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British View ISSN 2041-3963 Volume 10 Issue 1 2025
Impact factor 8

Comparative study of clinical and laboratory parameters using various protocols of controlled ovulation stimulation.

Mamadalieva D.M., Gafurova F.A.

Center for the Development of Professional Qualifications of Medical Workers, Department of Obstetrics, Gynecology and Perinatal Medicine, Tashkent

Abstract. The urgency of the problem of unsuccessful outcomes of the in vitro fertilization (IVF) program encourages the search for ways to optimize not only at the preparation stage, but also in the process of stimulation with gonadotropic drugs using monopreparation and combined schemes.

Keywords: assisted reproductive technologies, in vitro fertilization, ovarian stimulation protocols, recombinant gonadotropins, gonadoliberin agonists or antagonists.

Introduction.

According to the literature, during the entire reproductive period of a woman, follicles in the ovaries go through various stages of development, ranging from the primordial to the preovulatory. The growth and development of follicles occurs under the influence of various paracrine and endocrine factors. There is evidence of the effect of the level of anti-Muller hormone (AMH) on the quality of oocytes [5,6,9] and the relationship with the morphology of the embryo [8]. Hormones such as gonadotropins and anti-muller play an important role in follicle recruitment and inhibition of apoptosis processes. Considering that more than 99% of primordial follicles undergo atresia, the antiapoptotic effect of exogenously administered FSH during controlled stimulation in the in vitro fertilization program leads to the growth and maturation of several dominant follicles in one treatment cycle [7].

The use of gonadotropic hormones to induce superovulation made it possible to increase the effectiveness of IVF and embryo transfer (PE) in the 80s of the last century [2,8]. Recombinant drug analogues have a number of undoubted advantages, since their production technology does not require urine collection, the recombinant

product does not contain viral, protein, carbohydrate and steroid impurities, has high biochemical uniformity and consists of the most active fractions of the hormone, which, apparently, contributes to the production of significantly more mature oocytes and, accordingly, high-quality embryos. qualities. In order to optimize the IVF and PE method, new developments are currently underway, including the development of new drugs and the selection of adequate hormonal stimulation regimens.

The purpose of the study – optimize the selection of individual protocols of adequate hormonal stimulation protocols IVF.

Materials and methods.

257 women receiving infertility treatment in IVF programs at the Department of Assisted Reproductive Technologies at the Eramed Clinic from May 2021 to May 2023 were examined.

In accordance with the set goal and objectives for conducting a comparative analysis of the induced cycle, the studied patients were divided into 4 groups. Group 1A consisted of 60 patients who were stimulated with r-FSH with the addition of human menopausal gonadotropin (HMG) and the introduction of a GnRH agonist from the beginning of stimulation (day 2-3 of the menstrual cycle), group 1B included 54 patients who were stimulated with r-FSH with the addition of HMG and the introduction of a GnRH antagonist from the 6th-7th day of stimulation, group 2A included 50 patients who were stimulated with r-FSH with the addition of r-LH and the administration of a GnRH agonist from day 2-3, and group 2B consisted of 42 patients who were stimulated with r-FSH with the addition of r-LH and the administration of a GnRH agonist from day 6-7 of ovulation stimulation.

Follicle puncture was performed 36 hours after administration of the ovulatory dose of the trigger (Pregnil, Organon) under intravenous anesthesia and transvaginal ultrasound control using an adapter for attaching a puncture needle. Follicular fluid was aspirated using a special vacuum suction under a negative pressure of 130-150 mm of water column. The follicular fluid was placed under a stream of transmitted light on a worktable of a Zeiss binocular microscope. The obtained oocytes were cultured in Origio nutrient medium (Denmark) sequential culture system in droplets

under a layer of Origio mineral oil (Denmark) in special incubators at a temperature of 370C, a CO2 concentration of 5-6% and a gas humidity of 98-100% in the incubator. The resulting sperm was centrifuged after dilution (30 minutes) in an 80/40 silane particle density gradient (Suprasperm, Origio, Denmark). After removal of the filler fluid, the culture medium of Sperm Preparation Medium (Origio, Denmark) was layered on the precipitate. This step was repeated twice, then tubes with sperm sediment were placed in an incubator for activation. Fertilization was performed with activated spermatozoa. The sediment with actively motile spermatozoa (0.5 ml) was carefully selected and placed on a clean well of culture four-well cups in a CO2 incubator. 4 hours after the follicle puncture (40 hours after the ovulation trigger was introduced), the ICSI technique was performed. Developing embryos were cultured to the blastocyst stage in a sequential media system (ICM1 BlastAssist, Origio, Denmark) for 3-5 days separately from the left and right ovaries. Statistical data processing was performed on an individual computer using Microsoft Excel spreadsheets and the Statistica for Windows v.6.1 application software package, StatSoft Inc. (USA).

Results and Discussion.

The initial clinical and anamnestic and clinical and laboratory parameters of patients with various stimulation protocols were analyzed.

The data of the comparative analysis of the clinical and anamnestic parameters of the patients of the 4 study groups are presented in Table 1.

Based on the results of the analysis, it can be seen that the patients of all the studied groups were comparable in terms of clinical and anamnestic parameters. It is worth noting that group 1A patients had an older average age (36.1±3.9 years), and group 2A patients were more likely to have primary (35.7%) and longer-term (9.3±5.3 years) infertility than patients in other groups, but the differences were not statistically significant.

Table 1.

Characteristics of clinical and anamnestic parameters in patients with various stimulation protocols

Indicator	Group 1A r-FSH + HMG and GnRH agonist (from day 2-3) n=60	Group 1B r-FSH + HMG and GnRH antagonist (from day 6-7) n=54	Group 2A r-FSH + r-LH and GnRH agonist (from day 2-3) n=50	Group 2B r-FSH + r-LH and GnRH antagonist (from day 6-7) n=42
Age, years	35,7±4,3	34,2±4,1*	36,2±4,1	36,5±4^^
Menarche's age, years	13,6±1,4	13,6±1,5	13,4±1,3	13,8±1,4
MC duration, days	27,4±6,7	29,8±7,9*	29,2±7,6	27,6±6,7
Body mass index, kg/m^2	25,5±5,2	23,8±5,7	23,7±5,3^	25,1±6,1
Duration of infertility, years	9,7±4,9	11,7±5,7*	10,7±5,5	10,3±5,1
Primary infertility	19 (31,7%)	17 (31,5%)	18 (36%)	13 (31%)
OR	1,01 (0,46 – 2,23)		1,25 (0,52 – 3)	
Secondary infertility	41 (68,3%)	37 (68,5%)	32 (64%)	29 (69%)
OR	0,99 (0,45 – 2,19)		0,8 (0,33 – 1,91)	

Note – Statistically significant differences at * P<0.05, ** P<0.01, *** P<0.001 – to group A, ^ P<0.05, ^^ P<0.01, ^^^ P<0.001 – to the corresponding group 1.

The analysis showed that the studied patients had comparable data on the initial ovarian reserve, as indicated by basal levels of FSH, AMH, ovarian size and the number of antrum follicles. However, the number of antral follicles in all 4 groups corresponded to a low ovarian reserve. The average basal levels of blood hormones were within the limits of the nominative values. It should be noted that the level of estradiol in group 2B (66.4±68.1 pg/ml) was significantly higher than in groups 1A (49.5±58.9 pg/ml) and 2A (49.5±53.5 pg/ml) (p1A-2B=0.006; p2A-2B=0.034).

This fact can be explained by the fact that patients in group 2B had a slightly larger number of antrum follicles (6.1±3.1) (p>0.05) than patients in other groups, which contributed to a higher level of basal estradiol.

Table 2.

Characteristics of clinical laboratory and ultrasound parameters patients have different stimulation protocols

Indicator	Group 1A r-FSH + HMG and GnRH agonist (from day 2-3) n=60	Group 1B r-FSH + HMG and GnRH antagonist (from day 6-7) n=54	Group 2A r-FSH + r-LH and GnRH agonist (from day 2-3) n=50	Group 2B r-FSH + r-LH and GnRH antagonist (from day 6-7) n=42
Basal LH, mIU/ml	4,8±1,9	4,2±1,6	5±1,8	4,4±1,4*
Basal FSH, mIU/ml	7,5±2,2	6,9±2,4	8,1±2,5	6,6±2,2**
Basal E2, pg/ml	68,4±21,1	56,1±15,8 ***	81,7±29,8 ^^	85,6±31,7 ^^^
Basal P, ng/ml	14,9±4,8	11,1±3,9 ***	12,2±4,7 ^^	14,6±5,4 *^^^
Basal AMH, ng/ml	1,7±0,5	2,2±0,7***	1,3±0,4^^^	1,2±0,4^^^
Volume of the left ovary, cm^3	7,7±4,9	8,2±5,1	8,1±4,5	8,1±4,9
Volume of the right ovary, cm^3	7,6±3,8	7,2±4,1	7,3±4,3	6,6±4,4
The number of antral follicles in both ovaries	6,8±2,7	6,5±2,5	6,2±2,3	6,8±2,7

Note – Statistically significant differences at * P<0.05, ** P<0.01, *** P<0.001 – to group A, ^ P<0.05, ^^ P<0.01, ^^^ P<0.001 – to the corresponding group 1.

The analysis showed that the initial hormonal and ultrasound parameters of the ovaries in the patients of the two groups did not differ statistically. The average basal level of FSH, AMH, and ovarian volume corresponded to indicators of normal ovarian reserve. However, the number of antral follicles in both group 1 (r-FSH + HMG protocol) - 6.0±3.0, and in group 2 (r-FSH + r-LH) – 5.7±3.1 corresponded to indicators of low ovarian reserve (less than 5-7 follicles in both ovaries).

Conclusion.

Thus, the comparative analysis showed that the patients of the two groups were completely comparable in terms of clinical, anamnestic, laboratory and ultrasound

parameters, mainly related to late reproductive age and had a reduced ovarian reserve, which was a predisposing factor to a weakened ovarian response during stimulation.

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