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# Induction of Anovulation in Clomiphene Resistant Women with Endocrine Infertility

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**SUMMARY**

To evaluate the efficacy of letrozole and clomiphene citrate in combination with human menopausal gonadotropin (hMG) in clomiphene citrate-resistant infertile women with PCOS. Research methods: 60 women with resistance to clomiphene citrate, of which: 26 women received letrozole + hMG, 21 women received CC + hMG and 13 women received only hMG. All women were treated according to the same scheme during the cycle. All patients were given 75 IU hMG every other day until the dominant follicle appeared. Results of the study: the incidence of monofollicles was 84.6% in the letrozole + hMG group, 66.7% in the CC + hMG group and 53.8% in the hMG only group ($r<0.05$ for letrozole + hMG compared with the other two groups). The number of developing follicles (follicles larger than 14 mm) and the frequency of cycle cancellation due to ovarian hyperreactivity were lowest in the letrozole + hMG group. Ovulation and pregnancy rates were similar among the three groups. The mean length of induced days and the dose of hMG IU used were significantly lower in the letrozole + hMG and CC + hMG groups compared to the hMG alone group. Conclusion. Letrozole in combination with hMG is one of the most effective methods in women with clomiphene citrate resistant polycystic ovary syndrome and prevents complications such as ovarian hyperstimulation syndrome and multiple pregnancies.

Gonadotropins have been used for ovulation induction in clomiphene citrate (CC)-resistant women with infertility and polycystic ovary syndrome, but this has resulted in ovarian hyperstimulation, i.e., the development of multiple follicles. Ovarian hyperstimulation syndrome is a serious complication that reduces the effectiveness of treatment and the quality of life of women, even requiring intensive care[1,5].

Polycystic ovary syndrome (PCOS) is one of the main causes of anovulatory infertility, which accounts for 5-10% of women of reproductive age. Ovarian stimulation has been carried out for more than 60 years, and CC are used as the main drug for this. CC block estrogen-sensitive receptors in tissues and cells. Despite the higher ovulation rate in women receiving CC, the

frequency of pregnancy is much lower, which is a consequence of its antiestrogen effect on the endometrium and cervical mucus. On average, 25% of women with PCOS are resistant to clomiphene citrate [7].

In recent years, letrozole, an aromatase inhibitor, has been widely used as an alternative to CC for ovarian stimulation [2,3].

Letrozole is an aromatase inhibitor that prevents the conversion of androgen to estrogen. Because of this, there is a shortage of estrogen in the body, folliberin is stimulated in the hypothalamus, and FSH is produced a lot in the pituitary gland. Due to the increase in its concentration in the blood, folliculogenesis is stimulated in the ovary. Letrozole is an optimal tool for ovulation induction, because it does not block estrogen receptors in central and peripheral tissues, does not have a negative effect on the endometrium and cervical mucus. Usually, the growth of a single follicle leads to ovulation, which in turn prevents ovarian hyperstimulation [5,6].

In order to restore natural fertility, if there is no growth of the follicle due to the use of CC or there is no pregnancy, it is switched to gonadotropin drugs[6,7]. Over the past 10 years, gonadotropins have been used in "step-up" regimens, starting from low doses and gradually increasing the dose, that is, from 37.5IU to a maximum of 150IU. But the use of gonadotropins only for the purpose of restoring natural fertility leads to complications such as the growth of many follicles and, as a result, stopping the induction cycle, ovarian hyperstimulation syndrome, and multiple pregnancy.

Studies have shown that using CC in combination with hMG is more effective than using hMG alone to induce monofollicular growth. However, the combination of letrozole and hMG induces follicular growth, ovulation frequency, and CC do not lag behind hMG, but the pregnancy rate is higher, which depends on the antiestrogenic effect of CC [2,4].

**Research materials and methods:** from January 2021 to January 2023, women who applied to private clinics of Khorezm region "Zurriyat Shifo" and "Tsentr zdorovya" LLC due to infertility were examined. Of these, a total of 60 women with resistance to Clomiphene citrate were divided into 3 groups: Group I (n=26) letrozole + hMG; Group II (n=21) was given CC + hMG and group III (n=13) was a group of women who were given only hMG. Group I and II women were treated in the same scheme during the cycle. They received CC or letrozole for 5 days. All patients were given 75 XB hMG days until the dominant follicle. Group III women were given gonadotropin in a "step up" scheme, starting with a low dose and increasing it.

PCOS was diagnosed based on the Rotterdam criteria, i.e. women with at least 2 of the following 3 symptoms. These signs are: oligomenorrhoea or amenorrhoea, clinical and/or laboratory hyperandrogen status, and polycystic ovaries [17].

Women who received 100 mg CC for 5 days were considered resistant to CC if follicle growth or pregnancy was not observed for 3 cycles. The study criteria include: women under 38 years of age who are resistant to CC with PCOS, have not undergone any surgery on the small pelvic organs, have a normal body mass index, i.e. 18-25, have a spermogram that is fertile according to the criteria of WHO, women who have not used gonadotropin in the anamnesis.

The study criteria do not include: all types of anovulatory infertility except patients with anovulatory polycystic ovary, tube-peritoneal infertility, male infertility, ovarian failure and tumors, endometriosis.

**Study Design:** Consent was obtained from all patients participating in the study. A total of 60 infertile women who did not respond to clomiphene citrate with follicular growth during 3 cycles and did not become pregnant were included in the study. In patients with resistance, ovulation

stimulation was carried out with human menopausal gonadotropin or its combination with clomiphene citrate and letrozole. The choice of letrozole or clomiphene citrate was chosen at the discretion of the attending physician, there were no specific criteria for the choice of the drug. A combination of Letrozole and hMG was administered to 26 of 60 patients with clomiphene citrate resistance; In 21 patients, a combination of CC + hMG was used; 13 women received only human menopausal gonadotropin. In the first group, Letrozole 2.5 mg 2 times a day, Clomiphene citrate 50 mg 2 tablets (100 mg) a day were used for 5 days from the 3rd to the 7th day of the menstrual cycle, and from the 7th day, 75IU hMG was used every other day until the diameter of the dominant follicle was 18 mm. Ovulation induction to women in the third group was carried out from the 3rd day of the menstrual cycle with a dose of 37.5 IU in the "step up" mode, the maximum dose of hMG did not exceed 150 IU. The ovulation trigger was applied when the size of the dominant follicle reached 18-24 mm. Folliculometry was conducted by transvaginal ultrasound examination and was always performed by the same specialist and on the same machine. After determining the dominant follicle, their number and diameter of 14 mm and more follicles were counted, the amount of estrogen and VEGF in the blood was determined. If follicle growth was less than 0.5mm during 2 days, the dose of gonadotropin was increased by 37.5 IU. If follicle growth was 1 mm per day, hMG was kept at this IU dose. And based on their indicators, an individual ovulation trigger was selected to prevent ovarian hyperstimulation. Sexual intimacy is recommended 24-36 hours after using the ovulation trigger, for 2-3 days. Transvaginal US is performed 2 days after applying the trigger to confirm ovulation. After the corpus luteum was seen, 200 μg of micronized progesterone was given 2 times in order to maintain the second phase of the menstrual cycle. Pregnancy was confirmed when the fetal bladder was seen on US on day 21 after ovulation. Multiple pregnancy was considered if more than one fetus was detected.

At the end of the study, the following were evaluated: 1) Ovulation frequency (triggered when the leader follicle reached 18 mm);

1. the number of follicles with a diameter of 14 mm and more (counted on the day of applying the trigger);
2. The amount of estradiol and VEGF in the serum on the day of the trigger application;
3. the number of unsuccessful cycles: a) the follicle did not grow; b) follicle luteinization without ovulation; c) ovarian hyperreaction;
4. the amount of human menopausal gonadotropin (IU) consumed during the induction cycle;
5. the frequency of pregnancy, including the frequency of multiple pregnancies;
6. the number of people who developed ovarian hyperstimulation syndrome and in which group.

**Research results:** FSH, LH, AMH, estradiol (E2), total testosterone, free testosterone, cortisol, DHEAS, PRL, TTH, free T4, AT TPO, VEGF, and the number of antral follicles (3-9mm) in the ovary were determined by transvaginal ultrasound in all women in the early follicular phase.

Student's t test was used for statistical analysis. $r<0.05$ was considered statistically significant. In order to determine the predictors of monofolliculitis, the effect of a woman's age, body mass index, character of the menstrual cycle, free testosterone, LH/FSH ratio, number of antral follicles, index of insulin resistance (HOMA-IR) and the duration of treatment was analyzed.

A stimulation cycle was performed in 60 patients resistant to clomiphene citrate. In 6 of these, human chorionic gonadotropin was not administered because of the risk of ovarian

hyperstimulation, instead Decapeptil 0.2 was injected subcutaneously as a trigger. The total amount of hMG IU used in the first and second groups (letrozole + hMG and CC + hMG) was significantly less than the third group (hMG only) ($r < 0.05$). But this difference was not significant in the first and second groups. The frequency of ovulation was in 18 women (69.2)% in the first group, 14 women (66.7)% in the second group, and 8 women (61.5)% in the third group, and the difference between them was not significant.

The incidence of monofollicle was 84.6% in the first group, 66.7% in the second group, and 53.8% in the third group, which was higher in the first group (Letrozole + hMG) than the other groups ($r < 0.05$). The number of growing follicles (more than 14 mm in diameter) and the frequency of cycle interruption due to ovarian hyperreaction was the lowest in the first group. On the day of the trigger, serum estradiol levels were lower in the first group than in the other groups.

In the first group, there was no multiple pregnancy compared to the other groups. 1 multiple pregnancy was observed in the second group and 4 in the hMG group. Mild OHSS was more common in the hMG group than in the control group. Triplet pregnancy and ectopic pregnancy were not observed in any group.

Discussion. The results of this study showed that in women resistant to clomiphene citrate, the duration of stimulation days, the total amount of hMG, monofollicle growth, OHSS syndrome and multiple pregnancy did not develop in the letrozole + hMG group, indicating the superiority of this protocol over others. It is especially suitable for women who are at high risk of developing ovarian hyperstimulation.

In clomiphene citrate-resistant normal-weight women with PCOS, the primary goal of ovulation stimulation is to induce ovulation by inducing a monofollicle and, in turn, to restore natural fertility by avoiding multiple pregnancies with OHSS.

These results are consistent with the major benefits of letrozole in restoring monofollicular ovulation in women with PCOS. Letrozole is completely absorbed after oral administration, with an average half-life of 45 hours, while clomiphene citrate is retained in the serum for a long time and subsequently inhibits pregnancy by growing follicles.

**In conclusion,** it was found that the combination of hMG with letrozole reduces the duration of stimulation and the amount of hMG IU used for stimulation, which is considered convenient for patients on the financial side. In turn, this protocol prevents complications of ovulation induction such as ovarian hyperstimulation syndrome and multiple pregnancy by ensuring monofollicle growth.

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