SCIENTIFIC REVIEWS AND LECTURES

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MICROBIOME OF THE REPRODUCTIVE TRACT OF WOMEN AND INFLAMMATORY DISEASES OF THE PELVIC ORGANS

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The study of the microbiota of the uterus and placenta in clinically healthy women completely refutes the opinion that has existed for many years about their sterility. Recent studies have proved the relationship of the microbiota of the uterus and vagina with the frequency and characteristics of the clinical manifestations of inflammatory diseases of the pelvic organs. The literature review provides modern data on the genital microbiocenosis, describes the role of the most common microorganisms in the initialization of the inflammatory process. Features of the species composition of the microbiota of the uterus and vagina determine the tendency to chronicity of the inflammatory process and the severity of the negative impact on the reproductive health of women. The integral role of opportunistic microorganisms is described in the development of inflammatory diseases of the pelvic organs. A clinically healthy woman is dominated by lactobacilli in a vaginal microbiota, but a few conditionally pathogenic microflora may be present in the normal vaginal microflora: *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum,* yeast-like fungi of the genus *Candidaopobobus*, bacteriidae *Preobobus bacteria*, and bacteria representatives, *Megasphaera, Dialister, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia.* Some recent studies show that about 25% of healthy women have a "non-lactobacillary" type of physiological microbiocenosis, represented by a spectrum of anaerobic bacteria. Conditionally pathogenic microorganisms that are involved in the inflammatory process contribute to the excessive activation of mediators of inflammation of the macroorganism. The development of chronic forms is very often provoked wth long-standing non-specific inflammatory processes, which subsequently are difficult to respond to drug therapy. Untimely treatment of PID is associated with the deterioration of the patient's condition and long-term complications. However, even with timely treatment, distant complications may occur. One study showed that in women with PID, between the ages of 20 and 24, 18% will eventually develop chronic pelvic pain, 8.5% will have an ectopic pregnancy, and 16.8% will have infertility.

Keywords: microbiome, inflammatory diseases of the pelvic organs, chronic inflammatory processes in the pelvic organs, conditionally pathogenic microorganisms, infertility, reproductive health.

The study of the microbiome and its impact on human health has been the subject of active research in recent years. Microbiota is a collection of microorganisms present in a separate human biotope that are in symbiosis with the host organism [31, 33]. There is currently no clear understanding of the role of microbiota in maintaining physiological equilibrium and developing a pathological process in an organ. Studies on healthy volunteers using precision methods to determine the species composition of uterine microbiota and placenta in women show that they have their unique microflora, which completely refutes the long-standing view of their sterility. A W. Adrews study with co-authors of endometrial microflora composition in patients who had spontaneous premature birth and induced premature birth in history showed that there was no significant difference in microbial insemination of the endometrium. *Gardnerella vaginalis, Lactobacillus spp., Streptococcus viridians, Peptostreptococcus spp., Mycoplasma hominis, Ureaplasma urealyticum* were most frequently isolated. By cultural method, the state of microbiota of uterine cavity was evaluated in the work of M.N. Chertovsky and S.I. Kulinich in 2013. Microflora, represented by polymicrobic associations of opportunistic microorganisms, prevailed in most patients [8].

Relatively recently, a new approach has emerged to study the microbiota of the reproductive tract, particularly the uterine cavity, through molecule-genetic methods of study. In the S. Hilier study, in women with clinical signs of chronic pelvic pain, endometritis was confirmed histologically at 40%. As a result, a wide range of bacteria was obtained, represented by 63 different species, including 8 species of opportunistic microorganisms. The presence of true pathogens such as Neisseria gonorrhoeae and/or Chlamydia trachomatis has been associated with endometrite in 29% and 6% of cases. Among opportunistic microorganisms, G.vaginalis 35% and A.vaginae 22% were reliably identified in histologically confirmed endometritis. As a result of a study conducted by Franasiak J.M. et al., 15 bacterotypes of microorganisms were presented. In 90% of patients, a similar composition of uterine cavity microbiota was found, in which Bacteriodes xylanisolvens, B. thetaiotaomicron and B.fragilis dominated [31, 32].

Due to the data of the study of the vaginal microflora, lactobacilli predominate in a vaginal microbiota in a clinically healthy woman, despite this, the normal vaginal microflora may include a small number of conditionally pathogenic microflora representatives: Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum, yeast-like fungi of the genus Candidaopobobus bacterias, Preida mobius, bacterial bacteria, and bacteria representatives, Megasphaera, Dialister, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia. Some recent studies show that about 25% of healthy women have a "non-lactobacillary" type of physiological microbiocenosis, represented by a spectrum of anaerobic bacteria. All women with this type of microflora have a small number of representatives of lactoflora [7, 8].

A study by Mitchell M. et al. examined female uterus samples obtained after a hysterectomy. Microbial contamination of the uterine cavity was detected in 95% of patients, of which only 1 type of microorganism was found in 90% of patients. The most common species were: Lactobacillus iners, Prevotella spp., Lactobacillis crispatus [26]. Colonization of the uterine cavity by microorganisms was significantly lower than the vagina. Markers of inflammation in the endometrium did not differ significantly in women who did not find microorganisms in the uterine cavity compared with those who only found bacilli, or microbes associated with bacterial vaginosis (BV) were present.

Among violations of the microecology of the vagina, bacterial vaginosis occupies a leading position, makes up 30-

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80% of all infectious lesions of the vagina and shows a tendency to spread. Studies in this area indicate the presence of various obligate-anaerobic and facultative anaerobic microorganisms in patients with BV in 96.2% of cases. According to some authors, in 60% of cases, patients with confirmed colonization of the endometrium had violations of the vaginal microecology. The bacterial flora isolated in this case was of microaerophilic, obligate-anaerobic and facultative anaerobic origin. Determination in the microflora of the uterine cavity of such BV-associated representatives as Propionobacterium spp., Eubacterium spp., Peptostreptococcus spp., Bacteroides spp., Prevotella spp., Porphyromonas spp., Fusobacterium spp., Vellonella spp., Corppbacter. spp., Streptococcus spp., Enterococcus spp., Enterobacter spp., E. coli, Klebsiellaa spp., Gardnerella vaginalis, proves their participation in the development of inflammatory changes in the endometrium. It is shown that in the occurrence of inflammatory diseases of the pelvic organs (PID), a significant role belongs to the combined infection, in which 2-6 pathogens are involved with a predominance of representatives of obligate-anaerobic microflora. In 67.2% of cases, asymptomatic persistence of microorganisms occurs. Conditionally pathogenic microorganisms that are involved in the inflammatory process contribute to the excessive activation of mediators of inflammation of the macroorganism. With long-standing non-specific inflammatory processes, the development of chronic forms is very often provoked, which subsequently are difficult to respond to drug therapy. The chronic inflammatory process is an open gate for various viruses, the development of precancerous, cancerous processes due to a decrease in local immunity [1, 8, 33].

Inflammatory diseases of the pelvic organs (PID) are the most common diseases of the reproductive system in modern time in gynecology and have a negative impact not only on the reproductive health of women, but also on the overall incidence and quality of life [2, 3, 10, 12, 19].

Under current conditions, inflammatory diseases of the genital organs have special characteristics: an increase in the value of the conditionally pathogenic flora in the development of the pathological process, the absence of specific clinical symptoms, the transformation of the clinical picture in the direction of the erased forms and atypical course, the growth of antibiotic resistance of microorganisms, multi-focal inflammatory lesions, which creates significant difficulties in the diagnosis. “In mixed infections, some pathogens can create favorable conditions for the penetration, persistence and reproduction of other microbes, thereby increasing their pathogenicity” [4, 9, 11]. For example, the revealed “relationship between gonococcal infection and infection with M. hominis and U. Urealyticum: colonies of mycoplasmas and ureaplasmas grow on the surface of gonococcal colonies” [5, 6]. Also, some authors point to the “possibility of a synergistic action of U. urealyticum and G. vaginalis” [21, 23]. Ureaplasmas and mycoplasmas are often detected in patients with PID, but, despite this, their unconditional role in the development of the inflammatory process requires clarification. It is believed that these microorganisms are indicators of bacterial contamination of the genital tract, and not the main cause of the infectious process. According to some authors, ureaplasmas are found in 80% of women with symptoms of genital tract infection and in 51% of women with reproductive health problems.

The main trigger in the development of PID is microbial invasion. The cervix is one of the important structures that acts as a protective barrier to the spread of bacteria in the internal genital organs. The presence of pathogenic bacteria in the cervical canal can indicate both its syncretism and true colonization [22].

At present, in the etiology of PID, the frequency of occurrence of microbial associations in the form of biofilms is very high, which, according to various authors, is 52-96.7% [13].

Analyzing the situation today, it should be noted that the data on the frequency of STIs in Russia vary, which may be due to the incompleteness of the data provided by paid clinics. Moreover, according to the statement of the President of the Russian Society of Dermatovenerologists and Cosmetologists, director of the State Research Center of Dermatovenerology and Cosmetology Federal State Budgetary Institution of the Ministry of Health of Russia A. A. Kubanova at the XV All-Russian Congress of Dermatovenerologists and Cosmetologists held in 2015, “by 2014 the frequency of STIs for the last 10 years decreased by an average of 64%: syphilis - by 68%, gonococcal infection - by 49% ”[18].

The number of patients with PID in Russia includes about 60-65% who applied to medical institutions and 30% of patients hospitalized in a hospital [17, 18].

The highest PID incidence rate occurs at the age of 18-29 years, and is reliably comparable with an active sex life and with a low use of barrier methods of contraception. Between 2006 and 2013, there was a decrease in the prevalence of PID in the United States. The number of annual visits to emergency departments for PID has also decreased. Nevertheless, as of 2013, this indicator was still significant - 0.41% of all visits to the emergency department or from a total of 7.4 million visits [34]. Although the exact cause of the decrease in the prevalence of PID is unknown, it is believed that increased screening for sexually transmitted infections (STIs), leading to earlier detection and treatment, increased accessibility and adherence to antibiotics, and improved diagnostic testing may be contributing factors [27].

A study of PID in younger populations showed that adolescents are at even greater risk of PID and related complications. It is estimated that one in five cases of PID occurs in women younger than 19 years of age, and in one study, adolescents and young women aged 17–21 years were twice as likely to have PID as in other age groups. It is believed that an increased risk of PID in adolescents is secondary to a combination of behavioral and biological factors. In terms of behavioral risk, adolescents can have several sexual partners, have unprotected sex, and have short-term and high-frequency monogamous relationships [1, 28]. Biologically adolescents have a large fraction of the surface area for infection by microorganisms. Trent et al. also found in a PEACH (PID Evaluation and Clinical Health) study that adolescents under the age of 19 with relapsing PID are five times more likely to report chronic pelvic pain 7 years after the diagnosis of PID. In addition, adolescents in the PEACH study (PID Evaluation and Clinical Health) developed PID relapse in a shorter period of time than in adult women [24].

Inflammatory processes in the endometrium lead to its structural and functional inferiority, a violation of the receptor apparatus, which in turn causes premature termination of pregnancy.

Untimely treatment of PID is closely associated with the deterioration of the patient's condition and long-term complications. However, even with timely treatment, distant complications may occur. One study showed that in women with PID, between the ages of 20 and 24, 18% will eventually develop chronic pelvic pain, 8.5% will have an ectopic pregnancy, and 16.8% will have infertility [29, 30]. The problem of barren marriages has also become more and more relevant recently.

In the Russian Federation, the frequency of female infertility continues to increase and makes 517.5 per 100.000 female population. In addition, the number of ectopic pregnancy in the Russian Federation in the structure of the causes of maternal mortality reaches 3%, and in some years this figure can reach 6-7%.

An inseparable link of the complex mechanism of the onset and development of pregnancy is each organ of the female reproductive system, violations in any of which under the influence of infection can lead to infertility [15].

Inflammatory diseases of the pelvic organs take part in increasing the production of antisperm antibodies (ASAT). They are one of the known immunological factors preventing fertilization, enhancing sperm agglutination and gluing their heads to each other, which prevents them from moving through the cervical canal and blocks capacitation. The study of Yu.A. Petrov, which was conducted among women with infertility of inflammatory genesis, had high ASAT indicators, where the presence of all classes of immunoglobulins in the blood serum was significantly increased, which in turn could reflect the absence of physiological cyclicity among the indicators of the immune system. Elevated levels of IgM, IgA, IgG in cervical mucus cause the development of rejection reactions of the embryo.

Another cause of infertility due to chronic inflammation of the female genital organs is a violation of the receptivity of the endometrium and, as a result, endocrine dysfunction. A.R. Kotikov et al. data indicate the severity of the inflammatory process, which is inversely proportional to the level of expression of steroid hormone receptors - estrogen and progesterone. The inflammatory process inhibits local expression of markers of rapid proliferation. Moreover, a decrease in expression is most significant on the part of progesterone receptors, which explains the failure of the endometrium for blastocyst implantation [13, 14].

The cause of tubal-peritoneal infertility in 30-72% of cases is the pathology of the fallopian tubes of inflammatory genesis. Moreover, the peritoneal factor is present, only in 27% of patients with tubal infertility. Most patients with inflammatory changes in the fallopian tubes present a violation of their patency. As a result of cicatricial and sclerotic changes, obstruction occurs, as a result of the effects of infections on the tubular epithelium. With the progression of inflammatory infiltration of the walls of the tubes and atrophy of the ciliary epithelium of the mucous membrane, the occurrence of inflammatory obstruction of the fallopian tube, an excessively secreted secret stretches the walls of the tube, turning it into a hydrosalpinx. Due to squeezing of the epithelium, necrotic changes occur, which primarily cover the ciliary epithelium: its decylation occurs. If pus accumulates in the lumen of the tube, a pyosalpinx is formed. These anatomical and functional changes in the fallopian tubes significantly disrupt the advancement of the egg into the uterine cavity, and prerequisites for the development of an ectopic pregnancy or infertility arise [16].

Conclusion. Thus, the complex of changes arising in the reproductive organs of women in response to the vital activity of microorganisms can be reversible. However, the characteristics of the microbial landscape often determine the possibility of a manifestation of the inflammatory process, the nature of the clinical manifestations, the severity of pathomorphological disorders and the risk of developing reproductive function disorders, including infertility.

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