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CHARACTERISTICS OF THE MAIN LINKS OF IMMUNITY AND ENDOMETRIAL CYTOKINES IN WOMEN WITH REPRODUCTIVE DISORDERS

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Introduction. The involvement of many systems and levels of regulation in the processes of fertilization and gestation makes one pay attention to the changes occurring at all its levels.

Aim: to study and analyze changes in the indices of general and local immunity in women of reproductive age for the pathogenetic substantiation of therapeutic measures for reproductive disorders.

Materials and methods. The study included 50 patients with and reproductive disorders. Thirty-one healthy women with preserved fertility entered the control group included. All respondents underwent a questionnaire survey; general clinical, gynecological and laboratory-instrumental examination was carried out. The study followed the ethical principles and was approved by the local Committee on Biomedical Ethics. Statistical processing of the data obtained was performed using the StatSoft Statistica 6.1 (USA).

Results. Evaluation of indicators of cellular and humoral links of immunity showed a significant increase in the concentration of CD3 + (T-lymphocytes), CD3 + CD8 + / CD45 + (T-suppressors), phagocytic activity of neutrophils, NST -test sp., Ig M, and an increase in the studied pro- and anti-inflammatory cytokines. In the endometrium, with persistence of an infectious agent, a significantly high concentration of IL-8 and a decrease in IL-1 (β) were revealed.

Conclusions. The presence of the pathogen in the endometrium is characterized by a significant activity of the pro – inflammatory cytokine IL-8 and a decrease in IL-1(β). A decrease in progesterone, cortisol, NST sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8 can be attributed to the markers of reproductive disorders.

Keywords: immunity, endometrium, cytokines, reproductive disorders.

Introduction: The study of the problem of reproductive disorders is one of the important directions in reproductology. The percentage of infertility is constantly growing [2], miscarriage does not tend to decrease [6]. From a clinical point of view, pregnancy loss or their absence is becoming an increasingly significant problem in reproductology. The implantation process is very sensitive and requires compliance with a number of important conditions: a high degree of coordinated action between normal anatomical conditions, normal functioning of sex cells, an adequate hormonal environment of the embryo in the endometrium [8]. Taking into account the complexity of the process, the ambiguity of the pathogenetic mechanisms of reproductive disorders becomes obvious [4,3]. Adequate pregravid restructuring of the endometrium is the key to successful implantation. Multiple paracrine and autocrine regulatory factors are involved in the regulation of endometrial decidualization. The spatiotemporal regulation of the decidual process is strictly controlled by a variety of substances, such as growth factors, cytokines produced by various cellular structures of the endometrium including epithelial cells, stromal cells, local immune cells, and the vasculature [5,7].

Materials and methods: A cross-sectional study was conducted in the period 2011-2013 on an outpatient basis according to the patients' referral. When women were included in the study, the ethical principles set forth by the World Medical Association Declaration of Helsinki (1964, 2000) were followed. This study was approved by the local Committee on Biomedical Ethics. Eligible women participated after they signed an informed consent. This work was performed with the use of equipment of Collective research centre "Center for the development of progressive personalized technologies for health" SC FHHRP, Irkutsk.

A survey of 327 women of fertile age who complained of reproductive dysfunction was carried out. The patients underwent examination according to the standards of examination of infertile married couples (Kulakov V.I., 2006); the examination included general clinical, gynecological and laboratory-instrumental examination.

The criteria for inclusion in the group with reproductive disorders (RD) were: absence of pregnancy in patients with regular sexual activity without contraception for a year or more or miscarriage during the last year, or failure in assisted reproductive technologies programs. As a result, 223 (68%) women were diagnosed with infertility: primary infertility in 38% (125), secondary infertility in 30% (98), miscarriage was detected in 32% (104) women.

Criteria for inclusion in the control group: regular menstrual cycle, absence of neuroendocrine disorders and severe somatic pathology, presence of a pregnancy that ended in childbirth within the last year. The control group included 31 healthy women with preserved fertility.

Subsequently, there was formed a group of women (100 women) with suspected chronic endometritis who underwent minimally invasive manipulation - a pipel biopsy of the endometrium on the 4th-9th days of the menstrual cycle (middle proliferative phase) using a disposable intrauterine probe (Taizhou Kechuang Medical Apparatus Co., Ltd ", China) followed by a pathohistological examination (PHI) of endometrial tissue to verify or exclude the presence of signs of chronic inflammation of the endometrium. Finally, according to the results of the pathohistological examination, two groups were formed: the 1st group in-

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cluded 50 patients with reproductive disorders and chronic endometritis (mean age 30.5 ± 0.6 years), the 2nd group included 50 patients with reproductive disorders without chronic endometritis (mean age 30.2 ± 0.7 years).

This analysis included 50 women of fertile age with reproductive disorders (ICD 10 - N97.9, O03) and 31 women from the control group. The average age in the groups did not differ, it was comparable and was 30.2 ± 0.7 years (respectively, in the group of fertile women, 30.7 ± 5.9 years) (p≥0.05). The main criteria for inclusion in the main group were: the absence of pregnancy in patients with regular sexual activity without contraception for a year or more, miscarriage during the last year, absence of chronic endometritis based on the results of histopathological examination, and signing of informed consent. Exclusion criteria: presence of endocrine, genetic, hemostasiological, immunological causes, including the male factor, and the diagnosis of chronic endometritis verified by the results of a pathohistological examination (PHE) of the endometrium.

The main group, patients with reproductive disorders, was divided into two subgroups:

- a subgroup of 16 patients with RD with an infectious agent isolated from endometrial tissue
- a subgroup of 34 patients with RD with no infectious agent in the endometrial tissue.

Laboratory diagnostics for the presence of STIs (*N. gonorrhoeae, T. vaginalis, Ur. Urealyticum, M. hominis, M. Genitalium. Chl. Trachomatis*) was performed using the culture method. The polymerase chain reaction (PCR) method was used to diagnose a viral infection (HPV, HSV, CMV) in the material taken from the cervical canal. Microbiological studies of the vaginal biotope were carried out according to the guidelines (Order of the Ministry of Health of the USSR No. 535 of April 22, 1985 "On the unification of microbiological (bacteriological) research methods used in clinical and diagnostic laboratories of medical and preventive institutions". Ultrasound examination of the pelvic organs was performed using an Aloka-5500 machine with a 7 MHz vaginal transducer in two-dimensional imaging mode. Ultrasound examination of the pelvic organs was performed using an Aloka-5500 machine with a 7 MHz vaginal transducer in two-dimensional imaging mode. The concentrations of cytokines (IL - 1β, INF - γ, TNF - α, IL - 4,6,8,10) were determined in the endometrial tissue using the "Protein Contour" test systems (St. Petersburg), on the basis of the "sandwich" method using the enzyme immunoassay analyzer "Multiscan EX" (Germany) and expressed in PG / ml.

Blood sampling for hormonal studies was carried out on an empty stomach, from the 3rd-9th days of the menstrual cycle and in the second phase from the 20th-24th days of the menstrual cycle in accordance with generally accepted requirements. Determination of the concentration of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH) was carried out by radioimmunoassay using the analyzer "Immunotest" (kits of LLC "Dias", Russia). Enzyme immunoassay was used to determine the levels of testosterone ("Alcor Bio" kits, Russia); progesterone ("DRG ELIAS" kits, USA). The concentration of hormones PRL, LH, FSH was expressed in ng / ml; cortisol, testosterone - in pmol / l; progesterone - in nmol / l.

Statistical processing of the data obtained was performed using the StatSoft Statistica 6.1 application software package (USA) (the license holder is the Federal State Budget Scientific Institution "Scientific Centre for Problems of Family Health and Human Reproduction"). The distribution pattern (normality) was evaluated by Kolmogorov-Smirnov methods. Absolute and relative indicators (shares,%) were used for qualitative indicators. The significance of differences in unrelated samples was assessed using the Mann-Whitney criterion. For quantitative variables, the data in the tables are presented as M ± m, where M - the mean, m - the error of the mean. The difference was considered significant with a 95% confidence level ($p<0.05$). The analysis of the intragroup relationship of quantitative characteristics was carried out by the nonparametric Spearman correlation method. The relative risk (RR) was calculated using the criterion $\chi 2$ for a four-field table and one degree of freedom.

Results: As a result, 81 women with reproductive disorders, aged from 18 to 45 years agreed to participate and were surveyed. In the course of the survey, information was obtained about past diseases, somatic and gynecological morbidity. In the group of women with RD, there was a high rate of ovarian dysfunction 68% (ICD - 10, E28.9), the presence of chronic salpingo-oophoritis in 28% (ICD - 10, N70), scanty and rare menstruation was noted by 12% (ICD-10, N91) of respondents. Ten percent each accounted for heavy, frequent and irregular menstruation (N 92), primary dysmenorrhea (N 94.4), chronic inflammatory diseases of the cervix (N 72).

Comparative analysis of the concentration of pituitary hormones and sex hormones in patients with RD in comparison with those in women in the control group showed a significant increase in the concentration of prolactin, testosterone and a significant decrease in progesterone (Table 1).

Thus, the hormonal background in patients with reproductive disorders was characterized by the presence of hypoprogesteronemia, significant increase in PRL, cortisol, and testosterone. The concentrations of these indicators did not go beyond the reference values offered by the manufacturers of test systems for their determination.

The analysis of data on previous diseases in the examined women is presented in Table 2.

Compared with the control group, patients with RD were significantly more likely to have a history of kidney diseases ($p(\chi 2) = 0{,}021$), endocrine system diseases ($p(\chi 2) = 0.001$), allergic diseases ($p(\chi 2)=0.015$), surgical interventions on the pelvic organs ($p(\chi 2) = 0.0001$).

No significant differences were found in the structure of concomitant somatic pathology.

Anamnestic data showed that women with RD had ureaplasmosis in 50%, trichomoniasis in 36%, HSV in 32%, and chlamydia in 30%. Twenty-eight percent ($n=14$, $p(22) = 0.03$) of patients at the time of examination had conditionally pathogenic microflora in the cervical canal. In 9 women, it occurred as a monoinfection; mixed infection with predominance of two types of microorganisms was noted in 5 women. The most frequently observed were: low-risk HPV in 8%, Ur. Urealiticus, G. vaginalis, Candida, Staph. Epidermidis, E. Coli, Citrobacter spp., high-risk HPV 4% each. The number of microorganisms was in the range of 10^3–10^4 CFU / ml.

In 32% ($n = 16$, $p(\chi 2) = 0.0001$) of the patients, an infectious agent was detected from the uterine cavity; its content was in the range of 103-104 CFU / ml, E. coli was found with the highest frequency - in 12%, Candida - in 6%; Enterococcus faecalis, Staph. Epidermidis, Klebsiella 4% each.

Ur. urealyticum, Candida, E. coli, M. hominis, Streptococcus, Citrobacter spp., Enterococcus faecalis, low-risk HPV were detected in the control group as a monoinfection in isolated cases.

The results obtained in the study of Moreno I, Cicinelli E, Garcia-Grau I et al. (2018) show similar rates of pathogen

detection in patients with both chronic endometritis (CE) and in its absence (CE: 24/40 versus without CE: 14/25 [22]. Some studies have shown that 53% of women with infertility and miscarriage were observed to be completely free of lactobacilli [13].

The indicators of cellular and humoral immunity were determined and analyzed taking into account the presence and absence of an infectious agent in the endometrial tissue.

The results of the indicators characterizing the cellular and humoral immune response in patients in both study groups are presented in Table 3.

Evaluating the results of cellular and humoral immunity in patients with RD in comparison with the corresponding blood parameters of healthy women, there was a significant increase in the concentration of CD3 + (T-lymphocytes), CD3 + CD8 + / CD45 + (T-suppressors), a decrease in the phagocytic activity of neutrophils, NST - test sp., Ig M. Correlation analysis showed the presence of a strong positive relationship between IgM-IgA (r = + 0.77), which clearly indicates a decrease in immunity from the mucous membranes, and also showed the presence of a strong negative relationship between CD3 + CD4 + / CD45 + and CD16 + 56 + / CD45 + (r = - 0.77), which indicates the relationship of T-helpers and natural killers.

When comparing the indicators of the cellular and humoral links of immunity within the group, in the presence of an infectious agent and in its absence, no significant differences were found.

The state of local immunity was assessed by the levels of cytokines determined in the endometrial tissue. The results are presented in Table 4.

A 1.4-fold increase in the level of pro-inflammatory cytokines *IL-1 (β), INF - γ* was found in the endometrial tissue of women with reproductive disorders in comparison with similar indicators in healthy women. There was a 2.5-3 fold increase in *IL - 6, 8, 10; IL - 4* increased only in the group with no infectious agent. Assessing the cytokine status for the isolated infectious agent in the compared groups, a decrease in the concentration *of IL – 1(β), 6* and an increase in *IL – 8* were noted.

Using the discriminant equation, the contribution of the studied indicators was calculated, among which the following indicators were identified: a decrease in progesterone, cortisol, NBT sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8, which, with a high degree of probability, made it possible to include patients in the group with RD without chronic endometrial inflammation.

Table 1

Concentration of pituitary hormones and sex hormones in patients with reproductive disorders and control group

	Group with reproductive disorders n=50	Control group n=31
Prolactin (ng / ml)	424.1±213.22* 369 (155 и 914)	297.81±100.14* 274 (150 и 520)
LH (ng / ml)	4.67±2.84 4 (0.6 и 18.4)	4.2±1.43 3.8 (1.9 и 7.2)
FSH (ng / ml)	6.46±1.77 6.3 (3.3 и 10.2)	6.92±1.77 6.9 (3.7 и 10)
Estradiol (pM/l)	354.1±225.57 317.5 (90 и 987)	276.19±157.58 243 (110 и 980)
Progesterone (nmol/l)	43.05±19.69* 42.7 (3 и 84)	74.19±13.17* 75 (38.4 и 98)
Testosterone (pmol/l)	1.98±1.07* 1.8 (0.22 и 4.4)	1.41±0.88* 1.2 (0.6 и 3.7)
Cortisol (pmol/l)	644.2±242.77* 588.5 (148 и 1256)	387.74±97* 388 (214 и 589)

Significance level - * p <0.05.

Table 2

Characteristics of the previous diseases in women of the main and control groups

Premorbid background	group with RD абс./% *n* = 50	Control group abs./% *n* = 31	Significance level *p*(χ2)
Diseases of the ENT organs	5/10	5/16	
Gastrointestinal diseases	9/18	3/10	
Kidney diseases	6/12	1/3	0.021
Diseases of the endocrine system	11/22	2/6	0.001
Pathology of the thyroid gland	2/4	0/0	
Allergic diseases	6/12	1/3	0.015
Surgical interventions on the abdominal organs	6/12	2/6	
Surgical interventions on the pelvic organs	4/8	0/0	0.0001
Diseases of the cardiovascular system	3/6	2/6	

Discussion: The endometrium is tissue that undergoes monthly cyclical changes leading to menstruation, proliferation, secretion and decidualization under the influence of ovarian steroid hormones. There is a finely coordinated interaction between the circulating steroid hormones of the ovaries and the corresponding receptors in a variety of endometrial cell types [16,17]. Many researchers say that many factors involved in implantation have not yet been fully studied and, apparently, the endometrium plays a much more relevant role than other well-known factors [9, 11]. The endometrium contains a large number of immunocompetent cells, natural killer (NK) cells, macrophages, T cells and neutrophils whose composition and density fluctuate periodically [19,12]. Cycle-dependent changes in these subpopulations of leukocytes and their mediators are likely to play a significant role in implantation [11].

In addition, morphological changes in the endometrium are normally accompanied by focal activation of matrix metalloproteinases (MMPs) at the sites of menstrual lysis [20], by the enhancement of local expression of inflammatory mediators in the endometrium, for example, cyclooxygenase-2 (COX-2) [21], cytokines / chemokines (for example, cytokines-8 (IL-8), CCL-2) [5,1], as well as an increase in the level of local synthesis of prostaglandin [18].

An increase in the concentration of IL-1(β) stimulates the development of a whole complex of protective reactions of the body. The pro-inflammatory activity of IL-1(β) includes stimulation of lym-

Table 3

Characteristics of indicators of cellular and humoral links of immunity in patients with reproductive disorders taking into account the presence and absence of an infectious agent and in patients in the control group

indicators of Immunity	Patients with an isolated infectious agent, n= 16	Patients in the absence of an infectious agent, n=34	Control group n=31
CD3+/CD45+	75.33± 6.9	73.71±6.7	71.09±4.6
CD3+	*2057.88 ±454.9**	*2132±521.7**	*1462±348.4**
CD3+CD8+/CD45+	*30.33 ±5.02**	*29.45±5.07**	*22.25±3.4**
CD3+CD4+/CD45+	42.00 ±4.47	48.8±5.7	45.93±5.3
CD3+CD4+CD8+/CD45+	0.55 ±0.72	0.45±0.77	0.74±0.17
CD16+56+/CD45+	*10.77± 6.18*	*11.7±5.38*	*13.6±4.7*
CD19+/CD45+	*11.44 ±4.3*	*12.4±3.1*	*12.13±3.4*
Phagocytosis	*57.44 ±12.64**	*53.8±10.1**	*61.45±8.3**
NST-test sp.	*5.55 ±4.44**	*7.1±5.2**	*9.29±7.7**
NST-test ind.	27.88± 14.11	32.7±12.6	32.35±11.8
Ig G	12.85 ±3.89	14.3±4.9	14.26±4.2
Ig A	*2.12± 1.10*	*2.08 ±1.1*	*2.3±1.1*
Ig M	*2.30 ±0.82*	*1.88±0.9**	*2.6±0.8**
Circ.immune complexes	38.33± 11.13	41.4±16.6	40.74±14.1
T Help./ Suppres.	*1.41± 0.21*	*1.48±0.34*	*2.12±0.4*

Note: *p1-2<0.05. **p1/a-1/б<0.05

Table 4

Concentrations of cytokines in endometrial tissue in women with reproductive disorders and control groups depending on the presence or absence of an infectious agent

Indicators of local immunity local immunity	Patients with an isolated infectious n=16	Patients in the absence of an infectious agent n=34	Control group n=31
IL-1(β), pg/ml	34. 22± 37.72**(*)	44.46± 44.49**(*)	23.64±3.37*
IL-4,pg/ml	14.38 ± 12.98**	41.54 ± 81.22**(*)	13.71±1.93*
IL-6, pg/ml	83.85± 45.6**(*)	100.56 ± 98.13**(*)	39.53±3.81*
IL-8, pg/ml	99.55 ±102.56**(*)	81.31 ±71.82**(*)	23±2.42*
IL-10, pg/ml	70.4± 2.51*	76.51 ± 51.01*	26.67±4.61*
INF-γ, pg/ml	45.33± 70.01*	44.50± 50.21*	25.75±4.24*
TNF-α, pg/ml	16.33± 14.43	14.42 ± 20.24	9.48±0.85

phocytes, synthesis of prostaglandins, chemokines, and expression of endothelial adhesion molecules. Chemokines, in particular, a significant increase in IL-8 in the group of patients with an isolated infectious agent, enhances the migration of leukocytes to the site of inflammation and, together with other cytokines, increase their functional activity aimed at eliminating the pathogen and limiting the spread of the inflammatory process [10, 13, 20]. At the same time, pro-inflammatory cytokines activate connective tissue metabolism, stimulate the proliferation of fibroblasts and epithelial cells necessary for healing and restoration of tissue integrity [1], which contributes to maintaining a healthy endometrium.

Hypoprogesteronemia noted in patients with RD, in turn, enhances the local effect of cytokines and prostaglandins (PG) on endometrial stromal cells [15]. Previously published data from studies conducted on decidualized stromal cells of human endometrium in vitro, demonstrated the induction of inflammatory mediators, including IL-6, chemokines CCL11, CCL2, CXCL10 and CXCL8, and granulocyte macrophage colony stimulating factor (GM-CSF) in response to a decrease in progesterone levels. This cellular response is controlled by the action of the transcription factor NF-kB [10].

In addition, the lack of progesterone reduces the secretion of TGF-beta, a protein (a representative of cytokines) that controls proliferation, cell differentiation and other functions in most cells, is involved in the immune response by epithelial endometrial cells and, indirectly, acts on the stromal cells of the endometrium causing an increase in the production of PRL and integrin 3 necessary for decidualization, which we observe in patients with RD in relation to PRL [14]. In our study, similar results were obtained: a decrease in progesterone revealed an increase in the pro-inflammatory cytokine IL-6 and chemokine-IL-8 ($p<0.05$) as a specific cytokine-chemoattractant-responsible for the movement of white blood cells in the endometrium (recruitment, migration and activation) [1]. A significant increase in IL-10 and the normal concentration of IL-4 in patients with RD noted by us are due to the suppressive effect on the response of monocytes to endotoxin, in particular, by affecting the production of INF-γ by T-lymphocytes and, consequently, reducing the cytotoxicity of NK cells by inhibiting the reactions of cellular immunity [14].

On the part of the general link of the immune system, the revealed negative relationship of T-helpers and natural killer cells may be due to an increase in the production of inflammatory cytokines involved in the activity of NK cells, which play a decisive role in the local immune response at the early stages of implantation. The results obtained in the study indicate changes in the immune response characteristic of the immunological failure of the endometrium associated with reproductive disorders. The state of the endometrium in women with RD without CE can most likely be considered as an intermediate state between a "healthy" and "diseased" endometrium.

Conclusion: Reproductive disorders are accompanied by changes in the reactivity of the immune system in women at different levels of the immune response. The cytokine status in the presence of the pathogen in the endometrium is characterized by a significant activity of the pro – inflammatory cytokine IL-8 and a a low content of IL-1(β). A decrease in progesterone, cortisol, NST sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8 can be attributed to markers of reproductive disorders in the absence of chronic endometrial inflammation.

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LIPID PEROXIDATION IN THE DEVELOPMENT OF SOME SYMPTOMS OF POST-COVID SYNDROME

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The relationship of lipid peroxidation with sleep disturbance, anxiety and depression in residents of Yakutsk who recovered from COVID-19 was studied. It has been established that oxidative stress in COVID-19 due to an increase in the level of reactive oxygen species (ROS) in the body can lead to hypoxia and psycho-emotional disorders, such as anxiety and depression.

Keywords: COVID-19, malondialdehyde, lipid peroxidation, post-COVID effects, hypoxia, sleep, anxiety, depression, oxidative stress.

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Introduction. A novel coronavirus infection that causes severe acute respiratory syndrome COVID-19 has become a global pandemic with high morbidity and mortality [4,5].

The impact of the SARS-CoV-2 virus on the human body occurs primarily in the lungs, which causes pneumonia. Penetrating into the lower parts of the respiratory tract (small bronchi and alveoli) and begins damage to lung cells, provoking a strong inflammatory reaction, due to which the lungs cannot provide all organs and systems with sufficient oxy-