

The importance of the genital tract microflora in the endometriosis development

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Endometriosis is a common pathology among women of reproductive age. In the pathogenesis of its development a great importance is paid to the process of regulation of estrogens and other sex hormones, the implementation of the immune response at the general and local levels, the inflammatory response, and genetic background. In recent years, the role of the microbiota in different parts of the genital tract of the female organism has been studied not only from the standard approach of inflammatory diseases research of the reproductive organs and pathological vaginal discharge, but its contribution into the development of other gynecological diseases, in particular endometriosis, is presented.

The article is devoted to a review of scientific publications about researches devoted to the significance of the genital tract microflora in the pathophysiology of endometriosis. The article presents the concepts of states of eubiosis and dysbiosis, describes the features of the microflora of the lower (vagina, cervix) and upper parts (uterus, fallopian tubes) of the genital tract in healthy women. The data on the importance of *Lactobacillus* in maintaining an optimal state of acidity in the vaginal environment are presented.

The difference in the composition of the microbiota of the vagina, cervical mucus, uterine cavity and peritoneal fluid in women with and without endometriosis is revealed. The pathogenetic mechanisms of the role of the microbiota in the processes of endometriosis pathogenesis, namely, the regulation of the immune response and inflammation processes in this pathology, are described. It has been shown that in women with endometriosis there are differences in the microflora composition of the vagina, cervix, uterine cavity, peritoneal fluid, manifested by a decreased concentration of *Lactobacillus* and the presence of a variety of other microorganisms in relation to healthy women. The data about the role of gut microflora in patients with this pathology are also presented. The results of research about the diagnosis of various stages of endometriosis by studying the composition of the genital tract microbiota are described.

Keywords: endometriosis, pathogenesis, vagina, uterus, microbiota, microorganisms, vaginal microflora, microbiome.

Значення мікрофлори генітального тракту у розвитку ендометріозу

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Ендометріоз є поширеною патологією серед жінок репродуктивного віку. У патогенезі його розвитку важливе значення надається процесу регуляції естрогенів та інших статевих гормонів, реалізації імунної відповіді на загальному та локальному рівнях, запальній реакції, генетичному підґрунті. Останніми роками вивчається роль мікробіоти у різних відділах генітального тракту жіночого організму не тільки з позиції вивчення запальних захворювань репродуктивних органів та патологічних вагінальних виділень, але й виникнення та розвитку іншої гінекологічної патології, зокрема ендометріозу.

Стаття присвячена огляду наукових публікацій про значення мікрофлори генітального тракту у патофізіології ендометріозу. У статті наведено поняття станів еубіозу та дисбіозу, описані особливості мікрофлори нижнього (піхва, шийка матки) та верхнього (матка, маткові труби) відділів генітального тракту у здорових жінок. Представлено дані важливості *Lactobacillus* у підтриманні оптимального стану кислотності у піхвовому середовищі.

Детально розглянуті питання відмінності складу мікробіоти піхви, цервікального слизу, порожнини матки та перитонеальної рідини у жінок з та без ендометріозу. Наведено патогенетичні механізми ролі мікробіоти у процесах патогенезу ендометріозу, а саме – регуляції імунної відповіді та процесів запалення за даної патології. Зазначено, що у жінок з ендометріозом існують відмінності у складі мікрофлори піхви, шийки матки, порожнини матки, перитонеальної рідини, які проявляються зменшенням концентрації *Lactobacillus* та наявністю різноманіття інших мікроорганізмів щодо здорових жінок. Також представлено дані про роль мікрофлори кишечника у хворих із даною патологією. Описано результати досліджень стосовно діагностики різних стадій ендометріозу за допомогою вивчення складу мікробіоти генітального тракту.

Ключові слова: ендометріоз, патогенез, піхва, матка, мікробіота, мікроорганізми, вагінальна мікрофлора, мікробіом.

Microbiota of a woman's genital tract reflects the state of her gynecological and reproductive health [1]. Eubiosis means the state a healthy and balanced ecosystem. In the upper part of the genital tract it is characterized by the presence of >90 % *Lactobacillus* spp., *Bacteroides*, *Bifidobacterium*, *Pseudomonas*, a low microbial load, the ability to restore tissues, moderate immune stimulation, and in the lower part of the genital tract – a slight diver-

sity (α - β) of microflora, the dominance of *Lactobacillus* which corresponds to I, II, III and V types of microbial communities in the vaginal environment according to J. Ravel et al. [2].

Several types of microorganisms are included into the vaginal microbiota. The dominance of various species of *Lactobacillus* in the lower part of the genital tract is a sign of the health of the female reproductive system [3].

In healthy women a small variety of these microorganisms was found in the vagina [2, 4]. *Lactobacillus* provide stability of the vaginal environment [1, 2, 3, 5, 6]. However, the diversity of the composition of the vaginal microbiome is really large. The results of a metagenomic analysis of the vaginal microbiome of healthy women in the Chinese population, obtained by F. Liu et al., determined 111 types of microorganisms [7].

Lactobacillus contribute to the prevention of genital infections by maintaining optimal acidity in the vaginal environment [8, 9]. This is ensured by the fact that *Lactobacillus* and other enzymatic microorganisms synthesize lactic acid [6], for the production of which *Lactobacillus* use glycogen [4, 7]. In addition, a significant number of microorganisms in the vagina, including *Lactobacillus*, secrete amylase, which breaks down glycogen into simpler compounds that support the vital activity of bacterial populations [6].

Estrogen and progesterone also affect the composition of the vaginal microflora. Estrogens contribute to the accumulation of glycogen through the proliferation of vaginal epithelial cells. Progesterone promotes the lysis of vaginal epithelial cells and the release of glycogen, maintaining the pH of the vagina [10]. The mechanisms of the role of estrogens in vaginal immunity are still unclear [9]. However, scientists have established a connection between the immune system and the vaginal microbiota [9, 11].

There are endo- and exogenous factors that lead to changes in the composition of vaginal microflora – menstrual cycle, pregnancy, age, ethnicity, race, use of contraceptives, sexual activity, etc. [2, 5, 6, 8, 10, 12]. However, the results of B. Chaban et al. research demonstrated that during the menstrual cycle in healthy women the composition of the vaginal microbiota remains relatively stable [13].

A difference in the composition of microbial communities in the cervical canal, uterus, fallopian tubes, and peritoneal fluid compared to the vagina was found [14]. *Lactobacillus* also predominate in cervical mucus, but their percentage relative to the vagina is less [15]. According to the literature review, it was established that *Lactobacillus* species predominate, except for the vagina, in endometrium. Greater variability of *Lactobacillus* is observed in fallopian tubes and ovaries compared to the lower parts of the genital tract [2].

The uterine cavity is not sterile, as it was thought until recently. However, studies indicate that the microbial biomass of the endometrium is 100-10,000 times less than the bacterial content of the vagina [16]. I. Moreno et al. divided the endometrial microbiota into categories: *Lactobacillus* dominant (LD), in which the content of *Lactobacillus* spp. is >90%, and non-*Lactobacillus* dominant (NLD), which is characterized by the proportion of *Lactobacillus* spp. at the level of <90% and the rate of other bacteria is >10% [17]. The scientists have found that the microbial composition of the uterus differs from the vagina and contains up to 191 operational taxonomic units [17].

Dysbiosis is a non-homeostatic condition, the signs of which in the upper parts of the genital tract are a decrease in the content of *Lactobacillus* spp. (NLD) to less than 90 %, the detection of *Staphylococcus* spp., *Enterobacter* spp., a significant microbial load (infection), tissue dam-

age, immune stimulation [2]. In the lower parts, signs of dysbiosis are a significant diversity of microorganisms, the presence of type IV microbial community (*Anaerobes* species, *Gardnerella*, *Prevotella*, *Atopobium*) [2].

Bacterial vaginosis and anaerobic polybacterial dysbacteriosis are the most common changes in the vaginal microbiome [18]. Vaginal dysbiosis is known to be associated with increased sensitivity and susceptibility to human immunodeficiency virus, transmission of human immunodeficiency virus and other sexually transmitted microorganisms, an increased risk of development of inflammatory processes of the female genital organs, preterm labor, maternal infections during pregnancy and neonatal infections [18].

It has been established that the gut microbiota affects the intestinal environment, which influence on the distant organs [19]. Thus, changes in the composition of the gut microbiota can contribute to the development of such gynecological pathologies as polycystic ovary syndrome, endometriosis, and cancer [19, 20].

Endometriosis is a hormonally depended gynecological pathology, which is diagnosed in approximately 10 % of women in reproductive age. The reason of the pathology is the growth of the endometrium outside the uterine cavity [21]. The main symptoms of endometriosis are chronic pelvic pain, infertility, menstrual cycle disorders, and so on [22].

It was found that changes in estrogen metabolism lead not only to the development of endometriosis, but also they contribute to inflammation of the endometrium, changes in the vaginal microbiota, and genetic factors play an important role in the pathogenesis of the disease [23].

Researchers believe that the NLD microbiota is not only associated with adverse pregnancy outcomes or bacterial vaginosis, but can provoke an inflammatory response in the endometrium, which is one of the main factors in the development of endometriosis, so it should be considered that the changed endometrial microbiota or the dominance of NLD is related to this pathology [17].

The mechanisms of endometriosis, namely, disorders in the immunoregulatory functions of the microbiota due to dysbacteriosis have a lot of common signs with such diseases as inflammatory bowel disease, psoriasis, arthritis, and cancer [24]. It is known that dysbiosis in the intestines and vagina leads to changes in the functioning of the immune system, namely, to an increase of pro-inflammatory cytokines, damage of immune cells, which plays a role in the pathogenesis of endometriosis [24]. Immune dysregulation can subsequently contribute to the appearance of a chronic inflammatory process, which together with the activation of mechanisms of adhesion and angiogenesis, leads to the progression of endometriosis [24].

One of the explanations for the occurrence of endometriosis is the theory of the retrograde menstrual blood flow through the fallopian tubes to the abdominal cavity. The difference in the immune response in the peritoneal environment may be a hypothesis why in some cases endometrioid lesions appear, in particular, on the intestine and peritoneum [25, 26, 27, 28]. A more pronounced immune response will be in the cases of the intestinal dysbacteriosis, because intestinal bacteria stimulate neutrophils, acti-

vate CD4 T-cells, while the barrier function is disturbed, the release of microbial metabolites occurs, and this leads to inflammatory changes, an increase in the number of peritoneal macrophages, the ability of which is somewhat limited in phagocytosis of new implanted endometrial foci, thus a long-term inflammatory process develops, the persistence of foci and progression of endometriosis occurs [25, 26, 29, 30].

A study of W. Wei et al. indicates that there is a difference in the composition of the microbiota in different parts of the reproductive tract in women with endometriosis. In the lower parts, in particular, in the lower third of the vagina and the posterior vault, *Lactobacillus* predominate. Starting from the cervix and in the upper parts of the genital tract (endometrium, peritoneal fluid), a more pronounced diversity in the composition of the microbiota was found, namely, an increase in the number of operational taxonomic units, which may indicate the presence of a bacterial component in the development of the disease [31].

The association between the bacterial factor and endometriosis is emphasized by the studies of the groups of scientists W. C. Lin et al. and F. W. Tai et al., which demonstrated that women with infectious processes of the lower part of the genital tract or inflammatory processes of the internal genital organs in the anamnesis have an increased risk of endometriosis in 2-3 times [32, 33]. The results of the study of J. Kunaseth et al. confirm a similar proportion of *Lactobacillus* in the composition of the microbiota of the vaginal environment in women with adenomyosis (51.20 %) and women without adenomyosis (50.54 %) [34]. However, scientists have found an increased number of operational taxonomic units of vaginal microorganisms such as *Alloscardovia*, *Oscillospirales*, *Ruminococcaceae*, *UCG_002*, *Oscillospiraceae*, *Enhydrobacter*, *Megamonas*, *Moraxellaceae*, *Subdoligranulum*, *Selenomonadaceae* and *Faecalibacterium* in patients with adenomyosis [34].

The study of the vaginal microbiota for the determination of the endometriosis stage according to the updated recommendations of the American Society for Reproductive Medicine (revised American Society for Reproductive Medicine) is being considered. It was found that the vaginal and gut microbiota is associated with the degree of endometriosis and the presence of 1-2 stages of endometriosis can be most accurately assumed than 3-4 stages. At the same time, the operational anaerobic unit from the genus *Anaerococcus* was found to be the greatest prognostic criterion for establishing the stages of the disease [35].

It was found that women with endometriosis/adenomyosis and clinical manifestations of chronic pelvic pain had an increased number of *Clostridium butyricum*, *Clostridium disporicum*, *Alloscardovia omnicoles*, *Veillonella montpellierensis* in the vaginal environment compared to women with chronic pelvic pain without endometriosis/adenomyosis and women without chronic pelvic pain [36]. The presence of such microorganisms as *Clostridium butyricum*, *Clostridium disporicum*, *Alloscardovia omnicoles* and *Veillonella montpellierensis* in the vaginal environment, as well as the simultaneous deficiency of *Lactobacillus jensenii*, *Lactobacillus reuteri* and *Lactobacillus iners* can be considered as potential pathogens and markers

of chronic pelvic pain that occurs in women with the background of endometriosis/adenomyosis. When the relative amount of *Clostridium disporicum* exceeds 0.001105 % and *Lactobacillus reuteri* is less than 0.1911349 %, the differential diagnostic sensitivity and specificity are 81.08 % and 52.0 %, respectively. When CA125 in blood serum is included in the diagnostic algorithm, the sensitivity of the method increases to 89.19 %, but the specificity remains unchanged at the level of 52.0 % [36].

In women with endometriosis there is a tendency to the increased concentration of Firmicutes pathogens and a decreased in the content of Actinobacteria and Bacteroides bacteria in the cervix. In the late stages of endometriosis, deep infiltrative endometriosis, the presence of a high level of CA125, as well as in patients with a pronounced pain syndrome and infertility caused by endometriosis, there is an unstable content of *Lactobacillus* in the cervical canal in combination with an increase in the level of Streptococci and a decrease in the content of microorganisms of the *Dialister* group [37]. The study of K. Akiyama et al. presents that although *Lactobacillus* spp. prevailed in the cervical mucus in women with endometriosis, there was an increased content of such pathogens as *Corynebacterium*, *Enterobacteriaceae*, *Flavobacterium*, *Pseudomonas* and *Streptococcus* in the patients. Of these microorganisms, the highest concentration was determined for *Enterobacteriaceae* and *Streptococcus* [38]. A group of scientists head by B. Ata established that in the cervical environment in patients with III-IV stages of endometriosis there is an increased content of pathogenic bacteria (*Gardnerella*, *Shigella*, *Streptococcus*, *Escherichia*, *Ureaplasma*) [39].

In patients with endometriosis compared to healthy women there are changes in endometrial microbiota composition. Thus, there is a decrease in the concentration of *Lactobacilli* in the endometrium and an increase in the number of pathogens that contribute to the development of bacterial vaginosis and the high concentration of opportunistic bacteria are determined in the patients with endometriosis [24]. In women with endometriosis among the bacterial taxa in the endometrium microbiota gram-positive (*Actinobacteria* phylum, *Streptococcaceae*) and gram-negative microorganisms (*Oxalobacteria*, *Tepidimonas*) are often detected, while in patients with a pain syndrome that is not related to endometriosis, which was confirmed during surgery interventions, and persons with other benign gynecological pathology, often gram-negative pathogens (group *Burkholderiaceae* and *Ralstonia*) are established [40]. The endometrial microbiota in endometriosis is enriched by *Actinobacteria* phylum, *Oxalobacteriaceae* and *Streptococcaceae* families, and *Tepidomonas* genus relative to symptomatic patients without endometriosis [40].

In the women with endometriosis in the peritoneal fluid according to the results of W. Yaun et al. study the slight changes in the microbiota in relation to such pathogens as *Acidovorax*, *Devosia*, *Methylobacterium*, *Phascolarctobacterium*, *Streptococcus* was found [41], and research of S-R. Lee et al. indicates an increased content of *Acinetobacter*, *Pseudomonas*, *Streptococcus*, and *Enhydrobacter* and a reduced number of *Propionibacterium*, *Actinomyces*, and *Rothia* relative to control women [42].

However, scientific data regarding the importance of the microbiota of the genital tract in the genesis of endometriosis are controversial. According to the research of S. Hernandez et al. a similar composition of microorganisms in the vaginal environment, eutopic endometrium and endometrioid foci, consisting of *Lactobacillus*, *Gardnerella*, *Streptococcus* and *Prevotella*, was found between healthy women and patients with endometriosis. However, deep endometriosis foci have been detected to have a dissimilar bacterial composition with a lower number of *Lactobacillus* and a higher number of *Alishewanella*, *Enterococcus*, and *Pseudomonas* [43].

More and more studies are finding a relation between gut microbiota and endometriosis. Gut microflora can play a role in the mechanisms of endometriosis development through the processes of estrogen regulation and immune inflammation [26, 44, 45]. The studies on the animals suggest a two-way relationship between the gut microbiota and the onset and progression of endometriosis [23]. It was established that the assessment of the state of the gut microbiota is more informative for the diagnosis of endometriosis than the composition of the microbiota of the cervix [46].

Thus, it remains important to study the role of the genital tract microbiota in the development of endometriosis, which is confirmed by many researches.

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