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Research Article

THE MICROBIOLOGICAL COMPONENT OF CHRONIC ENDOMETRITIS

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Abstract:

Aim. The purpose of this study was to analyze the microbiological aspects of chronic endometritis in women with a history of reproductive loss.

Materials and methods. The study involved 480 women with a history of non-developing pregnancy, spontaneous miscarriage, artificial abortion, IVF failure with pathomorphologically verified CE (retrospective and prospective analysis). Microbiological research and DNA diagnostics of possible pathogens of CE, determination of embiotropic autoantibodies in blood serum (ELI-P-test), hysteroscopic and pathomorphological studies (aspirates and biopsies from the cervical canal and uterine mucosa) were carried out.

Results. During the study it was found out that the persistent conditionally pathogenic flora is likely to lead to progressively worsening changes in the general immune status, and the impaired immune resistance creates favorable conditions not only for the further growth of infections that caused the pathological process, but also for the involvement of new types of microorganisms in it (formation vicious circle). In this regard, CE is often characterized by polymicrobiality. In this case, there is a loss of the clinical specificity of the infectious process, which complicates both the diagnosis and the choice of adequate antibiotic therapy.

Keywords: chronic endometritis, macrotypes, diagnostics, autoantibodies, infection, microflora.

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INTRODUCTION:

Miscarriage and sterile marriage are critical aspects of modern health care. Among all the causes of these violations of fertility, special attention is drawn to chronic endometritis (CE), which, according to various estimates, is found with a high frequency - up to 60% of cases - in women with unsuccessful attempts at pregnancy, including in the case of extracorporal fertilization [1,2,3].

It has been proven that the chronic inflammatory process in the endometrium has an extremely negative effect on its morphology and functional state and leads to serious long-term complications: for example, CE can cause infertility, unsuccessful outcomes when using assisted reproductive technologies (ART), spontaneous abortion, complicated course gestational period [4,5,6,7].

The problem and difficulty for the practitioner is that CE is rather difficult to suspect and diagnose. The clinical picture is rather scanty and, most importantly, nonspecific symptoms. Meno- and metrorrhagias can often be observed, which are based on a violation of cyclic processes in the uterine mucosa and permeability of the vascular wall due to a chronic inflammatory process [8,9,10]. Also, patients may complain of pulling pains in the lower abdomen, the presence of pain associated with intercourse, serous and purulent discharge. A large proportion of women seek help from a specialist in connection with problems of conception. It was shown that in more than half of the cases with CE, disorders of the anxiety and depressive spectrum are observed [11,12,13].

Aspects such as erased symptoms, untimely, and sometimes incorrect diagnosis can lead to late initiation of treatment or the appointment of inappropriate therapy. The comprehensive examination of patients, including the use of modern laboratory and instrumental methods, will make it much more efficient to recognize CE and to fight it. To identify and identify the pathogen, microscopic, bacterio- and virological methods are used, as a material, endometrial scrapings, vaginal and cervical canal discharge are taken. Another diagnostic method is the morphological examination of the endometrium [14,15,16,17]. Characterized by the identification of inflammatory infiltrates, which are dominated by lymphoid cells. Often, with a long course of the disease, changes in the stroma are noted in the form of foci of fibrosis, sclerosis of the vascular walls. In chronic endometritis, the diagnosis can be confirmed by the determination of immunohistochemical markers: CD 68, CD 138, Ki-67 - the indicator of

proliferation processes, Syndecan-1, which is expressed at the late stages of B-lymphocyte differentiation and is involved in the processes of neovascularization, neoplasm and cell division. Also, the study can reveal the increase in collagen III and IV types [18,19,20,21].

Microbiological diagnostics was recognized as the "weak link" in CE detection: the rare detection of an infectious agent in samples of the uterine mucosa does not exclude its trigger role with subsequent elimination. The absence of microbial contamination of the endometrium may be associated with the difficulties in identifying a microbial culture, especially anaerobes [22,23]. The statement of the prevalence of non-gonococcal and non-chlamydial endometritis is confirmed by the facts of leukocytic infiltration of the mucous membrane in the presence of genitalia mycoplasma, viruses and Trichomonas in the cervical canal, as well as "superbugs" (E. coli, Enterococcus, Staphylococcus). The previously disputed role of opportunistic flora in the genesis of CE is confirmed by the facts of contamination with anaerobic cocci and vaginose-associated infections with the development of an inflammatory process in the uterine mucosa [24]. However, the possibility of contamination of endometrial samples with cervical and vaginal flora during the study should be excluded [25]. In modern conditions, CE is characterized by features: a change in the etiological structure with an increase in viral and opportunistic pathogenic flora [26,27]. This transformation is due to the widespread introduction of antibiotic therapy into medical practice, the lack of rehabilitation measures immediately after intrauterine interventions.

The purpose of this study was to analyze the microbiological aspects of chronic endometritis in women with a history of reproductive loss.

MATERIALS AND METHODS:

The study was conducted on the basis of the Rostov State Medical University. The study involved 480 women; 210 women with a history of non-developing pregnancy, spontaneous miscarriage, artificial abortion, IVF failure with pathomorphologically verified CE (retrospective analysis) and similar cohorts of patients (270 women) with early reproductive losses and different rates of morphological confirmation of CE (prospective analysis).

Microbiological research and DNA diagnostics of possible pathogens of CE, determination of embiotropic autoantibodies in blood serum (ELI-P-test), hysteroscopic and pathomorphological studies

(aspirates and biopsies from the cervical canal and uterine mucosa) were carried out.

RESULTS AND DISCUSSION:

Based on the hysteroscopic assessment of the state of the endometrium in early reproductive losses, it was established that endoscopic variants of CE (hyper-, hypoplastic and mixed) in the cohorts were presented with an equal frequency: 35.2, 33.1 and 31.9%.

The comprehensive microbiological study in endoscopic macrotypes of CE (mixed, hypo- and hyperplastic) showed that the detection of gram-positive microflora in the cervical canal was 71.2, 72.8 and 68.3%; in a smaller amount, gram-negative flora was determined - 27.4, 25.1 and 22.2%, respectively. Among the pathogenic microbial pathogens, enterococcus predominated - it was found in a third with the mixed variant of CE (32.9%), almost one and a half times more often with the hypoplastic macrotype (45.2%), twice - with hyperplastic (61.5 %).

Among other representatives of the facultative flora, attention is drawn to the high intensity of *E.coli* colonization (up to 10^5 CFU / ml): to the greatest extent - with the hyperplastic option (53.2%), in a third (34.7%) - with mixed, every fifth (19.6%) - with hypoplastic CE macrotype. The frequency of detection of streptococcus was comparable in all endoscopic variants (on average 15.5%), enterobacteria in every ninth with the mixed macrotype (11.4%), one and a half times more often in other macrotypes (on average 11, 2%). Bacterial-viral compositions of patients with CE, which determine mixed infection, were detected mainly in the hypoplastic variant - in two thirds (77.1%), somewhat less often in the hyperplastic variant (59.5%). With the mixed CE macrotype, such mixed mixtures were recorded only in half (53.4%).

Bacterial-mycotic associations were the prerogative of the hyperplastic macrotype (54.8%), while with mixed intensity of colonization with mixed mixtures, it was one and a half times less frequent (40.9%), hypoplastic - three times less (18.2%).

Infectious screening by PCR method showed the prevalence of high titer (more than 10^4 CFU / ml) representatives of opportunistic flora in the cervical secretion in the hypoplastic macrotype of CE in one third (36.7%) - *M. hominis*, half (44.2% each) - *U. Urealyticum* and *G. vaginalis*, a quarter (28.3%) - *C. albicans*. The lowest frequency of seeding with the indicated infections was noted in the mixed variant of CE in a quarter, of which (on average 25%) *U.*

urealyticum and *G. vaginalis* prevailed. High specific gravity *Ch. tracomatis* is the distinctive feature of the microbiota of every second patient with hyperplastic CE macrotype (41.2%), in other cases it is almost three times less common (on average 16.1%). The frequency of carriage of cytomegavirus infection was comparable (13.2, 15.8 and 14.7%) against the background of the prevalence of herpes simplex virus in hypo- and hyperplastic variants of CE (on average 58%). It is noteworthy that among the patients with CE there are figurants with sterile bacterial cultures from the cervical canal and negative PCR results - a quarter with a hypoplastic variant (24.1%), which is one and a half times more often than with mixed (15.8%), and twice - with hyperplastic macro-types (12.5%).

Microbiological data demonstrate that vaginal microbiocenosis in most patients with CE does not correspond to normal. The increased generation of strict anaerobes, observed in bacterial vaginosis, is a reservoir from which, under certain conditions, the further spread of microorganisms, their increased reproduction and, as the result, an infectious and inflammatory disease can occur.

The comparative analysis of the episodes of endometrial infection in different variants of CE was performed. The highest frequency of microbial persistence was observed in relation to bacterial-viral associations: for the overwhelming majority of women with hypoplastic CE macrotype (61.4%), half (53.2%) - with hyperplastic variant, every sixth (17.9%) - with mixed CE.

The predominance of bacterial-mycotic associations was found in hyperplastic macrotypes - in a third (32.5%) of women, while in hypoplastic ones, infectious agents were recorded to the lowest degree (7.2%).

Endometrial contamination with enterococcus was the most significant in the hyperplastic variant (26.1%), while in the rest it was found in 11.2% on average. With regard to enterobacteriaceae, no such dependence was established: the frequency was comparable for all CE macrotypes (4.2, 5.1 and 4.8%, respectively).

Infection of the endometrium with *Escherichia coli* in the cohort of women with the hyperplastic variant of CE was almost twice as high as the frequency in the remaining macrotypes (on average, 9.2%).

The analysis of the comparability of infections showed that the highest level of concordance between cervical and uterine cultures in relation to bacterial-

viral associations was typical for the cohort with a hyperplastic macrotype (68.1 and 53.2%, respectively). With the mixed macrotype, such a relationship was observed much less frequently (53.0 and 17.9%) than with the hypoplastic macrotype (77.2 and 50.4%, respectively).

A high level of concordance with respect to bacterial-mycotic associations prevailed in hyperplastic macrotypes (56.1 and 32.7%, respectively). The largest gap in the frequency of detection of infectious agents in the cervical canal and in the uterine cavity was characteristic of the mixed macrotype (40.8 and 9.9%), while in the case of hypoplastic one - one and a half times less often (18.5 and 7.1%).

The frequency of coincidence of the detection of enterococcus in the cervical canal and in the endometrium was the highest in hypoplastic macrotypes (43.5 and 34.3%, respectively). The level of concordance of endometrial and cervical enterococcus cultures in the mixed variant of CE (32.1 and 9.9%, respectively) exceeded that in hyperplastic (61.5 and 10.2%). The highest concordance in relation to *Escherichia coli* was found in hypoplastic macrotypes (19.8 and 12.1%, respectively), in hyperplastic (53.0 and 21.2%), the indicator exceeded that in the mixed variant of CE (34.9 and 7.8 % respectively). The level of endometrial cultures of epidermal staphylococcus in comparison with cervical cultures with different macrotypes of CE was the highest in comparison with streptococcus.

With regard to gram-positive flora, the highest concordance was found in women with hypoplastic macrotype: with 74% of infectious agents in the cervical canal from the uterine cavity, it was found almost one and a half times less (44%). A similar trend is observed in relation to gram-negative flora. Comparison of concordance between cervical and uterine cultures indicates a lower level for *Mycoplasma hominis* and *Ureaplasma urealyticum* in hypoplastic CE macrotype. The priority in this cohort belongs to *Gardnerella vaginalis*: 42.1 and 28.3%, respectively. In hyperplastic CE macrotype, the highest level of concordance was established for *Chlamidia trachomatis*: 42.2 and 17.1% for uterine and endometrial samples.

The frequency of *Candida albicans* shedding in the cervical canal and uterine mucosa was equally high for hyperplastic (18.2 and 10.9%) and mixed (11.8 and 7.7%, respectively) macrotypes.

Comparative analysis of the frequency of episodes of lack of growth of the cervical and endometrial flora stated that it was most pronounced in mixed (17.1 and 13.3%) and hyperplastic variants of CE (12.4 and 10.5%, respectively). With regard to the situation with the hypoplastic macrotype, the gap was more significant: 24.2 and 10.5%.

Ignoring the factor of infection of the lower parts of the genital tract, in most cases associated with asymptomatic persistence in the endometrium, definitely leads to miscarriage, which is especially significant from the standpoint of unsatisfactory results if there is a history of non-developing pregnancy, unsuccessful IVF attempts, and habitual miscarriages. Colonization of the endometrium with infectious agents in this case should be interpreted as an immune failure to eliminate microbial pathogens, which is realized in the form of activation of T-lymphocytes (T-helpers, natural killer cells) and macrophages. Thus, the role of the immune response in CE is one of the fundamental ones for the formation of a pathogenetic variant of inflammation of the uterine mucosa.

The high frequency of sterile endometrial specimens requires recognition of the existence of autoimmune endometritis, in which the role of microbes is secondary due to its elimination.

The results obtained reflect the high level of endometrial infection in cohorts with different macrotypes of CE.

A comparative analysis of the results of a microbiological study of the endometrium with variants of immunoreactivity tested on the basis of the ELI-P test showed that with a reduced production of embryotropic autoantibodies, opportunistic flora was most often sown with a mixed variant of CE (86.1%). With a hyperplastic macrotype, the probability of realizing the pathogenic properties of the saprophytic flora increased to 57.4%. With a hypoplastic macrotype, representatives of the opportunistic flora predominated in the cohort of hyperreactive (85.3%).

Infection of the endometrium with a specific pathogen turned out to be the prerogative of the hyperplastic variant: with a weak immune response - in 85.2% of women, with excessive production of embryotropic autoantibodies - almost twice less often (38.7%). With a mixed macrotype, a specific endometrial infection was detected in a third (33.6%) of hyporeactive patients, in every fifth (22.0%) with a hyperreactive immune response.

To the least extent, the frequency of endometrium infected with a specific pathogen was determined with hyperreactivity (8.9%).

Bacterial-viral associations prevailed in the cohort of hyperreactive (88.3%) and in half (49.8%) with reduced production of embryotropic autoantibodies in hypoplastic CE. With a mixed CE macrotype, the highest frequency of seeding of bacterial-viral associations was characteristic of almost half of women with hyperreactivity (42.7%), every fifth (23.6%) - with a weak immune response. The cohort of representatives with a hyperplastic CE macrotype was characterized by a dominant decrease in the production of embryotropic autoantibodies (61.6%), while other variants of the immune system's response to infection of the endometrium with bacterial-viral associations were recorded one and a half times less often (42% on average). Bacterial-mycotic associations prevailed in hyporeactivity: in half (52.0%) with hyperplastic CE macrotype, every seventh (13.9%) - with hypoplastic, almost a quarter (23.2%) - with mixed. The combination of these observations confirms the assumption that persistent bacterial and mixed infections and the presence of a chronic inflammatory process in the endometrium lead or are accompanied by both general immunosuppression and a decrease in the serum content (immunoreactivity) of specific embryotropic antibodies. Noteworthy is the absence of endometrial infection, mainly with a weak immune response: in 13.8% of women with hypoplastic and mixed macrotypes of CE, 11.9% - with hyperplastic. With excessive production of embryotropic autoantibodies, samples of sterile endometrium were distinguished by 9.0% of women with hyperplastic and mixed variants of CE and 6.6% - with hypoplastic. Similar results are consistent with the need to isolate the autoimmune pathogenetic variant of CE that we indicated.

CONCLUSION:

From the above, we can conclude that the persistent conditionally pathogenic flora is likely to lead to progressively worsening changes in the general immune status, and the impaired immune resistance creates favorable conditions not only for the further growth of infections that caused the pathological process, but also for the involvement of new types of microorganisms in it (formation vicious circle). In this regard, CE is often characterized by polymicrobiality. In this case, there is a loss of the clinical specificity of the infectious process, which complicates both the diagnosis and the choice of adequate antibiotic therapy.

List of symbols and Abbreviations:

CE - chronic endometritis.

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