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Original Article

# Clomiphene citrate plus cabergoline versus clomiphene citrate for induction of ovulation in infertile euprolactinemic patients with polycystic ovary syndrome: A randomized clinical trial

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ABSTRACT

*Objective:* To compare the effect of adjunctive use of cabergoline with clomiphene citrate (CC) in infertile polycystic ovarian syndrome (PCOS) patients with normal prolactin level.
*Study design:* A randomized clinical trial (NCT 02644304).
*Setting:* Assiut University Hospital, Assiut, Egypt.
*Materials and methods:* Infertile euprolactinemic PCOS patient were recruited and randomized in a 1:1 ratio to CC plus cabergoline or CC alone. All patients were evaluated by ultrasound examination for number, size of ovarian follicles and they were followed up for 3 consecutive cycles. The primary outcome of the study was the cumulative rate of ovulation in both groups allover the 3 cycles of treatment. The secondary outcomes included clinical pregnancy rate, miscarriage rate, multiple pregnancy rate, ovarian hyperstimulation rate and the rate of adverse effects of the study medications.
*Results:* One-hundred thirty patients were included (65 in each group). No statistical difference between both groups regarding the basal criteria. The cumulative ovulation rate in the CC plus cabergoline group was 76.7% versus 58.3% in the CC group ($p = .032$). Additionally, the largest follicle size in each cycle was significantly more in the CC plus cabergoline group ($p < .05$). Patients in the CC plus cabergoline group had a higher clinical pregnancy rate reaching 31.7% versus only 13.3% in patients of the CC group ($p = .004$). No difference between both groups as regard the miscarriage rate ($p = .74$), multiple pregnancy rate ($p = .83$), ovarian hyperstimulation rate ($p = .62$) and the rate of adverse effects of the study medications.
*Conclusions:* The use of cabergoline with CC in induction of ovulation in euprolactinemic infertile women with PCOS results in high ovulation rate, high pregnancy rate as compared to use of CC alone.


## 1. Introduction

Polycystic ovarian syndrome (PCOS) is considered the commonest cause of anovulatory Infertility worldwide [1]. Women with PCOS have an increased incidence of World Health Organization (WHO) group II anovulatory infertility [2]. Therefore, ovulation induction is performed to achieve repeated mono-follicular ovulation [3]. According to the Rotterdam criteria, PCOS is diagnosed by at least two out of three features: presence of oligo- or anovulation, evidence of clinical or biochemical hyperandrogenism and ultrasound appearance of polycystic ovaries [4].

Clomiphene citrate (CC) is the first and most widely used line of treatment options for women with PCOS. It is inexpensive, easy to use, carries low risk of complications and induces ovulation in more than 75% of women [5]. CC induces less response in hyperandrogenic, overweight and hyperinsulinemic women [2]. Adjunctive treatment was tried in those patients as use of metformin, glucocorticoids, dopamine agonists and aromatase inhibitors [6,7].

Hyperprolactinemia is evident in nearly 30–40% of PCOS women [8]. Dopamine agonists can induce ovulation in PCOS patients through reduction of the serum prolactin level. Moreover, they may induce ovulation in anovulatory patients with normal prolactin level [9]. This effect could be related to reduction of an occult hyperprolactinemia in PCOS patients [10].

Cabergoline is a dopamine receptor agonist, with higher affinity to dopamine D2 receptors and has the serum half-life of 43-h. A recent study reported an improvement in the uterine perfusion

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and a better ovulatory response in PCOS patients with its use [11]. The mechanism behind its effects is the ability to inhibit the vascular endothelial growth factor (VEGF) secretion in luteinized granulosa cells [12]. Additionally, it has an inhibitory effect on LH and androgen secretion [13].

No study has been previously conducted to evaluate the effect of CC plus cabergoline for induction of ovulation in infertile euprolactinemic PCOS patients. Therefore, this study was carried out to evaluate the effect of adjunctive use of cabergoline with CC in infertile PCOS patients with normal prolactin level.

## 2. Materials and methods

### 2.1. Study type, setting and duration

The current study was a single center randomized open label controlled trial (Clinical Trials. Gov: NCT 02644304) conducted in a University Hospital between the 1st of March 2015 and the 31st of December 2016. The Institutional Ethical Review Board approved the study, and we obtained a written informed consent from all participants before enrollment.

### 2.2. Study population

All women attended the Infertility Clinic of our hospital during the study period were invited to participate in the study. We included PCOS women <39 years, suffering from primary or secondary infertility, normal day 3 prolactin level < 20 ng/dl, no galactorrhea and body mass index (BMI) 18–30 kg/m$^2$. They were diagnosed as PCOS according to Rotterdam criteria [4] by the finding of at least two of the following criteria: ultrasound appearance of polycystic ovaries (12 or more follicles ranging 2–9 mm), hyperandrogenism (clinical and/or biochemical) and anovulation or oligoovulation (less than nine ovulatory cycles per year).

Women were excluded if they have diabetes mellitus, renal or liver disease, abnormal thyroid function tests, documented tubal factor or pelvic adhesions, elevated 17 alfa hydroxyprogesterone level and FSH more than 10 IU/L. We also excluded the women who started medications for weight reduction and those who their partner has abnormal semen parameters according to the world health organization parameters (WHO, 2010) [14]. Hysterosalpingography or office hysteroscopy was performed to confirm normal uterine cavity, and we excluded the patients with uterine abnormalities. Finally, Women were excluded if they were on other lines of infertility treatment or known to be hypersensitive to CC or cabergoline.

### 2.3. Sample size

Previous study by Tripathy et al. (2013) reported that the rate of ovulation in PCOS patients with CC was 69.4% [15]. We assumed that adding cabergoline to CC will increase the ovulation rate by 20%. The sample size was calculated using the OpenEpi, Version 3, open source calculator-SSMean program with 80% power and $\alpha$ error of 0.05. The estimated sample size in each group was 65 women (Odds ratio = 3.7).

### 2.4. Randomization

The randomization was done by computer-generated random table. Eligible women who gave their informed consent were randomized to either group I: (CC + cabergoline) or group II: (CC group). Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type. Allocation was never changed after opening the closed envelopes.

### 2.5. Study intervention

On cycle day 3, the study participants were approached by one of our researchers and the following data were collected: age, parity, BMI, duration of infertility and the results of basal investigations FSH, LH and prolactin.

Eligible participants were randomly allocated to one of two groups:

**Group I (CC + cabergoline):** patients received CC (Clomid®, Aventis, Egypt) 100 mg/day on two divided doses each 50 mg starting from cycle day 3 for 5 days plus cabergoline (Marvigoline®, Rameda Ph., Egypt) 1 mg on four divided doses each 0.25 mg every 3 days from cycle day 3 for 9 days and **Group II (CC):** patients received only CC (in the same dose and duration).

All patients were asked to return at Day 13 for follow up visit. When the leading follicle size 18 mm in diameter, 5000 IU of highly purified HCG (Choriomon®, IBSA, Lugano, Switzerland) was prescribed for intramuscular injection.

### 2.6. Follow up

In cycle day 13, all patients were evaluated by ultrasound examination through the same sonographer (Level II experience), who was blinded by their intervention group, using a SonoAce X8 machine (Medison, Korea) with transvaginal probe (4–8 MHz frequency). Transvaginal sonography (TVS) was done for evaluation of number, size of ovarian follicles at each side. All patients were followed up for 3 consecutive cycles.

### 2.7. Study outcomes

The primary outcome of the study was the cumulative rate of ovulation in both groups allover the 3 cycles of treatment. Ovulation was diagnosed when at least one leading follicle reaching 18 mm in diameter was observed by TVS at the follow up visit. The secondary outcomes included clinical pregnancy rate (defined as the number of the cases with at visualized gestational sac by ultrasound), miscarriage rate (the number of the cases with pregnancy loss within 12 weeks of gestation), the multiple pregnancy rate, ovarian hyperstimulation (OHSS) rate and the rate of adverse effects of the study medications.

### 2.8. Statistical analysis

All data were analyzed using SPSS software Chicago, IL, USA, version 21. Testing the normality of data distribution was done by the Shapiro-Wilk test. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. Quantitative data were presented in terms of, mean, standard deviation as they were normally distributed. For quantitative data, comparison between two groups was done using Independent T-test test. Level of significance "P" value was evaluated, where P value < .05 is considered of significant value.

## 3. Results

One-hundred forty-four patients were approached to participate in this study. Eleven women were excluded as they did not meet the inclusion criteria. Moreover, three women refused to participate in the study. The remaining 130 patients were randomly assigned to the two groups. Five patients in the each group did not complete the scheduled course of treatment or did not attend the follow up visits so they were excluded from the final analysis (Fig. 1, the study flowchart).

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