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FEATURES OF THE IMMUNE SYSTEM IN ENDOMETRIAL HYPERPLASIA IN THE PERIMENOPAUSAL PERIOD

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Tayanch so‘zlar: GE, PGE, CD25+, CD95+, IL-1β, IL-2, IL6, TNFα.
Ключевые слова: GE, PGE, CD25+, CD95+, IL-1β, IL-2, IL6, TNFα.

This article discusses the immunological features of the development of endometrial hyperplasia in women in the perimenopausal period. Markers of proliferation and apoptosis and pro-inflammatory cytokines in the blood serum were examined in women. They were divided into two groups (group 1 - HE, group 2 - recurrent HE turning to PHE), and it was revealed that in both groups of women, immunological changes were unidirectional, but more pronounced immunological changes were observed in the second group. Common properties for the studied groups were a decrease in the level of CD25+ and CD95+ cells and a significant increase in the level of IL-1β, IL-6, TNFα and a decrease in IL-2. Based on the results obtained, it cannot be unequivocally stated that the detected changes are directly related to the local processes of the reproductive organs in women with GE and possibly reflect the premorbid background of the patients. All this dictates the need for additional tests to study local immunity.

PERIMENOPOZAL DAVRDA AYOLLARDA ENDOMETRIYAL GIPERPLAZIYA RIVOJLANISHINING IMMUNOLOGIK XUSUSIYATLARI

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Ushbu maqolada perimenopozal davrda ayollarda endometriyal giperplaziya rivojlanishining immunologik xususiyatlari ko‘rib chiqiladi. Ikki guruhga bo‘lingan ayollarda qon zardobidagi proliferatsiya va apoptoz belgilari va yallig‘lanishga qarshi sitokinlar tekshirildi (1-guruh - GE, 2-guruh - qaytalanuvchi GE). Aniqlanishicha, ikkala guruhdagi ayollarda ham immunologik o‘zgarishlar bir yo‘nalishli bo‘lsa-da, ikkinchi guruhda aniqroq immunologik o‘zgarishlar kuzatilgan. O‘rganilayotgan guruhlar uchun umumiy xususiyatlar CD25+ va CD95+ hujayralari darajasining pasayishi va IL-1b, IL-6, TNFa darajasining sezilarli darajada oshishi va IL-2 ning pasayishi edi. Olingan natijalarga asoslanib, aniqlangan o‘zgarishlar GE bo‘lgan ayollarda reproduktiv organlarning mahalliy jarayonlari bilan bevosita bog‘liqligini va, ehtimol, bemorlarning premorbid fonini aks ettirishini aniq aytish mumkin emas. Bularning barchasi mahalliy immunitetni o‘rganish uchun qo‘shimcha testlarni o‘tkazish zarurligini taqozo etadi.

ОСОБЕННОСТИ ИММУННОЙ СИСТЕМЫ ПРИ ГИПЕРПЛАЗИИ ЭНДОМЕТРИЯ В ПЕРИМЕНОПАУЗАЛЬНОМ ПЕРИОДЕ

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В статье рассматриваются иммунологические особенности развития гиперплазии эндометрия у женщин в перименопаузальном периоде. Маркеры пролиферации и апоптоза, а также провоспалительные цитокины в сыворотке крови исследовали у женщин, разделенных на две группы (1-я группа - ПЭ, 2-я группа - рецидивирующая ПЭ, переходящая в ПГЭ). Выявлено, что в обеих группах женщин иммунологические изменения были однонаправленными, однако во второй группе наблюдались более выраженные иммунологические изменения. Общими свойствами для исследуемых групп были снижение уровня CD25+ и CD95+ клеток и достоверное повышение уровня IL-1β, IL-6, TNFα и снижение IL-2. На основании полученных результатов нельзя однозначно утверждать, что выявленные изменения напрямую связаны с местными процессами репродуктивных органов у женщин с ГЭ и, возможно, отражают преморбидный фон больных. Все это диктует необходимость проведения дополнительных исследований по изучению местного иммунитета.

Relevance. Today, with the increasing life expectancy of the population, the main causes of mortality in the general population and among the female population are cardiovascular diseases and cancer. In the structure of causes of mortality and disability, oncological pathology of the reproductive system occupies a leading place. Currently, according to world statistics, endometrial cancer (EC) ranks second among the causes of death in women of perimenopausal age, second only to breast cancer [2, 6, 18].

Throughout the world, in the structure of gynecological diseases in women of perimenopausal age, benign endometrial processes account for 60-70%, and therefore, prediction, early diagnosis and treatment of proliferative processes of the endometrium, which serve as a prerequisite for the development of endometrial cancer, is one of the preventive measures of this diseases [1, 5, 8, 12].

One of the key factors influencing the development of diseases, including hyperplastic processes in the reproductive organs, is the state of cellular and humoral immunity. Cytokines pro-

duced by immunocompetent cells play an essential role in regulating the immune response. They not only regulate the level of activity of the immune system, but also influence the interaction of the body's main biological systems, such as the nervous, immune and endocrine. It is believed that one of the most important and frequently damaged cells in the immune system are T helper cells, which produce cytokines [3, 7, 20].

The study of local immune mechanisms is of great interest for understanding the basic processes of the development of endometriosis. However, studying the systemic immune response in endometriosis also provides important information about the mechanisms of the disease, since the state of circulating cytokines often reflects the nature of immune disorders occurring locally in organs [4, 10, 15, 24].

Purpose of the study: studying the role of the cellular link and cytokine status in the development of hyperplastic processes in endometriosis in women during the perimenopausal period.

Materials and research methods. The studies were carried out in antenatal clinics in the city of Bukhara and the gynecological department in the period from 2022 to 2024. In accordance with the goals and objectives of the work, 114 women in the perimenopausal period were examined. Conventional clinical, laboratory, instrumental and immunological diagnostic methods were carried out. Group I consisted of 36 women with a physiological course of the perimenopausal period, group II included 40 women with HE, group III included 38 patients with recurrent HE with transition to PHE.

The following markers of immunocompetent cells (ICC) were determined: CD25+ - and CD95+ - lymphocytes. Expression of CD receptors was carried out in a rosette reaction using monoclonal antibodies of the LT series produced by Sorbent LLC, Russia.

Determination of the concentration of cytokines (IL-1β, IL-2, IL-6, TNFα) was carried out using the solid-phase “sandwich” method - a variant of enzyme immunoassay using a set of reagents from Vector-Best (Novosibirsk).

When working with the data, descriptive statistics methods were used: point estimates of the mean (M), standard deviation (SD) were determined. The normality of indicator values in the samples was checked graphically and using the Shapiro-Wilks test. When the distributions of values in samples deviated from the normal distribution, the nonparametric Mann-Whitney test for independent samples and the Wilcoxon test for dependent samples were used.

Research results. Analysis of the age distribution revealed that the age of women included in the groups ranged from 45 to 55 years and averaged 50±2.33 years, in the main group from 48.05±2.17 years, in the control group 49.2± 1.98 years ($p>0.05$). Based on these data, we can say that there is no significant difference between the ages of those examined in the control and main groups.

In addition, as a result of examining women in the selected groups, we found that the nature of menstrual function in both groups did not differ significantly. The average age of menarche in the main group was 14.0±0.85 and 14.5±0.92 years, in the control group 13.2±1.32 years ($p>0.05$). The duration of the menstrual cycle ranged from 25 to 32 days, on average it was 28-30 days in the main group, 26-27 days in the control group ($p>0.05$). The duration of bleeding did not have significant differences in the groups - 8.21±0.53 and 8.62±0.64 days, and blood loss in all was regarded as significantly heavy.

As can be seen from the Table 1, all gynecological pathologies and interventions were significantly more common in the third study group. Especially in this regard, the leading place is occupied by inflammatory diseases of the genital organs.

Since somatic pathology has an influence and is considered a risk factor for aggravating or provoking AUB of the perimenopausal period, its study is no less valuable. Systematizing the pathologies encountered in the study groups, we found that diseases of the gastrointestinal tract, endocrine system, and neurological diseases were diagnosed more than others; in the first place, anemia was competed with almost equal ratios by iron deficiency anemia (IDA) and hypertension. The list of diagnosed somatic pathologies is shown in Table 2.

A comparative analysis shows that in women of the main group, extragenital pathology is detected more often than in women in the control group, which is clearly visible in the Table 2, which once again proves that extragenital pathology affects the gynecological condition of patients.

To conduct immunological studies, we selected 50 patients diagnosed with endometrial hy-

1 table.

Gynecological diseases identified in comparative groups n=114, abs (%)

Diseases/interventions	I-group, (control group), n=36		II- group, main (women with HE), n= 40		III-group, main, (women with HE with transition to PHE), n=38	
	abs.	%	abs.	%	abs.	%
Metritis	1	2.38	1	2.77	2	5.88
Ovarian cyst	1	2.38	1	2.77	2	5.88
Adenomyosis	-	-	4	11.1	6	17.6
Myoma	-	-	10	27.7	11	32.3
Adnexit	1	2.38	1	2.77	1	2.94
Colpitis	2	4.76	2	5.55	3	8.82
Cystitis	1	2.38	2	5.55	1	2.94
TORCH infection	2	4.76	3	8.33	3	8.82
Mastopathy	3	7.14	4	11.11	4	11.76
Infertility	2	4.76	3	8.33	2	5.88
Surgeries on the genital organs	2	4.76	3	8.33	2	5.88
Erosion	2	4.76	3	8.33	4	11.76
DEK	1	2.38	1	2.77	1	2.94
Bottom line	18	42.85	26	72.2	27	79.4

*Note: *P≤0.05—the difference is significant compared to the control group.*

2 table.

Somatic pathology encountered in the study groups was n=112, abs (%).

Nosology	I-group, (control group), n=36		II- group, main (women with HE), n= 40		III-group, main, (women with HE with transition to PHE), n=38	
	abs.	%	abs.	%	abs.	%
Endocrine system diseases						
Diffuse goiter	12	40	21	52.5	18	39
Diabetes	-	-	5	13.8	8	23.5
Nervous system diseases						
	2	6.6	11	27.5	15	32.6
Lumbosacral radiculitis	-	-	-	-	1	2.17
NCD (neurocirculatory dystonia)	3	7.1	7	19.4	8	23.52
Neurosis	2	4.76	4	11.1	5	14.7
Chronic gastritis	3	7.1	8	22.2	10	29.4
Chronic cholecystitis	3	7.1	6	16.6	8	23.52
Others						
Anemia	21	50	34	94.4	30	88.2
Hypertension (HD)	5	11.9	10	27.7	12	35.2
Varicose veins	3	7.1	5	13.8	5	14.7
Chronic kidney disease	-	-	-	-	2	4.3

*Note: *P≤0.05—the difference is significant compared to the control group.*

perplasia in the perimenopausal period, who were divided into two groups:

- Group 1 – 27 patients diagnosed with endometrial hyperplasia (EH).
- Group 2 – 23 patients diagnosed with recurrent endometrial hyperplasia with transition to PHE.
- third group (control) – 20 healthy patients of similar age.

One of the risk factors for the endometrial hyperplasia development is the inflammatory process caused by persistent viral invasion. Since viruses attack the epithelial layers, the state of local protection of the organs of the reproductive system plays an important role in cases of endometrial hyperplasia. The mucous membranes, which function as a mechanical and functional barrier, also act as an immune filter. In this filter, humoral factors can be identified, such as immunoglobulins, cytokines, interferons, cellular T- and B-lymphocytes, macrophages and others. Levels of cytokines in biological fluids reflect the current state of the immune system [8, 9, 13, 17, 24].

It is known that abnormalities in the organs of the reproductive system can be associated with the development of immunological tolerance to various viruses, which can contribute to hyperplastic processes in the endometrium. One of the mechanisms leading to the formation of such tolerance includes cytokine-mediated suppression due to the predominance of Th2/Th3 cytokines. On the other hand, the predominance of Th1 cytokines may be associated with the level of viral load. However, some studies indicate that inflammatory processes may be associated not only with an increase in Th1 cytokines, but also with increased production of Th2 cytokines, as well as with a simultaneous increase in the levels of both types of cytokines. Thus, data on the production of various cytokines in endometrial pathology are multifaceted [11, 14, 19].

To clarify the role of early and late activation markers and cytokine status in the development of endometrial hyperplastic processes, we conducted a comparative analysis of previously studied activation markers in the examined groups.

A comparative analysis of the obtained data on the absolute values of CD25+ lymphocytes between groups revealed a decrease with progression from the control group (355.4 ±7.20µl) to the group with endometrial hyperplasia (285.8 ±5.73µl) and further to the group of women with recurrent endometrial hyperplasia transforming into a proliferative-hyperplastic form (245.4 ± 4.41 µl). A significant decrease in the level of CD25+ (abs) was observed by 1.24 times between the control group and the HE group, as well as by 1.16 times between the first group (HE) and the second (PHE).

The study showed that the number of CD95+ lymphocytes in the group of patients with recurrent endometrial hyperplasia turning into a proliferative-hyperplastic form decreased by 1.34 times (325.6 ±3.65µl compared to 436.5 ±6.19µl) compared to the control group.

A comparison of the relative values of CD25+ lymphocytes showed that the level of lymphocytes in patients with recurrent endometrial hyperplasia transitioning to proliferative-hyperplastic endometritis was significantly lower than in the control group and the group with HE, 1.29 and 1.18 times, respectively.

It is known that apoptosis is a genetically programmed death of cells in a living organism. Impaired apoptosis is important for carcinogenesis at all stages. At the initiation stage, mutated cells can die as a result of apoptosis, and the tumor does not develop. Inhibitors of apoptosis (except for the genes of the bcl-2 family) are increased production of gonadotropic hormones, their disordered secretion, accumulation of somatic cell mutation factors, aging of the body, metabolic disorders (oxidative stress), etc.[16, 21, 23, 25].

A comparative analysis of the relative value of CD95+ cells between the three groups revealed the following: in patients with endometrial hyperplasia (EH), there is a decrease in the relative number of CD95+ cells compared to the control group. In particular, the level of CD95+ cells was 23.7 ±0.62%, which is lower than the control group (25.3 ±0.68%). There is also a decrease in this indicator in patients with recurrent endometrial hyperplasia transitioning to a proliferative-hyperplastic form, where the level of CD95+ cells was 21.1 ±1.10%. The difference in the level of CD95+ cells between the HE groups and the control group was 1.06 times, between the groups of recurrent endometrial hyperplasia and the control - 1.19 times. (Fig. 1).

A comparative analysis of the level of cytokines in each examined group revealed the following: the level of interleukin-1β (IL-1β) in patients with endometrial hyperplasia (EH) was 17.9 ± 0.94 pg/ml, which significantly exceeds the level of the control group (6 .33 ±0.29pg/ml). The ratio between these groups was 2.83 times, indicating a significant increase in the level of IL-1β in the HE group. In the group of patients with recurrent

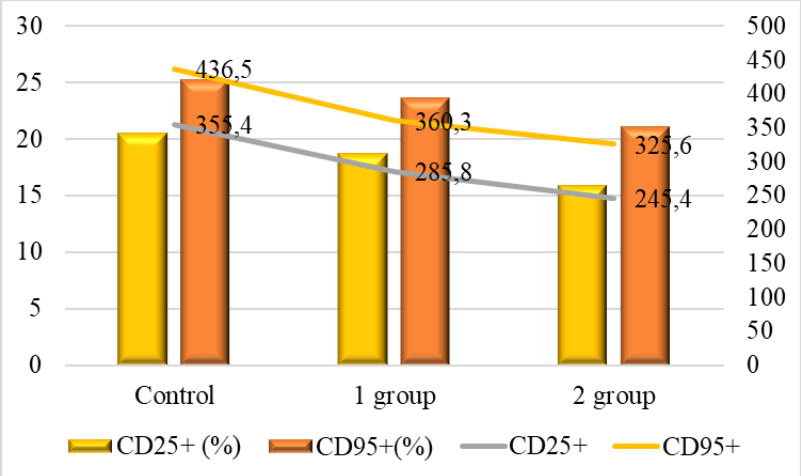

Figure 1. Comparative characteristics of activation markers among those examined (µl, %), (P≤0.05).

3 table.

The level of pro-inflammatory cytokines in examined patients pg/ml.

	IL-1β	IL-2	IL-6	TNFα
Control	6.33±0.29	8.75±0.34	5.67±0.32	25.8±1.41
HE (n=27)	17.9±0.94*	7.38±0.21	18.4±1.31*	55.2±5.66*
Rec. HE with lane on PHE (n=23)	21.3±1.01*	5.87±0.29	18.6±1.84*	67.9±5.23*

*Note: *(P≤0.05) significant compared to the control group.*

endometrial hyperplasia transforming into a proliferative-hyperplastic form, the level of IL-1β was 21.3 ± 1.01 pg/ml, which is also significantly higher than in the control group. The difference between recurrent HE with transition to PHE and the control group was 3.37 times.

The level of interleukin-2 (IL-2) in the HE group was 7.38 ± 0.21 pg/ml, which is 1.19 times lower than the level in the control group (8.75 ± 0.34 pg/ml). In the group of recurrent HE with transition to PHE, the level of IL-2 was also slightly lower than the control value, amounting to 5.87 ± 0.29 pg/ml. The difference between recurrent HE with transition to PHE and the control group was 1.49 times. Both groups with endometrial hyperplasia show decreased IL-2 synthesis.

The concentration of IL-6 was significantly increased in women with HE (18.4 ± 1.31 pg/ml) and in the second group with recurrent GE (18.6 ± 1.84 pg/ml) compared to the control group (5.67 ± 0.32). The difference between HE and the control group was 3.25 times, and between recurrent HE with transition to PHE and the control group - 3.28 times. Both differences are statistically significant (p≤0.001).

A comparative analysis between the two groups revealed that in patients of the first (55.2 ± 5.66 pg/ml) and second group (67.9 ± 5.23 pg/ml) the synthesis of TNFα significantly increased compared to the control group (25, 8 ± 1.41 pg/ml). The difference between the group of patients with HE and the control group was 2.14 times, and between recurrent GE with transition to PHE and the control group - 2.64 times (p≤0.05). (Table 3.)

Conclusions. Summarizing the results of our studies on the state of cytokines and markers of cellular activation and apoptosis, it should be noted that the detected changes in these indicators were common to various forms of endometrial hyperplasia. Since disturbances in the general immune system in endometrial hyperplasia are most often associated with concomitant diseases, and not with general mechanisms of development of hyperplastic processes in the endometrium, there is a need to study local immune reactions. For a better understanding the basic mechanisms of development of endometriotic lesions, studies of local immune processes are especially important. However, analysis of the systemic immune response in endometriosis also provides important data on factors contributing to the development of the disease, since the state of immunocompetent cells in the blood often reflects the direction of immune disorders at the local level.

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