

# Comparison of ovulation induction treatments in intrauterine insemination; A retrospective study in a tertiary center

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## Abstract

**Aim:** In this study, were compared of different ovarian stimulation drugs used in intrauterine insemination (IUI) cycles.

**Material and Methods:** The records of 3420 infertile patients who presented to the outpatient clinic were retrospectively analyzed. The patients were evaluated into three groups (n=421). 170 patients who received letrozole treatment were included in group 1, 50 patients who received Clomiphene citrate (CC) treatment were included in group 2, and 201 patients who received gonadotropins treatment were included in group 3.

**Results:** The mean numbers of follicles were in IUI cycles stimulated with the use of letrozole ( $1.5 \pm 0.6$ ), CC ( $1.6 \pm 0.6$ ), and gonadotropins ( $1.6 \pm 0.7$ ). After stimulation with letrozole, CC and gonadotropins, pregnancy rates were 13(7.6%), 6(12%) and 19(9.4%); Abortion rates were 2(1.1%), 1(2%) and 3(1.4%). Multiple pregnancy occurred in, 1/170 (0.58%), 1/50 (2%) and 2/201 (0.99%) in the letrozole, CC and gonadotropins groups.

**Conclusion:** After stimulation with treatment protocols; pregnancy rates, abortion rates, and multiple pregnancy rates were similar. The question that this study set out to answer was of effectiveness. Different ovarian stimulation protocols used in IUI programs, clinical opportunities, experience of the person, does affect the results of the study.

**Keywords:** Clomiphene citrate; gonadotropins; intrauterine insemination; letrozole; ovulation induction

## INTRODUCTION

It is a common method in infertile patients and accompanies natural cycles or ovarian stimulation cycles (1,2). CC binds to estrogen receptors and acts as a selective estrogen receptor modulator. As negative feedback from estrogen increases secretes gonadotropin hormones and induces follicular growth (3). Letrozole is another widely used oral ovulation drug with a different mechanism of action. It inhibits androgen-estrogen conversion, which leads to the secretion of follicle-stimulating hormone (FSH) through suppressed estrogen production (4). Gonadotropins have been used to induce ovulation in patients with CC-resistant polycystic ovary syndrome (PCOS). Multiple pregnancies may be more common in gonadotropin use (5).

In this study, were compared of different ovarian stimulation drugs used in IUI cycles.

## MATERIAL and METHODS

The records of 3,420 infertile patients who presented to the outpatient clinic were retrospectively analyses. The patients were divided into three groups (n=421). One hundred and seventy patients who received letrozole treatment were included in group 1, 50 patients who received CC treatment were included in group 2, and 201 patients who received gonadotropins treatment were included in group 3.

Female patients were between 18 and 39 years of age with PCOS and unexplained infertility (normogonadotropic normogonadism); had a healthy uterine cavity with at least one patent fallopian tube, and had a male patient with a semen specimen of at least 5 million sperm per milliliter (6) and no pathological findings (e.g. sub-mucous myomas, endometrial polyps,

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uterine septum, Asherman syndrome, endometriosis or hydrosalpinx. Exclusion criteria comprised; uncorrected thyroid disease; untreated hyperprolactinemia; allergy or contraindications to letrozole, CC and gonadotropins and hypogonadotrophic hypogonadism.

### Outcomes

Serum HCG levels were measured in the menstrual delay and fetal heartbeats were evaluated by transvaginal ultrasound and defined as clinical pregnancy.

### Drug Protocols

-CC (Serophene, Serono, Geneva, Switzerland) at 100 mg/d starting for 5 days (D3–D7) for one treatment cycle.

- Letrozole (Femara Novartis, Basel, Switzerland) at 5 mg/d starting for 5 days (D3–D7) for one treatment cycle.

-rFSH (Gonal-F 900 pen, Serono, Geneva, Switzerland) at 75 IU/d starting from day 3 for a different duration depending on the ovarian response.

Patients were evaluated with transvaginal ultrasonography on the seventh day of menstruation and after the diameter of the largest follicle reached 14 mm. If a dominant follicle was present, they received a human chorionic gonadotropin (HCG) trigger (Ovitrelle, single-dose, subcutaneous) when the follicle size reached 18–22 mm, followed by IUI 36–38 h later. (The insemination is applied on the average day of treatment).

The study protocol was approved by the regional ethics committee (336/2019).

### Statistical analysis

The mean  $\pm$  standard deviation (SD) was calculated for quantitative variables. Qualitative variables are presented as frequencies. The normality of the data was checked using the Kolmogorov–Smirnov test. The Student's t-test and Mann–Whitney U test were performed to compare continuous variables with and without a normal distribution in the groups. The proportional data were compared using a chi-squared test and Fisher's exact test. A p-value of  $< 0.05$  was considered significant. All statistical analyses were performed using R-software v.3.5.1 (R Statistics Software; Institute for Statistics and Mathematics, Vienna, Austria).

The Student's t-test were performed variables with a normal distribution (Age, BMI). Mann–Whitney U test were performed variables without a normal distribution (Pregnancy, Abortion, Twin fetuses).

## RESULTS

The mean numbers of follicles were in IUI cycles stimulated with the use of letrozole ( $1.5 \pm 0.6$ ), CC ( $1.6 \pm 0.6$ ), and gonadotropins ( $1.6 \pm 0.7$ ). After stimulation with letrozole, CC and gonadotropins, pregnancy rates were 13(7.6%), 6(12%) and 19(9.4%); Abortion rates were 2(1.1%), 1(2%) and 3(1.4%). Multiple pregnancy occurred in, 1/170 (0.58%), 1/50 (2%) and 2/201 (0.99%) in the letrozole, CC

and gonadotropins groups.

Groups 1 and 2 in Table 1, Groups 1 and 3 in Table 2, Groups 2 and 3 in Table 3 were compared.

**Table 1. Comparison of outcomes according to treatment groups**

	Group 1 Letrozole (n = 170)	Group 2 CC (n = 50)	P value
Age (y) (mean $\pm$ SD)	30.73 $\pm$ 6.95	30.73 $\pm$ 6.95	0.405
BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD)	21.2 $\pm$ 1.5	21.06 $\pm$ 1.3	0.410
Pregnancy, n (%)	13(7.6)	6 (12)	0.338
Abortion, n (%)	2(1.1)	1(2)	0.661
Twin fetuses, n (%)	1(0.58)	1 (2)	0.357

Data are mean  $\pm$  standard deviation or n (percentage). BMI: body mass index; CC: clomiphene citrate Age, BMI (The Student's t-test were performed variables with a normal distribution) Pregnancy, Abortion, Twin fetuses (Mann–Whitney U test were performed variables without a normal distribution)

**Table 2. Comparison of outcomes according to treatment groups**

	Group 1 Letrozole (n = 170)	Group 3 Gn (n = 201)	P value
Age (y) (mean $\pm$ SD)	30.8 $\pm$ 6.4	30.4 $\pm$ 6.3	0.609
BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD)	21.2 $\pm$ 1.5	21.2 $\pm$ 1.5	0.06
Pregnancy, n (%)	13(7.6)	19 (9.4)	0.538
Abortion, n (%)	2(1.1)	3(1.4)	0.793
Twin fetuses, n (%)	1(0.58)	2(0.99)	0.664

Data are mean  $\pm$  standard deviation or n (percentage). BMI: body mass index; Gn: Gonadotropins Age, BMI (The Student's t-test were performed variables with a normal distribution) Pregnancy, Abortion, Twin fetuses (Mann–Whitney U test were performed variables without a normal distribution)

**Table 3. Comparison of outcomes according to treatment groups**

	Group 2 CC (n = 50)	Group 3 Gn (n = 201)	P value
Age (y) (mean $\pm$ SD)	29.2 $\pm$ 6.4	30.4 $\pm$ 6.3	0.234
BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD)	21.06 $\pm$ 1.3	21.2 $\pm$ 1.5	0.566
Pregnancy, n (%)	6 (12)	19 (9.4)	0.338
Abortion, n (%)	1(2)	3(1.4)	0.661
Twin foetuses, n (%)	1 (2)	2 (0.99)	0.357

Data are mean  $\pm$  standard deviation or n (percentage). BMI: body mass index; CC: clomiphene citrate Gn: Gonadotropins Age, BMI (The Student's t-test were performed variables with a normal distribution) Pregnancy, Abortion, Twin fetuses

## DISCUSSION

We evaluated women undergoing IUI with ovarian stimulation. In this study, after stimulation with letrozole, CC, and gonadotropins; pregnancy rates, abortion rates, and multiple pregnancy rates were similar.

Diamond et al. associated with higher live birth and pregnancy rates when compared to gonadotropins, clomifen and letrozole (7). Many studies in the literature have suggested a similar or improved pregnancy rate with letrozole, as compared with CC or gonadotropin (8-10). For these different outcomes, the randomized design of the trial may be the timing of gonadotropin and the standard fertilization timing in all treatment groups (7). Huang et al. found that stimulation in an insemination, multiple pregnancy rates after letrozole were lower than gonadotropins or CC, but live birth rates were high. CC resulted more often in multifollicle in 49% of the patients, versus 18% and 24% for letrozole and gonadotropins, and when stratified for the number of follicles, letrozole had higher pregnancy and live birth rates than others (11).

214 patients undergoing three insemination cycles showed an improved ongoing pregnancy rate with the receiving of letrozole (33%) compared with CC (19%; OR 2.09, 95% CI 1.11–3.95) (12). Khanna, S.C. et al. did not find a difference between letrozole and clomifen in terms of pregnancy rates (13). Another two studies, the efficacy of letrozole and gonadotropins in the IUI cycle was shown to be similar (RR 1.2, 95% CI 0.4–3.2; and RR 0.7, 95% CI 0.3–2.0) (14,15). In this study, after stimulation with letrozole, CC and gonadotropins, pregnancy rates were 13(7.6%), 6(12%) and 19(9.4%); Abortion rates were 2(1.1%), 1(2%) and 3(1.4%). Multiple pregnancy occurred in, 1/170 (0.58%), 1/50 (2%) and 2/201 (0.99%) in the letrozole, CC and gonadotropins groups. Pregnancy rates, abortion rates, and multiple pregnancy rates were similar. Despite many studies on this subject, we have encountered different results. There is not yet a common decision as to which drug will be best applied in the IUI cycles (7,16). The present study has several limitations. First, although we increased the dose of gonadotropins, we kept the dose and duration of CC and letrozole constant. Second, we did not study neonatal outcomes because pregnancies were not followed up to delivery. Because patients can go to other hospitals after conception which affects our live pregnancy results.

## CONCLUSION

After stimulation with treatment protocols; pregnancy rates, abortion rates, and multiple pregnancy rates were similar. The question that this study set out to answer was of effectiveness. Different ovarian stimulation protocols used in IUI programs, clinical opportunities, experience of the person, does affect the results of the study.

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