

## RESEARCH ARTICLE

# The Outcome of using Clomiphene Citrate in Late Luteal Phase for stimulation of Ovulation in with Polycystic Ovary Syndrome Women

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### ABSTRACT

**Background:** Clomiphene citrate (CC) is one of the first and commonest drug management for treating ovulatory dysfunction in polycystic ovary syndrome (PCOS) patients as it is cheap, has minimum adverse effects, and needs less monitoring. There is a common difference concerning ovulation and pregnancy rates due to antiestrogenic properties that influence the endometrium and cervical mucus. In the present study, we compare the influence of late luteal phase clomiphene administration to the early follicular period on ovulation regarding total mature follicles, serum estrogen (E), and progesterone (P), the thickness of the endometrium, pregnancy and pregnancy loss rates.

**Patient and Methods:** this study conducted a randomized controlled trial involving 212 women with PCOS, conducted in a private clinic from 1st of May 2017 to 15th of September 2019. The first group's women were established with 100 mg of CC daily "early CC administration group" after medroxyprogesterone acetate (MPA) intended for 5 days (110 patients, 223 successions), while the second group, women in "late CC collection" established 50 mg of clomiphene citrate twice per day used for 5 days start on day three of the menstrual cycle (102 patients, 210 successions).

**Results:** There are no significant differences in the early CC group patients (group 1) (58.1% vs. 51.8%) in the ovulation rate in the early CC group patients. In group 1, the whole total of follicles during induction was significantly greater, and the thickness of endometrium with hCG injection was significantly greater (9.1–0.24 vs. 8.2–0.50 mm), while not significantly altered between Serum E2 and P. Getting pregnancy about 23/110 successions in the first collection (22.9%) and 17/102 rounds (14.7%) in the second Clomiphene Citrate collection; the variance was statistically not significant. The pregnancy loss rate was the same in both collections.

**Conclusion:** Management with luteal phase clomiphene citrate in PCOS patients resolved extra growth of the follicle and increased endometrial thickness, leading to a higher pregnancy rate.

**Keywords:** Clomiphene citrate, Induction of ovulation, Polycystic ovary syndrome.

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**Conflict of interest:** None

### INTRODUCTION

Polycystic ovary syndrome (PCOS) is a public heterogeneous endocrine complaint presented with multiple disorders in terms of menstrual disturbance, hyperandrogenism, and polycystic ovaries features in ultrasound.<sup>1</sup> The frequency of PCOS differs depending on either standard are to reach the diagnosis, its prevalence as 15-20% when the "European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine" criteria depends on.<sup>2</sup> Obvious signs contain hyperandrogenic, menstrual irregularity, and often infertility.<sup>3,4</sup>

Clomiphene citrate (CC) is found to be the first and commonest drug management for ovulation stimulation in PCOs women as it is inexpensive, has minimum adverse

effects, and needs less monitoring. Clomiphene Citrate has antiestrogenic properties that act by an increase in follicle-stimulating hormone (FSH) by negative feedback blockage, which prompts follicular growth. It encouraged a transient rise in LH and FSH during the management (CC peak), followed by a pattern of gonadotropins secretion closely approximating the pattern that appears in normal ovulatory cycles.<sup>5,6</sup>

While Clomiphene citrate is an effective drug in ovulation induction, there is a common inconsistency between pregnancy rates (PR) and the incidence of ovulation. This occurred due to anti-estrogenic properties that affect endometrium and cervical mucosa through the over secretion of luteinizing hormone (LH), or because of the adverse properties of CC level on oocytes and/or granulosa cells.<sup>7</sup>

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It has been found about 15% of patients who receive CC had unfortunately unfortunate post-coital test outcomes, so intrauterine insemination (IUI) was suggested.<sup>5</sup> It can be explained due to the increased long time effect of CC.<sup>8</sup>

If the trial occurs late in the menstrual phase, poor adverse properties are more likely to be prolonged to reach the peri-implantation time. Several readings stated when CC was ongoing on the first day somewhat than on the fifth day of the menstrual cycle had a better pregnancy rate.<sup>8,9</sup> Then, we will start CC even earlier; day 1 of menses had a good outcome.

*Aim of the Study:* This study uses luteal phase CC management to enhance stimulation inpatient with PCOS then measure the effect on androgenic hormones and follicular size.

**PATIENT AND METHODS**

*Study Design:* Randomized controlled test.

*Study Setting:* The study was done in the researcher’s gynecological private outpatient clinic, Diyala, Iraq, from November 2017 to March 2019.

**Study Group**

The sample included 210 women with Polycystic ovary syndrome, Analysis of PCOS was founded scheduled on reviewed 2003 agreement on diagnostic conditions and risk of health complication.<sup>9</sup>

**Inclusion Criteria**

The patient had done hysterosalpingography for them and found patent fallopian tubes and normal seminal fluid analysis for their husband.

Tools and methods of drug administration:

- Enrollment and consent: The study was accepted by the Ethics Committee, Medical College of Diyala, Iraq.<sup>10</sup> All the couples provided informed agreement prior to inclusion in the test. Enhance withdrawal vaginal bleeding was attained via medroxyprogesterone acetate (MPA) 10-mg tablets for 10 days prior to prompt.
- Randomization: women were then assigned randomly into two groups of treatment:

*First group:* first group CC collection (109 patients, 222 successions)

*Second group:* late or second CC collection (100 patients, 210 successions).

- 3-Intervention: the first group, “early clomiphene citrate collection” (109 patients, 222 cycles), established 50 mg of CC twice per day daily for 5 days beginning the following day after finishing MPA (prior withdrawal bleeding), while in the second group “late CC group” begun on day 3 of the menses (100 women, 210 cycles), established 100 mg of CC daily for 5 days.

*Follow-up:* All participants were observed by ultrasound (vaginal route) for the follicular size and the thickness of the endometrium on days 10, 12, and 13 of the period. Then hCG injection (Human chorionic gonadotropin injection (10,000 IU IM) was assumed when follicle measured more than 18 mm) with Measurement of Serum E2 (in picograms per milliliter) and serum progesterone was measured on days 21–23 of the phase. Women were educated that after hCG injection, have intercourse by 24–36 hours. Serum hCG was measured 2 weeks later.

- Results events were: number of developing, mature follicles and endometrial thickness (in millimeters) using transvaginal sonography, levels of serum E and serum, and incidence of conception and abortion.

**Statistical Analysis**

Facts found statistically studied by means of SPSS computer package (SPSS Inc., Chicago, IL) by Student’s t-test. Quantities were evaluated with the  $\chi^2$  test. Outcomes found such as mean and SE of the mean. The variances measured to be statistically significant if  $p < .05$  at 95% confidence interval [CI].

**DISCUSSION**

Clomiphene citrate has an anti-estrogenic effect on the hypothalamus, which prompts ovulation between 80% and 85%, and conception rates around 40% when managed for 5 days, beginning on the fifth day of the cycle.<sup>14-16</sup>

**RESULTS**

**Table 1:** patient characteristics: concern to time of life, period of infertility and body mass index (BMI), or their clinical presentation No significant statistical variances among the two individuals. While hormones as FSH and LH levels were higher significantly in the late or second CC group ( $p < .05$ ).

	Group 1 (n = 110)	Group 2 (n = 102)	t	p-value
Total of successions	223	210		
Mean Age (y)	24.1 ± 1.12	23.4 ± 2.9	0.25	.61
Mean Parity	0.5 ± 0.22	0.3 ± 0.14	0.39	.31
Mean Height (cm)	145.3 ± 4.11	147.1 ± 5.33	1.06	12
Mean Weight (kg)	73.2 ± 4.42	79.1 ± 3.22	2.51	0.078
Clinic presentation			$\chi^2$	
Oligo/anovulation	90 (81.8%)	85 (83.3%)	0.08	.76
Hyperandrogenism	55 (50.9%)	48 (47.1%)	0.31	.57
BMI (kg/m <sup>2</sup> ) body mass index	30.2 ± 3.24	31.4 ± 2.61	0.22	.81
FSH (IU /ML)	4.1 ± 1.77	6.1 ± 2.13	5.7	.0 <sup>3a</sup>
LH (IU / ML)	10.1 ± 2.863	12.3 ± 1.12	6.1	0 <sup>3a</sup> <sub>i</sub>

**Table 2:** effect of clomiphene citrate and hormones: more ovulating patients in the collection 1 (59.1% vs. 51.9%), which is not significant. The total number of follicles more than 14 and 18 mm in the early CC group was significantly more ( $p < .05$ ). Endometrial thickness at the period of hCG given was more significant ( $p < .05$ ). Rate of pregnancy had been occurred in (20.9%) cycles in group 1 and (15.7%) in the second group, which was statistically not significant ( $p > .05$ ).

<i>First clomiphene citrate collection</i>				
	<i>Second cc</i>	<i>Collection (n = 102)</i>	<i>t</i>	<i>p-value</i>
Sum of women	65 (58.1%)	53 (51.8%)	1.08	.28
Whole number of follicles	4.2 ± 0.42	2.7 ± 0.31	10.1	.001 <sup>a</sup>
follicles more than 14 mm	2.9 ± 0.18	1.6 ± 0.17	12.5	.001 <sup>a</sup>
follicles more than 18 mm	1.2 ± 0.15	1.4 ± 0.33	8.7	.01 <sup>a</sup>
endometrial thickness (before treatment	2.6 ± 0.33	3.7 ± 0.52	1.7	.09
Endometrial thickness at hCG	9.2 ± 0.21	7.9 ± 0.5	3.1	.036 <sup>a</sup>
Serum Estrogen	316.1 ± 60.21	270 ± 81.30	0.72	.56
Serum progesterone	11.1 ± 0.72	10.2 ± 1.12	0.32	.84
Conception per cycle	22/110(20.9%)	17/102(14.7%)	X <sup>2</sup> = 0.86	.30
Pregnancy loss	4. (16.4%)	3 (17.8%)	X <sup>2</sup> = 0.07	.75

In this study, we started with Clomiphene citrate before the start of menses, in the late luteal stage; this led to an increase in the ovarian response in ovulation induction. The total numbers and the numbers of mature follicles during stimulus were significantly more, which was different from the findings of Chung and Craig research,<sup>13</sup> in which there were no significant changes in ovulation results and pregnancy rate between individuals establish CC on the beginning of menses.

On the other hand, Bilijan and colleagues<sup>17</sup> started with Clomiphene citrate on the first day rather than on the 5th day of cycle 2 as they found a more fast growth of the follicle and a more PR.

While Marrs *et al.*<sup>18</sup> establish that the follicles numbers significantly improved, oocytes regained and impregnated in cycles in which CC was started on the fifth day.

Dhebashi *et al.*<sup>19</sup> initiate that, throughout therapy, gonadotropin levels increased for a period of 10–14 days after administration of clomiphene citrate in both collections, a result similar to outcomes in previous studies.

The total number of significant follicles (R14 mm) were noticeably higher in 5th-day women “second group” than 1st day “the first group.” These results can determine that women arranged for IVF or embryo transfer should be commended to start CC on day five of the period.

Follicles maturation “from the primordial to the preovulatory phase” typically takes a period of numerous months.<sup>20</sup> This should be recommended giving Clomiphene citrate in the later time of the luteal period prior cycle will find extrafollicular growth. While the pregnancy frequency was more in the early collection, the variance was statistically insignificant. Larger sample size is needed for a future study that may give a significant result for early administration of CC.

## CONCLUSION

This study proposes that early Clomiphene citrate treatment will lead to more growth of follicles than better endometrial thickness with higher pregnancy rate outcomes.

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