INFERTILITY AND ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

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Abstract. *When immune tolerance is disrupted due to infection, stress, hormonal imbalance, genital or extragenital diseases, and a number of other factors, the risk of infertility and miscarriage increases.*

Keywords: *tumor necrotizing factor (TNF)-α., polyfunctionality of cytokines.*

The immunosuppressive mechanisms that develop during pregnancy and support its course are very diverse [1]. In the formation of maternal immunocyte tolerance to fetal antigens, an important role is played by increased activity of CD4+Foxp3+-T-regulatory lymphocytes (Treg), interleukin (IL)-10 and indolamine 2,3 dioxygenase (IDO), which causes a decrease in cytotoxicity of CD16+CD56+ cells [2]. It was found that during pregnancy estriol induces IDO secretion in monocytes, through protein kinase A promotes an increase in the amount of Treg, inhibits the expression of the CD16+ molecule on natural killer cells (NK), thereby enhances fruit-preserving immune reactions [2]. Pregnancy-associated α2 glycoprotein (SBAG), trophoblastic β1 glycoprotein (TBG), α-fetoprotein (AFP) also have an immunosuppressive effect. Thus, AFP suppresses the expression of MHC II molecules, the phagocytic and antigen-presenting ability of macrophages, the production of antibodies by plasma cells, the proliferative response of lymphocytes to mitogen, the secretion of IL 1ß and tumornecrotizing factor (TNF)-α by monocytes, the activity of NK [1, 3]. Glucocorticoids in pregnant women affect the differentiation of T-helper lymphocytes (Th) by blocking the production of Th1 proinflammatory cytokines (TNF-α, interferon (INF)-γ) and stimulating the formation of Th2 immunosuppressive mediators (IL 4, IL 5, IL 10), which is important for maintaining gestational homeostasis and uncomplicated outcome of childbirth [1].

It is suggested that maternal-fetal relations are not limited only to the development of maternal tolerance to fetal antigens, but are complemented by complex cytokine interactions that control selective immune regulation, control of adhesion and vascularization processes during embryo implantation and pregnancy [4].

Currently, the high frequency of infertility is a significant medical and social problem in many countries of the world and, according to WHO, affects 96-186 million people [5]. In the regions of Russia, the frequency of infertility ranges from 17.2 to 24% [6], in Cameroon it is 19.2% [7], in Kazakhstan — 20% [8], in the capital of Ethiopia — 27.6% [9]. In France, 3.3 million people have been diagnosed with infertility [10].

Assisted reproductive technologies (ART) are actively used for the treatment of infertility: in vitro fertilization (IVF) and embryo transfer (PE), intracytoplasmic sperm injection into the oocyte (ICSI), intrauterine insemination (IUI), cryopreservation of gametes, embryos and others [6, 8]. The use of ART is indicated for ineffective infertility therapy for 12 months in women under 35 years of age or for 6 months at the age of a woman 35 years and older [6].

In Italy, in 2017, the proportion of children born as a result of the use of ART in the structure of all newborns was 2.7%, which, against the background of a decrease in the total birth rate, is a positive stable dynamic [11]. In 2018, about 150,000 ART was applied in France, which led to more than 25,000 births (>3% of children born) [12].

At the present stage, IVF is considered the most effective method of achieving pregnancy [6]. Thus, according to a study in Denmark [13], of the women who started infertility treatment with IUI, 35% gave birth within 5 years, 24% — after switching to the IVF program, 17% — after natural conception. On the contrary, after starting IVF treatment, 53% of women gave birth within 5 years, 11% — after natural conception and less than 1% — after IUI.

The five-year birth rate strongly depends on the age of women and ranges from 80% in women under 35 to 26% in women ≥40 years [13]. In particular, the frequency of pregnancy as a result of ART decreases significantly with increasing age of the patient and in women under 35 years of age is about 30%, after 35 years it decreases by 2 times, at 40 years does not exceed 10%, after 43 years of age it tends to zero. The probability of childbirth decreases with an increase in the number of unsuccessful ART cycles [6, 14].

The study of changes in immune parameters is relevant in different trimesters of pregnancy, as well as at the stage of pre-pregnancy preparation, especially when using assisted reproductive technologies. The importance of assessing immune and hormonal statuses is determined by the diagnostic value and prognostic significance of markers correlating with the course and outcome of pregnancy.

The purpose of this review was to analyze the available scientific data on the use of immune parameters to predict the effectiveness of assisted reproductive technologies.

Material and methods.

A review of foreign scientific papers presented in the scientific electronic library eLibrary and in the databases PubMed, Scopus, on prevalence, immunopathogenetic mechanisms, diagnosis of infertility. The keywords were "antibodies", "infertility", "colony-stimulating factor", "cytokine", "pregnancy prediction", "reproductive technologies", "in vitro fertilization", "antibodies", "infertility", "colony-stimulating factor", "cytokine", "pregnancy prediction", "reproductive technologies", "in vitro fertilization". A multi-criteria search was carried out on inventions, abstracts of patent documents in Russian and English on immunological prediction of the effectiveness of ART.

Immunocompetent cells as predictors of the effectiveness of ART.

Ovarian immunocytes due to cytokine secretion are able to regulate the processes of folliculogenesis, ovulation, development and regression of the corpus luteum, synthesis of steroid hormones [15].

Previously, it was proposed before IVF in women with tubal-peritoneal infertility in the luteal phase of the cycle to determine the relative number of CD95+ macrophages in the leukocyte infiltrate of the endometrial biopsy and, at a value of ≥ 48.8%, predict the onset of pregnancy with an accuracy of 80%, with a lower content — absence. Presumably, the large number of CD95+macrophages in the endometrium reflects adequate activation of macrophages necessary for successful implantation and pregnancy development [16].

A method has been developed for predicting the onset of clinical pregnancy in women with a body mass index ≥ 28.5 in the IVF program by assessing the relative number of peripheral blood mononuclears with highly polarized mitochondria before and after stimulation of superovulation

and measuring waist volume. According to Gorshilova V.K. and co-authors, the accuracy of predicting the onset of pregnancy according to the proposed logistic regression equation was 82.6% [17].

Previously, it was proposed to study the number of progesterone receptors in the mononuclear fraction of peripheral blood cells in infertile women in the treatment of infertility according to the standard long IVF protocol in the middle of the luteal phase of the menstrual cycle and predict the onset of pregnancy at a value > 700 [18].

It is known that uterine NK cells play an important role in the implantation process: activating and accumulating in the uterine glands and around the uterine arteries at the implantation site, they participate in vascular remodeling [19]. It is believed that the receptivity of the uterus is optimal with a sufficient number of activated NK cells [4]. Cytokine imbalance may be accompanied by the transformation of NK cells into lymphokine-activated killers (LAK) capable of lysing trophoblast cells [20], secreting TNF-α and INF-γ, which in high doses induce spontaneous abortion [19].

There is a known method for predicting the risk of early termination of pregnancy after IVF and PE in patients with tubal-peritoneal infertility according to the prognostic index (PI) based on the absolute number of leukocytes, lymphocytes, CD3+-, CD4+-, CD3–containing cd16+56+-populations of venous blood lymphocytes. At PI <-0.1, a favorable prognosis of pregnancy is made, at 0.1 < PI > -0.1 patients are included in the risk group for early termination of pregnancy, with PI > 0.1, a high risk of termination of pregnancy in the first trimester is predicted. Sensitivity and sensitivity to PI > 80% [21].

Cytokines as predictors of the effectiveness of ART.

The study of the quantitative level of cytokines in blood serum, ovarian follicular fluid and endometrium as mediators of intercellular and interstitial interactions is of undoubted scientific and practical interest in terms of establishing discriminatory levels of immune parameters specific to different trimesters of normal pregnancy, the threat of miscarriage, infertility. Difficulties in interpreting the content of immunomediators with determining their diagnostic and prognostic value are due to the diversity, pleiotropy and polyfunctionality of cytokines.

In the role of predictors of the effectiveness of ART, a number of researchers [15, 22] propose an assessment the content of interleukins, interferons, colony stimulating factors, TNF-α, growth factors with dominant pro- or anti-inflammatory activity. The data presented in the scientific literature are not unambiguous due to the dualism of the action of some cytokines (IL 1ß, IL 2, IL 6, INF-γ) under microenvironment conditions [4, 23, 24].

Previously, it was found that with premature birth and with premature rupture of the fetal membranes, the levels of IL 1ß and IL 6 increase. At the molecular level, it was revealed that the expression of caspases 8 and 9 was induced in the amnio-chorion under the action of IL 1ß and IL 6, caspases 2 and 3 under the stimulation of IL 1ß, as well as DNA fragmentation. Consequently, IL 1ß is an inducer of apoptosis of human fetal membranes cells to a greater extent than IL 6, and an increase in its amount correlates with early termination of pregnancy [23].

An association with non-pregnancy due to IVF was revealed with the content of IL 2 ≥ 15 pg/ml, IFN-γ ≥ 11 pg/ml in the follicular fluid. A probable explanation for the unfavorable outcome is the IL 2–induced activation of cytotoxicity of CD3+CD4-CD8+– and CD3-CD16+56+-cells. In addition, an increase in the amount of IFN-γ was accompanied by a decrease in the frequency of crushing and formation of blastocysts [22].

There is evidence of an association of increased serum levels of soluble IL 2 α (IL 2 sR-α) and INF-γ receptors with miscarriage after IVF. In Fasouliotis S.J. et al. [24] it was shown that the content of IL 2 sR-α in patients with miscarriage in the early stages significantly exceeded the amount of the receptor in women with normal pregnancy, and at marker values ≥ 1000 pg/ml, an unfavorable pregnancy outcome was predicted. The frequency of embryo implantation was lower in IFN-γ-positive patients (37.6%) compared with IFN-γ-negative women (50%), while the risk of an unfavorable pregnancy outcome during IVF was twice as high in the former. There was no dependence of pregnancy outcome on TNF-α level.

According to N.O. Motovilova et al. [15], after IVF in women with infertility, the onset or absence of pregnancy was not accompanied by significant differences in the content of granulocytic (G-CSF) and granulocytic-macrophage (GM-CSF) colony–stimulating factors in the follicular fluid. Weak positive correlations were noted between the level of GM–CSF and the number of follicles growing during gonadotropic stimulation, the number of eggs obtained during ovarian puncture. At the same time, on the contrary, a weak negative relationship between the content of GM–CSF in the ovarian follicular fluid and the frequency of fertilization was revealed, presumably due to the effect of ovarian stimulation by gonadotropins on the oocyte.

There are data on the participation of GM–CSF in the interaction of the oocyte and somatic (granulose) cells, in the activation of follicle growth, progesterone synthesis, proliferation and differentiation of blastocyst cells, embryo, in the formation of tolerance of maternal immunocytes to fetal antigens [1, 15].

The expression of G-CSF and its receptor is determined in granulosa cells of the ovaries, in the decidual membrane, trophoblast [15]. The amount of G-CSF in the blood serum increases in the first phase of the natural menstrual cycle and during ovarian stimulation with gonadotropins, promoting follicle growth and ovulation [15]. A. Salmassi et al. a direct relationship was established between the frequency of pregnancy and the content of G-CSF in the blood during follicle puncture [25]. N.O. Motovilova et al. a moderate positive correlation was found between the content of G-CSF in the follicular fluid and the age of infertile women, presumably resulting from the adaptation of the ovaries to gonadotropin stimulation [15]. The combined assessment of the amount of G-CSF in the follicular fluid and the condition of the embryos allows predicting the onset of pregnancy in the IVF program at cytokine values ≥ 410 pg/ml and the presence of morphologically good quality embryos, the sensitivity of the method is 80%, specificity is 83% [26]. Previously, a method was proposed for predicting the effectiveness of IVF programs based on serum levels of IL 8 and lactoferrin (LF) in tubal-peritoneal infertility associated with chronic endometritis [27]. On the day of follicle puncture in the IVF program, the number of markers is determined in blood serum by solid-phase enzyme immunoassay and a high probability of a positive IVF result is predicted at a concentration of LF < 1.8 mcg/ml, IL 8 < 10 pg/ml, a negative result at a content of LF > 2.0 mcg/ml and IL 8 > 10 pg/ml with recommendation of cryopreservation and delayed embryo transfer.

There is a way to predict the outcome of the IVF and PE program: in the follicular fluid, the amounts of TNF-α, fibroblast growth factor-β are determined and PI is calculated using the formula. With a value of PI < 0.3038, a favorable outcome of in vitro fertilization is predicted, with PI ≥ 0.3038 — an unfavorable outcome [28].

In patients of late reproductive age, a decrease in the expression of vascular endothelial factor (VEGF) was found, contributing to endometrial vascularization disorders [29].

Pregnancy glycoproteins for evaluating the effectiveness of ART.

When studying the quantitative level of TBG secreted by the cells of the syncytial layer of the trophoblast and placenta, statistically significant differences were obtained in pregnant women with IVF, depending on the outcome of the use of ART [30]. About 60% of pregnant women after IVF and only 3.3% of patients with spontaneous pregnancy had a reduced concentration of TBG. At the same time, the threat of premature birth was associated with a twofold decrease in the serum amount of glycoprotein, and the elimination of clinical signs was accompanied by a 56% increase in the marker, but without reaching the values of healthy pregnant women. In prognostic terms, the probability of spontaneous termination of pregnancy is 100% with a decrease in the level of TBG by 5 times or more from the initial one, 30-33% — with a reduction by 2-4 times [30].

In the work of Maltseva N.V. et al. It was shown that in women with tubal infertility before the IVF programs, the serum content of α2 macroglobulin (MG) did not differ from the values of healthy non-pregnant women, as a result of IVF, 50% of patients with the amount of MG 2.75–4.55 mmol/l and 36% — with a concentration of MG < 2.75 mmol/l became pregnant [31].. The use of gonadotropins led to an increase in MG levels in half of infertile women, pregnancy—associated α2 glycoprotein (ABG) - in 18%. In all pregnant patients after IVF, the amount of ABH increased 7 times relative to non-pregnant women and 4 times when compared with the level during physiological pregnancy. The MG/ABG ratio negatively correlated with the fact of pregnancy in women with tubal infertility in IVF programs.

For predicting early fetal losses during induced pregnancy in women with pregnancy in the IVF program, it is recommended to determine the level of immune complexes MG-immunoglobulin (Ig) G and LF-IgG in the follicular fluid and with the amount of MG-IgG < 0.6 mcg/ml, LF-IgG < 0.8 mcg/ml predict a high probability of early termination of pregnancy [32]. The method is intended for timely assessment of the risk of reproductive loss and the appointment of intensive support of the luteal phase according to indications immediately after oocyte sampling.

In infertile women, before ovarian stimulation in ART programs, IgM, IgG to progesterone and estradiol are detected in the blood serum in half of cases, which is combined with a fivefold decrease in the frequency of implantation; the accuracy of the method exceeds 70% [33]. With the help of artificial intelligence, models for predicting pregnancy outcomes in patients after the use of ART have been developed. It has been shown that a higher IgG titer to cardiolipin without exceeding the discriminatory level is associated with the birth of a live child [34].

Conclusions.

The development and preservation of pregnancy is facilitated by the complex regulation of immune reactions in the female body. Maternal-fetal relations are not limited to the development of tolerance to fetal antigens: suppressive mechanisms are supplemented by changes in the cytokine profile and immunocompetent cells that activate and control the processes of adhesion and vascularization during embryo implantation and pregnancy.

Due to infection, stress, hormonal imbalance, genital or extragenital diseases, and a number of other factors, immune interactions in the mother-fetus system are disrupted and the risk of miscarriage and infertility increases.

In the treatment of infertility, ART is actively used, of which IVF is considered the most effective method of achieving pregnancy.

To predict the effectiveness of ART, an assessment of immune parameters can be successfully used, especially in combination with sex hormones and characteristics of the embryo

state. Studies of the quantitative level and functional state of immunocompetent cells, cytokines and their receptors, pregnancy glycoproteins, autoantibodies to sex hormones and other antigens, immunogenetic markers are relevant.

The determination of some of the immune parameters in peripheral blood, serum, and follicular fluid is comparable in sensitivity, specificity, and allows predicting the result of the use of ART with high accuracy. A number of immunocytes and cytokines statistically significantly differ in content in the studied material at different stages of pre-pregnancy preparation and pregnancy.

Thus, the study of immune indicators in infertile women is relevant, has diagnostic value and prognostic significance, can contribute to the timely correction of therapy and ART programs.

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