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Clomiphene citrate vs Letrozole as first line ovulation induction drug in infertile PCOS women

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ABSTRACT

Background: *Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy resulting in anovulatory infertility in young women as in recent years have seen a significant rise in women presenting with PCOS . Despite wide acceptance of clomiphene citrate (CC) as the first-line drug for ovulation induction in women with polycystic ovaries (PCOS), a significant proportion of women do not respond to this treatment. In addition, CC use is known to have several disadvantages, including a discrepancy between ovulation and conception rates. Recent studies have suggested that letrozole, an aromatase inhibitor, can be used for ovulation induction and is associated with higher pregnancy rates and less complications than CC treatment in women with PCOs.*

Aim of study: *To compare the efficacy of letrozole and clomiphene citrate (CC) for ovulation induction in infertile women with polycystic ovarian syndrome (PCOS).*

Materials and methods: *The prospective randomized trial was conducted between February 2023 and February 2024 at Lamis IVF center in Misrata-Libya. 103 infertile PCOS patients were randomly selected for the study . All patients were selected started 5 mg letrozole (52 patients) or 100 mg clomiphene citrate (51 patients) twice daily starting day 2 to day 6 of menstrual cycle. When at least one mature follicle (with a mean diameter ≥ 18 mm) was observed, 10000 IU of human chorionic gonadotrophin (hCG) were given subcutaneously to trigger ovulation.*

Results: *The mean age, Body Mass Index (BMI), duration of infertility in both Clomiphene Citrate (CC) and Letrozole groups were similar. Ovulation rate was 67.3% in letrozole group and 58.8% in CC, which was not significant. There was no statistically significant difference between Endometrial thickness (CC 7.99 ±2.4, Let 8.69 ± 2.14) and days of ovulation (CC 13.6 ± 2.1; Let 13.1 ± 2.4). Mono-*

follicular development (CC 56.6% , Let 80 %) and Pregnancy rate (CC 11.7%, Let 28.8%) were significantly higher in letrozole group.

***Conclusion**: Letrozole is a better alternative for ovulation induction in anovulatory women with PCOS as pregnancy rates are higher and chances of multiple pregnancy are less because of high monofollicular growth. We recommend letrozole over clomiphene citrate as an ovulation induction drug in women with infertility and PCOS, although the quality of the evidence is mixed.*

Introduction:

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy resulting in anovulatory infertility in young women. Recent years have seen a significant rise in women presenting with PCOS.

Polycystic ovary syndrome (PCOS) affects approximately 20–33%,[1-4] of women of reproductive age, and is a leading cause of infertility.

According to the Rotterdam consensus [5], polycystic ovarian syndrome (PCOS) is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary).

Despite wide acceptance of clomiphene citrate (CC) as the first-line drug for ovulation induction in women with polycystic ovaries (PCOs), a significant proportion of women do not respond to this treatment. In addition, CC use is known to have several disadvantages, including a

discrepancy between ovulation and conception rates.[6,7] Recent studies have suggested that letrozole, an aromatase inhibitor, can be used for ovulation induction and is associated with higher pregnancy rates than CC treatment in women with PCOs.[8]

Anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus. On the other hand , Letrozole is an aromatase inhibitor that prevents androgen to estrogen conversion. The antiestrogenic effects of clomiphene are not found with letrozole.6,9-11

Recent studies have suggested that letrozole, an aromatase inhibitor, can be used for ovulation induction and is associated with higher pregnancy rates than CC treatment in women with PCOs.[8]

Aim of the study

To compare the efficacy of letrozole and clomiphene citrate (CC) for ovulation induction in infertile women with polycystic ovarian syndrome (PCOS).

Materials and Methods

The prospective randomized trial was conducted between February 2023 and February 2024 at Lamis IVF center in Misrata Libya . 103 infertile PCOS

patients were randomly selected for the study. PCOS was diagnosed according to Rotterdam criteria.

All patients were selected started mg letrozole (52 patients) or 100 mg clomiphene citrate (51 patients) twice daily starting day 2 to day 6 of menstrual cycle. Follicular development was monitored using transvaginal ultrasound from day 10 onwards. When at least one mature follicle (with a mean diameter ≥ 18 mm) was observed, 10000 IU of human chorionic gonadotrophin (hCG) were given subcutaneously to trigger ovulation.

Pregnancy was diagnosed using β-hCG levels obtained 2 weeks after timed intercourse, and ultrasound was performed 2 - 4 weeks after a positive pregnancy test to confirm clinical pregnancy by the presence of cardiac activity.

Results :

- A total of 103 women with PCOs were enrolled into the study. Of these, 51 received CC and 52 received letrozole.
- The demographic characteristics and endocrine status of the study participants are shown in Table 1; there were no statistically significant differences between the two groups.

TABLE 1: Demographic characteristics of patients with polycystic ovaries assigned to receive either clomiphene citrate or letrozole for ovulation induction

	CLOMIPHENE CITRATE (N = 51)	LETROZOLE (N = 52)	P VALUE
AGE (YEARS)	31.8 ± 5.6	30.0 ± 6.0	0.12
MEAN INFERTILITY PERIOD (YEARS)	5.4 ± 3.7	4.8 ± 2.4	0.34
BODY MASS INDEX (KG/M 2)	27.7 ± 4.1	28.0 ± 5.0	0.75

- The ovulation rate was 58.8% in CC group and 64.4% in Let group (P = 0.57).
- There was no statistically significant difference between the two groups in endometrial thickness on the day of HCG (CC 7.8 ± 2.4 mm, Let 8.6 ± 2.2 mm P = 0.08).

TABLE 2 : OVULATION RATE & ENDOMETRIAL THICKNESS

	CLOMIPHENE CITRATE (N = 51)	LETROZOLE (N = 52)	P VALUE
OVULATION RATE	58.8%	64.4%	0.57
ENDOMETRIAL THICKNESS (MM)	7.8 ± 2.4	8.6 ± 2.2	0.08

- Table 3 summarizes the responses of the women in the two groups to ovarian stimulation .
- Mono-follicular development was seen in 80% of ovulatory cycles in the letrozole group compared with 53.3% in the CC group (P=0.02).
- Meanwhile multi-follicular development was significantly higher in patients who received clomiphene citrate

TABLE 3 : Responses to ovarian stimulation

	CLOMIPHENE CITRATE (N = 51)	LETROZOLE (N = 52)	P VALUE
MONO-FOLLICULAR DEVELOPMENT %	53.3%	80%	0.022
MULTI-FOLLICULAR DEVELOPMENT %	46.7%	20%	0.022

- History of Laparoscopy In the clomiphene group, (Table 4) 68.6% of patients had a prior history of having undergone laparoscopy as part of infertility workup compared to 61.5% in the letrozole group. The p value of 0.45 showed no significant difference in the distribution of patients in the two groups.

TABLE 4 : Comparison of laparoscopy based on drug

LAPAROSCOPY	CLOMIPHENE CITRATE (N = 51)	LETROZOLE (N = 52)	P VALUE
YES	68.6%	61.5%	0.45
NO	31.4%	38.5%	0.45

- Pregnancy occurred in 6 out of 51 (11.8%) in CC group and in 17 out of 52 (32.7%) in the Let group, the difference was highly statistically significant (P = 0.02) [Table 5].
- There were no twin pregnancies in either category.

TABLE 5 : Outcome of treatment

	CLOMIPHENE CITRATE (N = 51)	LETROZOLE (N = 52)	P VALUE
PREGNANCY RATE %	11.8%	32.7%	0.02
MULTIPLE PREGNANCY %	NONE	NONE	

discussion:

Clomiphene citrate (CC) has been used for ovulation induction since 1960s. It is still considered first-line drug for anovulatory PCOS women. However, clomiphene resistance (15-20%), endometrial thinning, and poor cervical mucus (15-50% of cases) makes it ineffective in many situations.[12-16] Letrozole, which is an aromatase inhibitor, has been explored as a good alternative by many researchers, but the evidence about its efficacy as compared to clomiphene is conflicting.

Letrozole creates an estrogen-deficient environment by blocking conversion of androgens to estrogens. This releases the pituitary from negative feedback of estrogens and releases FSH. Also, an added positive effect is increased follicular sensitivity to FSH through amplification of FSH receptor gene expression.[17-20] Thus, ovulation induction by letrozole should be better than by CC in terms of follicular growth and endometrial development.

Letrozole has also been shown to be effective in ovulation induction in CCresistant PCOS women.[21] Hyper-insulinemia, which is closely associated with PCOS, is thought to be one of the causative factors for CC resistance. The prevalence of insulin resistance in PCOS is close to 50%.[22] This could be one more reason for letrozole to be a better first-line drug compared to clomiphene citrate.

Multiple developing follicles appear on day 7 but, because letrozole does not deplete estrogen receptors, unlike CC,[23] normal negative feedback occurs centrally as the dominant follicle grows and estrogen levels increase. This results in FSH suppression and atresia of smaller follicles, and mid-cycle mono-ovulation occurs in most patients. Mono-ovulation is the major advantage of using aromatase inhibitors for ovulation induction. A drug that consistently results in a single ovulation is particularly desirable in patients with PCOs, who are often hyperresponsive to onadotrophins.[24] In addition, aromatase inhibitors do not have negative effects on endometrial thickness or cervical mucus.[8]

A double-blind, randomized trial comparing the use of an aromatase inhibitor with CC for ovarian stimulation in 49 women with unexplained infertility found that patients receiving the aromatase inhibitor had increased endometrial thickness compared with those receiving CC.[25] An almost threefold increase in pregnancy rate was observed in patients who received aromatase inhibitor treatment compared with those who received CC treatment (16.7% versus 5.6% per patient, respectively); this difference was not statistically significant, but the number of patients studied was small.

In a well-designed study comparing CC with letrozole in patients with PCOs, letrozole produced a significantly thicker endometrium on the day of hCG administration and no apparent adverse effects on the endometrium were seen with letrozole treatment.[8] In women with PCOs who did not have an adequate response to CC, ovulation occurred in 75% of the letrozole treatment cycles and clinical pregnancy was achieved in 17% of the cycles.

Mitwally and Casper showed a similar effect of letrozole on the endometrium.[26] Cortinez et al.[27] found normal morphological features of the endometrium and full expression of pinopodes during the implantation window when letrozole was used. On the other hand, no significant difference was noted in other studies in regard to the effect of either drug on the endometrium.[28,29]

Al Fouzan et al.[30] reported better results in the letrozole group [for the number of developing and mature follicles] than in the clomiphene citrate group.

In a study published in Journal of Human Reproductive Sciences showed ovulation rate was 60.78% with CC and 73.08% with letrozole, which was not statistically significant (P = 0.398). Others reported similarly, Badawy et al.[31] (CC 70.9%, Let 67.5%), Bayer et al.[32] (CC 74.7%, Let 65.7%), and M. Zeinalzadeh et al.[33] (CC 72%, Let 86%). In majority of the studies, no statistically significant difference is found between CC and letrozole in ovulation rate. Multi- follicular development was statistically significantly higher in outstudy (CC 45.16%, Let 20.51%, P = 0.027). This is expected and corroborated by number of studies.[31-33] Letrozole resulted in monofolliculogenesis in 79.49% of cases, which is optimal for ovulation induction in PCOS women. However, where multiple follicular development is needed, letrozole may be inadequate.

The mean endometrial thickness was slightly higher in letrozole group, 7.65 ± 2.1 compared to CC 7.61 ± 1.96. Badawy et al.[31] in their study of 438 patients with 1063 cycles, one of the largest studies comparing CC and letrozole, reported statistically significantly higher endometrial thickness in CC group (9.2 ± 0.7) vs. letrozole (8.1 ± 0.2, P = 0.021). They attributed this effect to greater number of mature follicles and higher serum E_2 levels. Mitwally and Casper[26] found letrozole associated with greater endometrial thickness. Cortinez et al.[34] found normal morphologic features of endometrium and full expression of pinopodes during implantation window when letrozole was used. Few studies have shown no significant difference between the two groups with regard to effect on endometrium.[35,36] In a recent study by Banerjee et al.,[37] 147 Indian women with PCOS were compared between letrozole (2.5 mg) Vs. clomiphene (100 mg). Mean endometrial development was 8.72 ± 11.41 mm in letrozole and 8.78 ± 1.16 mm in CC group (P = 0.004).

Pregnancy rate per cycle was astonishingly high with letrozole in our study (21.56%) Vs. (7.84%) (P = 0.015) Badawy et al.,[31] , with 438 women (1063 cycles), reported slightly better pregnancy rate in CC group (15.1%) letrozole and 17.9 % in CC group). Bayer et al.,[32] with 74 women, Zeinalzaden et al.,[33] with 107 women, both reported slightly better pregnancy rates with letrozole; however, no statistically significant difference between the two groups.

In a meta-analysis by He and Jiang,[38] the clinical efficacy and safety of letrozole was compared with clomiphene for ovulation induction in PCOS women. This is one of the largest meta-analysis of the subject published. Six RCTs involving 841 patients were analyzed. There were no significant differences in pregnancy rate, abortion rate, and multiple pregnancy rate between the two groups. The evidence from ovulation rate was not enough to support either of the drugs.

In our study, ovulation rate was 58.8% with CC and 64.4% with letrozole, which was not statistical-

ly significant (P = 0.57). In majority of the studies, no statistically significant difference is found between CC and letrozole in ovulation rate.

Multi- follicular development was statistically significantly higher in our study (CC 46.7%, Let 20%, P = 0.022). This is expected and corroborated by number of studies. Letrozole resulted in monofolliculogenesis in 80% of cases, which is optimal for ovulation induction in PCOS women. However, where multiple follicular development is needed, letrozole may be inadequate.

The mean endometrial thickness was slightly higher in letrozole group, 8.6 ± 2.2 compared to CC 7.8 ± 2.4 .

Regarding tubal patency , In the clomiphene group, 68.6% of patients had a prior history of having undergone laparoscopy as part of infertility workup compared to 61.5% in the letrozole group. As rest of the patients undergone HSG which showed patent free tubes .

Semen analysis among all patients in this study was within normal .

There was no instance of ovarian hyperstimulation syndrome in either group.

Conclusion:

- Letrozole is a better alternative for ovulation induction in anovulatory women with PCOS as pregnancy rates are higher and chances of multiple pregnancy are less because of high monofollicular growth.
- We recommend letrozole over clomiphene citrate as an ovulation induction drug in women with infertility and PCOS, although the quality of the evidence is mixed.

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