

**DIFFERENCIAL IMMUNOKORRECTION IN WOMEN WITH GENITAL ENDOMETRIOSIS**

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**Abstract:** *56 patients with genital endometriosis were examined. Of these, 26 had internal endometriosis, and 30 had external genital endometriosis. 18 practically healthy women made up a control group. All examined women were examined the state of the immune system (cellular immunity, phagocytosis and cytokine status). It was found that in patients with endometriosis, the level of T-lymphocytes and its subpopulation composition were reduced, and the level of killer activity varied in different ways depending on the form of genital endometriosis. Functional activity of neutrophils changed only in the group of women with EGE.*

**Keywords:** *genital external and internal endometriosis, immune status, phagocytosis, cytokines.*

To clarify the fundamental mechanisms of endometrioid foci development, the study of local immune processes is of the greatest interest. However, the study of systemic immune response in endometriosis also provides important information on pathogenetic factors of disease development, as the functional state of circulating immunocompetent cells can reflect the direction of immune disorders occurring at the local level.

**The aim of the study.** Study of some parameters of congenital and adaptive immunity in peripheral blood in women with genital endometriosis.

**Material and methods:** We observed 26 women with internal genital endometriosis (IGE) and 30 patients with external genital endometriosis (EGE), whose diagnosis was verified at the stage of clinical and instrumental examination, including therapeutic and diagnostic laparoscopy.

All patients were comparable in age, complaints, history, gynecological and extragenital pathology, degree of disease spread (II-III degree according to the American Society of Fertility r-AFS classification) [5]. Indicators of 18 almost healthy women with normal reproductive function, who were admitted for planned surgical sterilization, served as a control group for immunological research.

Immunological studies were carried out by studying the level of lymphocytes for identification of CD3, CD4, CD8, CD16, CD20, CD25 and CD95 differentiation clusters on the surface using monoclonal antibodies of LT series (Sorbent LLP, Moscow, Russia). Functional activity of phagocytes was studied in the NST-test. The level of pro- (IL-1p, IL-2, IL-6, IL-8,

IFN $\gamma$ ) and anti-inflammatory (IL-4) cytokines in blood serum was studied by ELISA (test-systems Titokin, St. Petersburg, Russia).

**Results and discussion:** The age of the observed women ranged from 21 to 39 years of age. Women with HGE had an average of 4.7 years of age and women with EGE had an average of 2.8 years of age.

The study of somatic anamnesis showed that dysmenorrhea, acute and chronic adnexitis, uterine myoma, wearing of uterine spirals, colpitis, bacterial vaginosis and dysfunctional uterine bleeding (DU bleeding) were the most frequent of all gynecological diseases.

Among the obstetric and gynecological operations performed there were ovarian surgeries on different ovarian cysts, conservative myomectomy, reconstructive plastic surgeries on uterine malformations, caesarean section, suturing of perforation holes in the uterus, ectopic pregnancy, etc. Such operative interventions as cervical surgeries (diathermosurgical and cryosurgical manipulations) were found only in 2 women.

The study of complaints from patients of two groups showed that all women had painful menstruation of different intensity. Pains had a cyclic periodicity, increased before the menstrual period and were weakened and disappeared after them.

Depending on the form of the disease various additional symptoms of endometriosis were recorded. Thus, menstrual dysfunction in the form of DUB was observed in 76,5% of women with IGE. DUB was accompanied by irregular cycle, masking intermenstrual excretions (51%), abundant monthly (19%) and bleeding (6.5%).

During menstruation, nausea (30%), vomiting (11%), fever (7%), leukocytosis (19%), high YBK (17%) and low hemoglobin levels (27%) were often observed in women with both IGE and EGF.

The overall condition of women has deteriorated significantly due to the fact that endometriosis has had a negative impact on the work of all internal organs. Patients felt weak (45%), their ability to work decreased (27%), irritability appeared due to constant pain, abundant blood loss caused dizziness (25%), tachycardia and shortness of breath (15%).

One of the serious complications of endometriosis is the absence of pregnancy for more than one year (primary infertility) and secondary infertility.

In case of endometriosis due to hormonal disorders there is often no ovulation or there is a lack of accuracy of the second phase of the cycle. Thus, in 58,8% of women with IGE the insufficiency of the second phase of the cycle prevailed, and in 32,3% of patients with EGE the prevalence was higher.

Hormonal background in 42% of women with ovarian endometriosis was characterized by the increase of follicle stimulating (FSH) and luteinizing hormone (LH) level, which indicates the damage of ovarian follicular apparatus and decrease of ovarian reserve. In 8% of patients there was an increase in estrogen level, prolactin (10%), in 70% of the examined patients there was a decrease in progesterone content.

Study of the nature of pain syndrome in women with various forms of endometriosis has shown that depending on the localization of places of hemorrhage there are additional symptoms of the disease. So, at 44,7 % of patients with adenomyosis strengthening of the pains irradiating in a back pass, during sexual intercourse (dyspareunia) was marked.

In 15 (71,4%) women with EGF the focus of endometriosis was in the posterior douglas space. Patients complained more often of pain during the act of defecation. When the focus of endometriosis was located on the wall of the bladder, there were complaints of pain during urination.

The results of immunological studies showed that the number of CD3+ and SB4+ lymphocytes in women with EGF in peripheral blood decreased significantly and the content of CD16+iaieTOK increased sharply in comparison with the data of healthy women ( $p<0.01$  in all cases).

Changes in the phenotypic profile of peripheral lymphocytes in internal endometriosis had a different direction (Table 1). In this group of women, we noted a significant decrease in the content of SB8+cells and an increase in the number of CD 16+ lymphocytes compared to the control group ( $p<0.05$ ).

Table 1

Population composition of peripheral blood lymphocytes in women with endometriosis,  $M\pm n$

Indicators. %	Control group.. p=18	I GE, p=27	E GE, p=31
CD3+	55,8±1,9	50.7±1.4*	48,4±1,7*
CD4+	35.6±1.4	31,3±1,1	28,6±1.2*
CD8+	21,8±1,0	20.8±0.8	17.1±0.6*
CD 16+	13,6±1,1	8.7±0.5*	21.9±1.3*
CD20+	15,7±0,9	16.3±0.7	13,7±0.8
CD45RA+	54,3±1,4	48,8±1,2*	38,3±1.5*
CD25+	18,3±1,4	16.3±1.4*	15.3±1.4
CD95+	26,8±1,6	19,8±1,6*	23,8±1,6

Note. \* - $p<0.05-0.001$  compared to the control group. - (Table 2).

The level of functional activity of peripheral neutrophils was also estimated by us according to the indicators of spontaneous and winterized NST-test with calculation of phagocytic reserve index.

The analysis of the obtained results showed that the NST-activity of neutrophils in the spontaneous NST-test was increased beforehand in the peripheral blood of patients with NGE, and the index of the dye recovery activity was increased in comparison with the

similar parameters in the peripheral blood of healthy women (accordingly,  $p < 0.01$ ;  $p < 0.05$ ). In addition, in patients with NSE there was a slight decrease in the reserve of functional activity of neutrophils, which was estimated with the help of phagocytic reserve index ( $p < 0.05$ ).

Table 2

Indicators of functional activity of peripheral blood neutrophils in women with endometriosis

Indicators	Control group n=18	I GE, n=27	E GE, n=31
HCTc, %	16,8±1,52	22,5±1,7*	26,8±1,63*
HCTc, и.а.в.	0,24±0,05	0,31±0,03*	0,38±0,02*
HCTз, %	38,3±2,4	37,4±2,0	37,9±2,0
HCTз, и.а.в.	0,86±0,06	0,83±0,04	0,81±0,03
ИФР	1,46±0,3	0,89±0,2	0,64±0,1 *

Note. \* -  $p < 0.05-0.001$  compared to the control group.

Changes in the parameters of the NST-test stimulated by zymozan in peripheral blood of women with NGE compared to those of healthy women were not observed ( $p < 0.05$ ). When comparing the indices of functional activity of peripheral blood neutrophils in patients with HGE and healthy women, we also found no significant differences. The number of NSF-positive peripheral neutrophils in the spontaneous and stimulated NSF test in women with internal genital endometriosis corresponded to the normative values.

Thus, the results obtained by us indicate that the functional activity of neutrophils changed only in women with IGE. Probably, it is connected with AMGF-a2 microglobulin of fertility, or glycodelin, which level in serum of endometriosis patients increases considerably (Posiseeva JI.B. et al., 1998).

We have also studied the peculiarities of cytokines synthesis in blood serum in women with external and internal endometriosis. The obtained results indicate that in women with internal endometriosis the level of IL-10 was 3.2 times higher than the control values ( $p < 0.01$ ). At the same time, the number of IL-2 had only a tendency to decrease. The content of anti-inflammatory cytokine IL-4 was 2.2 times lower than the control values ( $p < 0.01$ ).

Table 3

Synthesis of cytokines in peripheral blood serum in women with endometriosis, M±n

Indicators, %	CONTROL GROUP, n=18	IGE, n=27	EGE, n=31
ИЛ-1 В	21.5±2,2	69,7±2.4*	73.4±2.7*
ИЛ-2	8,95±1,7	7,3±1,8	5.6±1,5*
ИЛ-4	20.9±2.4	9.4±1.3*	15,8±1.6*
ИЛ-6	27,9±2,5	17,4±1,0*	19,8±1,4*
ИЛ-8	16.3±1.9	25.3±2.0*	29,7±2,3*
IFN $\gamma$	18,7±2,7	15,6±1,0	9.7±,9*

Note. \* -  $p < 0.05-0.001$  compared to the control group.

The IL-6 and IFN $\gamma$  levels were also below control ( $p < 0.05$  in both cases). Analysis of the data of women with external endometriosis showed that the levels of proinflammatory cytokines IL-1p and IL-8 in them were sharply increased ( $p < 0.05$ ), and the content of IL-2, IL-4, IL-6 and IFN $\gamma$  was lower than the control values ( $p < 0.05$ ).

Summarizing the data on phenotypic, cytokine profile and phagocytes of peripheral blood, it should be noted that the changes in the studied parameters were common for different forms of endometriosis. Apparently, systemic immune disorders in endometriosis are more associated with concomitant clinical symptoms, which are different for a particular form of endometriosis, and less reflect the general mechanisms of ectopic endometrium development.

The obtained results convincingly prove the necessity of including immunocorrectors into the complex therapy depending on the endometriosis localization, clinical course and immune system parameters.

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#### CONCLUSION:

56 patients with genital endometriosis were examined. Of these, 26 had internal endometriosis and 30 had external genital endometriosis. All tested women studied the state of the immune system (cellular immune response, phagocytosis and status of cytokines). It was noted that in patients with endometriosis the level of T- lymphocytes and their subpopulation composition decreased, and the degree of activity of killers changed in different directions depending on the form of genital endometriosis. Functional activity of neutrophils changed only in the group of women with TGE.

**REFERENCE:**

1. Selkov S.A., Yarmolinskaya M.I., Pavlov O.V. i dr. Sistemniie I lokalnie urovni reguliyasii immunopatogenicheskix prosessov u pasientok s narujnim genitalnim endometriozom. //Jurn.akush.i jen. bol. - 2005. - T. LIV, NO. 1. - pp. 20-28.

Solodovnikova N.G., Niauri D.A. Rol faktorov immunnoy sistemi v patogeneze narujnova genitalnogo endometrioza. //Beul. Federalnogo sentra serdsa, krovi i endokrinologii im. V.D. Almazova. - 2011. - №6. - S. 23-28.

3. Shishkov D.N. Rol immunnix narushenie v razvitii besplodiya pri malix formax narujnogo genitalnogo endometrioza: Avtoref. dis. ...kand. med. Nauk. -Ivanovo, 2007.

4. Bohler, N.S. et al. Endometriosis markers: immu-nologic alterations as diagnostic indicators for en-dometriosis (in Russian) // Reprod. Sci. - 2007. - Vol. 14, №6. - P. 595-604.

5. Burney R.O. The genetics and biochemistry of en-dometriosis // Curr. Opin. Obstet. Gynecol. - 2013. -Vol. 25.-P. 280-286. \*

6. Podgaec S. et al. Endometriosis: an inflammatory disease with a Th2 immune response component // Human Reproduction. - 2007. - Vol. 22, №5. - P. 1373-1379.  
Buyanova S.N., Shchukina N.A., Gorshilin A.V. Reproductive prognosis in patients with purulent inflammatory diseases of small pelvis: problems and solutions. Russian messenger of obstetrician-gynecologist. 2009; 2: 65-68.

7. Zubkov M.N. Collection, transportation of biological material and interpretation of microbiological research results. Clinical microbiology and antibacterial chemotherapy. 2004; 6; 2: 143-154.

8. Kisina V.I., Kanishcheva E.Yu., Dmitriev G.A., Yakovlev V.P. Clinical, microbiological and morphological features of chronic inflammatory diseases of small pelvis organs in women. Sexually transmitted infections. 2002; 2: 10-14.

9. Identifier of Bergie bacteria. Edited by Hault J., Krieg N., Sneeta P., Steely J., Williams S. Moscow: "Mir". 1997; T.1-2.

10. Ross J.D.S. European guidelines for inflammatory diseases of the pelvic organs and perihepatitis // Sexually transmitted infections. 2002; 2: 34-37.

11. Utkin, E.V.; Kulavskiy, V.A. Main reasons of development and modern tendencies in the clinical course of the inflammatory diseases of the pelvic organs in women. Russian messenger of obstetrician-gynecologist. 2008; 1: 40-44.

12. Yaglov V.V. Inflammatory diseases of the pelvic organs. Gynecology. 2006; 4: 46-47.

13. Bohm M.K., Newman L., Satterwhite C.L., Tao G., Weinstock H.S. Pelvic inflammatory disease among privately insured women, United States, 2001-2005. Sex Transm Dis. 2010; 37(3): 131-136.