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New approaches to the prevention of pregnancy loss in women after extracorporal fertilization

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Abstract

The renewal of reproductive function of women suffering from infertility is an extremely topical problem. The last decades have been characterized by the increasing proliferation of assisted reproductive technologies for the treatment of infertile couples in our country and throughout the world. Women with induced pregnancy are among the high risk groups for miscarriage and other complications of gestational process and childbirth.

The Objective: of this study was to optimize the program of pre-gravida preparation in patients with infertility, included in the program of auxiliary reproductive technologies, with risk factors for implantation disorder.

Materials and methods of the study: A comprehensive examination of 100 women with infertility was performed; they were divided into observation groups, taking into account the suggested approaches to pre-conceptual preparation: the main group receiving a comprehensive pathogenetically grounded pre-gravida program and a comparison group that received the standard scheme of preparation for the program of assisted reproductive technologies. The control group included 30 women whose pregnancy occurred in the natural cycle and with uncomplicated course. There was performed general clinical examination, ultrasound examination, determination of hormonal and immunological status.

Results of the research and their discussion: The positive effect of the proposed pre-conceptual preparation on the prevention of complications of pregnancy in women after assisted reproductive technologies is confirmed by the normalization of clinical, immunological, hormonal and endothelial status, the state of the fetoplacental complex and the newborn.

Conclusion: The proposed pre-gravida preparation in women with induced pregnancy by normalizing the balance of hormonal, immunological and endothelial factors can reduce the proportion of gestational complications, accelerate the regress of clinical signs of the threat of abortion and promote the successful prolongation of pregnancy in women with subchorionic hematoma

Keywords: infertility, miscarriage, auxiliary reproductive technologies, pre-gravida preparation

1. Introduction

The significance of the problem of perinatal consequences of infertility treatment is increasing today, due to the fact that on the one hand, there is the invariably high proportion of infertile couples in the population, and on the other hand, there is an increasingly assisted reproductive technologies' (ART) spread ^[1]. According to various data, the course of pregnancy, which occurred as a result of the treatment of infertility with the help of extracorporal fertilization (IVF), has significant differences from that in the physiological pregnancy. The use of different methods of complementary reproductive technologies (ARTs) in solving the problem of infertility is only the first step, followed by the next one, extremely important – providing of carrying of a pregnancy and the birth of a healthy child ^[2]. However, despite the modern laboratory and medical program provision, the successful implantation of embryos in one transfer does not exceed 20-35%. In this case, the incidence of miscarriage after the use of ART, according to various authors, varies from 11 to 66%, which reduces the effectiveness of infertility treatment ^[3]. If in natural fetation 15% of pregnancies are interrupted, after fertilization in IVF-ET cycles – 30%, with 75% of spontaneous abortions occurring in the last trimester. The combination of factors associated with age, etiology and pathogenesis of infertility, the nature and duration of pre-treatment, the state of physical health, the contingent of women with IVF belongs to a group of high risk of miscarriage of pregnancy and other complications of gestational processes and childbirth ^[4].

In the modern period, the recognition of the role of immunological disorders, endothelial dysfunction, hereditary thrombophilia and antiphospholipid syndrome (APS) in the development of pregnancy complications such as habitual miscarriage, gestosis, chorion

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detachment, antenatal fetal death, fetal growth retardation syndrome, premature detachment of the placenta, has been recognized as a significant achievement of the modern medical science. It was established that the cause of the obstetric pathology development in 70-75% of cases is the hereditary and acquired abnormalities of hemocoagulation. Taking into account the peculiarities of the physiological adaptation of the hemostasis system to the pregnancy, the absolute majority of genetic and acquired forms of thrombophilia clinically manifest itself during the gestational process and, as it turned out, not only in the form of thrombosis, but also in the form of typical obstetric complications [4, 6]. Performance of the IVF protocol is a serious hormonal load, and in connection with an increase of estrogen levels, rapid non-physiological changes in the hemostasis system, this procedure is a provocative factor in the occurrence of hypercoagulable syndrome, which can lead to arterial and venous thrombosis [5].

Only in the course of comprehensive pre-gravida screening of the state of the hemostasis system, the detection of existing hematogenous thrombophilia, the study of immunological and hormonal status, the determination of the level of endothelium-damaging factor of homocysteine and markers of endothelial dysfunction, timely and adequate influence on the process of pathological intravascular blood coagulation as a potential factor, is possible, that violates the process of implantation and placentation. In the course of ovulation stimulation and at the onset of pregnancy, the correction of the revealed violations will help to find new ways to increase the effectiveness, safety and productivity of the IVF program.

Objective

of our study – is to optimize the program of pre-gravida preparation of infertility patients included into the program of auxiliary reproductive technologies with risk factors for implantation disorder.

Materials and Methods of the Study

100 women with infertility of hormonal and tube-peritoneal genesis, whose pregnancy was obtained using IVF with embryo transfer, were examined. Depending on the method of pre-conceptual preparation and the pregnancy management, women were divided into two clinical groups: the first clinical group (comparison group) included 50 pregnant women who received the standard pregnancy schedule before and after IVF; the second clinical group (the main group) included 50 patients who were performed the proposed pre-gravida preparation, which included the prescription of a multivitamin preparation with curative content of folic acid, amino acid L-arginine aspartate, a hepato-cardioprotective medicine – tiotriazoloni, omega-3 fatty acids and hormonal support with dydrogesterone. The approach to optimization of pre-gravida preparation using this complex was based on the following positive pharmaceutical effects of these medicines. The amino acid L-arginine aspartate has anti-hypoxic, cytoprotective, antioxidant, detoxification and membrane-stabilizing effect. Hepato-cardioprotective medicine tiotriazoloni causes anti-ischemic, antioxidant, membrane-stabilizing and immune-modulatory effects. Omega-3 fatty acids have hypolipidemic properties, as well as moderate anticoagulant, anti-aggregate, anti-inflammatory and immune-modulatory effects. In addition to hormone-regulating effect, dydrogesterone is characterized by immune-modulating effect.

At the stage of the positive outcome of ART and in the onset

of pregnancy, the complex of medicated agents contained a multivitamin preparation with high levels of folic acid, omega-3 fatty acids, and hormonal support for dydrogesterone up to 18 weeks of gestation. The control group included 30 women whose pregnancy occurred in the natural cycle and with uncomplicated gestational period.

A general clinical examination, ultrasound examination, determination of hormones levels (estradiol, progesterone, chorionic gonadotropin), as well as an evaluation of endothelial dysfunction and cytokine profile of blood serum was performed in parallel with an immunoassay assay. Statistical processing of the research results was performed using the standard program “STATISTICA 6.0”, taking into account Student’s criterion.

Results of the Study and Their Discussion

The average age of women in the control group was 24.5 ± 0.8 years, the main group and the comparison group – was 31.1 ± 0.62 years and 31.5 ± 0.65 years respectively. Thus, the age group of women included in the ART program showed that more often, early reproductive loss was observed in patients over the age of 30, which was 48.27% of cases. In the main group and in the comparison group, firstly pregnant women were 28 (56%) and 27 (54%) respectively, in the control group – 22 (73.3%). An important risk factor of local chorion detachment – is the increase in the number of pregnancies in the anamnesis (more than three in history, accustomed miscarriage, more than three abortions (artificial and spontaneous), etc.).

A thorough analysis of the obstetric-gynecological anamnesis of patients with induced pregnancy has shown that abortions took a significant place, with more than a third of women having two and more instrumental abortions ($p < 0.05$). In the control group there was one case of artificial abortion (3.3%). It should also be noted in 21.0% of cases of involuntary miscarriage and unsuccessful in vitro fertilization attempts that were observed in study groups.

Infertility of endocrine genesis was noted in 48% of women, tubal-peritoneal – in 24% of women, combined genesis – 28%. Evaluation of the effectiveness of ART programs in this category of patients allowed marking in 18% of cases more than three attempts of IVF in history, in 67% of observations, the IVF program was performed for the first time.

It should be noted that the impairment of lipid metabolism and overweight in women included in the ART programs was 5.6 times more frequent than in the control group ($p < 0.01$). Studying the structure of extragenital morbidity, a significant proportion of cardiovascular morbidity (25%), thyroid gland disease (30%), and urinary tract disease (26%) were found. Attention is drawn to the fact that there is 2%-fold increase of percentage of operative small pelvic operations in patients with infertility included in the ART program.

The most common gynecological diseases were chronic genital infections, which occupied the leading place with regard to structural significance: it was the pathology of the uterine cervix and inflammatory diseases, and their share was 5.0 times higher than those in the control group ($p < 0.05$).

In an ultrasound examination, signs of the threat of abortion (local hypertonic myometrium, the presence of chorion detachment in the form of subchorionic hematoma) were observed in the main group in 8 (16%), in the comparison group – in 21 (42%) of the pregnant women, in the control group of segmental uterine contractions and areas of chorion detachment are not defined. Our observations noted the

largest proportion of subchorionic hematomas in terms of (8.2 ± 1.2) weeks. In addition, subchorionic hematomas were detected in 7 (14.0%) women in the main group, while in the comparison group – in 13 (26.0%) women. Detachment of chorion was accompanied by clinical symptoms of the threat of abortion in the form of bloody discharge; asymptomatic course was noted in 3.0% of patients. The death of the embryo was observed in 7 women (14.0%) in the main group and 12 (24.0%), while anembryonia – in 5 (5.0%) cases. The results of the performed clinical analysis demonstrated the predominance of reproductive losses in the early terms of 5-7 weeks of pregnancy – 52 (63.41%).

Studying the hormonal profile, low levels of progesterone were detected – 1.5 times compared with control data, estradiol and β -HGT levels were almost 2.0 times higher than those in women with natural pregnancy. The performance of optimized pre-gravida preparation allowed marking the normalization of the hormonal balance in women of the main group, and also prolonging the pregnancy with the presence of subchorionic hematoma in 5 (15.15%) women versus 2 (8.7%) of the comparison group, that is, to improve the effectiveness of clinical pregnancies in 1.8 times.

Analyzing the cytokine profile, it should be noted in this category of patients in the main group the growth of level $il-1\beta$ in 1.5 times, while in the comparison group – in 4 times, against the data of control. The level of $TNF-\alpha$ in the main group exceeds the control indices 1.7 times, whereas in the comparison group it is almost 3.5 times higher. The normalization of the level of anti-inflammatory interleukin-4 in the main group was noted, while in the comparison group it remained 2.5 times lower. It is important that in women from the risk group implantation disorder, there was a very high $TNF-\alpha$ indices and depression of IL-4 synthesis, which is characterized by immunosuppressive activity and providing mechanisms for implantation of the embryo. While in women of the main group with a successful attempt of the embryo implantation, IL-4 level was within the reference limits, which in our opinion, would increase the effectiveness of the IVF program and prolong the pregnancy. Thus, it has been established that in the group of pregnant women with infertility treated with ART, there is an imbalance not only in hormonal homeostasis, but also in the immune chain of regulation of the activity of the organism adaptation processes, which causes the expediency of the use of the medication immune-modulatory effect. During the study of the concentration of endothelin-1 in women of the main and comparative groups a statistically significant (3.7 times) increase of this indicator was determined in the main group against the data of the comparison group. Regarding the content of nitrogen oxide metabolites, in women of the main group and the comparison group, this figure was 38.29 ± 0.97 $\mu M/l$ and 26.96 ± 1.17 $\mu M/l$, respectively, which is significantly lower than that of women in the control group – 41.02 ± 1.57 $\mu M/l$. Thus, in women with induced pregnancy and the presence of chorion detachment, an increased production of endothelin-1 and decreased synthesis of nitric oxide were found. At the same time, there was revealed a probable difference in the indices of women from the comparison group, whose gestational period was complicated by chorion detachment and the formation of subchorionic hematoma, against the indices in women of the main group with signs of the threat of abortion.

The proposed pre-gravida preparation in women with induced pregnancy by normalizing the balance of hormonal,

immunological and endothelial factors can reduce 2.0-fold the proportion of gestational complications, accelerate the regress of clinical signs of the threat of abortion and contribute to the successful prolongation of pregnancy in this category of patients.

Analyzing the course of pregnancy in women of the main group and the comparison group, a decrease in the percentage of placental dysfunction in 2.0 times, pre-eclampsia in 2.9 times, an increase in the incidence of urgent completion of pregnancy and the percentage of operative delivery in 2.0 times, reduction in the frequency of non-pregnancy and premature childbirth in 2.3 times. 75.75% of newborn babies were born satisfactorily without symptoms of asphyxia in women receiving the pre-conceptual preparation, and 24.25% of newborns were in moderate asphyxia, while in the comparison group, these indices were 44.79% of children and 65.21% of children respectively.

Thus, the positive effect of the proposed pre-conceptual preparation as for the proportion of gestational complications in women after IVF is confirmed by the normalization of clinical, immunological, hormonal and endothelial status, the course of labor and the state of the newborn.

Conclusions

The proposed pre-gravida preparation in women with induced pregnancy by balancing of immunological and endothelial factors improves microcirculatory processes, accelerates the regress of signs of the abortion threat and facilitates the successful prolongation of pregnancy in women with subchorionic hematoma.

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