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# THE USE OF THE PRP THERAPY TO ACTIVATE FOLLICULOGENESIS IN WOMEN OF THE LATE REPRODUCTIVE AGE IN PROGRAMS OF ASSISTED REPRODUCTIVE TECHNOLOGIES

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## ABSTRACT

The rate of infertility in married couples of reproductive age in this country makes up from 10 to 15%, in some regions this value is close to 20% - a critical level that has a negative impact on demographic figures. The rate of pregnancy depends directly on the women's age and decreases by 3.3 times starting from the age of 19 and by the age of 48. The decrease in the ability to conceive is accounted for by subtle mechanisms related to the deterioration of the quality of oocytes. The patients who are prepared for an extracorporeal fertilization program (ECF) and do not respond to controlled ovarian hyperstimulation protocols are considered to be poor respondents. Many studies focused on the development of an optimal treatment method. However, none of the approaches seems to be effective enough to guarantee a successful use. Platelet-rich plasma is a new and promising method that is successfully used in the reproductive science to solve a number of medical problems. All the patients whose common features were low oocyte output and poor embryo quality as well as failed ECF attempts were offered a treatment method of autologous PRP therapy after their written consent. Three months later, one obtained astonishing results, which by the markers of biochemical infertility alone could be classified as a complete biological phenomenon and are also characterized by improved embryo quality. The results of hormonal homeostasis show a decrease in the level of the follicle-stimulating hormone by 67.33% while the level of the anti-muellerian hormone is 75.18% higher. Thus, the use of the PRP therapy in poor respondents helps them to overcome their problematic reproductive barrier.

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**Introduction.** The rate of infertility in married couples of reproductive age in this country makes up from 10 to 15 %, in some regions this value is close to 20% - a critical level that has a negative impact on demographic figures. The rate of pregnancy depends directly on the women's age and decreases by 3.3 times starting from the age of 19 and by the age of 48 [1,2].

A significant part of women seeking treatment for infertility at the clinics that use assisted reproductive technologies (ART) are women of the late reproductive age [3,4].

Indeed, the postponing of marriage and pregnancy by women of reproductive age has led to an increase in the rate of age-related infertility in recent years. The ovarian reserve of such women is

significantly reduced, often close to zero. Besides, such women usually have a positive gynecological anamnesis (endometriosis, uterine fibroids, surgeries on small pelvis organs, etc.).

The key factors influencing the efficiency of ART attempts include a reduced ovarian reserve (age factor, surgeries on ovaries, endocrine disorders) and ovarian insufficiency with normal gonadotropin levels. To improve the ovarian response in patients of the late reproductive age with a low ovarian reserve, various stimulation methods are offered: the use of short stimulation protocols, the reduction of the dose of gonadotropin-releasing hormone agonists (GnRH-a), the use of gonadotropin-releasing hormone antagonists (GnRH-ant), etc. [5,6,7]. However, the key component of these modified protocols is the increase of the dose of gonadotropin, i.e. a more aggressive ovarian stimulation. The efficiency of these strategies arouses doubt [8].

**Research aim.** Assessment of the efficiency of the use of the PRP therapy to activate folliculogenesis in women of the late reproductive age by means of hormonal and ultrasound examination of the ovarian function.

**Research data.** The research was aimed at establishing whether the quantity of follicles in women of the late reproductive age would increase after the intraovarian injection of autologous PRP.

The research was conducted on 42 women affected by infertility and aged between 35 and 44 (average age  $37.6 \pm 4.2$  years). The functional condition of the hypophysial and ovarian system was examined with the use of hormonal, biochemical and ultrasound methods. The retrospective analysis of data included the indicators of the socioeconomic situation, somatic, gynecological, obstetrical and allergological anamnesis. All the women underwent a complete clinical and laboratory examination.

All the women underwent transabdominal and transvaginal ultrasonography of the small pelvis organs (convex sensors of 3-5 and 5-9 MHz) with the use of an SSD-500 diagnostic ultrasound scanner. When examining ovaries, one measured their volume and the ovarian-uterine index (OUI) according to S.G. Khachkaruzov's method (1999).

The levels of hormones in blood serum was measured with the use of immunoenzyme assay on the 2-3d day of the menstrual cycle.

The research results were processed by means of the applied program package Exel-2007 and Statistica 5a. In the course of statistical analysis, we calculated the significance level ( $p$ ), with 0.05 being the critical value.

#### **Research results.**

The experience of use of ART shows that the use of inducers of folliculogenesis in the most common stimulation protocols (usually long stimulation protocols) allows the maturation of no more than 3 follicles (or none at all) in 20 to 30% of patients in the first treatment cycle. A decreased ovarian response to inducers of folliculogenesis is referred to as poor or low. Our task was to find a simple and effective way of use of the PRP therapy, which in its turn would stimulate ovulation, to activate folliculogenesis in women of the late reproductive age with a low ovarian reserve by rejuvenation of ovaries with autologous PRP, stimulating and differentiating stem cells, with the formation of new follicles, to ensure the stimulation of folliculogenesis in a way that would be not too aggressive, economically reasonable and at the same time would increase the prospects of pregnancy. The set objective of activation of folliculogenesis in women of the late reproductive was accomplished by the infusion of autologous PRP, which, according to the invention, implied the activation of intracellular and signaling pathways that induced the mechanisms of reparation by proliferation and differentiation of cells of mesenchymal origin in women of the late reproductive age with a low ovarian reserve (poor response, failed ECF attempts, low oocyte output and poor embryo quality).

The suggested method, consisting of 2 stages, enables the activation of intracellular and signaling pathways. In the first stage, 20 ml of blood is collected from every patient and placed into a vessel with sodium citrate that prevents platelet aggregation, with subsequent transvaginal injection of 4 ml of the obtained material directly in each ovary with a puncture needle under sonographic control. The course of treatment implies 4 injections and lasts for three months. The stimulating effect is reached if the platelet concentration in PRP exceeds 1,000,000/ $\mu$ l.

The mean numbers of oocytes before and after the PRP injection were 0.64 and 2.1 respectively. Two patients had spontaneous conceptions. The third patient reached clinical pregnancy and gave birth to a healthy child in June 2018. The results of this research are probably the first report on the influence of the intraovarian PRP injection on the increase of the ovarian response, even on spontaneous responses of women with a poor ovarian response.

Intraovarian PRP injection is a new treatment approach for patients of the late reproductive age with a low ovarian reserve. In our research, the said method led to successful pregnancy and live birth in 18 patients, which makes up 42.8%. The analysis of the indicators of hormonal homeostasis revealed an increase in the basic levels of gonadotropins in women of the late reproductive age, namely of FSH by 3 times to  $12.8 \pm 1.5$  IU/l and of LH by 2.8 times to  $12.6 \pm 1.4$  IU/l, while the level of AMH ranged from 0.7 to 0.9 ng/ml. After 3 months of the suggested therapy, the levels of FSH decreased to  $7.8 \pm 1.2$  IU/l and of LH to  $8.1 \pm 1.4$  IU/l, while AMH ranged from 1.1 to 1.3 ng/ml. Before the treatment, the level of estradiol in blood serum was decreased by 2 times to  $0.13 \pm 0.02$  nmol/l and after the treatment, it increased to  $0.22 \pm 0.03$  nmol/l, which corresponded with the levels in the early follicular phase of the menstrual cycle. As for the number of antral follicles, it clearly correlates with the patients' age. Thus, in women aged between 36 and 41, the mean number of follicles was  $4.5 \pm 1.7$ , in women aged between 42 and 44, the mean number of follicles was  $3.7 \pm 1.4$  in 75 (27.6%) cases. After the suggested therapy, the number of antral follicles increased statistically significantly to  $8.4 \pm 1.5$  in women aged between 36 and 41 and to  $7.6 \pm 1.2$  in women aged between 42 and 44.

Thus, after 3 months of the suggested therapy, the levels of the examined hormones did not differ from the levels in healthy women of reproductive age, which confirms the efficiency of the treatment.

**Conclusions.** Judging by the totality of significant features, we have obtained a new technical solution that ensures a qualitatively new result, including the improvement of blood supply in tissues owing to improved angiogenesis and the activation of folliculogenesis in ovaries, with the formation of new follicles, in women of the late reproductive age, and may be used in ART programs. This result is sufficient for the set objective to be accomplished.

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