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COMPARISON OF EFFICACY OF LETROZOLE AND CLOMIPHENE CITRATE IN OVULATION INDUCTION IN PAKISTANI WOMEN WITH PCOS

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Abstract:

Objective*: To compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) for ovulation induction in women with polycystic ovary syndrome (PCOS).*

Design: *Prospective randomized trial.*

Setting*.Tertiary care hospitals of Sialkot and Gujrat,Pakistan.*

Patient(s): *The study comprised a total of 110 infertile women with PCOS.*

Intervention(s): *Patients were randomized to treatment with 5 mg of letrozole daily (60patients) or 100 mg of clomiphene citrate daily (50 patients) for 5 days starting on day 3 of menses. Intercourse time was decided 24 to 36 hours after hCG injection.*

Main Outcome Measure(s): *Number of follicles, Duration of stimulation (d), endometrial thickness, and pregnancy and miscarriage rates.*

Result(s): *In both groups mean age, parity, and duration of infertility were similar. The total numbers of follicles during stimulation were similar between the two groups (5.7 ±0.3 in the letrozole group, 4.5 ± 0.4 in the CC group). The number of follicles >14 mm and 18 mm were significantly higher in the letrozole group. The duration to reach a dominant follicle was 9.6 ± 0.4 days in the letrozole group and 10.8 ± 0.9 days in the CC group .there was no significant difference in the endometrial thickness between the two groups. The pregnancy rate per cycle was 15.5% in the letrozole group and 12% in the CC group. Twenty pregnancies in letrozole group are presently ongoing. 6 of 20 pregnancies in the CC group resulted in a miscarriage. No miscarriage was see in the letrozole group, but we encountered two ectopic pregnancies.*

Conclusion: *In conclusion, the results of this study suggest that letrozole, are safe and equally efficacious to clomiphene citrate in terms of ovulation. Higher miscarriage were seen in CC group participants but both CC and letrazole groups had same preganancy rates among PCOS women.*

Key words: *Superovulation, ovulation induction, PCOS.*

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in young women. It manifests itself in a variety of clinical ways and 55% to 75% of PCOS patients are infertile due to chronic anovulation [1-3].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. [4] Clomiphene citrate (CC) is still the standard drug for inducing or augmenting ovulation. It is not, however, equally successful in all situations. Clomiphene resistance, which refers to persistence of anovulation after standard CC therapy, occurs in 15% to 20% of patients [5]. In addition, CC use is known to have several disadvantages, including a discrepancy between ovulation and conception rates. [4,6].Gonadotropin is an alternative drug for superovulation. However, it is associated with a higher risk of ovarian hyper stimulation syndrome (OHSS) and multiple pregnancies [7]. It is also more expensive than CC and the injectable route is inconvenient. Letrozole is an aromatase inhibitor that has been widely used in women with breast cancer [8]. It works by suppressing estrogen (E) production, and recently it has been used to induce ovulation. In previous study used [9] letrozole (2.5 mg daily for 5 days) in 12 women with inadequate response to CC. Ovulation occurred in 9 of 12 cycles and 3 patients conceived. 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. [10]

The purpose of our study is to compare the effects of letrozole with CC in women undergoing ovulation induction.

MATERIAL AND METHOD:

One hundred and ten infertile PCOS patients at the age group of 18–40 attending the Gynaecology & Obstetrics OPD of tertiary care hospitals of Gujrat and Sialkot,Pakistan were the target population for this study. Study was conducted between the duration of January 2018 to January 2019. Protocol of the study was approved by the institutional ethics committee, and informed consent was filled by all study participants.

Inclusion criteria:

Women with primary infertility and PCOs with no other known cause of infertility were enrolled into the study. All patients had a history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2 – 10 mm in diameter and hyperechogenic stroma.

Exclusion criteria:

Patients who had hyperprolactinemia, thyroid disorder, male factor infertility, known or suspicious tubal factor infertility (endometriosis and pelvic inflammatory disease), patients with a history of liver and kidney failure, cardiovascular diseases, diabetes or patients who consumed metformin or drugs effecting insulin secretion or clomiphene citrate in the previous 2 months.

Ovulation induction:

Participants were allocated to receive either 100 mg CC or 2.5 mg letrozole daily for 5 days starrting on day 3 of the menstrual cycle. On day 3 of the menstrual cycle Transvaginal ultrasound examination was performed before treatment was commenced. by using transvaginal ultrasound from day 10 onwards Follicular development was monitored. When at least one mature follicle (with a mean diameter ≥ 18 mm) was observed, 10 000 IU of human chorionic gonadotrophin (hCG) were given subcutaneously to trigger ovulation. Pregnancy was detected 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.

Statistical analysis:

A group t-test or the Student's t-test was used to compare data as appropriate. Proportions were analyzed using the 2 test. Results were expressed as mean and standard error of the mean. P-value less than 0.05 was considered to be statistically significant.

RESULTS:

A total of 110 women with PCOs were enrolled into the study. Of these, 50 received CC and 60 received letrozole. The demographic characteristics The mean age, parity, and duration of infertility in both groups of patients were similar and endocrine status of the study participants are shown in Table 1; there were no statistically significant differences between the two groups. Table 2 summarizes the responses of the women in the two groups to ovarian stimulation. The total numbers of follicles during stimulation were similar between the two groups (5.7 ±0.3 in the letrozole group, 4.5 ± 0.4 in the CC group). The number of follicles >14 mm and 18 mm were significantly higher in the letrozole group (3.0 ± 0.1 for letrozole and 1.5 ±0.1 for CC) (Table 2). The duration to reach a dominant follicle was 9.6 ± 0.4

days in the letrozole group and 10.8 ± 0.9 days in the CC group .there was no significant difference in the endometrial thickness between the two groups. The pregnancy rate per cycle was 15.5% in the letrozole group and 12% in the CC group. Twenty pregnancies in letrozole group are presently ongoing. 6 of 20 pregnancies in the CC group resulted in amiscarriage. No miscarriage was see in the letrozole group, but we encountered two ectopic pregnancies. One twin pregnancy occurred in the CC group and none in the letrozole group.

Table 1: demographic Characteristics of patients undergoing ovualation induction with letrozole and with clomiphene citrate (CC)

	Letrozole	CC
Age	32.5± 0.7	33.3± 0.5
Parity	0.4 ± 0.2	0.3 0.1
Body mass index	2.2 ± 0.7	2.4 ± 0.9
Duration of infertility	2.9 ± 0.3	3.1 ± 0.3
Mean baseline LH level (range)	5.61IU/l (1.59–35.57)	5.98 IU/l (1.59–35.57)
Mean baseline FSH level (range)	2.97 IU/l (1.39–12.6)	4.44 IU/l (0.8–15)
Mean baseline TSH levels (range)	3.7 mIU/l (1.05–5.1)	3.52 mIU/l (2.2–6.89)

Table 2: ovulation induction with letrozole and with clomiphene citrate (CC).

	Letrozole	CC	95% CI	P value
Total number of follicles	5.7± 0.3	4.5 ±0.4	0.5 to 1	0.087
Number of follicles of 14 mm	3.0 ±0.1	1.5± 0.1	0 to 0.5	0.04
Number of dominant follicles	2 ±0.1	0.9± 0.1	0 to 0.5	0.01
Pretreatment endometrial thickness (mm)	5 0. ±0.1	4.9± 0.1	-0.5 to 0.3	0.056
Endometrial thickness at hCG (mm)	6.8± 0.2	8.2± 0.6	-1.1 to 0.2	0.68
Duration of stimulation (d)	9.6 ±0.4	10.8 ±0.9	-1 to 0.5	0.77

DISCUSSION:

Letrozole is potentially a new drug for ovulation induction or superovulation. The use of CC is associated with endometrial thinning in 15%–50% of patients [11-13]. This could be due to prolonged E receptor depletion in the endometrium [11,14,15]. Compared with CC, letrozole is associated with a thicker endometrium [16].It suggests that letrozole has minimal effect on the endometrium. Perhaps, this is due to its rapid and reversible action on the endometrium allowing the endometrium to respond well to increasing E in the late follicular phase. Such findings could be attributed to the mechanism of action of letrozole. As an aromatase inhibitor, it works by decreasing the conversion of androstenedione (A) and T to E in the ovary. The decrease in circulating E increases gonadotropin secretion [17-21]. Compared with CC, the use of 7.5 mg of letrozole daily for 5 days leads to a slightly higher number of developing follicles. However, there was no difference in the pregnancy rates or in the endometrial thickness between the CC and the letrozole group. This is in contrast with the effect of a lower dose of letrozole on the endometrium [16,22].

Miscarriage rate was higher in the CC group. Perhaps, this is due to the different mechanism of action between letrozole and CC. In our previous study, we reported that the addition of letrozole (5 mg daily for 5 days) to gonadotropin is associated with a thinner endometrium than gonadotropin alone [23]. In the present study, the endometrial thickness was the same in the letrozole group and in the CC group. We found that the number of the mature follicles is significantly higher in the letrozole group compared with the CC group. This is in agreement with the previous report [19] that letrozole improves ovarian response to FSH in poor responder women. In our previous study, no difference was found in the pregnancy rate between the FSH group and the letrozole/FSH group (20.9% vs. 21.6%) [23]. The higher number of mature follicles in the letrozole group did not result in a higher pregnancy rate. Perhaps, this is related to inadequate quality of endometrium in the letrozole group. A larger study is needed to clarify this matter.

CONCLUSION:

In conclusion, the results of this study suggest that letrozole, are safe and equally efficacious to clomiphene citrate in terms of ovulation. Higher

miscarriage were seen in CC group participants but both CC and letrazole groups had same preganancy rates among PCOS women.

REFERENCE:

1. Kovacs G, Wood C. The current status of polycystic ovary syndrome. Aust NZ J Obstet Gynecol 2001;41:65–8.
2. Guzick D. Polycystic ovary syndrome. Symptomatology, pathophysiology and epidemiology. Am J Obstet Gynecol 1998;179:89–93.
3. Slowey MJ. Polycystic ovary syndrome: new perspective on an old problem. South Med J 2001;94:190–5.
4. Randall JM, Templeton A: Cervical mucus score and in vitro sperm mucus interaction in spontaneous and clomiphene citrate cycles. Fertil Steril 1991; 56: 465 –468.
5. Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. Clin Obstet Gynecol 1985;12:605–32.
6. Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H: Effects of clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. Fertil Steril 1997; 67: 256 – 260.
7. Kettel LM, Roseff SJ, Berga SL, Mortola JF, Yen SS. Hypothalamicpituitary-ovarian response to clomiphene citrate in women with polycystic ovary syndrome. Fertil Steril 1993;59:532– 8.
8. Pfister CU, Martoni A, Zamagni C, Lelli G, De Braud F, Souppart C, et al. Effect of age and single versus multiple doses, pharmacokinetic of letrozole (Femara) in breast cancer patients. Biopharm Drug Dispos 2001;22:191–7.
9. Mitwally M, Casper R. Use of aromatase inhibitor for ovulation induction in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305–9.
10. Rabau E, Serr DM, Mashiach S, Insler V, Salomy M, Lunenfeld B. Current concepts in the treatment of anovulation. Br Med J 1967;4: 446 –9
11. Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Hum Reprod 1990; 5:670 – 4.
12. Yagel S, Ben-Chetrit A, Anteby E, Zacut D, Hochner-Celnikier D, Ron M. The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate. Fertil Steril 1992;57: 33– 6.
13. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. Fertil Steril 1993;59:756 – 60.
14. Opsahl MS, Robins ED, O'Connor DM, Scott RT, Fritz MA. Characteristics of gonadotropin response, follicular development, and endometrial growth and maturation across consecutive cycles of clomiphene citrate treatment. Fertil Steril 1996;66:533–9.
15. Eden JA, Place J, Carter GD, Jones J, Alaghband-Zadeh J, Pawson ME. The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. Obstet Gynecol 1989;73:187–90.
16. Mitwally M, Casper R. Use of aromatase inhibitor for ovulation induction in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305–9.
17. . Weil SJ, Vendola K, Zhou J, Adesanya OO, Wang J, Okafor J, Bondy CA. Androgen receptor gene expression in the primate ovary: cellular localization, regulation, and functional correlations. J Clin Endocrinol Metab 1998;83:2479 – 85.
18. Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. J Clin Endocrinol Metab 1999;84:2951– 6.
19. Vendola K, Zhou J, Wang J, Famuyiwa OA, Bievre M, Bondy CA. Androgens promote oocyte insulin-like growth factor I expression and initiation of follicle development in the primate ovary. Biol Reprod 1999;61:353–7.
20. Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest 1998;101:2622–9.
21. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril 2002;77:776 – 80.
22. Sammour A, Biljan MM, Tan SL, Tulandi T. Prospective randomized trial comparing the effects of letrozole and clomiphene citrate (CC) on follicular development, endometrial thickness and pregnancy rate in patients undergoing superovulation prior to intrauterine insemination [Abstract 291]. 57th Annual Meeting of the American Society for Reproductive Medicine, October 20 –25, 2001, Orlando, FL

23. Healey S, Tan SL, Tulandi T, Biljan M. Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril 2003;80;1325–9.