



## IMMUNOHISTOCHEMICAL FEATURES OF THE ENDOMETRIUM IN MISCARRIAGE

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<p><b>Received:</b> October 10<sup>th</sup> 2022 <b>Accepted:</b> November 10<sup>th</sup> 2022 <b>Published:</b> December 24<sup>th</sup> 2022</p>	<p>The problem of miscarriage continues to occupy one of the first places among the most important tasks of practical obstetrics and gynecology and is of great medical and social importance. Immunohistochemical and ultrastructural features of the endometrium in case of miscarriage are important for pathoanatomical diagnosis and gynecological practice. Data on the expression of steroid receptors, proteins that regulate the cell cycle, are important diagnostic signs of miscarriage.</p>

**Keywords:** endometrial immunohistochemistry, miscarriage, vascular endothelial growth factor.

In recent years, the problem of protecting the health of the population has acquired a special medical, demographic and social significance. In modern Russia, the state and society are more than ever interested in the successful completion of each pregnancy. However, the number of spontaneous abortions annually reaches 180 thousand or > 15-20% of all desired pregnancies. At the same time, the frequency of non-developing pregnancy (NP) remains consistently high and amounts to 45-88.6% of cases of spontaneous miscarriages in the early stages [3].

The causes of miscarriage are numerous and it is often not possible to isolate the leading factor. Up to 80% of reproductive losses occur in the first trimester [1]. In fact, the number of women with miscarriage may be somewhat higher, since a part of spontaneous miscarriages occurs even before a woman visits a gynecologist due to the fact of pregnancy. About 1-2% of women suffer from recurrent miscarriage. Habitual miscarriage may be associated with the presence of chromosomal abnormalities, antiphospholipid syndrome, as well as immune and endocrine disorders [3]. Among the causes of premature termination of pregnancy, one of the leading places is occupied by inflammatory diseases [4]. However, in 50% of cases, the cause of the miscarriage is unknown. Therefore, the study of the causes of miscarriage is still one of the urgent problems in obstetrics and gynecology.

Immunohistochemistry (IHC) is a method for detecting the exact localization of a particular cellular or tissue component (antigen) by binding it to labeled antibodies. Albert Coons in 1941 for the first time received fluorescein-labeled antibodies and applied them for diagnostic purposes.

To analyze the results of immunohistochemistry, the histological H-score method is used according to the

formula:  $HS = 1a + 2b + 3c$ , where a is the percentage of weakly stained cells, b is the percentage of moderately stained cells, c is the percentage of strongly stained cells, 1, 2, 3 - staining intensity expressed in points. The degree of expression of E2 and P-receptors is assessed: 0-10 points - no expression, 11-100 points - weak expression, 101-200 points - moderate expression, 201-300 points - pronounced expression [4].

In addition to the above method, the Allred Score method is used for the immunohistochemical evaluation of the endometrium. Calculated by the formula: AS (Allred Score)  $= a + b$ , where a is the intensity of staining (from 1 to 3: 1 - weak; 2 - moderate; 3 - strong staining), b - from 1 to 5, depending on the percentage stained cells (1 - 1%; 2 - 2% - 10%; 3 - 11% - 33%; 4 - 34-70%; 5 - 71-100%). The result can range from 0 to 8 points maximum.

Miscarriage (NB) is a multifactorial disease, in most cases, the cause of abortion in the 1st trimester is an endocrine pathology, primarily an inferior luteal phase that occurs due to hypersecretion of luteinizing hormone (LH), hyposecretion of follicle-stimulating hormone (FSH), hypoestrogenism, hyperandrogenism, damage to endometrial receptors (for example, in chronic endometritis with a high level of cytotoxic cells IL1 $\beta$ , IL8, CD20 and the pro-inflammatory cytokines they produce, as a rule, normal hormone levels are maintained) [4].

In the normal endometrium, depending on the phase of the menstrual cycle, the subpopulation composition of leukocytes, the expression of steroid hormones, growth factors in the cells of the glands and the stroma of the endometrium change. The most significant cyclic changes were found in the nuclei of epithelial cells compared to stromal cells. The maximum sensitivity of



the epithelium of the endometrial glands to estrogens as a result of a pronounced expression of E2 (estrogen receptors) was noted in the middle and late phases of proliferation. High sensitivity of the glandular epithelium to progesterone was revealed in the middle, late phases of proliferation.

The dynamics of the expression of receptors for E2 outstrips the expression for P (progesterone receptors) both in the epithelium of the glands and in stromal cells by one stage in each phase of the menstrual cycle.

In chronic endometritis, a more than 2-fold increase in the expression of estrogen and progesterone receptors in the nuclei of cells of the glandular epithelium was noted compared to normal endometrium. Quantitatively, progesterone receptor expression was found on average in more cells than estrogen receptor expression. The ratio of steroid receptors E2/P in the epithelium in chronic endometritis is 0.97, which differs significantly from the values in normal endometrium - 1.42. The E2/P ratio in stromal cells was 0.41 and 0.58, respectively. The presence of changes in the ratio of steroid receptors in the endometrium indicates, first of all, dysfunctional disorders of tissue reception against the background of chronic inflammation [2].

It is important to note the interdependence of the listed causes of non-developing pregnancy, for example, the level of progesterone has a direct effect on the cytokine system. With a low content of progesterone or damage to the receptors, a low level of the progesterone-induced blocking factor was revealed. Under these conditions, the mother's immune response to the trophoblast is realized with a predominance of type 1 Th, producing mainly pro-inflammatory cytokines TNF- $\alpha$ , IFN- $\gamma$ , IL-1 and IL-8, which have a direct embryotoxic effect and contribute to abortion in the 1st trimester. During physiological pregnancy, Th2 type cytokines predominate in the blood, including IL-4, which block the reactions of cellular immunity and promote trophoblast invasion.

An important role in the pathogenesis of non-developing pregnancy is given to oxidative stress, a universal pathological process. Products of lipid peroxidation are involved in the cascade of destructive changes in cell membranes and, under conditions of inadequacy of the antioxidant system, modulate the immune response and other adaptive reactions of the body.

In recent years, due to the development of new technologies and the possibility of using complex research methods, the attention of scientists began to attract the immunological aspects of spontaneous abortion, which are expressed by pathological changes at various levels of the immune system in 40-50% of

cases, as well as an inadequate response of the mother's body to paternal antigens.

Modern studies have shown that the material obtained as a result of curettage of the walls of the uterine cavity provides more information for diagnosing the causes and adequate subsequent treatment of women with this pathology. Histological analysis makes it possible to identify etiopathogenetic variants of non-developing pregnancy against the background of inflammatory, endocrine, immune, genetic changes or their combination. It is very important to assess the state of the endometrium during the morphological examination of the scraping, i.e. the adequacy of its gestational changes. According to Glukhovets B.I., Glukhovets N.G., et al. (2001), in non-developing pregnancy, underdevelopment of decidual tissue is often observed due to progesterone deficiency [6].

Along with the morphological study of the endometrium, the assessment of its functional activity is of great importance. The endometrium is the main target tissue for ovarian steroid hormones - estradiol, which stimulates the proliferation of stromal and glandular cells in the follicular phase of the menstrual cycle, and progesterone, which causes secretory transformation of the endometrium in the luteal phase [5].

**CONCLUSION:** The revealed changes require further study of the problem by pathomorphologists, obstetrician-gynecologists, immunologists to determine the pathomorphological mechanisms of the development of non-developing pregnancy in each couple. This will allow obstetricians-gynecologists to focus on a detailed examination of a married couple and conduct a comprehensive prevention of miscarriage. Immunohistochemistry makes it possible to more accurately diagnose and monitor the effectiveness of hormonal treatment, provides an individual approach to the patient and, therefore, allows optimizing hormone therapy regimens. The established morphological and immunohistochemical features of chronic endometritis emphasize the importance and necessity of a comprehensive study of scrapings and biopsy specimens in the algorithm for examining patients with infertility and miscarriage.

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