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DIFFERENTIAL IMMUNOCORRECTION IN WOMEN WITH GENITAL ENDOMETRIOSIS

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Abstract: 52 patients with genital endometriosis were examined. Of these, 22 had internal endometriosis, and 30 had external genital endometriosis. 21 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.

Introduction

According to modern data, external genital endometriosis (EGE) is diagnosed in 30% of women of reproductive age, 38.8% of patients suffering from pelvic pain syndrome, 50% of women with infertility, and the frequency of its detection on autopsy material reaches 53.7%.

According to the literature, endometriosis is one of the main causes of female infertility, ranked second after inflammatory diseases of uterine appendages. Meanwhile, up to now, there is no single idea of infertility pathogenesis associated with endometriosis. The most probable causes of infertility in endometriosis are: disorders in the system of hypothalamus-pituitary ovaries, leading to anovulation, immunological changes in the peritoneal fluid, adversely affecting the mobility and fertilizing capacity of sperm, as well as tubal-peritoneal factor due to the obstruction of uterine tubes, developing due to the adhesion process

The multifactorial infertility in endometriosis appears to be the cause of low frequency of fertility restoration in patients using conventional methods of treatment for this disease. According to the literature data, only surgical removal of the EGE centers with the separation of adhesions and restoration of uterine tubes patency allows to get pregnancy in 20 - 30% of patients. Complex surgical and hormonal treatment of the EGE increases this index up to 39 - 50% due to the decrease in the frequency of recurrences of the disease, however, anovulation that occurs against the background of hormonal therapy in the most favorable period for conception (the first 6 months after the removal of endometriosis foci), does not allow to achieve more significant results.

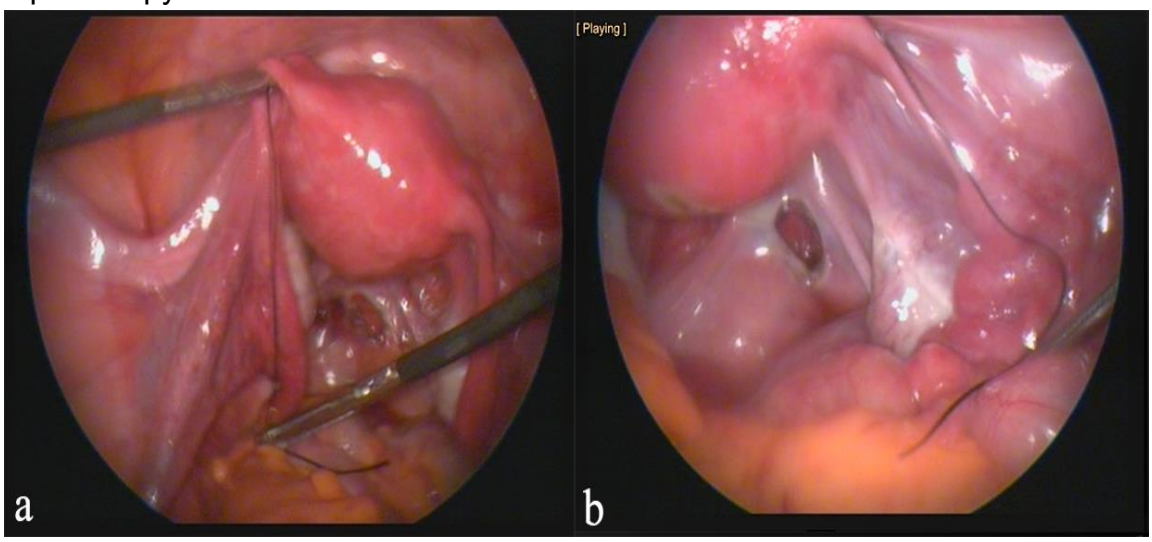
Insufficient efficacy of the existing methods of treatment of the EGE with respect to the restoration of fertility in patients with infertility determines the relevance of further study of this problem, taking into account all aspects of infertility pathogenesis occurring in this disease. In modern notions about the nature of immune disorders in the case of EGE, the use of immunotropic drugs is an important step in the complex therapy of infertility that occurs in this pathology. However, until now, the immune component of infertility associated with the EGE is undeservedly ignored.

In the overwhelming majority of works immunomodulating preparations were used as an addition to the postoperative hormonal treatment of the EGE, which does not allow to evaluate objectively - their advantages and disadvantages in the treatment of this disease and associated infertility. In our opinion, the pathogenetically grounded and experimentally confirmed scheme of selective immunotherapy of infertility associated with the EGE will allow to form a new direction in solving the actual problem of obstetrics and gynecology, which determined the purpose of our study.

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.

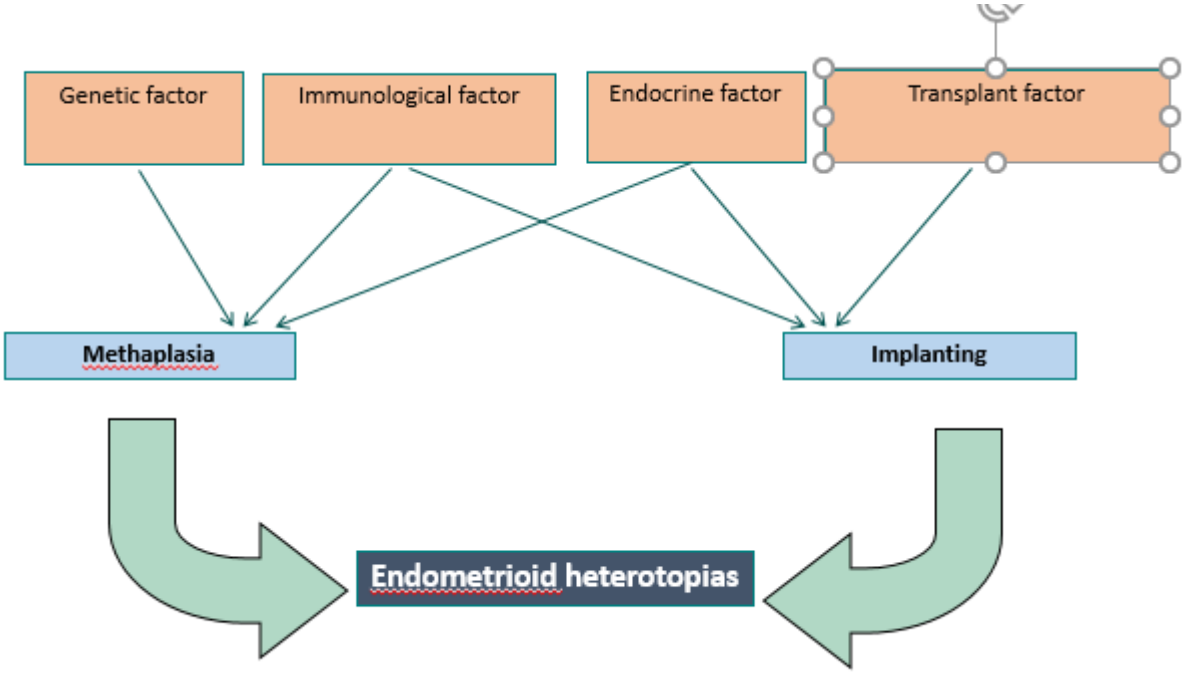
Material and methods: We observed 22 women with internal genital endometriosis (IGE) and 30 patients with external genital endometriosis (EGE), whose diagnosis was verified at the stage of clinical and instrumental examination, including therapeutic and diagnostic laparoscopy.



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 21 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- ip, IL-2, IL-6, IL-8, IFNy) 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 HGE 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 selection, 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 mesical 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. DUBwas 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 УВК (17%) and low hemoglobin levels (27%) were often observed in women with both IGE and EGF.

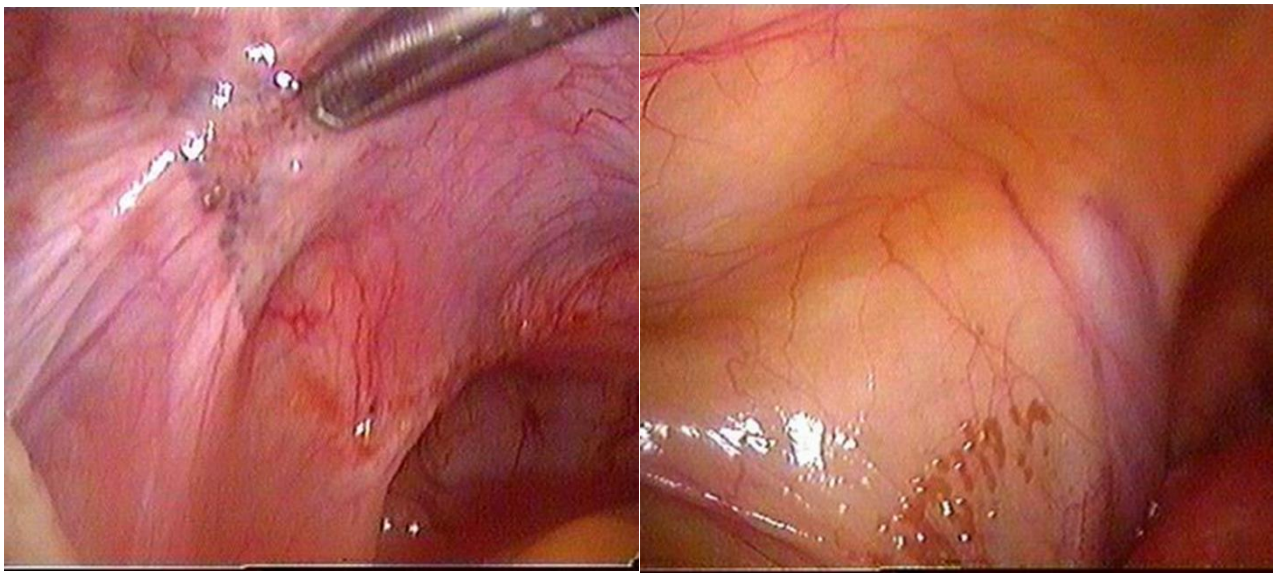
The overall condition of women has deteriorated significantly due to the fact that endometriosis has had a negative impact on the work of all internal organs. Patients felt weak (45%), their ability to work decreased (27%), irritability appeared due to constant pain, abundant blood loss caused dizziness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

Indicators. %	Control group..p=18	IGE, p=27	EGE, 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 the 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). Besides, 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).

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 the 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.

Table 2

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

Indicators	Control group p=18	IGE, p=27	EGE, p=31
NSTs, %	16,8±1,52	22,5±1,7*	26,8±1,63*
NSTs, и.а.в.	0,24±0,05	O,31±O,03*	0,38±0,02*
NSTi, %	38,3±2,4	37,4±2.0	37,9±2,0
NSTi, in quan.	0,86±0,06	0,83±0,04	0,81±0,03
IER	1,46±0,3	0,89±0,2	0,64±0.1 *

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

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 ($p<0.01$).

The IL-6 and IFNy 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 IFNy was lower than the control values ($p<0.05$).

Table 3

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

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

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

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. 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:

52 patients with genital endometriosis were examined. Of these, 22 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.

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