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CHANGES IN THE LOCAL AND SYSTEM IMMUNE RESPONSE IN WOMEN WITH CHRONIC ENDOMETRITIS

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Abstract.

Aim: *To analyze the features of changes in the immune response both at the local and systemic levels in patients with chronic endometritis (CE). Assess the state of cellular and immune components of the immune system in women with CE.*

Materials and methods: *The study reveals in detail the variability of immunological rearrangement in 450 women with different macro types of CE (hypoplastic, hyperplastic, mixed). The following indicators were analyzed to assess the state of the immune system: T-lymphocytes (CD 3+), B-lymphocytes (CD 20+), T-helpers (CD 4+), NK-cells (CD 16+), cytotoxic T-cells (CD 8+), rFAS-CD 95+ (apoptosis receptor), phagocytosis activity of monocytes and neutrophils. The above parameters were evaluated in the control group. There were 65 women with an early reproductive loss in history, but without chronic endometritis.*

Results: *The results of the data showed that the greatest decrease in resistance and inhibition of immunological rearrangement was observed in a cohort with a hyperplastic variant of CE. Hyperreactivity of the immune system was characteristic of women with mixed macro types. The pro-apoptotic orientation of changes, inhibition of cellular and humoral units was revealed in a cohort with hypoplastic macro types of CE. The role of persistent microbial pathogen in the development of immune deficiency was studied. The results of the study detail the importance of destructive-inflammatory, autoimmune processes, the imbalance of the cellular and humor parts of the immune system in the initiation and maintenance of CE.*

Conclusions: *The detailed study of the reaction of cellular and humoral defense factors, both at the local and systemic levels, will optimize the choice of pathogenetic therapy, interrupt the vicious cycle of persistent chronic inflammatory process in endometrial tissues, and also make an individual selection of rehabilitation measures in women with a complicated obstetric history.*

Key words: *chronic endometritis, immune response, macro types, immunological rearrangement, diagnostics.*

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INTRODUCTION:

Chronic endometritis (CE) is one of the main problems of modern gynecology. Despite the widespread prevalence of this pathology and long-term history of the study, modern methods of diagnosis and pathogenetically determined therapy do not allow complete elimination of the infectious agent and extirpation the chronic inflammatory process [12,22,27,30]. The danger of CE is the increased risk of adhesion in the pelvis, miscarriage, infertility, failed attempts at in vitro fertilization (IVF) and purulent-septic complications [9,24,25]. Currently, there is a tendency toward an increase in the number of patients with CE [3]. According to various observations, CE is recorded in 0.4-66.3% of cases, while the majority of patients (about 88%) belong to the group of women of childbearing age [5.29]. Infertility as one of the complications of CE is detected in 60-65% of women susceptible to this disease [17,18,23].

The causes of CE are currently considered to be infection of the genital tract, invasive procedures on the organs of the reproductive system (curettage, hysteroscopy, IVF, hysterosalpingography), early onset of sexual activity, promiscuous sexual life, use of intrauterine contraceptives, vaginal dysbiosis, preceding abortion, and violation of the immune system [3,4,5,14]. The key causes of the chronic course of the inflammatory process in the uterine cavity are the depletion of the phagocytic and specific immune systems, leading to the manifestation of local and general immunosuppression, the imbalance in the hormonal system, which contributes to the increase in the association of opportunistic microorganisms that cause CE in more than half of patients [19, 20]. The inflammatory process in the endometrium contributes to the persistence of infectious agents due to the formation of a comfortable living environment (blood clots, necrotic tissue, fibrin deposits) and low immunogenicity of the conditionally pathogenic flora [11].

Thus, the relationship between immune system disorders and CE becomes apparent, however, the exact mechanisms leading to the long-term maintenance of inflammatory and autoimmune reactions in endometrial tissue have not been fully studied [16]. Disruption of compensatory-adaptive reactions and suppression of immune defense factors are associated with the action of exo- and endogenous toxins, adhesion factors (pili, proteins, lipoteichoic acid of the cell wall) and enzymes produced by infectants, as well as the increase in the microflora structure of facultative and obligate anaerobes (*Peptostreptococcus spp .*, *Actinomyces spp.*, *Bifidobacterium spp.*, *Veillonellae spp.* and others), their waste products (nitrosamines) and the decrease in *Lactobacillus* (*L. acidophilus, L. plantarum, L. casei, L. fermentus,* etc.), which provide immunoprotection due to the shift of ph to acidic side (4.4 - 4.6), which increases the activity of oxidation-reduction, and competitive blockade of nutrients and adhesion loci; which leads to a decrease in local resistance of the endometrium in patients [6,7,8,10].

Among the components of pathogenesis of CE in modern studies, special attention is paid to hemodynamic disorders in the vasculature of the small pelvis and organs of the reproductive system, a change in the number of lymphoid cells in the endometrium, a decrease in the functional activity of the phagocytic system, and the appearance of inactive white blood cells that do not provide complete phagocytosis (suppression of fusion of phage and lysosomes, inactivation of lysosomal enzymes), excessive production of cytokines (TNF-α, interleukins - 1,6,17,18), activating the prothrombinase complex CS, which leads to a predominance of the effects of the coagulation system, thrombosis and detachment of the trophoblast or placental insufficiency [13,15,26,28]. Opinions about the effect of the chronic inflammatory process in the uterus on the state of the systemic and local immune response remain controversial [21,26,28]. The study of changes in local immunity in patients with CE caused by various infectious agents, the research of activation of the reactions of the humoral and cellular components of immune system, as well as impaired immunoreactivity and resistance, will help to correct the course of the inflammatory process in the endometrium, to choose the optimal, pathogenetically determined, most effective treatment regimen for women with various histological macro types of CE and various pathogens, as well as to interrupt the vicious circle of chronic sluggish diseases of the reproductive system.

MATERIAL AND METHODS:

The study was conducted on the basis of the Rostov State Medical University. The study involved 515 women with a complicated obstetric history (failed IVF attempts, missed pregnancy, induced abortion, spontaneous abortion). The criterion for inclusion in the study was the confirmation of the diagnosis of chronic endometritis in all women particularly in 450 patients. The control group included 65 women with reproductive losses, but without CE.

All subjects underwent a hysteroscopic examination. Based on the data obtained by histological analysis of biopsy specimens and aspirates, among women with verified CE, 3 variants (macro types) of the course of the chronic inflammatory process in the endometrium were identified by assessing the thickness of the mucous membrane, vascular network reaction, morphological structure and the presence of polyps [1]. In most patients (47.1%), the mixed macro type was observed, characterized by the alternation of pathologically altered areas with normal; the second most common was the hyperplastic macro type (30.9%) with polypous endometrial hypertrophy; in the third place is the hypoplastic macro type (22%), which is characterized by depletion of the vascular pattern, a marked decrease in the thickness of the mucosa in all phases of the menstrual cycle, intrauterine adhesions.

Also, all women included in the study, regardless of the presence of CE, were evaluated the parameters of the immune system using an EPICS-XT cytometer manufactured by «COULTER» (USA). Peripheral blood lymphoid cells were studied by multiparameter bicolor cytofluorometry using FITC-labeled monoclonal antibodies («Sorbent-Service», Russia). Assessment of the concentration of immunoglobulins M, G, A was carried out using sera specific for one of human Ig (I.I. Mechnikov Research Institute) (N. Novgorod) according to one of the precipitation reaction methods - radial immunodiffusion in molten agar gel with determination of the diameter of the precipitation ring (mm). The study of the bactericidal ability of white blood cells and the usefulness of phagocytosis was based on the method proposed by the laboratory of clinical immunology of the Institute of Immunology of the Ministry of Health of the Russian Federation. The state of the enzyme system of NADPH oxidase of neutrophils, which provides the bactericidal properties of macrophages, as well as processes of cell division and differentiation, was assessed using the microscopic method - a spontaneous sample with nitroblue tetrazolium (NBT test), which characterizes the state of non-specific immunity. The stimulated (induced) NBT test made it possible to determine the activity of phagocytes by enhancing oxidative reactions with activated granulocytes and monocytes in vitro.

Among the indicators of the immune system assessment, the following markers were identified: T-lymphocytes (CD 3+), B-lymphocytes (CD 20+), T-helpers (CD 4+), NK-cells (CD 16+), cytotoxic T-cells (CD 8+), rFAS-CD 95+ (the so-called "death receptor" responsible for programmed cell death), the activity of phagocytosis of monocytes and neutrophils.

RESULTS:

Analysis of the state of the local immune response in patients with CE revealed that the lowest T-lymphocyte count (CD 3+ marker) was recorded in women with a hyperplastic variant (0.81 ± 0.05) and was 1.7 times lower than in healthy women of the control group, this indicator corresponded to the norm (1.41 ± 0.03) ($p < 0.05$). In women with the mixed CE macro type, the content of T-lymphocytes (CD 3+) had a slight deviation from the norm (1.29 ± 0.03) ($p < 0.05$).

Further study of the immunoregulatory index (IRI), which reflects the ratio of the subpopulation markers CD 4 + / CD 8+ (T-helper cells and cytotoxic T-cells, respectively), in patients with the hyperplastic macro type found that this indicator was reduced (0.91 ± 0, 03) in comparison with the control group (1.7 ± 0.02). Moreover, the decrease in IRI in all cases was due to a decrease in the activity of T-helpers. Their activity was 2 times less than in the control group — 0.47 ± 0.05 and 0.9 ± 0.01, respectively, which may reflect impaired development of the cellular and humoral immune response.

The change in the content of NK cells, which at the late stages of development acquire signs of normal killers (in addition to CD 3+ markers, CD 16+ markers appear) and take part in the initiation and maintenance of the inflammatory response from the endometrium, in cohorts with hyperplastic and mixed macro types were most pronounced . In the first case, an increase in CD 16+ was recorded almost 2 times (0.36 ± 0.04), compared with healthy women (0.2 ± 0.02); in the second case, the increase in this marker was not so pronounced (0.27 ± 0.03) ($p < 0.05$).

The smallest changes in the cellular component of the local immune response were observed in the group of women with the hypoplastic macro type. Markers of subpopulations of T-helper cells, cytotoxic T-cells, and IRI corresponded to normal values in healthy women. At the same time, this cohort showed a decrease in the membrane marker of normal-blood B-cells (CD 20+) - 0.14 ± 0.03, which is 2 times less than in the control group - 0.29 ± 0.007 ($p < 0, 05$).

Assessment of the status of the antibody-dependent immune response showed an increase in its activation and tension in all women with CE regardless of the

variant. The increase in highly avid and low-affinity IgG reached the highest values in the cohort with the hypoplastic macro type (13.0 ± 0.4), in second place with the hyperplastic (12.5 ± 0.034), slightly less in the mixed-variant group (11.9 ± 0 , 2) ($p < 0.05$). The increased content of highly specific IgA localized on the uterine mucosa was most pronounced in the cohort with the hyperplastic variant (2.4 ± 0.25), in the second place with the mixed (2.2 ± 0.2), and in the third with the hypoplastic (2.01 ± 0.15) ($p < 0.05$). However, an increase in the level of these immunoglobulins and circulating immune complexes (CICs) led to the conclusion about the maximum activation and intensity of the antibody-dependent immune response in the group with the mixed CE macro type.

Assessment of the phagocytic activity of leukocyte cells revealed that the activity of neutrophil phagocytosis was more pronounced in patients with a hyperplastic variant than in healthy women and women with the mixed macro type (4.0 ± 0.2 versus 3.5 ± 0.15 and 3.45 ± 0.17) ($p < 0.05$). In a cohort with the hypoplastic macro type, neutrophil phagocytosis activity was 1.2 times less than in the control group and 1.4 times less than in women with a hyperplastic variant (2.9 ± 0.2) ($p < 0.05$).

The systemic immune response to the prolonged presence of an infectious agent (PCR) in the female body that causes a chronic inflammatory process on the part of the endometrium was evaluated by a change in the level of leukocytes, monocytes, lymphocytes, CIC and other indicators. So, the general restructuring of the immune system with a change in the leukocyte formula was most pronounced in the cohort with the hyperplastic variant. The decrease in leukocytes was characteristic of women of this group with a positive PCR test to a greater extent than in the absence of detection of pathogens (6.86 ± 0.37 versus 7.4 ± 0.2) ($p < 0.05$). In the control group, this indicator was 1.2-1.4 times less (5.54 ± 0.12) ($p < 0.05$).

An increase in leukocyte cells was observed with the hypoplastic macro type in the absence of an infectious agent (6.5 ± 0.2) ($p < 0.05$), but with a negative PCR test this parameter was comparable to the values obtained in the control group (5.8 ± 0.27 and 5.68 ± 0.1, respectively).

At the same time, an increase in the number of leukocytes against the background of an infectious agent was recorded only in a cohort with the mixed CE macro type (6.8 ± 0.3 versus 5.7 ± 0.17) ($p < 0.05$).

A change in the lymphocytic component of immune system in the absence of an infectious agent in the hypoplastic variant of CE had a significant deviation from the norm (2.3 ± 0.1) in comparison with the data obtained with a positive PCR test (1.9 ± 0.17). The variability of the deviations of the data on the number of lymphocytes from the indicators in the control group of healthy women had the same tendency in patients with the hyperplastic macro type (2.63 ± 0.2 and 1.91 ± 0.15, respectively) ($p < 0.05$).

The change in the level of neutrophils in the presence of an infectant was of a uniform nature. In the presence of the pathogen, the neutrophilic reaction from the endometrium was more pronounced than in women without an infectious agent with mixed (4.41 ± 0.2 vs 3.7 ± 0.22) and hyperplastic (4.1 ± 0.39 and 4, 6 ± 0.15) CE variants. It should be noted that, regardless of whether the PCR test was positive or negative, the neutrophil content in the cohort with the hyperplastic macro type was higher than in women from the control group (3.36 ± 0.21) ($p < 0.05$).

The response of monocytes in the case of detection of the causative agent of infection was not overly expressed in any of the groups of subjects. With the mixed macro type, the monocyte level was 0.27 ± 0.02; in women with a negative PCR test, the values were similar - 0.35 ± 0.015 ($p < 0.05$).

The same trend was observed in the cohort with the hypoplastic variant. This parameter in the case of a positive PCR test confirming the presence of an infectious agent was less and amounted to 0.31 ± 0.035 than in the absence of a microbial pathogen (0.44 ± 0.06) ($p < 0.05$).

In cohorts with hyper- and hypoplastic macro types, the severity of increased activity of T-lymphocytes (CD 3+) was minimal. In patients with a mixed variant of CE, this parameter was increased in case of detection of an infectious pathogen and amounted to 1.3 ± 0.1, and in its absence 1.1 ± 0.03 ($p < 0.05$).

The determination of the content of the T-helper subpopulation marker (CD 4+) led to the conclusion that in the cohort with the mixed variant, the CD 4+ values were increased in the case of a positive PCR test with detection of an infectant in relation to the group without infected endometrium (0.8 ± 0 , 1 against 0.68 ± 0.08) ($p < 0.05$).

Similar results were obtained in the group of women with hyperplastic macro types: with a positive result of the PCR test, the CD 4+ reaction indicators exceeded the data of the negative PCR test by 1.6 times (1.2 ± 0.15 and 0.75 ± 0.04, respectively) (p <0.05).

Inhibition of a subpopulation of cytotoxic T cells, manifested by a decrease in the level of the marker CD 8+, in the case of infected endometrium was detected in only one cohort - with a mixed variant of CE. The values of CD 8+ with a positive PCR test result were 0.51 ± 0.035, in the absence of an infectious agent - 0.55 ± 0.07 (p <0.05).

The detailed study of the T helper cells subpopulation marker of CD4 + revealed a pronounced decrease in this indicator in the cohort with a mixed CE type with a positive PCR test result (0.16 ± 0.03) compared with the group in which there was no infection of the endometrium (0, 2 ± 0.045); moreover, both values exceeded those in the control group (0.27 ± 0.015) (p <0.05).

The study of the response of NK cells (natural killers) was carried out by evaluating the subpopulation marker CD 16+. As a result of the obtained data, a twofold decrease in this indicator was revealed with the hypoplastic macro type in the presence of an infectious agent (0.13 ± 0.015 versus 0.29 ± 0.1 in the absence of pathogen isolation according to PCR) (p <0.05).
An inverse pattern was revealed by studying the cluster line of CD 16+ NK cells in the remaining groups. However, in a cohort with a hyperplastic variant, this parameter was most close to that of healthy women (0.35 ± 0.07 and 0.26 ± 0.05, respectively).

The content of lymphocyte apoptosis receptors, the marker of which is rFAS-CD 95+, was variable in the study groups with CE and the control group. A general tendency for a decrease in this indicator in women without confirmed infectious endometrial lesions was revealed. In the hyperplastic variant, this indicator was 1.42 ± 0.31 versus 2.8 ± 0.18 (p <0.05), which is 2 times less than in the control group (2.79 ± 0.35). In the cohort with the mixed macro type, 1.37 ± 0.27 vs 1.8 ± 0.6.

In the study of rFAS-CD 95+ indices, opposite values were found in the cohort with the hypoplastic variant. An increase in the level of rFAS-CD 95+ was observed in women with the hypoplastic macrotype CE with the presence of a microbial pathogen 1.5 times more often than with negative PCR results (2.51 ± 0.7 vs 1.65 ± 0.16) (p <0.05).

In a cohort with the mixed CE macro type, an inhibition of the immune system response during endometrial infection was noted. So, with a positive PCR test, the activity of neutrophil phagocytosis was 3.45 ± 0.3, and in the absence of an infectious agent, 3.93 ± 0.21. In women with a hyperplastic variant, monocyte phagocytosis activity was less pronounced, however, the trend continued to decrease when microbial pathogens were detected (0.25 ± 0.015 with a positive PCR test versus 0.37 ± 0.01) (p <0.05).
A similar trend was found in the analysis of AF Mo. and AF N. in the group of women with the hypoplastic macro type CE. In the presence of an infectant, the phagocytic activity of monocytes was less pronounced (0.25 ± 0.025 versus 0.31 ± 0.013 in the case of a negative PCR test). The phagocytic activity of neutrophils in this group of women is 3.04 ± 0.17 and 3.27 ± 0.2, respectively (p <0.05). In addition, all the studied parameters were reduced in comparison with the data of the control group (0.25 ± 0.015 and 3.23 ± 0.1, respectively).

In all groups of women with CE and the presence of an infectious agent, a decrease in leukocyte killing activity was detected. The greatest change in the indicators of the bactericidal ability of leukocytes was observed in a cohort with a hyperplastic variant. With a positive PCR test result, this indicator was 1.5 times lower than in the absence of an infected endometrium (37.9 ± 0.55 versus 56.1 ± 1.5, respectively) (p <0.05).

The level of circulating immune complexes, on the contrary, was increased in all patients with CE compared with healthy women (37.1 ± 5.2). The highest CICs content was determined in cohorts without the detection of microbial pathogens; when they were detected, the indicators were slightly lower. So, in the group of women with the mixed macro type, the above values were 86.1 ± 8.5 and 74.2 ± 3.1, respectively, with the hyperplastic variant - 75.2 ± 9.6 and 56.9 ± 2.51, respectively.

In the cohort with the hypoplastic macro type CE, CICs level was increased compared to the control group, regardless of the detection or absence of infectious agents: 59.1 ± 6.9 with a positive PCR test and 60.9 ± 7.3 with a negative PCR test.

A study of the results of a test with nitro-blue tetrazolium, which reflects the bactericidal activity of phagocytes, revealed a decrease in the spontaneous NBT test in women with all types of CE and infected endometrium, except for the hypoplastic macro type, in which there was no sharp change in the indicators regardless of the presence of the microbial pathogen: 9.82 ± 1.60 - upon detection of an infectious agent and 10.6 ± 1.29 in the case of a negative PCR test result.

In a cohort with the mixed macro type, the results of this test were inferior to those of healthy women. In the presence of signs of an infected endometrium, 8.51 ± 1.55, in the absence of an infectious agent, 9.98 ± 1.09 ($p < 0.05$), in healthy women, 0.25 ± 1.2 ($p < 0, 05$).

An induced test with nitro-blue tetrazolium revealed a general orientation of the indicators; their variability was insignificant. Only in a cohort with the mixed macro type, with a positive PCR test result, an increase was found compared to the absence of detection of microbial pathogens (23.9 ± 4.95 and 17.1 ± 1.3, respectively) ($p < 0.05$). The results were higher than in the control group (17.9 ± 1.48) ($p < 0.05$).

The change in the humoral immune response in all women with CE and a positive PCR test was the same and showed an increase in IgA compared with the control group (1.20 ± 0.12) ($p < 0.05$). In patients with the hypoplastic macro type and the presence of an infectious pathogen, the IgA increase was less pronounced (2.74 ± 0.23 when the microbial agent was detected and 1.85 ± 0.29 when the PCR test was negative) ($p < 0.05$) than women with other macro types of CE. The second place in terms of the number of immunoglobulins of this class was a group of women with a mixed variant (2.31 ± 0.18 versus 2.07 ± 0.15 outside the detection of an infectious agent) ($p < 0.05$). The highest IgA values were found in a cohort with thr hyperplastic macro type and infected endometrium (2.61 ± 0.28 versus 2.34 ± 0.21 with a negative PCR test result).

The IgM content in patients with thr mixed macro type, regardless of the results of the PCR test, was significantly higher than in the group of healthy women (1.68 ± 0.01). In infected endometrium, the IgM level was 1.5 times higher and amounted to 2.53 ± 0.06, in the absence of an infectious agent - 1.71 ± 0.15 ($p < 0.05$). In the cohort with the hypoplastic macro type CE, there was a tendency for IgM to decrease with a positive PCR test (1.55 ± 0.12) and increase with a negative result (2.09 ± 0.18) ($p < 0.05$). In the hyperplastic variant of CE, regardless of the results of the PCR test, the concentration of this class of immunoglobulins in the blood serum was higher than in the control group, however, their level also prevailed in women without signs of endometrial infection (2.1 ± 0.25 against 2.36 ± 0 , 12) ($p < 0.05$). Studies of IgG levels revealed a downward trend in this indicator in almost all patients with CE and infected endometrium compared with the group of healthy women (10.39 ± 0.5) ($p < 0.05$). With a hypoplastic variant and a positive PCR test, the concentration of IgG was 11.51 ± 1.69 and 12.82 ± 1.71 - with a negative; with a mixed 11.22 ± 0.57 and 13.15 ± 2.78, respectively ($p < 0.05$). Only in the cohort with the hyperplastic macro type, an increase in IgG level was more pronounced in the detection of an infectious agent (12.27 ± 0.52) than in its absence (10.39 ± 0.45) ($p < 0.05$).

DISCUSSION:

The analysis of the data revealed the variability of the directivity of the immunological response in patients with various chronic endometritis macro types.

The greatest decrease in resistance and suppression of the immune response was observed in a cohort with the hyperplastic macro type of CE, which was reflected in the indices of the cellular component of the immune system (the level of “apoptosis receptors” - rFAS-CD 95+, T-lymphocytes and markers of their subpopulations, decrease in the concentration of monocytes, inhibition of functional white blood cell activity). Positive results of the PCR test allowed us to confirm the participation of a persistent microbial pathogen in maintaining the chronic inflammatory process, which also impeded the development of a normal immune response in this group of women.

The reverse situation was observed in a cohort with the mixed CE macro type. The reaction of the immune system in this group of women was most pronounced, which was reflected in the indicators of both cellular and humoral components (absorption capacity of monocytes, IgM, markers of T-cell subpopulations: CD 3+, CD 4+, CD 16+, spontaneous NBT test).

The multidirectional changes in the immune response were detected in women with the hyperplastic macro type CE. In this group, on the one hand, there was an inhibition of the humoral component of the immune

system (according to the level of immunoglobulins of classes M and A), NK cells and the bactericidal activity of neutrophils, and on the other hand, the proapoptotic orientation of immunological rearrangement.

CONCLUSIONS:

The detailed study of the reaction of cellular and humoral defense factors, both at the local and systemic levels, will optimize the choice of pathogenetic therapy, interrupt the vicious cycle of persistent chronic inflammatory process in endometrial tissues, and also make an individual selection of rehabilitation measures in women with a complicated obstetric history (unsuccessful IVF attempts, missed miscarriage, artificial termination of pregnancy, spontaneous abortion).

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