ANALYSIS OF CELLULAR IMMUNITY IN WOMEN DIAGNOSED WITH EXTERNAL GENITAL ENDOMETRIOSIS

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Annotation. *Endometriosis remains a "mysterious" condition, as its precise etiology has not yet been fully elucidated. Proposed etiological factors include congenital predisposition, environmental influences, epigenetic mechanisms, as well as autoimmune and allergic components. The most widely accepted pathogenetic theory suggests that endometriotic lesions arise through retrograde menstruation, whereby menstrual blood flows through the fallopian tubes into the peritoneal cavity, allowing exfoliated endometrial cells to implant and proliferate.*

Key words*: endometriosis, dienogest, cellular immunity.*

АНАЛИЗ ПОКАЗАТЕЛЕЙ КЛЕТОЧНОГО ИММУНИТЕТА У ЖЕНЩИН С НАРУЖНО-ГЕНИТАЛЬНЫМ ЭНДОМЕТРИОЗОМ

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Аннотация. *Эндометриоз – «загадочное» заболевание, и его точная причина до сих пор не установлена. Среди этиологических факторов перечислены врожденные, средовые, эпигенетические, аутоиммунные и аллергические факторы. Считается, что первичным механизмом образования очагов эндометриоза является ретроградная менструация, т. е. прохождение менструальной крови по фаллопиевым трубам в брюшную полость и имплантация отслоившихся клеток эндометрия.*

Ключевые слова: *эндометриоз, диеногест, клеточный иммунитет.*

TASHQI GENITAL ENDOMETRIOZI BOR AYOLLARDA HUJAYRAVIY IMMUNITET KO‘RSATKICHLARINING HOLATI

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Izoh*. Endometrioz "sirli" kasallik bo'lib, uning aniq sababi hali ham noma'lum. Etiologik omillarga kongenital, ekologik, epigenetik, otoimmun va allergik omillar kiradi. Endometrioz o‘choqlarini shakllantirishning asosiy mexanizmi retrograd hayz, ya'ni hayz qonining fallop naylari orqali qorin bo‘shlig‘iga o‘tishi va eksfoliatsiyalangan endometriyal hujayralarning implantatsiyasi deb ishoniladi.*

Kalit so'zlar*: endometrioz, dienogest, hujayra immuniteti.*

Endometriosis is a chronic gynecologic disease characterized by the development and presence of histological elements like endometrial glands and stroma in anatomical positions and organs outside the uterine cavity. The main clinical manifestations of the disease are chronic pelvic pain and impaired fertility. The localization of endometriosis lesions can vary, with the most commonly involved focus of the disease being the ovaries, followed by the posterior broad ligament, the anterior cul-de-sac, the posterior cul-de-sac, and the uterosacral ligament.[1] Endometriotic nodules also affect the intestinal tract and the urinary system, like the ureter, the bladder, and the urethra. Nevertheless, endometriosis is not limited to the pelvis but can damage extra pelvic structures like the pleura, the pericardium, or the central nervous system [2]. The main theories utilized to explain the pathogenesis of endometriosis are Sampson's theory, the coelomic metaplastic theory, the stem cell theory, the Müllerian remnant theory, and the vascular and lymphatic metastasis theory. Endometriosis has a number of features that distinguish it from other diseases: cyclicity, similar to the regularity of the ovario-menstrual cycle; the absence of a connective tissue capsule in the focus of endometriosis; tendency to infiltrating growth associated with the enzymatic activity of endometrioid foci. A feature of endometriosis is its ability to metastasize, i.e., the transfer of endometriosis cells by implantation through the lymphatic and blood vessels to other organs and tissues located at a considerable distance from the primary focus [2, 5, 8].

The first scientific reports on the problem of endometriosis are traditionally attributed to the middle of the 19th century. Around the same time, the first hypotheses about the origin and development of endometrioid heterotopias appeared. According to the literature, at the moment there are at least 11 different concepts. However, endometriosis

still remains a mystery to researchers, since its etiology and pathogenesis have not been fully established [3, 4, 16].

A review of studies indicates a steady increase in the incidence of genital endometriosis over the past 10-15 years, which has become one of the leading in the structure of gynecological pathology [1,6]. Identified by a number of authors, significant disorders of the immune status in patients with endometriosis [2, 14] made it possible to make an assumption about the participation of immune mechanisms in the pathogenesis of this disease, develop methods for early diagnosis, and outline ways of immunocorrective therapy. Regardless of localization, endometriosis affects not only the function of the affected, adjacent and distant organs, but also the entire body as a whole. Most researchers [1, 3, 8] consider immunological changes in endometriosis as a secondary reaction of the immune system to the developing focus of endometriosis. However, some of them indicate the possibility of the primacy of these disorders and their participation not only in the development of infertility and anovulation, but also in the occurrence of endometriosis [2, 4, 7].

At the same time, there are not enough studies devoted to a comparative analysis of the response of a woman's immune system depending on various methods of treating endometriosis. According to the European Society of Human Reproduction and Embryology (ESHRE) (2022) guidelines, the most commonly prescribed treatments for endometriosis include drugs that alter the hormonal milieu, either by suppressing ovarian activity or by acting directly on steroid receptors and enzymes present in lesions. These drugs include progestogens, antiprogestogens, combined oral contraceptives (OCPs), gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, levonorgestrel intrauterine devices (LNG-IUD), danazol, and aromatase inhibitors. All these hormone treatments lead to a clinically significant reduction in pain compared with a placebo [7,9]. Dienogest is a new generation of progestin carrying the pharmacological specialties of 19-norprogestin and progesterone derivatives. It has been shown that dienogest has strong progestogen, androgenic, mineralocorticoid, and glucocorticoid effects [5,11,15].

The purpose of our study is to determine the optimal approach for evaluating the effect of dienogest treatment using Visanne, by assessing clinical outcomes and analyzing changes in selected cellular immunity indicators

Material and methods. 102 women diagnosed with external genital endometriosis and 20 healthy women who made up the control group were examined. All surveyed were of fertile age (mean age of patients 27.8 years, in the control - 26.9) without severe extragenital pathology. Of the total number of patients, the first group consisted of 50 (36.5%) women who, against the background of traditional therapy, used Vizanna in a cyclic regimen, and the 2nd group included 52 (38.0%) women who, against the background of traditional therapy received the drug Visanne in a continuous mode. In group 1, 16 (55.2%) out of 29 had primary and 5 (17.2%) secondary infertility, 8 (27.6%) had no impaired fertility. In group 2, respectively, in 20 (64.5%) and 6 (19.4%), in 3 (9.7%) fertility was not impaired, and 2 (6.5%) girls aged 16 and 17 years were under the age of marriage.

The diagnosis of endometriosis was verified by the characteristic clinic of the disease, ultrasound data and histological studies.

The content of populations of CD3+ - T-lymphocytes, CD20+ - B-lymphocytes, subpopulations of CD4+ - T-helpers and cytotoxic CD8+ - T-lymphocytes in the peripheral blood was determined using monoclonal antibodies. The value of the immunoregulatory index (IRI) was determined by calculating the CD4+/CD8+ ratio. In addition, the percentage of antigen-binding lymphocytes (ASL) specifically sensitized to tissue antigens of the brain, liver, kidneys, ovary, endometrium, and myometrium was determined in all subjects in the peripheral blood. Tissue-specific antigens from the listed organs were obtained according to the method of H. Werner [15]. Determination of ASL to tissue antigens of organs was carried out by the method of F. Yu. Garib and M. V. Zalyalieva [3].

The obtained data were subjected to statistical processing using a statistical analysis software package with the calculation of the arithmetic mean (M), standard deviation), standard error (m), the statistical significance of the measurements obtained when comparing the average values was determined by the criterion (t) Student. Significance level $P<0.05$ was taken as statistically significant changes.

Results and discussion. In patients with endometrioid lesions, there are significant changes in both local immunity factors and immunological components in the circulating blood.

Analysis of the T-link showed that the total pool of T-lymphocytes before treatment was significantly reduced in both groups compared with the control.

30-36 days after treatment, this indicator increased significantly in both groups ($P<0.05$), but not reaching the level of the control group in all positions.

The number of B-lymphocytes before treatment was also reduced compared to the control in both groups. After treatment, there was a similar dynamic to the recovery of the indicator without significant differences. The picture of the content of T-helpers and T-suppressors showed the same dynamics. (Table 1).

Table 1.

Cellular immunity parameters before and after treatment

Indicators	Control Groups	Timing	Groups of patients with endometriosis	
			1st group	2 group
CD3	59,6±1,1	Before treatment	34,9±1,1*	36,6±1,1*
		After	43,3±1,3*♦	42,8±1,1*
CD20	19,2±0,8	Before treatment	14,1±0,6*	14,7±0,5*
		After	17,3±0,4*♦	16,9±0,4*♦
CD4	31,9±0,7	Before treatment	17,1±0,8*	18,6±0,7*
		After	25,2±0,5*♦	26,5±0,7*♦
CD8	21,7±0,5	Before treatment	16,4±0,5*	17,1±1,9*
		After	19,4±0,4*	21,1±0,3*
Immuno-regulatory index	1,5±0,05	Before treatment	1,1±0,04*	1,1±0,03*
		After	1,5±0,04♦	1,5±0,03*♦

*Note: * - differences relative to the control group (* - P<0.05); • -P<0.05) differences relative to before treatment are significant*

The inclusion of Jeannine in traditional therapy in a continuous regimen turned out to be more effective, as shown by the analysis of immunological parameters after treatment

An analysis of the parameters of antigen-containing lymphocytes is presented in Table 2. Before the intervention, statistically significant differences were established in almost all studied ASL parameters (except for ASL-brain) in 2 groups compared with control values. At the same time, the highest rates were found for tissue antigens of the ovaries, endometrium and myometrium. For extragenital organs, the indicators of ASL-liver, - myocardium, - endocardium dominated.

After treatment with Visanne, there was a significant trend towards a decrease in all studied ASL parameters in both groups. However, by the second examination period, the parameters of ASL-ovary, endometrium, and myometrium were still significantly higher than the control ones (Table 2).

The conducted studies allow us to suggest that significant immunological changes in the body of patients with endometriosis arise as a result of the influence of endometrioid disease.

Table 2.

Dynamics of ASL indicators in patients with endometriosis

Indicators	Control Groups	Timing	group of patients with endometriosis	
			1st group	2nd group
Liver	2,03±0,04	Before treatment	4,93±0,50*	5,42±0,65*
		After	2,37±0,31♦	2,40±0,37♦
Brain	1,11±0,07	Before treatment	1,01±0,16	1,20±0,40
		After	0,96±0,08	1,01±0,10
Endocardiumд	1,98±0,04	Before treatment	4,63±0,59*	5,03±0,57*
		After	2,04±0,22♦	2,07±0,47♦
Myocardium	2,01±0,03	Before treatment	4,04±0,46*	5,23±0,54*
		After	1,74±0,20♦	1,63±0,42♦
kidneys	1,88±0,03	Before treatment	3,89±0,41*	4,68±0,55*
		After	2,09±0,23♦	2,00±0,29♦

Lungs	1,32±0,07	Before treatment	4,19±0,69*	3,90±0,37*
		After	1,45±0,29♦	1,39±0,31♦
Endometrium	1,82±0,04	Before treatment	7,37±0,88*	6,42±0,75*
		After	2,81±0,47*♦	2,95±0,51*♦
Myometrium	1,63±0,05	Before treatment	6,07±0,94*	6,23±0,61*
		After	2,87±0,21*♦	2,73±0,36*♦
Ovary	1,45±0,04	Before treatment	8,44±0,92*	7,93±0,74*
		After	3,67±0,36*♦	3,52±0,60*♦

*Note: * - differences relative to the control group (* - P<0.05); • -P<0.05) differences relative to before treatment are significant*

The conducted studies allow us to suggest that significant immunological changes in the body of patients with endometriosis arise as a result of the influence of endometrioid disease. This may be indicated by a clear trend towards the restoration of the main clones of immunocompetent cells after the intervention. Probably, the main trigger of immunosuppression is the content of endometrioid heterotopias.

Conclusions.

1. Comparative analysis of ASL indicators, confirming the above assumption, indicates a continuing significant level of cell destruction in the internal genital organs 30-36 days after treatment, regardless of its nature.

2. The clinical results of the study, coupled with the analysis of immunological parameters, make it possible to characterize the drug Visanne as a method of choice for the treatment of external genital endometriosis, especially among women with a satisfactory generative history.

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