



Comparison of letrozole and clomiphene citrate efficacy in terms of ovulation induction and pregnancy rate.

Nadia Sharif¹, Uzma Manzoor², Saadia Bano³, Uzma Shahzaad⁴

1. FCPS
Associate Professor Obst & Gynae
Independent Medical College,
Faisalabad.
2. FCPS
Assistant Professor Obst & Gynae
Independent Medical College,
Faisalabad.
3. FCPS
Associate Professor Obst & Gynae
Independent Medical College,
Faisalabad.
4. FCPS
Associate Professor Obst & Gynae
Independent Medical College,
Faisalabad.

Correspondence Address:

Dr. Nadia Sharif
Department of Obst & Gynae
Independent Medical College,
naadiasharif@hotmail.com

Article received on:

12/02/2021

Accepted for publication:

16/04/2021

ABSTRACT... Objective: To compare the efficacy of Letrozole and clomiphene citrate in Patients of Anovulation polycystic ovarian syndrome with Infertility. **Study Design:** Randomized Controlled Trial **Setting:** Department of Obstetrics and Gynecology Independent Medical College Faisalabad. **Period:** 30-09-2019 to 29-6-2020. **Material & Methods:** This study included 100 patients with 50 patients in each group. Group A received 2.5 to 5mg letrozole in each cycle from day 3 to 7. Group B received clomiphene citrate 50 to 100 mg incremental dose depending on ovarian response. Both Drugs were given for consecutive 3 to 6 cycles to see response. Main outcome Measure included optimal follicle size (> 18mm), endometrial thickness, and pregnancy rate. Epidemiological data and efficacy outcome measures were recorded on a Performa. Statistical analysis was done using SPSS version 13. Chi-square test applied and p-value <0.05 was considered significant. Both group included primary infertility patients. **Results:** The mean age of patients was 28.03+ 3.02 years. Mean age of group A patients was 29.04+3.44 and 28.47+3.90 group B patients. Mono ovulation in group A patients (88.9%) and 27 in group b patients (60.0%). The mean endometrial thickness was 9.6mm + 1.6 in letrozole group and 6.9mm + 1.2 in clomiphene citrate group A. In group A 18% got pregnant from Letrozole group and 1.1% from the group B. **Conclusion:** Efficacy was significantly higher in group A Patients received letrozole as compared to patients echo received clomiphene citrate. The effects of Letrozole showed better outcome in terms of Ovulation Induction Endometrial Thickness and Pregnancy rate.

Key words: Clomiphene Citrate, Endometrial Thickness, Letrozole, Ovulation Induction.

Article Citation: Sharif N, Manzoor U, Bano S, Shahzaad U. Comparison of letrozole and clomiphene citrate efficacy in terms of ovulation induction and pregnancy rate. Professional Med J 2021; 28(5):749-754.
<https://doi.org/10.29309/TPMJ/2021.28.05.6497>

INTRODUCTION

Infertility is defined as the inability to conceive despite regular unprotected sexual intercourse over a specific Period of time, usually 1-2 years.¹ The cumulative spontaneous pregnancy rate for a couple is approximately 57 percent after three months, 72 percent after six months, 85 percent after one year and 93 percent after 2 years. It has been estimated that infertility effects 9 percent of couples, of Whom 70 percent suffer from Primary Infertility with no previous conception and 30 percent Secondary infertility have achieved a previous pregnancy (Regardless of outcome of that pregnancy). The most common cause of primary Infertility is now male factor closely followed by ovulatory disorders.² The tubal disease is the most common cause of Secondary

Infertility Pakistan is a highly populated country, still infertility affects 30% of Pakistan population with the prevalence of Primary Infertility 5 % and 18 % Secondary Infertility.³ Ovulation induction is one of the most successful treatment of infertility due to anovulation.⁵ Polycystic Ovarian syndrome is most common disorders, often Complicated by chronic anovulatory Infertility.⁴ It is characterized by ovarian dysfunction, and its clinical manifestations may include obesity, increased Insulin resistance and compensatory hyperinsulinemia, oligo/anovulation and infertility. PCOS (polycystic ovarian syndrome) may represent the largest under addressed segment of the female cause of infertility. For years clomiphene citrate is used as a first-choice drug for Ovulation induction in

patients with PCOS associated anovulation. It is not, successful in all situations. It is a selective estrogen receptor modulator (SERM). It reduces negative feedback effect of circulating estrogen, there by triggering Hypothalamic Gonadotropin-releasing hormone (GNRH) reaction and increase of pituitary gonadotropins follicle-stimulating hormones (FSH) and Luteinizing stimulating hormones (LH) leading to follicular selection and ovulation in 5-12 days after the last dose.⁶ It is not however equally successful in all cases and many lead to resistance in ovulation in 15-20% of the patients. Clomiphene citrate may have a negative effect.⁷ In addition Clomiphene citrate has a negative effect on cervical mucus and endometrium.

The alternative treatments to Clomiphene citrate are insulin sensitizing drugs such as letrozole (Aromatase inhibitor). They have attracted attention for ovulation Induction as the discrepancy between ovulation and pregnancy rates with Clomiphene citrate has been attributed to its anti-estrogenic action and estrogen receptor depletion. The aromatase inhibitors suppress estrogen production and there by mimic the central reduction of negative feedback through which Clomiphene citrate works.⁸ The adverse effects on endometrium and cervical mucus are considerably less than Clomiphene citrate. There are reports of higher pregnancy rate with lower incidence of multiple pregnancies.⁹

The aim of this study was to compare efficiency of letrozole and clomiphene citrate in attaining optimum follicle size (> 18mm) increase in endometrial thickness receptive after implantation and pregnancy. This study will provide information for selecting the most appropriate and efficient drug for ovulation induction in primary infertility patients with anovulation.

MATERIAL & METHODS

The randomized controlled study was conducted At Department Gynecology and Obstetrics, Independent medical college, Faisalabad for a period of 9months starting from 30-sep-2019 to 29-june-2020. The study was approved by the institutional Ethical Committee. Total 100 patients

were included in this study after informed consent.

Inclusion Criteria

All patients with anovulatory primary infertility due to POCS. The subjects must have tubal patency ensured by either laparoscopically or by hysterosalpingography and have at least one patent tube.

Exclusion Criteria

Male infertility, liver, renal or Diabetes. Women with history of any Gynecological Disease.

The patients were divided into two groups each comprised of 50 patients. Study Group A was given Letrozole 2.5-5 mg once a day from Day 3 to 7 of menstrual cycle. Study Group B was given Clomiphene 50mg / 100mg from day 3 to 7 of menstrual cycle.

All patients were followed for 6 months of pregnancy during this period. Both groups were followed by transvaginal ultrasound for follicle tracking on day 12 of the menstrual cycle. At least one follicle of >18mm was considered adequate, Injection HCG (10,000IU) was given intramuscularly and advise to have coitus for 24-36 hours after HCG injection. If adequate size of follicle not achieved in one cycle then subsequently dose is incremented to 5mg in next cycle. In case of group B clomiphene citrate was given at doze of 50mg in first cycle. If follicle not achieved incremental dose to 100mcg in next cycle in same pattern as done for group A.

Ultrasound screening was done in order to monitor the size of follicle and later on to confirm ovulation, number of follicle and size, endometrial thickness and pregnancy rate. The outcome measured were optimal follicle size endometrial thickness (>6mm), ovulation follicle and pregnancy rate. And patient is called for Urine pregnancy test on day 35 or if she misses her period. All variables are articulated as mean + standard deviation and Qualitative test were expressed as Frequencies in percent. The statistical analysis was done by SPSS and P value <0.05 was considered statistically significant.

RESULTS

The mean age in study was 28.03+ 3.02 years. Mean age of group A patients was 29.04+3.44 and 28.47+3.90 group B patients. P value >0.05, Difference not statistically significant. The age distribution in both groups is given in Table-I.

Age in (years)	Group A (Letrozole)	Group B (Clomiphene Citrate)
	Frequency (%)	Frequency (%)
20-25	22(44%)	20(40%)
26-30	16(32%)	8(16%)
31-35	10(20%)	20(40%)
36-40	2(4%)	2(4%)

Table-I. Age stratification in both groups.

The duration of infertility was recorded in Table-II and the duration of Infertility in present study was not statistically significant between two groups.

In years	Group A (Letrozole)	Group B (Clomiphene Citrate)
	Frequency (%)	Frequency (%)
1-2	12(24%)	10(20%)
2-4	16(32%)	14(28%)
4-6	10(20%)	12(24%)
6-8	10(20%)	10(20%)
8-10	2(4%)	4(8%)

Table-II. Duration of infertility.

Comparison of Endometrial Thickness was done in our Patients. More in group with letrozole as compared to clomiphene citrate. In group A the mean endometrial thickness was 9.6 + 1.6mm and in group B it was 6.9 + 1.2 mm and statistically significant with p-value < 0.001.

Ovulation which meant achieving of desired size of follicle >18 mm diameter. In case of clomiphene citrate group induction done in 155 cycles of 50 Patients and among them ovulation occur in only 75 cycles. The difference of ovulation rate in both groups was significant statistically (P<0.01). The rate ovulation was found to be more in letrozole group than clomiphene citrate.

	Group A (Letrozole)	Group B (Clomiphene citrate)
Ovulation	Frequency (%)	Frequency (%)
Occurred	41(81.65%)	33(65.51%)
Not Occur	9(18.34%)	17(34.48%)

Table-III. Percentage of successful ovulation.

The letrozole group conception rate was need to double as compared to patient who reserved clomiphene citrate. The difference between two groups is statistically significant value (P<0.05) Table-IV.

	Group A (Letrozole)	Group B (Clomiphene citrate)
	Frequency (%)	Frequency (%)
Not Conceive	28(57%)	32(64%)
Conceived	22(43%)	18(36%)

Table-IV. Percentage of pregnancy rate or successful conception rate.

DISCUSSION

A randomized double trial by s Fisher SA Raid RL, Van Vugt DA, Casper RF showed the most common cause of infertility in women is anovulation.¹¹ There are many drugs used for ovulation induction in patients with PCOD anovulation infertility. The first line oral treatment is non-steroidal selective estrogen receptor modulators (SERM).¹⁰ Since 1962 it has been the drug of choice for oral ovulation induction over the last 50 years.¹² Unfortunately there is a group of women resistant to clomiphene citrate and fail to ovulate. Letrozole is another drug which is found to be very effective in ovulation induction in patients with an ovulatory infertility and having polycystic ovarian disease.

Letrozole increases FSH levels and therefore increases the number of mature follicles.¹³ It does not have adverse endometrial effects as clomiphene citrate has due to its antiestrogen effects. Its half-life is shorter than clomiphene citrate, so it also increases pregnancy rate due to its effects on endometrium. Abu Hashim said that: Clomiphene citrate is not equally effective in all situations for induction of ovulation.¹⁴

Stephanie and co-workers demonstrated that the aromatase inhibitors "Letrozole is equivalent to clomiphene for stimulation of Follicular growth in normal ovulatory women. Significant number of follicles were observed in cycles stimulated with 2.5 mg letrozole compared with cycles stimulated with 100 mg clomiphene.¹³ Elnashan et al (2006) reported an ovulation rate of 54.6% and pregnancy rate of 25% with letrozole induction in clomiphene citrate resistant women PCOS.¹⁶ Ganesh et al (2000) reported the ovulation rate of 79.3% with letrozole.¹⁷ This data is comparable to ovulation rate of 88.9% in one study.¹⁵

Mitwally and Casper used Letrozole for ovulation induction and reported 75% success when letrozole was used.¹⁸ Another study by Legro et al randomly assigned 750 women with anovulatory infertility and PCOS to receive ovulation induction with either clomiphene citrate as letrozole for 5 consecutive cycles.¹⁹ He observed ovulation in 61.7% of letrozole group patient verses only 48.3% in clomiphene citrate patients. ($P < 0.001$). In our study Ovulation occurred in 81.65% of patients.

Similarly, the conception rate was significantly higher in Letrozole group as compared to patients who receive clomiphene citrate. Owing to favorable effect of letrozole on endometrium verses clomiphene antiestrogen effects. In another study by Tom Tanbo²⁰ letrozole treatment resulted in higher ovulation, pregnancy with a lower multiple pregnancy rate. Study by Ratnabali Chakra vortyard Amitoj Athwal also showed similar outcome of rate of ovulation and pregnancy in patients had ovulation induction with letrozole 37.8% had ovulation in letrozole group verses 13% in clomiphene citrate group. The conception rate 24% in letrozole as compared to 15% in clomiphene citrate taking patients.^{21,22}

A study by vadenemek oriji and kennedy Nyengidiki showed similar results for rate of ovulation in patients offered letrozole as compare to clomiphene citrate with ovulation rate of 81% verse 76% in respective groups.²³

The limitation of study was that it is a single center

study and the pregnancy was not followed for nine months to estimate successful pregnancy rate. Increased period of follow up with multiple centers would improve the data of study.

CONCLUSION

Our study showed that letrozole has excellent pregnancy rates compared to clomiphene citrate. Letrozole should be considered as par with clomiphene citrate as first line drug for ovulation induction in patients sufferings from anovulatory infertility due to PCODS.

Copyright© 16 April, 2021.

REFERENCES

1. Luesley DM, Kilby M, editors. **Obstetrics & Gynaecology: An evidence-based text for MRCOG.** CRC Press; 2016 Mar 30.
2. Edmonds K. **Dewhurst's Textbook of Obstetrics & Gynaecology.** John Wiley & Sons; 2018 Nov 12.
3. Saoji AV. **Primary infertility problems among female have been a source of concern in India lately.** Innovative J Med Health Sci. 2014 Jan; 4(1):332-40.
4. Ledger WL, Atkin SL, Sathyapalan T. **Long term consequence of polycystic ovary syndrome Green top Guideline,** No 33 November 2014.
5. Norwitz ER, Schorge JO. **Obstetrics and Gynecology at a glance.** John Wiley & Sons; 2013 Oct 14.
6. Khan RL, Khan YL. **Textbook of Gynaecology.** 6th edition. 2017.
7. Bao SH, Sheng SL, Peng YF, Lin QD. **Effects of letrozole and clomiphene citrate on the expression of HOXA10 and integrin alpha v beta 3 in uterine epithelium of rats.** Fertil Steril. 2009 Jan; 91(1):244-8. doi: 10.1016/j.fertnstert.2007.11.024. Epub 2008 Feb 4. PMID: 18249394.
8. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. **The management of anovulatory infertility in women with polycystic ovary syndrome: An analysis of the evidence to support the development of global WHO guidance.** Hum Reprod Update. 2016 Nov; 22(6):687-708. doi: 10.1093/humupd/dmw025. Epub 2016 Aug 10. PMID: 27511809.
9. Casper RF, Mitwally MF. **Review: Aromatase inhibitors for ovulation induction.** J Clin Endocrinol Metab. 2006 Mar; 91(3):760-71. doi: 10.1210/jc.2005-1923. Epub 2005 Dec 29. PMID: 16384846.

10. Beck JL, Boothroyd C, Proctor M, Farquhar C, Hughes E. **Oral anti-oestrogens and medical adjuncts for subfertility associated with anovulation.** Cochrane Database Syst Rev. 2005 Jan 25; (1):CD002249. doi: 10.1002/14651858.CD002249.pub3. Update in: Cochrane Database Syst Rev. 2009; (4):CD002249. PMID: 15674894.
11. Fisher SA, Reid RL, Van Vugt DA, Casper RF. **A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women.** Fertil Steril. 2002 Aug; 78(2):280-5. doi: 10.1016/s0015-0282(02)03241-7. PMID: 12137863.
12. Sipe CS, Davis WA, Maifeld M, Van Voorhis BJ. **A prospective randomized trial comparing anastrozole and clomiphene citrate in an ovulation induction protocol using gonadotropins.** Fertil Steril. 2006 Dec; 86(6):1676-81. doi: 10.1016/j.fertnstert.2006.05.048. Epub 2006 Sep 27. PMID: 17007849.
13. Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T. **A randomized trial of superovulation with two different doses of letrozole.** Fertil Steril. 2006 Jan; 85(1):161-4. doi: 10.1016/j.fertnstert.2005.07.1283. PMID: 16412748.
14. Abu Hashim H, Shokeir T, Badawy A. **RETRACTED: 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 Sep; 94(4):1405-1409. doi: 10.1016/j.fertnstert.2009.07.985. Epub 2009 Sep 3. Erratum in: Fertil Steril. 2020 Sep; 114(3):667. PMID: 19732888.
15. Hughes E, Collins J, Vandekerckhove P. **Clomiphene citrate for ovulation induction in women with oligo-amenorrhoea.** Cochrane Database Syst Rev. 2000; (2):CD000056. doi: 10.1002/14651858.CD000056. Update in: Cochrane Database Syst Rev. 1996; (1):CD000056. PMID: 10796477.
16. Elnashar A, Fouad H, Eldosoky M, Saeid N. **Letrozole induction of ovulation in women with clomiphene citrate-resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/follicle-stimulating hormone ratio.** Fertil Steril. 2006 Feb; 85(2):511-3. doi: 10.1016/j.fertnstert.2005.08.016. PMID: 16595244.
17. 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 Jan; 26(1):19-24. doi: 10.1007/s10815-008-9284-4. Epub 2009 Jan 7. PMID: 19127427; PMCID: PMC2649330.
18. Mitwally MF, Casper RF. **Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate.** Fertil Steril. 2001 Feb; 75(2):305-9. doi: 10.1016/s0015-0282(00)01705-2. PMID: 11172831.
19. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; **NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome.** N Engl J Med. 2014 Jul 10; 371(2):119-29. doi: 10.1056/NEJMoa1313517. Erratum in: N Engl J Med. 2014 Oct 9; 317(15):1465. PMID: 25006718; PMCID: PMC4175743.
20. Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. **Ovulation induction in polycystic ovary syndrome.** Acta Obstet Gynecol Scand. 2018 Oct; 97(10):1162-1167. doi: 10.1111/aogs.13395. Epub 2018 Jul 24. PMID: 29889977.
21. Sammour A, Biljan MM, Tan SL, Tulandi T. **Prospective randomized trial comparing the effects of letrozole (LE) and clomiphene citrate (CC) on follicular development, endometrial thickness and pregnancy rate in patients undergoing super-ovulation prior to intrauterine insemination (IUI).** Fertility and Sterility. 2001; 3(76):S110.
22. Chakravorty R, Athwal A, Sur D, Saha R. **A prospective, randomized trial comparing the effects of letrozole versus clomiphene citrate for induction of ovulation and pregnancy rate in women with polycystic ovary syndrome.** Fertility Science and Research. 2016 Jul 1; 3(2):93.
23. Oriji VK, Nyengidiki K. **Ovulation induction in women with polycystic ovary syndrome: What is the optimal option?.** In Debatable Topics in PCOS Patients 2017 Dec 20. IntechOpen.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Nadia Sharif	Main Author	<i>Nadia Sharif</i>
2	Uzma Manzoor	Co-Author	<i>uzma manzoor</i>
3	Saadia Bano	Co-Author	<i>Saadia</i>
4	Uzma Shahzaad	Co-Author	<i>Uzma Shahzaad</i>