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ANALYSIS OF HORMONAL CHANGES DURING DIFFERENT OVARIAN STIMULATION PROTOCOLS USED IN ART PROGRAMS

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Abstract
Despite the diverse results of studies and meta-analyses regarding the effectiveness of individual drugs, analysis of data on folliculogenesis and oogenesis shows that LH levels during ovarian stimulation have a significant impact on the quality of oocytes and the likelihood of successful embryo implantation. Studies show that insufficient LH content can negatively affect reproductive outcomes. The article presents the results of a comparative analysis of various methods of ovulation stimulation. The choice of ovarian stimulation protocol in ART programs should be based on consideration of the hormonal status of the patient. The optimal LH content and the combination of gonadotropins contribute to improving the quality of oocytes, the success of fertilization and pregnancy.

Keywords: Infertility, ovulation stimulation, hormonal status, human menopausal gonadotropin, recombinant gonadotropins, assisted reproductive technology protocols.

Introduction

In the modern world, the problem of infertility in couples of reproductive age continues to be relevant, ranging from 17.2% - 24.0%. This situation creates not only medical difficulties, but also entails significant social and economic consequences [1]. A key stage of assisted reproductive technology (ART) programs is to achieve an adequate number of mature oocytes capable of successful fertilization. Stimulation of ovarian function and selection of high-

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quality oocytes make it possible to form embryos suitable for further transfer into the uterine cavity.

In the process of ovarian stimulation, various pharmacological drugs are used that have a stimulating effect on the processes of folliculogenesis [2]. When choosing these drugs, an objective assessment of the patient's initial reproductive condition and the specific effects of specific gonadotropins are taken into account.

The most popular drugs used in ART protocols include highly purified human menopausal gonadotropins (hMG) with preserved LH activity, recombinant follicle-stimulating hormone (r-FSH) created using genetic engineering, as well as combined drugs containing r-FSH and r-LH. Advanced genetic engineering technologies have made it possible to create drugs combining r-FSH and r-LH, thereby expanding the horizons of individualized stimulation in clinical practice. Despite the diverse results of studies and meta-analyses regarding the effectiveness of individual drugs, analysis of data on folliculogenesis and oogenesis shows that LH levels during ovarian stimulation have a significant impact on the quality of oocytes and the likelihood of successful embryo implantation. Studies show that insufficient LH content can negatively affect reproductive outcomes [4].

The purpose of the study

Conducting a comparative study to analyze the effectiveness of different protocols and strategies for stimulating ovarian function by using urinary and recombinant gonadotropins in order to optimize the outcomes of assisted reproductive technology (ART).

Materials and Methods

The study included 114 patients from a total group of 257 women undergoing infertility treatment at the ART department of the Eramed Clinic. The patients were retrospectively analyzed after puncture or embryo transfer procedures. The review included the main parameters characterizing the stimulation protocol, such as duration, dosage, and outcomes of fetal cycles. The data were compared for two groups: patients with GnRH antagonists (34.2%) and GnRH agonists

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(65.8%). On average, the duration of stimulation was 9 days (antGnRH) and 10 days (aGnRH). The average dosage of gonadotropins was 2151 IU (antGnRH) and 2295 IU (aHnRH).

On the day of application of the ovarian follicle final maturation trigger, chorionic gonadotropin (HCG) was used in 89.2% of cases, while the average number of preovulatory follicles was 8.9 (AHRH) and 9.3 (antGnRH). In the subgroups of women of older reproductive age (40-43 years), there was a decrease in the number of follicles.

When the follicle diameter was ≥ 17 mm, the patients were assigned a trigger for the final maturation of oocytes. In 89.2% of cases, a preparation of chorionic gonadotropin (HCG) was used. 35 hours after the introduction of the ovulation trigger, oocytes were collected, followed by an assessment of their quality using transvaginal puncture of the follicles. Fertilization of the obtained oocytes was performed by IVF (48.5%) and ICSI (51,5%). All stages of cultivation were carried out in multi-gas incubators.

Embryotransfer into the uterine cavity was performed on the 3rd and 5th days after fertilization. The support of the luteal phase and the management of the posttransfer period were carried out in accordance with generally accepted methods [5]. On the 14th day after embryo transfer, the level of the beta subunit of human chorionic gonadotropin (β-hCG) was assessed. With a positive result of beta-hCG, 21 days after the transfer, the patients underwent ultrasound of the pelvic organs to confirm clinical pregnancy. Further management and monitoring of pregnancy was carried out individually, taking into account the specifics of each clinical case.

The analysis of cycle parameters after stimulation in women in protocols with GnRH antagonists and GnRH agonists was carried out. In the group with GnRH agonists, the duration of stimulation was 10 days, while in the group with GnRH antagonists it was 9 days. The average dosage of gonadotropins in the group with aGnRH was 2295 IU subcutaneously, and in the group with antGnRH – 2151 IU subcutaneously. On the day of the oocyte final maturation trigger, the average number of preovulatory follicles in the group with AHRH was 8.9; in patients of older reproductive age (40-43 years) – 7.3. In the group with antGnRh, the

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average number of dominant follicles on the day of trigger administration was 9.3, while in the group of older reproductive age (40-43 years) it was 6.9. The incidence of degenerative oocytes was comparable in different age categories and did not exceed 5%. The relative number of blastocysts of good quality was 59.9%, and in the group of older women this figure was 54.6%.

The rate of clinical pregnancy, calculated on the basis of embryo transfer, in group 1 (25-29 years) It was 44.4%, and in the group of patients of older reproductive age (40-43 years) – 25.0%. The incidence of progressive pregnancy according to ultrasound of the pelvic organs per protocol at 12-13 weeks of age was 86.0% in the 1st subgroup (25-29 years) and 66.0% in the 2nd group (40-43 years). The average frequency of live fetal delivery for embryo transfer without protocols was 31.5% in the 1st group (25-29 years old), and in the older age group (40-43 years old) - 15.0%. Thus, CHMG+rFSH therapy proved to be effective regardless of the age of the patients, including the group of patients of older reproductive age, as evidenced by the high percentage of clinical pregnancy and the birth of live children.

Results and Discussion

Initially, higher efficacy of drugs containing only FSH (p-FSH) was shown in studies by N. Out et al. [6]. However, the analysis of larger-scale data has called into question the advantage of r-FSH in comparison with CHMG. A meta-analysis by P. Levi Setti et al., which included 13 studies and data from 3,970 patients, did not reveal the benefits of any particular drug in terms of the effectiveness of ART programs [7].

There is evidence that CHMG, obtained from the urine of postmenopausal women, is excreted from the body for a longer time and has more physiological properties than p-FSH [8]. Modern purification techniques in the production of urinary gonadotropins minimize the risk of allergic reactions and provide comparable therapeutic properties compared to r-FSH preparations [9]. The results obtained correspond to the present studies, since none of the patients had any allergic reactions during ovarian stimulation with hCG. In a study by R. Frydman et al. It has been shown that highly purified hMG and r-FSH have

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similar efficacy in relation to CHF and the frequency of live fetal delivery in patients aged 18 to 38 years during ovarian stimulation as part of ART programs [10].

The results of this study showed that in patients of older reproductive age, the use of hCG to stimulate ovarian function also remains effective. It was noted that the NNB in this group was 25%, and in the group of 35-39 years – 37.7%.

Data from several studies demonstrate that in women with low LH levels, the frequency of early reproductive losses increases and amounts to 31.1%, while in the group with normal LH levels, this indicator is 16.3% ($p = 0.01$), which confirms the important role of LH in ensuring adequate folliculogenesis and pregravidar transformation of the endometrium [1-4]. The average CHF in patients in the Menopur group in this study was 39.3%, which is comparable to the high efficiency of ART programs [5]. In the studies of P. Lehert et al. It has been shown that in patients of older reproductive age, the level of active LH receptors decreases, which leads to a decrease in the activity of androgens that affect the sensitivity of follicles to FSH [6].

Despite the fact that some studies do not confirm the results for the group of patients of older reproductive age, in women with reduced ovarian reserve, the use of the LH component for ovarian stimulation may be justified, which is confirmed by the data of the Cochrane Review published in 2017 [7-9]. A separate group of patients who are often preferred in using r-FSH for ovarian stimulation in the ART program includes women at risk for ovarian hyperstimulation syndrome (OHSS) and patients with polycystic ovary syndrome (PCOS). However, the results of recent studies have shown that in patients at risk of OHSS, exogenous PH can lead to atresia of medium-sized follicles and prevent the development of clinically significant OHSS [20, 21]. It has been established that the use of hCG in patients with elevated LH levels on the background of PCOS does not provoke an increase in LH levels and does not worsen treatment results [12, 13]. It is important to note that in this study, the risk of OHSS was recorded in only 83 patients (2.0%), and none of the study participants had clinically significant OHSS.

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It was also noted that the LH activity in Menopur is more associated with hCG, which is contained in it in a higher concentration than in other menotropins. Data are described that hCG provides higher rates of reproductive outcomes in patients in the ART program, which explains the high CHF and childbirth in women in the Menopur group in this study, including patients with a "poor response" [12]. Thus, speaking about the benefits of gonadotropins, it should be noted that even with low levels of endogenous LH, the physiological properties of this hormone are preserved and ensure adequate growth and development of the follicle, as well as obtaining high-quality eggs, and this is confirmed in a number of studies. However, highly purified human menopausal gonadotropins turn out to be no less effective than recombinant FSH, and probably do not exceed their effectiveness in terms of the frequency of pregnancy and gestation [14].

Conclusion

The choice of ovarian stimulation protocol in ART programs should be based on consideration of the hormonal status of the patient. The optimal LH content and the combination of gonadotropins contribute to improving the quality of oocytes, the success of fertilization and pregnancy. Ongoing research in the field of hormone therapy provides an opportunity to improve individualized approaches to stimulation and increase the effectiveness of ART methods.

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