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Original Article

Clomiphene citrate Versus Cabergoline in Ovulation Induction by letrozole: A randomized clinical trial Study on of Infertile Polycystic Ovary Syndrome Women

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ABSTRACT

Background: Polycystic ovarian syndrome (PCO) is among the most common reasons for infertility in women of reproductive age.
Objective: to examine two pharmaceutical regimens for infertile women with polycystic ovarian syndrome.
Method: In this randomized clinical trial, 60 infertile women with PCO were randomly assigned into two arms, each having 30 subjects. The first arm received Clomiphene citrate (CC) followed by letrozole. The second arm received letrozole followed by cabergoline. Following the procedures, outcomes of biochemical pregnancy and incidence of the complications were recorded along with other baseline characteristics and laboratory data.
Results: Concerning age, weight, height, and BMI, both arms were matched. In terms of follicle quantity and size, as well as endometrial thickness, with no statistical differences among the study arms, although the cabergoline-letrozole regimen demonstrated a considerably higher success rate in the treatment of infertility. The endometrial examination revealed three-layered and transparent endometrium in both arms, although it was statistically more common in the letrozole-cabergoline arm (P = 0.001). The successful pregnancy was achieved in 9 cases (30%) in the first arm and 7 (23.3%) in the second arm (P=0.54), with no significant difference in adverse maternal events.
Conclusion: The letrozole-cabergoline regimen appears to be more successful in inducing ovulation in infertile women with PCOs. Other trials should be conducted over longer periods of time and at varied dosages to provide a more exact evaluation of its effect.

GRAPHICAL ABSTRACT

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Introduction

Fertility refers to a couple's ability to reproduce, and infertility is the ineptitude to conceive after one year of cohabitation and intercourse without the use of contraception, and it is a complete and inherent inability to reproduce. Female individuals of couples who have never become pregnant are diagnosed with primary infertility, whereas those who have a history of fertility are diagnosed with secondary infertility [1]. PCO syndrome is so prevalent in reproductive-age females. This syndrome affects about 4% of women of childbearing age and about 5 to 10% of the general population [2,3]. Ovulation induction is a fertility therapy that involves the prescription of medicines to trigger or control ovulation, or to increase the number of eggs produced throughout a cycle, to enhance the chances of pregnancy [4]. Ovulation induction can be achieved medically or surgically in women with PCOS. There is no definitive protocol for inducing ovulation in these patients, but the logical approach is to use the least invasive method first line [4]. In the past, CC, a weak synthetic estrogen, was used as the first line of treatment for infertility in cases of anovulation, as well as the primary treatment for unexplained infertility [5]. Although clomiphene leads to ovulation in 80% of patients, about 50% of them become pregnant [6]. In these patients, due to the hypersensitivity of the ovaries to gonadotropins, there is a risk of multiple pregnancies (7 to 10% of clomiphene use can be associated with twins) and ovarian hyperstimulation syndrome (OHSS) [7,8]. Letrozole, an aromatase inhibitor, is now used as a choice to induce ovulation. Compared with clomiphene, side effects of letrozole are rare and occur with continued use [9]. The benefits of letrozole over clomiphene have been examined by characteristics such as the overall number of follicles, endometrium thickness, conception rate, the incidence of ovarian hyperstimulation syndrome, and the risk of miscarriage in numerous studies comparing the two medications [10-11]. PCO patients have been shown to have higher resistance to uterine blood flow and lower ovarian resistance than healthy individuals. cabergoline is a dopamine receptor agonist [12-13]. Recent studies have reported improvements in uterine perfusion and better ovulation with cabergoline in PCOS patients [14-15]. In a 2008 study [15], In high-risk individuals, cabergoline was shown to be a beneficial drug for preventing serious OHSS. In high-risk patients, cabergoline proved more efficacious versus albumin in avoiding OHSS [16]. Given that Iranian women with anti-müllerian hormone (AMH) level more than 6.95 ng/ml are at a higher risk of suffering OHSS [17,18] and induction of ovulation after administration of exogenous gonadotropins in women with PCO, significantly increases the risk of OHSS. In this study, we decided to compare regimens of CC + letrozole with letrozole + cabergoline evaluating outcomes of infertility treatment and reducing the complication of OHSS.

Materials and Methods

Trial design and participant

The current randomized controlled in which study samples were infertile women with PCO who were referred to the Jahrom University of Medical Sciences' affiliated women's clinic in 2020 (for 6 months). The current investigation was done under the Helsinki declaration after acquiring ethical approval from the affiliated medical university ethics board (ethics code: IR.JUMS.REC.1399.051) and clinical trial protocol approval code (IRCT20200122046221N2).

Criteria for inclusion in the present study include Infertile women with PCO who have not had a history of pregnancy after 12 months without contraception; women with no ovulation; infertility at the age of 15-45 years; diagnosis of infertility with no Ovulation, which was diagnosed according to standard criteria of normal hysterosalpingography results with open fallopian tubes; and signing the informed written consent. In contrast, the exclusion criteria of the present study include uterine and adnexal pathology such as leiomyoma, endometriosis, etc., hyperprolactinemia, hyperthyroidism or hypothyroidism, previous genital surgery, appendicitis, peritonitis, genital tuberculosis, abnormal pelvic anatomy, liver or kidney dysfunction, diabetes mellitus or accidental high blood sugar above 140 mg/dl, taking drugs that

interfere with ovulation, or allergy to prescription drugs, and FSH above 9 in the initial stages of the follicular phase.

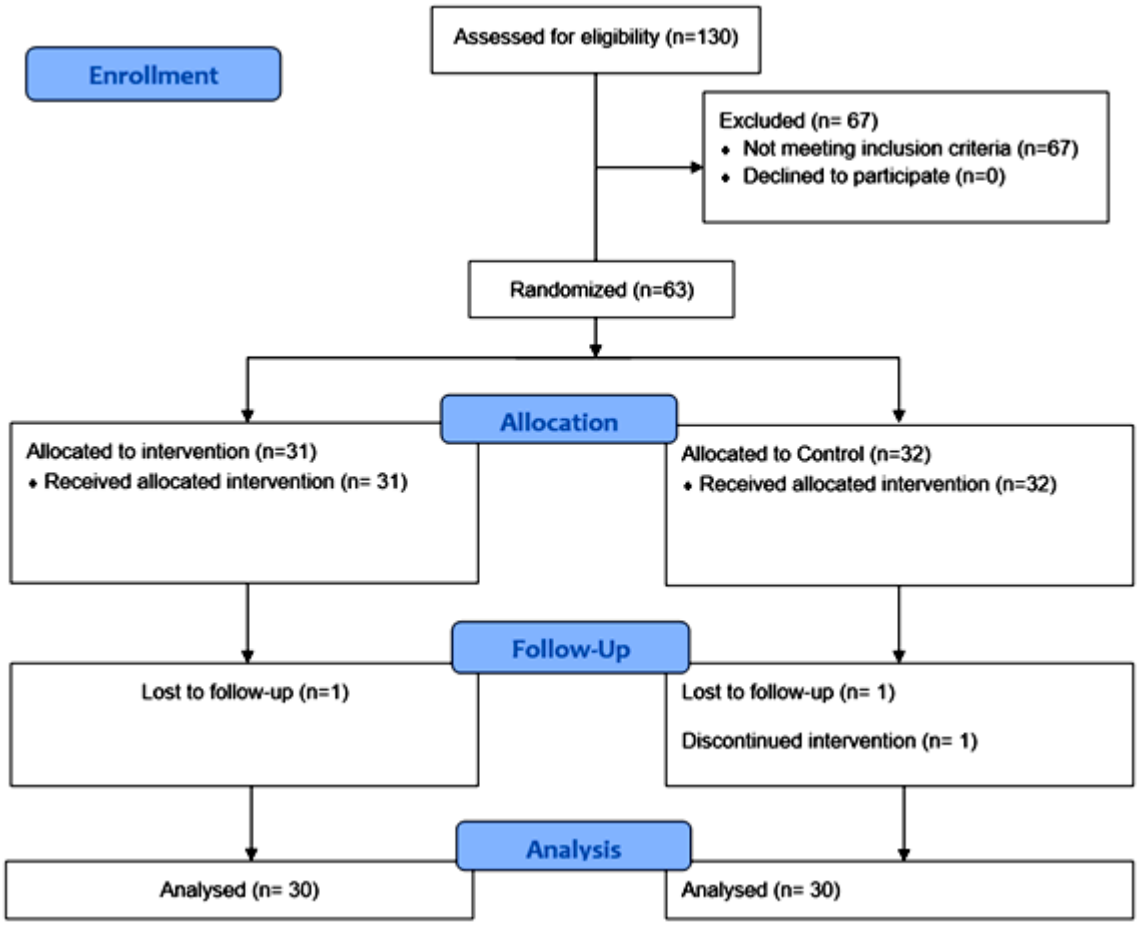

Figure 1: The consort flow diagram of the study is presented below

Intervention

In the present study, 60 infertile women with PCOS were allocated into two arms of 30 patients using a simple randomization method using a random number table (using Random Allocation Software). Concealment was done centrally by one of the statistical consultants so that the researcher did not interfere in assigning the samples to the arms. Calculating the sample size of the two arms A and B to receive the regimen based on Rasekh et al. study [19] and the means and deviation of the criteria achieved in this study using the difference between the means. Based on this, 30 subjects in each arm were calculated to fit study. Arm A received two clomiphene 50 mg (100 mg) tablets from the 3rd to the 7th day of menstruation, one tablet per day, and then two 2.5 mg letrozole tablets (5 mg in total) from the eighth to the eleventh day of menstruation [19]. Arm B received two Letrozole 2.5 mg tablets daily (5 mg in total) from the third to the eleventh day, and then one 1 mg cabergoline tablet daily from the eighth day until the eleventh day [20-21].

Data collection

A questionnaire containing questions about the demographic characteristics of patients including age, height, weight, blood pressure, etc. was completed. The condition of the patients' ovaries and uterus was also examined. After the intervention, information about the number of follicles, the size of the grown follicles, and the thickness of the endometrium were collected.

On days 8 and 12 of the menstrual cycle, transvaginal ultrasound was performed to check the number of follicles, the size of the follicles that have grown, and the thickness of the endometrium. If the size of the follicle was more than 18 mm, the 5000 to 10,000 units HCG ampule was injected depending on the number and size of the follicle [19, 22]. Ovulation release was assessed based on ultrasound to follow the response to treatment. HCG injections were

injected into each patient from the two arm s, who responded to the treatment and the follicle size was larger than 18 mm and the endometrial diameter was more than 8 mm. Other criteria of the HCG injection were that endometrium should have three layers and a transparent pattern, to release the follicle. Pregnancy diagnosis of patients was based on ultrasound results and ß-HCG titer tests.

Statistical analysis

Following data gathering, descriptive statistics (mean, standard deviation, count, and percentage) and inferential statistical tests (Chi-square, Mann-Whitney, and Friedman tests) were used to analyze the data utilizing SPSS software version 21. P<0.05 was used as the level of significance.

Results and Dissection

Sixty subjects participated in the study in two arm s receiving CC-letrozole (n=30) and letrozole-cabergoline (n=30). The results showed that the CC-letrozole and letrozole-cabergoline arm s were similar in terms of age, weight, height, and body mass index. The mean age in the CC-letrozole arm was 30.07±6.48 and in the letrozole-cabergoline arm was 31.7±5.56 years (P=0.299). The CC-letrozole arm had a mean weight of 63.87±11.73 kg and the CC-letrozole arm had a mean weight of 67.87±11.04 (P=0.179).

There was a substantial difference between the CC-letrozole and letrozole-cabergoline arm s, in follicle size in the first period of treatment on the 12th menstrual day (p-value= 0.047) but in the other periods, there was a significant difference that did not exist (P<0.05), as shown in Table 1. The results of the Friedman test showed that in both arm s, the follicle size before treatment to the follicle size at 8 and 12 menstrual periods was significantly increased in all periods (p<0.001). Paired tests revealed a significant difference in the follicle size in the first, second and third treatment periods and the follicle size before treatment; it increased significantly in both arm s (P<0.001) (Table 1).

Table 1: Comparison of the frequency of follicle size at different times in CC-letrozole and letrozole-cabergoline arm s

			CC-letrozole		Letrozole-Cabergoline		p
			N	%	N	%	
3rd day of menstruation		2-5 mm	6	20.0	4	13.3	0.492
		6-10 mm	24	80.0	26	86.7	
8th day of menstruation	**First treatment cycle***	Too small**	19	63.3	13	43.3	0.166
		proper ***	10	33.3	17	56.7	
		Too large****	1	3.3	0	0.0	
	Second treatment cycle*	Too small	18	62.2	14	48.3	0.121
		proper	8	27.5	15	51.7	
		Too large	3	10.3	0	0.0	
	Third treatment cycle*	Too small	16	55.2	11	37.9	0.096
		proper	11	37.9	18	62.1	
		Too large	2	6.9	0	0.0	
12th day of menstruation	**First treatment cycle***	Too small	6	20.0	1	3.3	0.047
		proper	14	46.7	13	43.3	
		Too large	10	33.3	16	53.3	
	Second treatment cycle*	Too small	7	24.1	3	10.3	0.169
		proper	22	75.9	26	89.7	
	Third treatment cycle*	Too large	5	17.2	4	13.8	0.589
		Too small	24	82.8	25	86.2	

* Significant difference with baseline (3rd-day results) in all cells, P<0.0001. ** 11-15 mm. ***16-20 mm. ****21-25 mm.

The results in Table 2 showed that there was no significant difference between the CC-letrozole and letrozole-cabergoline arm s in the number of follicles at different times of menstruation (P-value <0.05). The results of the Friedman test showed that in the CC-letrozole and letrozole-cabergoline arm s, the number of follicles before treatment to the number of follicles at 8 and 12 menstrual periods was significant (P-value <0.001) (Table 2).

Table 2: Frequency of number of follicles at different times in CC-letrozole and letrozole-cabergoline arm s

			CC-letrozole		Letrozole-Cabergoline		P
			N	%	N	%	
3rd day of menstruation		**0-5**	2	6.7	6	20.0	0.710
		6-10	5	16.7	7	23.3	
		11-15	17	56.7	15	50.0	
		16-20	6	20.0	5	16.6	
8th day of menstruation	**First treatment cycle***	**0-3**	14	6.7	12	23.3	0.300
		4-6	16	16.7	18	33.3	
	Second treatment cycle*	**0-3**	11	48.2	9	31.03	0.302
		4-6	18	62.06	20	68.96	
	Third treatment cycle*	**0-3**	13	44.8	10	34.4	0.308
		4-6	16	55.17	19	65.5	
12th day of menstruation	**First treatment cycle***	**1**	8	26.6	3	10.0	0.386
		2	7	23.3	9	30.0	
		3	10	33.3	12	40.0	
		4	5	16.6	6	20.0	
	Second treatment cycle*	**1**	6	20.6	3	10.3	0.380
		2	12	41.3	10	34.4	
		3	8	27.5	12	41.3	
		4	3	10.3	4	13.7	
	Third treatment cycle*	1	3	10.3	4	13.7	0.300
		2	10	34.4	11	37.9	
		3	13	44.8	11	37.9	
		4	3	10.3	3	10.3	

* Significant difference with baseline (3rd-day results) in all cells, P<0.0001.

The pregnancy rate in the CC-letrozole arm was 30% and in the letrozole-cabergoline arm was 23.3%, but the pregnancy rate between the CC-letrozole and letrozole-cabergoline arm s was not statistically significant (P-value=0.542). Ovarian hyperstimulation syndrome after three cycles of treatment in all women participating in the study in letrozole-cabergoline arm s was negative, but in the CC-letrozole arm during three cycles of treatment one case was reported, where the difference remained insignificant (Table 3).

Table 3: Comparison of the final end-points

		CC-letrozole		CC-letrozole		P
		N	%	N	%	
Ovarian hyperstimulation syndrome	yes	1	3.3%	0	0	0.990
	No	29	96.7%	30	100%	
Pregnancy after the first treatment cycle	yes	1	3.3%	1	3.3%	0.990
	No	29	96.7%	29	96.7%	
Pregnancy after the second treatment cycle	yes	0	0	0	0	-
	No	29	100%	29	100%	
Pregnancy after the third treatment cycle	yes	8	27.6%	6	20.7%	0.542
	No	21	72.4%	23	79.3%	

In women with PCOS, ovulation induction can be achieved medically or surgically. There is no fixed protocol for induction of ovulation in these patients, but the logical approach is to use the least invasive method first [23]. OHSS is the most serious complication of infertility treatment. Every ovulation-induced patient is at risk for OHSS, although some are more at risk than others [24]. Before treatment on the third day of menstruation, the majority of women (86%) had follicle sizes in the 10-6 mm range, which we found in both arms following treatment. On the eighth day of menstruation, the majority of people with follicle sizes in the range of 15-15 mm received all three periods of treatment in the CC-letrozole arm, and on the twelfth day of menstruation, the majority of people with follicle sizes in the range of 16-20 mm received the first period of treatment in the CC-letrozole arm. The second and third treatments were 21-25 mm in length. The results demonstrate that letrozole-cabergoline therapy reacts better to follicle growth to achieve the required ovulation size, with more patients in this arm having follicles bigger than 16 mm in size during all three treatment periods. These findings are consistent with those of El-Gharib *et al*. (2015), who evaluated the effects of letrozole plus tamoxifen vs CC in 60 infertile women. They claimed that the oocytes in the letrozole arm were in excellent condition [25]. In research of Sameh Al-Shoraky *et al*. (2020), they discovered that patients treated with letrozole 23 (46 percent) had more dominating follicles with a mono-follicular shape than patients treated with CC 14. (28 percent). It has been noticed [26]. The letrozole-cabergoline regimen had a better effect on the number of dominant follicles in the menstrual cycle, which is consistent with Badawy et alfindings. .'s (2008). It has been claimed that (2.5 mg per day for 10 days) is more effective than the conventional regimen (5 mg per day for 5 days) [15]. Letrozole was shown to be more successful than clomiphene in triggering ovulation and boosting the number of follicles that recovered upon ovulation, according to Mitwally *et al*. (2001). [27]. There was a significant difference in endometrial thickness in the first, second, and third treatment periods and endometrial thickness before treatment in the CC-letrozole and letrozole-cabergoline arms in our research (P>0.001). Our findings suggest a superior response to letrozole-cabergoline therapy in terms of increasing endometrial thickness during all three treatment periods, with more persons in this arm achieving endometrial thickness more than 7 mm in each of the three treatment periods. These results are consistent with the result of Al-obaidi *et al*. (2019) that showed a significant effect of letrozole on endometrial thickness relative to CC [28]. The use of letrozole to induce ovulation in patients with polycystic ovary syndrome has a better effect on endometrial thickness than CC. The results of Harira (2018), which compared letrozole and clomiphene on 172 women with unexplained infertility, stated that letrozole was significantly more effective than clomiphene on endometrial thickness [29].

From before therapy at 3 menstruation to after treatment at 8 and 12 menstruation, the status of the endometrium changed in three layers in our study. Our findings show that at days 8 and 12, the majority of women in the letrozole-cabergoline arm had three-layered and transparent endometrial conditions and that there was a statistical difference (p-value 0.05) between the letrozole-cabergoline arm and the CC-letrozole arm in the frequency of endometrial condition Three-layer and clear in the letrozole-cabergoline arm. Li wang *et al*. (2019) found that endometrial volume, vascular index (VI), endometrial flow index (FI), and vascular flow index (VFI) on the day of HCG injection and 7-9 days following ovulation were all increased. In individuals with polycystic ovarian syndrome, transfer to the letrozole arm was considerably higher, and letrozole boosted endometrial absorption when compared to clomiphene [30]. The endometrial response to letrozole was substantially better than that to CC, according to the findings of research by Baruah *et al*. (2009). [31]. In our study, the pregnancy rate in the CC-letrozole and letrozole-cabergoline arms are similar and desirable in both methods, but there is no significant difference (p-value=0.54), which is consistent with Liang Guo jun *et al*. (2016) who

found that cabergoline is an effective way to prevent OHSS but has no effect on pregnancy rate [32]. According to Esinler *et al*. (2013), administering half of our administered dose of cabergoline daily for 8 days was a highly successful strategy for reducing moderate to severe OHSS without decreasing the pregnancy rate [33]. After three cycles of therapy, all women in the letrozole-cabergoline arm tested negative for OHSS; however, one case was identified in the CC-letrozole arm over the three treatment cycles. This finding is following Hortu *et al*. [2020], who found that cabergoline can effectively lower the occurrence of OHSS in ovulation-inducing therapy [34]. Corbett and his colleagues [2014] Doctors at an infertility clinic reported a substantial decrease in the occurrence of hyperstimulation syndrome after using a dosage of 0.5 mg cabergoline every 3 days for a total of 4 doses from the start date of the Machu egg release medication. Since the introduction of cabergoline as a prophylactic strategy, severe ovaries have been reported [35]. In a paper, Tang *et al*. (2016) stated that dopamine agonists reduce the incidence of moderate to severe OHSS in women at high risk for this complication compared with placebo or no treatment [36].

Conclusion

Finally, our findings revealed that the use of the letrozole-cabergoline regimen is a more effective method with fewer side effects to induce ovulation in infertile women with PCOS. Also, the use of this treatment compared to other treatments has fewer side effects. Enjoys. Due to the limited sample size and study time, it is suggested that in future studies, the effect of letrozole-cabergoline regimen on pregnancy rate, reduction of ovarian hyperstimulation syndrome, miscarriage, and the presence or absence of side effects on the fetus. Since this treatment regimen is easily accessible and has fewer side effects, it is recommended that other studies be performed over longer periods and at different doses to find a more accurate measure of its effect.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

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Conflict of Interest

We have no conflicts of interest to disclose.

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