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MICROBIAL LANDSCAPE OF THE ENDOMETRIUM IN PATIENTS WITH CHRONIC ENDOMETRITIS.

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Annotation: The aim of the study was to investigate the microbiological features of chronic endometritis (CE) in women of reproductive age. A total of 76 patients with histologically confirmed CE were examined, divided into two groups according to the degree of inflammation activity. Real-time PCR with the Femoflor-16 kit was used to analyze the endometrial microbiota. In patients without CE, the microbiota was predominantly represented by Lactobacillus spp. (85.0%) and Eubacterium spp. (60.0%). In moderate CE, Streptococcus spp., Staphylococcus spp. and Enterobacteriaceae spp. were detected more often, while associations of Mobiluncus spp./Corynebacterium spp. and Gardnerella vaginalis/Prevotella bivia/Porphyromonas spp. were less common ($p < 0.05$).
Key words: chronic endometritis; women of reproductive age; endometrium; microbiota; microorganisms.

Chronic endometritis (CE) remains a pressing issue, especially among women of reproductive age, which maintains high interest in the study of this pathology. The prevalence of CE varies from 3% to 98% according to various studies. Modern studies focus on the study of etiology, pathogenesis, effectiveness of antibacterial therapy and criteria for assessing treatment. Particular attention is paid to the role of microbial associations, especially aerobic-anaerobic ones. It has been established that associations of microorganisms are more aggressive than monocultures. More than 20 types of opportunistic microorganisms (129 strains) were identified in the endometrium, including obligate anaerobes (61.4%: bacteroides, eubacteria, peptostreptococci, etc.), microaerophiles (31.8%: genital mycoplasmas and diphtheroids), and facultative anaerobes (6.8%: group B and D streptococci, epidermal staphylococcus).

Inflammation of the endometrium often changes the composition of the cervical canal microbiome. However, there are opinions that the microbial factor does not play a decisive role in the development of CE, since the frequency of endometrial contamination in complex microbiological studies is 52.7%. Nevertheless, the results of modern studies confirm the participation of representatives of the vaginal and cervical flora in the infection of the endometrium. At the same time, intrauterine infections caused by Neisseria gonorrhoeae or Chlamydia trachomatis are not always associated with chronic pelvic pain in histologically proven CE. Studies have shown ambiguous results in assessing the correspondence of cultures from the uterine cavity, cervical canal and vagina, including differences in the type of pathogens. This indicates a possible influence of the cervical canal microbiome on the development of inflammatory processes in the uterine cavity in non-pregnant women. However, the isolation of pathogens in inflammatory diseases of the pelvic organs remains a difficult task in modern conditions.

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The aim of this study was to identify the microbiological characteristics of chronic endometriitis in women of reproductive age.

Materials and methods of the study.

The study involved 76 women with histologically confirmed chronic endometritis (CE). The following inclusion criteria were used: age from 18 to 45 years, presence of histologically verified active CE, detection of an infectious pathogen or association of microorganisms from the lesion (endometrium), as well as the absence of sexually transmitted diseases at the time of the study.

Exclusion criteria were: use of hormonal, antibacterial or immunomodulatory drugs (systemically or locally), postpartum or post-abortion periods. All participants provided written informed consent, and the study protocol was approved by the local ethics committee.

The control group included 20 gynecologically healthy women who sought pregnancy planning.

Patients with CE were divided into two groups depending on the degree of activity of the inflammatory process and the results of the morphological study of the endometrium:

• Group 1 - 36 women (47.4%) with a low degree of CE activity,

• Group 2 - 40 women (52.6%) with a moderate degree of CE activity.

The age of the participants ranged from 19 to 40 years, averaging 27.8 ± 1.07 years. The age characteristics of the groups were comparable, with the most common age range being from 22 to 30 years.

The patients were examined using a standard method, including collection of passport data, life and disease history, complaints, as well as a general clinical and gynecological examination.

A double-lumen catheter was used to obtain the contents of the uterine cavity, preventing contamination of the samples with vaginal and cervical canal microflora. Real-time polymerase chain reaction (PCR) was used to analyze the types and amounts of endometrial microbiota using the Femoflor-16 reagent kit (NPO DNA-Technology, Moscow). DNA was extracted from 100 µl of the sample using the Proba-GS reagent kit (NPO DNA-Technology, Moscow) according to the instructions. Numerical data were tested for normality using the Kolmogorov-Smirnov test. Quantitative indicators were processed statistically, the arithmetic mean (M) and its error (SE) were calculated. The statistical significance of differences between values was determined using Student's t-test, with the minimum acceptable significance level being $p<0.05$.

Results and discussion.

Among the examined patients, the largest number were office workers (44.7%) and housewives (42.1%). Among the extragenital diseases, acute respiratory viral infections (39.5%) and urinary tract infections (34.2%) were common. According to the anamnesis, spontaneous miscarriages, abortions and ectopic pregnancy were recorded in 23.7%, 40.8% and 6.6% of women, respectively. Pregnancy loss was reported by 43.4% of patients. Of the gynecological diseases, ectopia (28.9%) and chronic cervicitis (26.3%) were most common. Inflammatory diseases of the uterus and appendages, including complications after abortions or childbirth, were reported in 39.5% of cases.

The average duration of chronic endometritis was 3.6±0.8 years. The main complaints of patients included lower abdominal pain (43.4%), painful menstruation (57.9%), abnormal vaginal discharge (24.4%), painful intercourse (25.0%), irregular menstrual cycle (36.8%), cyclic and acyclic bleeding (25.0%) and infertility (22.4%).

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Microbiological analysis of the endometrium showed different frequencies of microorganism detection among the examined groups. In patients with a low degree of chronic endometritis activity (group 1), Staphylococcus spp. (52.8%), Streptococcus spp. (50.0%) and the Enterobacteriaceae family (47.2%) were most often detected. In women with a moderate degree of activity (group 2), these microorganisms also prevailed. In this group, Staphylococcus spp. occurred in 65.9%, Streptococcus spp. and the Enterobacteriaceae family in 62.5%. Among women without chronic endometritis, Lactobacillus spp. (85.0%) and Eubacterium spp. (60.0%) dominated, while Staphylococcus spp. were detected in 40.0% of cases.

Comparative analysis showed that the frequency of Staphylococcus spp. detection in patients of groups 1 and 2 was 2 times ($p<0.05$) and 1.5 times ($p<0.05$) higher than in the control group. Significant differences in the frequency of Streptococcus spp. between patients with chronic endometritis and the control group were revealed: in women of group 1, the frequency of this microorganism was 10 times higher ($p<0.001$), and in patients of group 2 it was 10.5 times higher ($p<0.001$). Bacteria of the Enterobacteriaceae family, which includes both representatives of normal microflora and pathogenic microorganisms, were also frequently encountered. In groups 1, 2 and the control group, the Enterobacteriaceae family was identified in 47.2%, 62.5% and 30.0% of cases, respectively. Compared with the control group, in patients of group 1 its frequency was 1.6 times higher ($p<0.05$), and in patients of group 2 it was 2.1 times higher ($p<0.05$).

When studying the endometrial biocenosis, associations of microorganisms were revealed. In the control group, the association Ureaplasma (urealytikum+parvum) (40.0%) and Lachnobacterium spp. + Clostridium spp. (25.0%) were frequently encountered. In patients with low CE activity (group 1), these associations were encountered in 22.2% of cases. In women with moderate CE activity (group 2), the association Ureaplasma (urealytikum+parvum) was recorded in 22.5% of cases, and the association Lachnobacterium spp. + Clostridium spp. — in 15.0% of cases. Thus, the association Ureaplasma (urealytikum+parvum) in chronic endometritis was less common than in the control group. In patients with low and moderate activity of chronic endometritis, the frequency of this association was lower than in the control group by 1.8 times ($p<0.05$), respectively. The frequency of detection of the association Lachnobacterium spp. + Clostridium spp. in groups 1 and 2 compared to the control group was reduced by 1.1 and 1.7 times ($p<0.05$). Statistically significant differences were also observed between the control group and the group of women with moderate activity of CE in the frequency of detection of associations Mobiluncus spp. + Corynebacterium spp. and Gardnerella vaginalis/Prevotella bivia/Porphyromonas spp., where in patients of the second group the frequency was reduced by 2.0 times ($p<0.05$).

When compared with low CE activity, with moderate CE activity, the endometrial microbiota was characterized by an increase in the frequency of detection of streptococci and staphylococci by 1.2 times, as well as enterobacteria by 1.3 times. When comparing the frequency of microorganism associations between groups 1 and 2, a statistically significant difference was found in relation to the associations Mobiluncus spp. + Corynebacterium spp. and Gardnerella vaginalis / Prevotella bivia / Porphyromonas spp., which were found 1.7 times less frequently with moderate CE activity ($p < 0.05$). Our results again confirmed that the uterine cavity is not sterile, which is consistent with literature data. In the endometrial microbiota of women without chronic endometritis, normocytosis representatives prevailed, such as Lactobacillus spp. (85.0%) and Eubacterium spp. (60.0%). Eubacterium spp. are gram-positive bacteria of the family

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Eubacteriaceae of the order Clostridiales. The genus Eubacterium is highly heterogeneous and includes various species with different phenotypes. The literature describes that these bacteria are found in the vagina of both healthy women and those suffering from bacterial vaginosis. However, their role in endometrial colonization has not yet been fully determined.
Conclusions. Thus, in patients without morphological signs of chronic endometritis, lactobacilli and eubacteria predominated in the endometrium, while in patients with CE, the endometrial microbiota was characterized by a decrease in the frequency of detection of lactobacilli and an increase in the frequency of detection of staphylococci, enterobacteria, and streptococci.

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