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# Optimization of Treatment for Women with Infertility

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***Abstract*---**Annotation. Up to 20-25% of women with PCOS are resistant to clomiphene citrate. The aim of the study is to optimize the baseline ovarian response in clomiphene-resistant women to ovulation induction with minimal drug costs. Materials and methods of research: the study included 40 clomiphene-resistant women with PCOS. For women in group I, we used clomiphene citrate 100mg + human menopausal gonadotropin (HMG)37.5 IU / day. Group II received only HMG 37.5 using a low dose escalating protocol. The use of this protocol enables monofollicular growth and a decrease in the risk of multiple pregnancies and, in turn, is the prevention of ovarian hyperstimulation. The results of the study showed that in group I compared with group II, the frequency of ovulation was significantly higher (60% versus 35%). Conclusions. The combined administration of CC + HMG in clomiphene-resistant women with PCOS compared to the use of HMG alone, gives higher ovulation rates and lower financial costs.

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***Keywords***---clomiphene citrate (CC), human menopausal gonadotropin (HMG), infertility, ovulation stimulation, treatment.

## Introduction

Infertility is a global problem of the community, family and medicine. In a joint WHO / World Bank Disability Report of June 9, 2011, it was noted that infertility is the eighth most common serious global disorder, followed by maternal sepsis and unsafe abortion [WHO, World Bank. World Report on Disability. Geneva, World Health Organization, 2011]. Endocrine infertility accompanied by anovulation is the most common form of endocrine disorders in women of reproductive age [1,2,5]. It has been proven that ovulation induction is the main treatment for fertile women with PCOS [4,5,7,8]. According to the WHO, from 10 to 15% of married couples suffer from infertility. In the conditions of Central Asia, where families with many children are widespread and this is traditionally encouraged, childlessness is considered a great misfortune and often leads to the disintegration of the family [1,6,8]. Up to 20-25% of women with PCOS are resistant to clomiphene citrate [2,3,9].

## Materials and Method

Our randomized trials were conducted at the central polyclinic in Urgench from 2018 to 2020. It included 40 clomiphene-resistant women with PCOS. In group I (n = 20) women, we used clomiphene citrate 100mg + human menopausal gonadotropin (HMG)37.5 IU / day. Group II (n = 20) received only HMG 37.5 using a low dose escalating protocol. Informed written consent was obtained from all patients. The protocol for this study was approved by our board of the Urgench branch of the Tashkent Medical Academy. 52 clomiphene-resistant women with PCOS applied to the central polyclinic of the city of Urgench. Of these, 47 met the inclusion criteria and 7 of them refused to participate in the study. Randomization was carried out using a computer of random numbers, and the distribution of groups was carried out according to a simple random distribution rule. Patients were randomly assigned CC + HMG (20 cases, group I), and only HMG (20 cases, group II). The statistician performed the randomization, and the nurse coordinator performed the patient registration and group assignment for the study.

Women were considered clomiphene resistant if ovulation did not occur when taking CC at a dose of 150 mg / day. PCOS was diagnosed based on the Rotterdam criteria, in which at least 2 of the following three criteria were met: 1) oligomenorrhea (a cycle lasting 35 days or more) and / or amenorrhea (no menstruation for 6 months or more); 2) hyperandrogenism (defined as the Ferriman-Gallvi index of more than 8) which is clinically manifested by acne / hirsutism and / or biochemical - the determination of testosterone in the blood serum of more than 0.7ng / mg; 3) sonographic manifestations of polycystic ovary: if the ovary contains 12 or more follicles with a diameter of 2 to 9 mm and / or the volume of the ovaries is more than 10 ml.

Inclusion criteria are, clomiphene citrate resistant women with PCOS aged 20 to 38 years, BMI, no previous ovulation induction, partners with normal sperm counts according to WHO standards, opening of the fallopian tubes (confirmed by hysterosalpingography in the previous 6 months), without operations on the genitals. The exclusion criterion is the presence of any factors of infertility, except for CC-resistant women with PCOS. The study also included measurement of blood pressure, abdominal circumference, hormonal study of the serum of patients such as basal FSH, LH / FSH ratio, free testosterone (T), insulin, progesterone, AMG on the 3rd day of the menstrual cycle. HDL High Density Lipoproteins, serum estradiol was determined on the day of ovulation trigger administration. Insulin resistance (HOMA-IR) was determined as follows: HOMA-IR = fasting insulin (IU / ml) x fasting glucose (mol / l) / 22.5. Ultrasound of the ovaries with a transvaginal sensor on the 2nd - 3rd day of the menstrual cycle to assess the number of antral follicles with a diameter of 2 to 9 mm (in an amount of 12 or more is considered polycystic) and an assessment of the volume of the ovary, which is determined by measuring three perpendicularly directed ovarian diameters and applying the formula: D1xD2xD3x0.5236 .

Patients who qualified for ovulation induction treatment fell into World Health Organization (WHO) classes 1 and 2 and usually had failed prior ovulation induction efforts with clomiphene citrate for at least three cycles. Patients received ovulation induction with gonadotropin only for a maximum of four cycles. This treatment algorithm was contractually determined with HMO-I but was uniformly applied to all patients within the CHR system. Patients who did not conceive with up to four gonadotropin cycles were advanced into in vitro fertilization.

**Results**

Table 1 shows the results of clinical and laboratory studies of both groups, which reflects the average age of a woman, type of infertility, BMI, abdominal circumference, ovarian volume, type of menstruation disorder, hormonal and biochemical studies (Table 1).

Table 1
Results of clinical and laboratory studies

| | Group I (CC + HMG) | Group II (HMG) | *P* |
|---|---|---|---|
| Number of women | 20 | 20 | |
| Age | 21-22 | 23-24 | 0.78 |
| Type of infertility: | | | 0.09 |
| primary | 12 | 15 | |
| secondary | 8 | 5 | |
| Duration of infertility (in years) | 3-4 | 3-4 | 0.86 |
| Menstrual irregularities: | | | 0.79 |
| - Amenorrhea | 1 | 3 | |
| - Oligomenorrhea | 19 | 17 | |
| Hyperandrogenism | 12 | 11 | 0.68 |
| BMI | 22,3±5,4 | 24,2±5,7 | 0.68 |

| | | | |
|---|---|---|---|
| Ovarian volume (cm3) | 11,7±6 | 12,2±5 | 0.46 |
| FSH | 5,4±1,75 | 5,4±1,72 | 0.93 |
| LH | 5,58±4,2 | 6,53±3,7 | 0.09 |
| LH / FSH | 1,02±0,57 | 1,02±0,72 | 0.05 |
| Free testerone | 1,6±2,6 | 2,2±3,2 | 0.15 |
| Fasting insulin | 11,5±12,2 | 14,4±12,6 | 0.10 |
| Fasting glucose | 99,9±15,6 | 100,6±21,4 | 0.73 |
| HOMA-IR | 2,8±2,6 | 3,4±3,4 | 0.19 |
| HDL | 40,7±16,7 | 38,8±14,6 | 0.32 |
| Triglycerides | 138±68,3 | 132,8±75,0 | 0.49 |

Analysis of the data obtained showed that older women predominate among clomiphene-resistant patients, there were no significant differences in LH levels, clomiphene-resistant patients had low E2 levels, and 7 out of 18 women had previously undergone laparoscopic ovarian cauterization. It was also noted that in the group of clomiphene-resistant patients there were women in whom pregnancy was previously achieved using CC, but it was not developing. This fact may serve as confirmation that clomiphene-resistance is most likely not an initial condition, but is formed in the process of long-term unsuccessful infertility treatment. At the next stage of work in groups 1 and 2, ovulation was induced by direct ovulation inducers. The results of the ovulation induction by CC+HMG and HMG did not differ significantly in many parameters, possibly due to the small number of patients in the groups. But the results were significantly different from the induction of ovulation by clomiphene citrate. The size of the leading follicle against the background of drug administration was 20.1 ± 0.3 mm, the thickness of the endometrium was 9.9 ± 0.4 mm.

Upon reaching a dominant follicle of 18 mm and an endometrial thickness of at least 8 mm, ovulation triggers were prescribed (hCG at a dosage of 5000 IU+Decapeptyl 0.2). Ovulation was diagnosed in 100% of cases after 2 ± 1 days. Moreover, in cycles with CC+HMG induction, ovulation occurred spontaneously in 3 cases, which made it possible not to inject trigger. In order to support the luteal phase of the cycle, the secretory transformation of the proliferative endometrium, the secretion of proteins, the preparation of the endometrium for the invasion of the trophoblast, the rest of the uterus by reducing prostaglandins and oxytocin, we used endogenous micronized progesterone Utrozhestan, the chemical structure of which is 100% identical to endogenous progesterone. Gestagen was administered vaginally at a dosage of 200 mg 2 times a day. In the middle of the luteal phase, ultrasound was performed: the size of the corpus luteum was 17.4 ± 0.6 mm.

As our study showed, group I CC + HMG) received a lower dose of HMG (532.5 ± 315) and the duration of stimulation days (12.34 ± 4.5) was less than in group II (18.42 ± 6.2 days of stimulation). The number of growth of the middle and dominant follicle, the thickness of the endometrium, the number of ovulations and the frequency of pregnancy are shown in Table 2.

Table 2
Induction cycle indicators with results

| | Group I (CC + HMG) (n = 20) | Group II (HMG) (n = 20) | *P* |
|---|---|---|---|
| Total hMG dose (IU) | 414,5±315 | 939,5±585 | *P*<0.001 |
| Length of days of stimulation | 11,34±4,5 | 17,42±6,2 | *P*<0.001 |
| Large follicle count (≥16mm) | 1,6±0,3 | 1,5±1,5 | 0.62 |
| Average follicle size (12-15mm) | 1,1±0,98 | 1,8±2,03 | 0.005 |
| The amount of hMG on the day of trigger administration | 4,79±1,88 | 5,5±1,65 | 0.02 |
| Estradiol on the day of trigger administration | 465,49±377,95 | 296,88±255,45 | 0.0013 |
| Endometrial thickness (mm) | 9,6±2,5 | 10,1±1,8 | 0.15 |
| Ovulation rate | 18 | 12 | *P*<0.001 |

The study showed that the dose of gonadotropin preparations for obtaining ovulation can be reduced by the simultaneous administration of CC + hMG. HMG can be recommended for women with a history of hyperstimulation syndrome (OHSS), as well as for patients with high blood LH levels and women at risk of developing OHSS. After the second stage of the study, a group of patients was identified in whom the induction of ovulation by direct and indirect inductors was ineffective for the restoration of reproductive function: absence of ovulation, insufficiently prepared endometrium for implantation of the ovum, lack of growth of the dominant follicle in the ovaries during induction of ovulation with normal ovarian reserve. In addition, endoscopic ovarian surgery, previously performed in 10 of the patients, and IVF methods in 2 patients, were ineffective. These patients were regarded as the most difficult for reproductive rehabilitation. Thus, the presented results indicate the need for further study of the effectiveness of conservative treatment of infertility in PCOS under the condition of comprehensive preliminary preparation before the induction of ovulation and the differentiated use of ovulation inducers, taking into account the clinical and anamnestic characteristics of patients, the results of laboratory examination and analysis of the ovarian response.

**Conclusion**

The combined administration of CC + hMG in clomiphene-resistant women with PCOS compared to the use of hMG alone, gives higher ovulation rates and lower financial costs of drugs. The use of this protocol enables monofollicular growth and a decrease in the risk of multiple pregnancies and, in turn, is the prevention of ovarian hyperstimulation.

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