrate associative relationships and do not allow us to unambiguously establish causal mechanisms. A promising direction is the use of vaginal microbiome characteristics as potential biomarkers of reproductive health and predicting the results of reproductive treatment. The data obtained indicate the importance of the vaginal microbiome for maintaining reproductive homeostasis and justify the need for further prospective and randomized studies to clarify causal mechanisms, identify the most informative microbiome markers and develop personalized approaches to correct dysbiotic disorders.

Key words: vaginal microbiome, *Lactobacillus*, endometrial microbiome, dysbiosis, reproductive health.

ORCID and contributionship:

Shuba S. S.: <https://orcid.org/0009-0006-0974-4649>^{BD}

Sidashenko O. I.: <https://orcid.org/0000-0003-2750-026X>^{ABDEF}

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The authors declare no conflict of interest.

Corresponding author

Sidashenko Olha Ihorivna
Dnipro University of Technology
Ukraine, 49005, Dnipro, 19 av. Dmytra Yavornytskoho
Tel.: +380502112520
E-mail: microb.sidashenko@gmail.com

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article.

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Якимчук М. М., Пинда М. Я., Якимчук О. М.

РЕДОКС-ІМУННІ МЕХАНІЗМИ РЕМОДЕЛЮВАННЯ АЛЬВЕОЛЯРНОЇ КІСТКИ ПРИ ГЕНЕРАЛІЗОВАНОМУ ПАРОДОНТИТІ ЗА УМОВ ТИРЕОЇДНОЇ ДИСФУНКЦІЇ: СУЧАСНІ ПАТОГЕНЕТИЧНІ АКЦЕНТИ

Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України
(м. Тернопіль, Україна)

yakymchuk_asp@tdmu.edu.ua

Генералізований пародонтит є хронічним імунізопальним захворюванням, за якого локальна відповідь на мікробну біоплівку трансформується у стійке ушкодження сполучної тканини та резорбцію альвеолярної кістки. Тиреоїдна дисфункція може змінювати інтенсивність цих процесів через вплив на системний метаболізм, редокс-гомеостаз, цитокинову відповідь і кісткове ремоделювання. Мета – узагальнити сучасні дані щодо ролі оксидативного стресу та остеοімуних механізмів як потенційного патогенетичного зв'язку між тиреоїдною дисфункцією і генералізованим пародонтитом. Проведено систематизований наративний аналіз рецензованих публікацій 2020-2026 років, присвячених патогенезу пародонтиту, тиреоїдній регуляції кісткової тканини, окисно-відновним механізмам, системі RANK/RANKL/OPG, цитокинам та клінічним асоціаціям тиреоїдної патології з пародонтальним статусом. Сукупність даних свідчить, що надлишкова генерація активних форм кисню при пародонтальному запаленні активує NF-κB, MAPK та інші редокс-чутливі шляхи, посилює продукцію IL-1β, IL-6 і TNF-α, матриксних металопротеїназ та остеокластогенез. Тиреоїдні гормони і тиреотропін додатково впливають на оборот кісткової тканини, остеοгенну диференціацію клітин періодонтальної зв'язки та метаболічну активність імунних клітин. Експериментальні роботи демонструють вираженіший цитокиновий дисбаланс і деструкцію сполучної тканини при поєднанні пародонтиту з гіпер- або гіпотиреозом, а метааналізи 2024-2025 років підтверджують гірші пародонтальні показники у пацієнтів із тиреоїдними захворюваннями. Редокс-імуна дисрегуляція є біологічно обґрунтованим механізмом, через який тиреоїдний статус може модифікувати перебіг генералізованого пародонтиту, однак наявні клінічні дані переважно асоціативні й потребують підтвердження проспективними та експериментальними дослідженнями.

Ключові слова: генералізований пародонтит, тиреоїдна дисфункція, оксидативний стрес, RANKL/OPG, альвеолярна кістка.

Зв'язок публікації з плановими науково-дослідними роботами.

Робота є фрагментом планової науково-дослідної роботи кафедри дитячої стоматології Тернопільського національного медичного університету імені І. Я. Горбачевського МОЗ України «Удосконалення лікування та профілактики захворювань зубів і пародонта в осіб різного віку та соматичного стану» (номер державної реєстрації 0123U100066).

Вступ.

Сучасне розуміння генералізованого пародонтиту вийшло далеко за межі уявлення про локальну бактеріальну інфекцію. Мікробна біоплівка залишається необхідним пусковим чинником, однак ступінь руйнування тканин визначається характером і тривалістю відповіді організму господаря. Хронічна активація вродженої та адаптивної імунної системи підтримує продукцію прозапальних медіаторів, протеолітичних