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Effect of Therapy Using the "Modified Protocol" on the Effectiveness of Treatment of Infertility in Women with a Poor Ovarian Response

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Abstract: The "modified" protocol of treatment for women with infertility, who demonstrated a high probability to develop poor ovarian response to the controlled ovarian stimulation, was designed and proposed to be used in practice of human reproduction. The pre-protocol diagnostics of poor ovarian response is based on the diagnostic criteria of color Doppler mapping, which were established during the examination of the women who repeatedly consulted us to receive infertility treatment using the auxiliary reproductive techniques, for whom the previous attempts of infertility treatment failed and who were diagnosed with poor ovarian response after a controlled ovarian stimulation. The final results of using the "modified" protocol (the number of preovulatory follicles, the number of punctured oocytes and the number of cultivated embryos) attest to the positive effect for treating women with a risk of developing the poor ovarian response syndrome.

Key words: Infertility % Women % Ovarian stimulation % Ovarian response syndrome.

INTRODUCTION

Poor ovarian response is a response of the follicular apparatus, which is inadequate to the controlled ovarian stimulation (COS), when after the standard therapeutical doses of follicle-stimulating agents are introduced, the reproductive medicine physicians manage to cultivate single preovulatory follicles and subsequently obtain single oocytes after puncture. Hence, sometimes it is impossible to obtain even single viable embryos (since embryo selection cannot be performed) to conduct embryo transfer, the final stage of extracorporeal fertilization (*in vitro* fertilization) [1, 2, 3].

Absolutely all reproductive medicine clinics encounter the problem of poor ovarian response; they typically elaborate their own approaches to overcoming the pathological response of the ovarian follicular apparatus [4], thus "modifying" the conventional protocols of treatment for infertility using the auxiliary reproductive techniques [5, 6, 7, 8, 9, 10]. We have elaborated our own "modified" protocol of treating female patients with poor ovarian response. It is based on the following principles of affecting the ovaries: the temporary "rest" of the ovaries (and, therefore, of the follicular apparatus), normalizing blood circulation in the ovarian tissue and improving the rheological properties of blood supplied to the ovarian tissue.

METHODS

The principle of ovarian "rest" is based on prescribing hormone medications with estradiol valerate as the major active ingredient to female patients for at least three menstrual cycles preceding to the stimulation protocols. On day 21 of the third menstrual cycle after the administration of the medication containing estradiol valerate was started, the women were prescribed dexamethasone (1 mg), long-acting form of nitroglycerin - nitrogranulong (2.9 mg intravaginally) along with an intravenous infusion of the drug containing pentoxifylline (100 mg in 400 ml of Ringer's solution) as the major active ingredient at an infusion rate of 20–30 drops/min.

Under the ultrasonographic control (performed every second day, beginning on day 21 of the cycle preceding the cycle when the stimulation was begun), a female patient received injections of recombinant follicle-

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stimulating hormone (FSH) – follitropin "- at the initial dose of 25 IU; the FSH dose was subsequently individually corrected so that follicles with the diameter of at least 2–3 mm were obtained by days 2–3 of the next menstrual cycle. Starting on day 2 of the menstrual cycle in which ovarian stimulation was performed, a gonadotropin-releasing hormone antagonist was prescribed (at a dose of 0.5 mg/day during 6–8 days). Folliculogenesis in this case was conducted due to the administration of follitropin " at a dose of 300 IU and menopausal gonadotropin at a dose of 150 IU for the subsequent 5 days; the dose was then prescribed individually depending on the response obtained. After the diameter of the dominant follicle reached 14 mm, a gonadotropin-releasing hormone antagonist was prescribed at a dose of 0.25 mg/day until the chorionic gonadotropin trigger dose (10 000 IU intramuscularly) for final oocyte maturation was prescribed. A single subcutaneous injection of 75 IU of recombinant lutropin (LH) was given the same day the chorionic gonadotropin trigger dose was administered.

RESULTS AND DISCUSSION

In order to perform a dynamic assessment of the efficiency of pharmacological components of the "modified" protocol, the following parameters were determined: the changes in the ovarian volume during the treatment period (Figs. 1 and 2); the antral follicle count prior to the conductance of the protocol after the pre-protocol therapy; the number of preovulatory follicles that responded to the stimulation protocol and attained the value required for puncturing; and the number of oocytes obtained by puncture (Table 1). The total number of women who received therapy using the "modified" protocol was 32. The pre-protocol therapy had no positive results in 4 cases; these women became the candidates for *in vitro* fertilization in the oocyte donation programs.

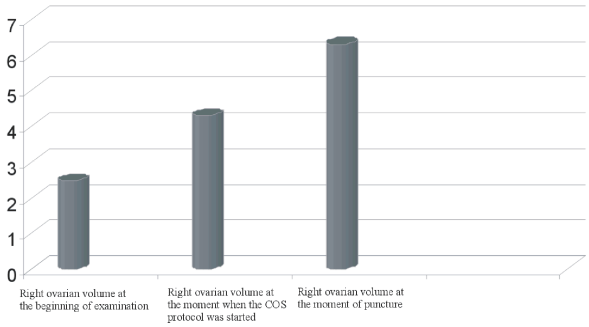

Fig. 1: Ultrasonic parameters of the right ovarian volume (cm^3)

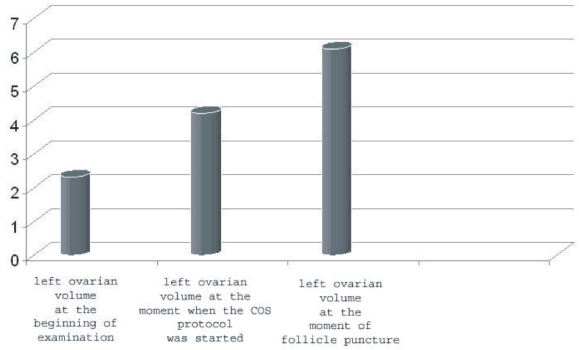

Fig. 2: Ultrasonic parameters of the left ovarian volume (cm^3)

The ovarian volume increased by 75–80% as compared to the initial ovarian volume.

The conventional procedure of oocyte insemination was carried out in 27 female patients (84.4%) for oocyte fertilization. Intracytoplasmic sperm injection into an oocyte was used in 5 cases (15.6%) due to low sperm count of their husbands.

According to the tentative results of the treatment using the "modified" protocol, the total frequency of oocyte fertilization in female patients was 86.4%. The frequency of cases when the oocytes remained unfertilized was 5.9%, which indirectly attests to

Table 1: Parameters of the ovarian response to the "modified" protocol and embryogenesis

Parameter	Count
Antral follicle count in the beginning of the examination	4.18±0.49
Number of preovulatory follicles obtained after the pre-protocol therapy and treatment conducted according to the "modified" treatment protocol	6.55±0.6
Number of oocytes obtained by puncture	5.97±0.34
Number of unfertilized oocytes	0.32±0.14
Number of oocytes showing signs of polyspermia by the end of day 1 after the fertilization (oocyte insemination)	0.41±0.12
Number of oocytes obtained by the end of day 3 of cultivation	5.15±0.21
Number of embryos showing signs of fragmentation	0.41±0.11
Number of embryos obtained by the end of day 5 of cultivation	4.65±0.43

the positive effect of the drugs used in the "modified" protocol on the fertilization process. The frequency of development of polyspermia (simultaneous fertilization by at least two spermatozoa) was 7.8% of the cases when the embryonic development was observed; the frequency of embryo fragmentation was 7.8%. After the cultivation for 5 full days, the embryo count was 4.65±0.43. The total blastocyst count was 147. Among these blastocysts, 133 (90.4 %), 12 (8.2 %) and 2 (1.4 %) were allocated to grades A, B and C, respectively. The percentage of blastocysts of the best grade (A) was high (90.4 %). With allowance for this fact, it was possible in most cases to separate the resulting embryos into several embryo transfers (the native embryo transfer as the final stage of the therapy and subsequent cryo-embryo transfer if the first embryo transfer failed).

It should also be mentioned that the positive aspect of the therapy using the "modified" protocol (along with the resulting embryos that can be used for embryo transfer) is that the number of female patients with the non-follicular type of the ovarian structure decreased from 15 (13.8%) to 4 (3.7%). In other words, the type of the ovarian structure has become follicular after the combined pre-protocol therapy, which allowed using the ovarian stimulation protocol in 11 (10.1 %) women.

The average duration of the controlled ovarian stimulation with gonadotropins until the follicles attained the size corresponding to that of the preovulatory follicles (at least 18 mm in diameter) was 9.1±0.7 days. The total dose of gonadotropins used for stimulation of the female patients was 1044 FSH ampoules; the average number of FSH ampoules per patient was 29±0.8. On day 5 after the puncture for oocyte retrieval, an embryo transfer of one grade A embryo was performed in 24 (75.0 %) female patients "on demand"; the embryo transfer of two grade A embryos in 5 (15.6 %) patients, two grade A and B embryos in 2 (6.3 %) patients and three grade A, B, C embryos in 1 (3.1 %) patient was performed. After 39 (26.5%) embryos were transferred into the uterus, the remaining 108 (73.5%) embryos were subjected to cryofreezing using either a programmable freezer or the vitrification procedure and were used as an embryo reserve for the women in whom the embryo transfer using native embryos failed.

The other positive effects of the pre-protocol treatment were the attenuation of the signs of vaginal dryness and increased libido, which was mentioned by all the female patients who had these symptoms prior to the treatment (this fact was also noted by the other physicians providing treatment using these protocols [9, 10]).

It has been known from the follow-up history that biochemical pregnancy occurred in 17 (53.1%) patients on day 15 after the embryo transfer. The clinical pregnancies (confirmed by ultrasound screening) were subsequently observed in 12 (37.5%) women; 2 (5.6%) pregnancies were terminated through spontaneous abortion at 4 and 7 weeks of gestation, respectively. Thus, the frequency of final positive results of the treatment among the female patients was 31.3%, which corresponds to 10 patients with the progressing intrauterine pregnancy. Seven (19.4%) women underwent a planned caesarean delivery. One (2.8%) female patient expressed an intention to give birth without assistance and delivered a child at 39 weeks of gestation (physiological birth). Two (5.6%) patients experienced preterm labor: at 33 and 35 weeks of gestation, respectively. All the children delivered demonstrated no signs of pathology and are developed according to their age.

With allowance for the high outcome of production of viable embryos suitable for embryo transfer (86.49%) and high percentage of pregnancies (37.5%), we consider it reasonable to use the elaborated "modified" protocol to treat women with a high risk of the development of poor ovarian response during controlled ovarian stimulation.

CONCLUSIONS

Due to its pharmacological components, the elaborated "modified" protocol in some cases allows achieving the conversion of the non-follicular ovarian structure into the follicular one, thus making it possible to perform controlled ovarian stimulation to these women.

The "modified" protocol allows one to use relatively low doses of the follicle-stimulating hormone during the ovarian stimulation, which has a positive economic effect on the treatment procedure.

The percentage of the output of the best quality (grade A) blastocysts is also high (90.4%).

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