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IMMUNOLOGICAL CHARACTERISTICS OF THE ENDOMETRIUM IN WOMEN WITH IMPAIRED FERTILITY

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The main morphological criterion of chronic endometritis is the presence of inflammatory infiltrates consisting mainly of lymphoid elements and plasma cells with focal or diffuse location in the stroma and glands. Immunological research allows to evaluate the phenotypic composition of endometrial cells, identify the number of cytotoxic cells that limit embryo implantation and contribute to reproductive dysfunction, and determine the need for complex therapy.

Key words *: endometrium, chronic endometritis, immunomorphology, reproductive disorders.*

Inflammatory diseases of the pelvic organs are the most common cause of women's health problems. Chronic endometritis occupies a special place in the structure. Many researchers note an increase in the frequency of pathological changes in the endometrium in the population of women of reproductive age. The frequency of chronic endometritis varies widely from 0.2 to 66.3%, but on average is 14%. The main contingent of patients with chronic endometritis are women of reproductive age 25-35 years. Data on the frequency of chronic endometritis among gynecological patients are variable (from 2.5 to 85%), primarily due to certain difficulties in diagnosis, clinical and morphological verification [15,18].

The mechanism of pregnancy termination in these patients is associated with the changes that occur in the endometrium as a result of disruption of secretory transformation processes caused by insufficient production or inadequate response of the target organ to progesterone. In the endometrium, there is underdevelopment of glands, stroma, vessels, insufficient accumulation of glycogen, proteins, growth factors, excessive amount of proinflammatory cytokines, which leads to inadequate

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development of the ovum, and as a result, miscarriage occurs [16,20]. A significant role in the development of chronic endometritis belongs to disorders of local and general immunity, manifesting inflammatory complications after childbirth and abortions. Long-term stimulation of immunocompetent endometrial cells by an infectious agent leads to decompensation of the regulatory mechanisms of local homeostasis, which maintains the persistence of the infectious process. Chronic activation of cellular and humoral proinflammatory reactions is accompanied by increased production of cytokines and other biologically active substances, causing microcirculation disorders, exudation and deposition of fibrin in the endometrial stroma, which forms connective tissue fibrinous adhesions in the stroma and/or intrauterine synechiae of varying degrees of severity [4,19].

There are many risk factors for the development of chronic endometritis, including one of the significant ones being various types of intrauterine manipulations. Medical abortions, curettage of the uterine cavity walls, endometrial biopsy, hysteroscopy , hysterosalpingography , hydrosonography , insemination, in vitro fertilization contribute to the development of chronic endometritis in 95% of cases [6,7]. The clinical picture of chronic endometritis is usually not very specific and largely reflects the depth and duration of pathomorphological changes in the uterine mucosa. A number of authors have noted that the main symptom of chronic endometritis (in 93% of cases) is perimenstrual bleeding. Among the clinical symptoms, a special place is occupied by infertility (mainly secondary), unsuccessful IVF attempts and miscarriage [11,13]. Diagnosis of chronic endometritis is based on the analysis of clinical symptoms, anamnesis data, echographic picture and morphological examination of the endometrium [5,10,12].

The “gold standard” for diagnosing chronic endometritis is a morphological examination of the endometrium, which should be a mandatory part of the examination algorithm for patients with reproductive dysfunction [5,15,16].

Diagnostic curettage or biopsy of the uterine mucosa is performed in the middle and late phases of proliferation, on days 7-11 of the menstrual cycle. Generally accepted morphological criteria for the diagnosis of chronic endometritis: - The

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presence of inflammatory infiltrates consisting mainly of lymphoid elements and plasma cells with a focal nature of the arrangement - around glands and vessels. The diffuse nature of the arrangement of lymphoid elements is also not excluded. Infiltrates are located mainly in the functional layer, but their basal arrangement is also very typical.

– Formation of lymphoid follicles in the functional layer of the endometrium.

– Focal fibrosis of the stroma, which occurs during a long-term chronic inflammatory process in the endometrium and sometimes affects large areas.

– Sclerotic changes in the spiral arteries with the formation of tangles of spiral arteries.

– Dystrophic changes in the endometrial glands. Changes in the glandular and stromal components do not correspond to the days of the menstrual cycle.

Morphometric analysis provides a quantitative assessment of the endometrium. In tubal- peritoneal infertility and miscarriage caused by chronic endometritis, there is a discrepancy between the histological picture of the endometrium and the day of the menstrual cycle. The absence of decidua-like metamorphosis and weak development of muscular and capillary vessels in the luteal phase [2,21].

The totality of morphological changes in the endometrium affects the receptivity of the endometrium and limits the possibility of embryo implantation, affecting the overall effectiveness of infertility treatment using assisted reproduction methods and miscarriage [9]. The endometrium contains a large number of immunocompetent cells, the phenotypic composition of which is important for the immunological balance between the embryo and the endometrium. Immune reactions occurring in the endometrium participate in the implementation of the protective function when infectious agents penetrate the uterine cavity, as well as in the full implantation and development of the embryo [17]. Endometrial epithelial cells are capable of independent secretion of cytokines, chemokines and cell adhesion molecules. Their functional activity largely depends on the state of the endometrial

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stromal cells. The results of several studies show that stromal cells indirectly provide the effect of estrogens on endometrial epithelial cells [9,23].

Today, the method of identifying specific antigens of plasma cells and endometrial lymphocyte subpopulations using immunohistochemical research is widely used [17].

immunocytes are represented by an association of macrophages, NK cells, neutrophils, leukocytes and immunoglobulin-producing cells. When detecting The following lymphocyte subpopulations are distinguished: CD3+ – T-lymphocytes, CD4+ – T-helpers, CD8+ – T-suppressors, CD14+ – monocytes/macrophages, CD16+ – natural killer cells (NK), CD45 – leukocytes, CD56+ – NK, BGL, CD95+ – Fas antigen, apoptosis marker, CD138 – plasma cells, excluding mature B-lymphocytes [16].

The most numerous population of lymphocytes present in the endometrium are large granular lymphocytes (LGL), which many authors consider to be decidual NK cells (CD56+). In the proliferative phase of the cycle, their share is about 8% of all endometrial cells, in the secretory phase – 60%, and in the early stages of pregnancy – more than 70% [2,19].

It has been established that under the influence of ovarian hormones, not only does the number of NK cells in the endometrium increase, but their activation with the expression of chemokines occurs [8]. In the uterine mucosa, macrophages can reach 10% of the total number of leukocytes [15].

This indicates a significant role of macrophages in the processes of implementing the immune response. It is also interesting that after implantation, macrophages leave the chorion invasion zone and are practically absent from the decidual tissue, being detected only in the periplacental blood flow [9].

The functional activity of endometrial macrophages is largely subject to hormonal influences. The ability of estrogens to induce macrophage activity has been established. In addition, macrophages do not have nuclear receptors for progesterone, and their sensitivity to the influence of progesterone is due to cross-linking of progesterone with glucocorticoid receptors [23].

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The population of NK cells (CD56+), T lymphocytes (CD3+) and macrophages (CD14+) of the endometrium are the main sources of cytokines, due to which the dominance of the Th-2 type of immune response is maintained during pregnancy. The detection of NK cells in large quantities around the invasive cytotrophoblast allowed us to talk about their participation in the isolation of embryonic antigens from the mother's immune system, limiting the expansion of trophoblast in the uterine tissue and the reorganization of spiral arteries during pregnancy [8,20].

It has been proven that NK cells can enhance the inflammatory response through macrophages and generation of cytokines that activate cytotoxic T lymphocytes. The ability of NK cells of the endometrium to produce a number of biologically active molecules has also been established: γ-IFN, TNF-α, IL-8, IL-10, TGF-β1. With insufficiency of the NK link of the endometrium, an increase in episodes of viral infections and herpes infection in particular is noted [16,17]. Changes in the number of NK cells in the endometrium against the background of bacterial -viral infection and inflammation lead to an imbalance of secreted cytokines and the prevalence of the Th-1 type of immune response, which causes a limitation of trophoblast invasion and termination of pregnancy [10,11].

The works of domestic and foreign authors have shown that chronic endometritis is characterized by a complex of immunomorphological changes. In the proliferative phase on the 7-11th day of the cycle, a reliable increase in the number of monocytes/macrophages (CD14+) and NK cells (CD56+) was detected in the endometrium. A slight increase in the total number of T lymphocytes (CD3+) is noted. The levels of T helpers (CD4+) and T suppressors (CD8+), as well as their ratio, do not differ from the indicators in healthy women. An increase in the number of NK cells (CD56+) and macrophages (CD14+) in the endometrium of women with reproductive pathology characterizes the intensity of the inflammatory process in the tissue and is an unfavorable factor that prevents normal adhesion and implantation of the blastocyst, as well as further development of the trophoblast . The number of CD95+ cells (apoptosis markers) significantly exceeds the similar indicator in healthy

women, and indicates a high level of programmed cell death against the background of chronic inflammation in the endometrium [2,19]. Chlamydial -associated endometritis is characterized by a high content of B-lymphocytes in the endometrial stroma, which diffusely infiltrate the endometrial stroma, and in 11% of cases form focal dense lymphoid clusters of the lymphoid follicle type. Incomplete secretory transformation of the glands, lag and development of fibrosis of the endometrial stroma are noted [22].

Conclusions. Thus , the destructive effect of immunocompetent cells on endometrial tissues leads to the formation of chronic autoimmune endometritis. The result of a long pathogenetic chain is a violation of implantation in IVF and embryo transfer programs and miscarriage. pregnancy. Given the complexity of the structure and the ability to cyclic transformation, these changes are especially pronounced and difficult to correct in the endometrium. At the same time, the receptivity of the endometrium consists of many factors, each of which requires assessment. Pathogenetically based therapy of chronic endometritis in women with reproductive dysfunction allows restoring the structure and functional activity of the endometrium, restoring the phenotypic composition of immunocompetent cells and leveling out the factors that prevent the onset and normal development of pregnancy.

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экспериментального вагинита, вызванного химическим агентом. Материалы и методы. Экспериментальные исследования проведены на кроликах самках массой 2800-3000 г. Оценивались следующие показатели: ph-метрия влагалища, полуколичественная оценка площади поражения слизистой оболочки влагалища в баллах, оценка микробиоциноза с помощью современного экспресс-теста Фемофлор-16, цитологические и морфологические данные. Результаты. Фармакотерапия экспериментального лечения вагинита с помощью Куркувир показал достоверное снижение, (1).

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