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ORIGINAL ARTICLE

Comparison of the Efficacy of Letrozole and Clomiphene Citrate in women having Anovulatory Infertility

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ABSTRACT

Aim: To compare the efficacy of letrozole and clomiphene citrate in women having anovulatory infertility.
Study design: Randomized Controlled Trial.
Place and duration of study: 16th October 2020 to 15th September 2021 in Department of Obstetrics & Gynecology, Shahida Islam Medical Complex Lodhran.
Methods: In our study 112 patients between ages 18 to 40 years with anovulation were included. Patients having H/O previous pelvic surgery, raised prolactin and TSH levels were excluded. These women were divided into02 groups i.e. Group A (clomiphene citrate) & Group B (letrozole), by lottery method and the effectiveness was noted in both groups.
Results: Mean age of women in group A was 24.53±6.12 years and in group B was 25.37±6.33 years. Majority women included in our study, 78(69.64%) were between ages 18 to 30 years. Duration of infertility was 3.28±2.11 years. Mean infertility duration in group A was 3.63±2.10 years and in group B was 3.79±2.14 years. The efficacy of drug shownin Group A was 9(8.03%) while in Group B was 18(16.07%) (p-value = 0.005).
Conclusion: We concluded from this study that letrozole is proved to be more efficacious than clomiphene citrate in anovulatory infertility.
Keywords: Anovulation, Infertility, Letrozole, Clomiphene Citrate, Conception Rate

INTRODUCTION

Hypothalamic-pituitary-ovarian (HPO) axis maturation results in ovulation. Out of the commonest causes of female infertility is ovulation dysfunction, almost in 30-14% of cases[1,2]. Insufficient estrogen levels leads to ovulation dysfunction because of failure to have LH surge, thus any condition leading to decreased levels of estrogen leads to anovulation. First-line agents used of ovulation-induction therapy targets the HPO-axis[3,4,5,6] i.e., clomiphene citrate and letrozole are 02 most commonly using oral agents for the said purpose. Injectable fertility medications can also be used but, the oral drugs are used most commonly.

Selective estrogen-receptor modulator i.e. Clomiphene citrate, antagonizes the negative feedback of estrogen at the hypothalamus leading to ovulation[7], but it has disadvantages of low efficacy, high multiple-pregnancy rate and unwanted side-effects like mood changes, hot flushes and blurring of vision[4,7].

A non-steroidal aromatase inhibitor i.e. Letrozole, blocks estrogen synthesis, so directly affects HPO axis leading to improved pregnancy rates. Letrozole results in monofollicular ovulation, thus, lower multiple-pregnancy rates andreduced side-effects[6,7]. Previously many studies[1,2,4,5] concluded that letrozole and clomiphene citrate significantly differ in their efficacy in terms of ovulation, pregnancy and live birth rates. A higher rate of pregnancy noted in letrozole group as compared to Clomiphene citrate. Ibrahim MI[8]concluded letrozole to be more efficacious as a pregnancy rate of 23.07% in the LTZ group and 10.68% in the CC group was shown.

In clomiphene citrate resistant cases the letrozole do proves to be benificial[1,4,7,9]. However its use as first line therapy needs further studies[3,6,10]. Thus we found a need to study and find out the first line treatment for ovulation induction that can be given to the patients for better results in anovulatory infertility.

MATERIALS & METHODS

It was a Randomized controlled trial conducted in the Department of Obstetrics & Gynecology, Shahida Islam Medical Complex Lodhran since, 16th October 2020 to 15th September 2021. Total number of patients was divided into two groups A and B with 56 patients in a group. The appropriate sample size for the study was based on an analysis of sample size by taking P=50%, α = 0.05 1-β =80%, with the consideration of effectiveness in clomiphene group being 10.68%, while 23.07% in letrozole group.[8]Sample was selected by Non-probability, consecutive sampling technique.All patients with anovulatory infertility having age (18-40) years, who gave informed consent, their prolactin and TSH levels were checked, were included in the study. Patients having any previous pelvic surgery, high levels of TSH and prolactin and known to allergic to the drugs were excluded.

After approval from ethical review committee a total of 112 infertile patients with anovulation presenting to OPD in Shahida Islam Medical Complex, fulfilling the inclusion/exclusion criteria were selected. After taking informed consent and getting their prolactin and TSH levels checked, all selected cases were divided in to two groups by lottery method. Group A patients were advised CC (50mg) orally twice a day for 5 days from day 2 of her menstrual cycle and Group B women were prescribed letrozole (2.5mg) orally on day 3to day 7 of menstrual cycle once daily for 5 menstrual cycles. All patients were evaluated after each cycle to check conception confirmed by β-HCG in urine after 05 days of the first missed menstrual period and effectiveness of each group was noted.

Statistical analysis: Data analysis was done by SPSS 20.0. Quantitative variables i.e.; Age of patients and duration of infertility was analysed by Mean and Standard Deviation while, Qualitative variables i.e., efficacious (yes/no) was assessed by calculating percentages and frequencies. Chi Square test was applied to compare efficacy in both groups. P value ≤0.05 was considered to be significant.

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RESULTS

In the study women were of 18 to 40 years of age with mean age of 28.06 ± 6.05yrs. Mean infertility duration was 3.42±2.01yrs. The

efficacy of drug in Group A (CC group) was 09(16.07%) vs Group B (LTZ group) was 19 (33.92%) as shown in the following tables (I &II) (p value=0.005).

Table-I: Age and duration of infertility in both groups (n=112).

	Group A (n=56)	Group B (n=56)	Total (n=112)
Age in years			
18-30	36(65.04%)	37(66.07%)	73(66.0%)
31-40	20(35.71%)	19(33.04%)	39(35.97%)
Mean ± SD	28.01 ± 6.02	28.12 ± 6.03	28.06 ± 6.05
Duration of infertility			
< 5 years	35(64.28%)	34(61.61%)	69(61.60%)
>5 years	21(36.61%)	22(38.09%)	43(38.39%)
Mean ± SD	3.12 ± 2.19	3.70 ± 2.34	3.42 ± 2.01

Table II: Efficacy in both groups

Efficacious	Group A (n=56)	Group B (n=56)
Yes	9(16.07%)	19(33.92%)
No	47(83.92%)	(3766.07%)

P value is 0.005 which is statistically significant.

DISCUSSION

Anovulation is the commonest cause of infertility, many drugs are used for ovulation induction. First line drug used for this purpose is Clomiphene Citrate (Non-Steroidal SERM)[11]. Over the last 50 years clomiphene citrate is the drug of choice for ovulation induction[12]. However, 20-25% women showed resistance to CC[13]. In contrast to clomiphene citrate, Letrozole leads to formation of multiple mature follicles[14], thus leading to increased pregnancy rates.We conducted study to compare the efficacy of letrozole and clomiphene citrate in terms of achieving pregnancy.

Women with ages 18-40 years were included in the study with mean age of 26.7±6.19. Most womeni.e;74(66.07%) were between ages 18yr to 30yr. Mean age in Group A was 28.01±6.02 and that of Group B was 28.06±6.05. We found pregnancy rate in Group A as 09(16.07%) and in Group B 19(33.92%). P value = 0.005 which is statistically significant.

Ibrahim MI[8] studied and found pregnancy rate of 10.68% in clomiphene citrate group and 23.07% in letrozole group. Few studies suggests that clomiphene along with metformin should be the first line treatment for anovulatory infertility, but further studies are needed toevaluate effects of metformin with letrozole vs metformin with clomiphene citrate[15].

Garg N in his study concluded that letrozole has much higher efficacy in terms of ovulation induction as compared to CC.[16]Another studyconcluded after evaluating 19 trials, a higher ovulation rate in women with Polycystic Ovarian Syndrome in letrozole group than the women in clomiphene citrate group. Thus resulting in higher pregnancy rates and live births[17]. In Hussain et al[18] study, pregnancy rate was higher in the Letrozole group vs the CC group, 25.3% and 16% respectively. A meta-analysis by Polyzos et al studied role of aromatase inhibitors, summed up the previous literature[19,20].

Mehmet Nafi Sakar et AL, recommends letrozoleas first-line treatment for ovulation induction in women with PCOS having anovulatory infertility[21]. Abu Hashim in his study concluded that CC is not an effective agent for ovulation induction in every circumstances[22]. A recent study, conducted in 2022, showed that the women in letrozole group had much higher cumulative live births i.e.; 36 of 50(72%)as compared to 28 of 50 (56%) in clomiphene group[23].

Bansal et Al conducted a study recently and concluded that letrozole is more significant agent for ovulation induction than clomiphene citrate in patients with anovulation as higher pregnancy rates were found in letrozole group. This study also showed that letrozole is associated with monofollicular ovulation[24].

Hu S along with his companions concluded after a meta analysis of nine randomized control trials that; letrozole resulted more significant in terms of ovulation rate, pregnancy rate and live births. However, clomiphene citrate and letrozole showed no significant difference in terms of multiple pregnancy and miscarriages[25].

CONCLUSION

We concluded from this study that letrozole is proved to be more efficacious than clomiphene citrate in anovulatory infertility.

Keywords: Anovulation, Infertility, Letrozole, Clomiphene Citrate, Conception Rate
Conflict of interest: Nil

REFERENCES

1. Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, et al. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J Hum Reprod Sci. 2012;5:20-5.
2. El-Gharib MN, Mahfouz AE, Farahat MA. Comparison of letrozole versus tamoxifen effects in clomiphen citrate resistant women with polycystic ovarian syndrome. J Reprod Infertil. 2015;16:30-5.
3. Eftekhar M, Mohammadian F, Davar R, Pourmasumi S. Comparison of pregnancy outcome after letrozole versus clomiphene treatment for mild ovarian stimulation protocol in poor responders. Iran J Reprod Med. 2014;12:725-30.
4. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril. 2009;92:849-52.
5. Sakhavar N, Kaveh M, Sadegi K. The impact of letrozole versus clomiphene citrate on uterine blood flow in patients with unexplained infertility. J Family Reprod Health. 2014;8:1-5.
6. Kamath MS, George K. Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. Reprod Biol Endocrinol. 2011;9:86.
7. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: a prospective randomized trial. J Hum Reprod Sci. 2012;5:262-5.
8. Ibrahim MI, Moustafa RA, Abdel-Azeem AA. Letrozole versus clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. Arch Gynecol Obstet. 2012;286:1581-7.
9. Banerjee Ray P, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Arch Gynecol Obstet. 2012;285:873-7.
10. Akbari S, Ayazi RM, Ayazi RF. Comparing of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles. Iran J Reprod Med. 2012;10:29-32.
11. Brown J, Farquhar C, Beck J, Boothroyd C, Proctor M, Hughes E. Oral anti-estrogen and medical adjuncts for subfertility associated with anovulation. Cochrane Database Syst Rev. 2009;1 CD002249. [PubMed]
12. Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. J Assist Reprod Genet. 2009;26:19–24.
13. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotropins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertil Steril. 2007;88:879–885.
14. Landeras J, Herrero J, Navarro E, Neyro JL, Salvador C, Tur R, et al. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Hum ReprodUpdate. 2008;14:571–582.
15. Behnoud N, Bahrami R, Kordafshari G, Farzaneh F, Kenari HM. Management of early menopause using traditional Persian medicine: a case report. International Journal of Women's Health and Reproduction Sciences. 2019;7(2):231-6.
16. Garg N, Vanitha VG. A Comparative Study of Letrozole Vs Clomiphene Citrate as First Line for Anovulatory Infertility–An Institutional Experience. Asian Research Journal of Gynaecology and Obstetrics. 2019 Apr 11:1-8.
17. Tsiami AP, Goulis DG, Sotiriadis AI, Kolibianakis EM. Higher ovulation rate with letrozole as compared with clomiphene citrate in infertile women with polycystic ovary syndrome: a systematic review and meta-analysis. Hormones. 2021 Sep;20(3):449-61.

18. Hussain NHN, Ismail M, Zain MM, Yeu PC, Ramli R, Mohammad WMZW.Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. Open J Obstet Gynecol 2013;3:11-7.
19. Polyzos N, Tsappi M, Mauri D, Atay V, Corinovis I, Casazza G: Aromatase Inhibitors for infertility in polycystic ovary syndrome. The beginning or the end of a new era?. Fertil Steril. 2008, 89: 278-280.
20. Polyzos N, Tzioras S, Badawy AM, Valachis A, Dritsas C, Mauri D: Aromatase Inhibitors for female infertility: a systemic review of the literature. Reprod Biomed Online. 2009, 19: 456-471.
21. Sakar MN, Oglak SC. Letrozole is superior to clomiphene citrate in ovulation induction in patients with polycystic ovary syndrome. Pakistan Journal of Medical Sciences. 2020 Nov;36(7):1460.
22. Abu Hashim H, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril. 2010;94:1405–1409.
23. Pandya MR, Patel K. P-596 Comparative efficacy of Letrozole (5 mg) versus Clomiphene citrate (100 mg) for ovulation induction among infertile women. Human Reproduction. 2022 Jul;37(Supplement_1):deac107-548.
24. Bansal S, Goyal M, Sharma C, Shekhar S. Letrozole versus clomiphene citrate for ovulation induction in anovulatory women with polycystic ovarian syndrome: A randomized controlled trial. International Journal of Gynecology & Obstetrics. 2021 Mar;152(3):345-50.
25. Hu S, Yu Q, Wang Y, Wang M, Xia W, Zhu C. Letrozole versus clomiphene citrate in polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Archives of gynecology and obstetrics. 2018 May;297(5):1081-8.