

Optimization of Ovulation Induction in Clomifene Resistant Patient with Infertility

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ABSTRACT

Annotation: Up to 20-25% of women with PCOS are resistant to clomiphene citrate.

Aim: 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+ recombinant follicle-stimulating hormone p FSH 37.5 IU / day. Group II received only p FSH 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 hyper stimulation.

Results: The study showed that in group I compared with group II, the frequency of ovulation was significantly higher (60% versus 35%).

Conclusion: The combined administration of CC + rFSH in clomiphene-resistant women with PCOS compared to the use of rFSH alone, gives higher ovulation rates and lower financial costs.

Introduction

It has been proven that the induction of ovulation is the main method of treatment in infertile women with PCOS [1-3]. According to the WHO, from 10 to 15% of married couples suffer from infertility. In the conditions of Central Asia, where large families are common and this is traditionally encouraged, childlessness is considered a great misfortune and often leads to family disintegration [4,5]. Up to 20-25% of women with PCOS are resistant to clomiphene citrate [6,7].

Materials and Research Methods

Our randomized trials were carried out in the central polyclinic of Urgench from 2018 to 2020. It included 40 clomiphene-resistant

women with PCOS. In group I (n = 20) women, we used clomiphene citrate 100mg + recombinant follicle-stimulating hormone p FSH 37.5 IU / day. Group II (n = 20) received only p FSH 37.5 using a low dose escalating protocol. Informed written consent was obtained from all patients. 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) Oligo menorrhoea (a cycle lasting 35 or more days) and / or amenorrhoea (absence of menstruation for 6 or more months);
- 2) Hyperandrogenism (defined as a 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 presence operations on the genitals. The exclusion criterion is the presence of any factors of infertility, except for CV-resistant women with PCOS. The study also included the 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: $HOMA-IR = \text{fasting insulin (IU / ml)} \times \text{fasting glucose (mol / l)} / 22.5$. 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: $D1 \times D2 \times D3 \times 0.5236$.

Results of the Study

Table 1: Results of clinical and laboratory studies.

	Group I (CC + rFSH)	Group II (rFSH)
Number of women	20	20
Average age	21-22	23-24
Infertility type:		
Primary	12	15
secondary	8	5
Duration of infertility (in years)	3-4	3-4
Violation of menstruation:		
-Amenorrhea	1	3
-Oligomenorrhea	19	17
Hyperandrogenism	12	11
BMI	31,3±5,4	33,2±5,7
Ovarian volume (cm ³)	13,7±6	14,2±5
FSH	5,4±1,75	5,4±1,72
LH	5,58±4,2	6,53±3,7
LH / FSH	1,02±0,57	1,02±0,72
Free testosterone	1,6±2,6	2,2±3,2
Fasting insulin	11,5±12,2	14,4±12,6

(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). As our study showed, group I (CC + rFSH) received a lower dose of rFSH (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). The study showed that the dose of gonadotropin preparations for obtaining ovulation can be reduced by the simultaneous administration of CC + rFSH.

Table 2: Induction cycle indicators with results.

	Group I (CC + rFSH)	Group II (rFSH)
Total rFSH dose (IU)	532,5±315	1057,5±585
Length of days of stimulation	12,34±4,5	18,42±6,2
Large follicle count (≥16mm)	1,6±0,3	1,5±1,5
Average follicle size (12-15mm)	1,1±0,98	1,8±2,03
The amount of FSH on the day of hCG administration	4,79±1,88	5,5±1,65
Estradiol on the day of hCG administration	465,49±377,95	296,88±255,45
Endometrial thickness (mm)	10,6±2,5	11,1±1,8
Ovulation frequency	16	8
Number of pregnancies	8	7

Conclusion

The combined administration of CC + rFSH in clomiphene-resistant women with PCOS compared to the use of rFSH alone, gives higher ovulation rates and lower financial costs. 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 hyper stimulation.

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