ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

Comparing Letrozole versus Clomiphene for PCOS-Related Infertility — A Single-Center Study

DOI: dx.doi.org

Shayla Sharmin[1*], Jahanara Rahman[2], Atiquzzaman[3]

Received: 19 November 2024
Accepted: 28 November 2024
Published: 15 December 2024

Published by:
Gopalganj Medical College,
Gopalganj, Bangladesh

*Corresponding Author

ABSTRACT

Introduction*: Polycystic Ovary Syndrome (PCOS), a common endocrine disorder affecting women of reproductive age, is characterized by hyperandrogenism, anovulation, and polycystic ovaries. Infertility is a frequent consequence of PCOS, primarily due to anovulation. Letrozole and Clomiphene Citrate, two widely used medications for treating PCOS-related infertility.* ***Objective:*** *Purpose of this study to compare the efficacy and safety of Letrozole vs. Clomiphene Citrate for PCOS-related infertility.* ***Methods and Materials****: A single-center RCT was conducted in OPD of Dhaka National Medical College in Bangladesh from 1st January 2022 to 31st December 2022. Total 160 patients diagnosed with PCOS with infertility according to Rotterdam criteria were recruited and randomly assigned into two groups after taking written informed consent. The women were followed by Ultrasound to monitor follicular development, endometrial thickness, ovulation, and pregnancy outcomes.* ***Results:*** *While both groups had similar distributions of infertility types and endometrial thickness, a significant difference was observed in follicular development (p = 0.002). Group A had a higher rate of mono-follicular development, while Group B showed more multi-follicular development. No significant difference was found in ovulation rates (p = 0.796), but Group A had a significantly higher pregnancy rate than Group B (p = 0.000961).* ***Conclusion****: letrozole is better than clomiphene citrate in patients with PCOS with subfertility where letrozole users demonstrated significantly higher pregnancy rates than clomiphene citrate users. So letrozole should be considered as first line treatment option for ovulation induction in patients with PCOS with subfertility.*

Keywords: *Infertility, PCOS, Letrozole, Clomiphene Citrate, Endometrial Thickness*

(The Insight 2024; 7(1): 360-366)

1. *Assistant Professor, Department of Gynae and Obstetrics, Dhaka National Medical College, Dhaka, Bangladesh*
2. *Professor, Department of Gynae and Obstetrics, Dhaka National Medical College, Dhaka, Bangladesh*
3. *Associate Professor, Medicine Department, Dhaka National Medical College, Dhaka, Bangladesh*

INTRODUCTION

Hormone imbalance is a complex disorder associated with PCOS. Although the precise etiology is unknown, inflammation, insulin resistance, and hereditary factors are thought to have a role. The word "polycystic" describes a condition in which the ovaries have several little sacs filled with fluid, known as cysts. But frequently, the symptoms are not caused primarily by these cysts.

The diverse disorder known as polycystic ovary syndrome (PCOS) is frequently linked to oligo anovulation and clinical or biochemical hyperandrogenism brought on by ovarian malfunction. The primary factor contributing to this syndrome's status as the leading cause of anovulatory-associated infertility in developed nations is still ovarian dysfunction[1,2]. Although the exact cause of PCOS is unknown, it is thought to be the result of interactions between one or more environmental variables and genetics[3].

Several study results point to a genetic propensity among family members, even though the exact function of several genes is still unknown[4,5]. PCOS has recently been associated with the promoter -1031(T/C) polymorphism in tumour necrosis factor-alpha[6,7]. PCOS can present clinically as anything from a simple menstrual issue to a serious disruption of metabolic and reproductive processes. Cardiovascular disease and type 2 diabetes are more common in women with PCOS[8].

The symptoms of PCOS in women determine how to treat them. These could be indications of androgen malfunction, menstruation problems, or infertility linked to ovulatory failure. Losing weight raises the chance of ovulation and pregnancy and enhances the endocrine profile. Menstrual cycle normalization and ovulation can happen with as low as 5% of the starting weight lost. In addition to medication and surgery, lifestyle changes (diet and exercise) are part of the treatment for obesity. Novovulation in PCOS is associated with low levels of follicle-stimulating hormone and the termination of antral follicle development during the last phases of maturation. Medication options for treating this include clomiphene citrate, tamoxifen, metformin, letrozole, aromatase inhibitors, glucocorticoids, and gonadotropins. Surgical options include laparoscopic ovarian drilling[9]. A new therapy option that can challenge CC for ovulation induction in anovulatory women is letrozole, a non-steroidal aromatase inhibitor[10,11].

Clomiphene citrate is a non-steroidal selective modulator of the estrogen receptor with a strong anti-estrogenic effect that causes a prolonged depletion of estrogen receptors. For women with hypothalamic-pituitary dysfunction linked to normal basal levels of endogenous estradiol, clomiphene citrate (CC) has exhibited an exceptionally long history of use as the initial line of treatment for irregular or missing ovulation (WHO group II)[12]. Numerous studies have demonstrated that levozole is as effective as clomiphene, if not more so in terms of ovulation and pregnancy rates[13].

GENERAL OBJECTIVE

This study aims to evaluate the comparative efficacy and safety of Letrozole and Clomiphene Citrate in treating polycystic ovary syndrome (PCOS)-related infertility.

Specific Objectives:

1. To compare the ovulation rates induced by Letrozole and Clomiphene Citrate in women with PCOS with infertility.
2. To evaluate the pregnancy rates achieved with Letrozole and Clomiphene Citrate.

MATERIALS AND METHOD

A single-center, double-blind, randomized controlled trial (RCT) was *conducted* in the OPD of Dhaka National Medical College in Bangladesh from January 1, 2022, to December 31, 2022.

Eligible patients were randomly assigned to one of two groups using a computer-generated randomization sequence. To ensure allocation concealment, a researcher conducted the randomization process independently without involvement in the study, patient enrollment, or data collection.

A total of 160 patients diagnosed with PCOS with infertility according to Rotterdam criteria were recruited and randomly assigned into two groups after taking written informed consent. **Group A** included 80 patients receiving Letrozole, while **Group B** included 80 patients receiving Clomiphene Citrate for 6 menstrual cycles. Women were randomly assigned to receive Letrozole (Group A) 2.5 mg twice daily on the 2nd – 6th consecutive days of the menstrual cycle or Clomiphene Citrate (Group B) 50 mg twice daily on the 2nd – 6th consecutive days of the menstrual cycle. Transvaginal ultrasonography with folliculometry was performed on day 12 to monitor follicular development, endometrial thickness. Later on further follow up of the patient's done to monitor ovulation rate and pregnancy outcomes.

Ethical approval:

Ethical approval for the study was obtained from the Institute Ethics Committee.

Inclusion Criteria:

- Age: 20-35years old
- Fertility: Primary subfertility
- Husband with normal semen analysis
- Patent both tubes on hysterosalpingography
- Conception: No conception for at least one-year in spite of regular sexual intercourse

Exclusion Criteria:

- Age: < 20 years old or > 35years old
- Patients with hyperprolactinemia, thyroid disease, male subfertility, unexplained infertility
- Uterine Conditions: Uterine fibroid, ovarian cyst, pelvic endometriosis, PID
- Hypersensitivity: History of hypersensitivity to study drug

Statistical analysis:

All data were entered in SPSS version 23 and were utilized for all data analysis. For comparison Chi – square test was used between qualitative variables.

<0.05 P – value was considered statistically significant.

RESULTS

Table I presents a comparative analysis of basic socio-demographic characteristics between Group A and Group B. No significant differences were observed in the mean ages (Group A: 28.3 ± 2.8 years; Group B: 27.6 ± 3.2 years) or the mean ages of marriage (Group A: 21.5 ± 2.1 years; Group B: 20.8 ± 2.7 years) between the two groups (p>0.05 for both comparisons). There was no significant difference in the duration of infertility between the groups (Group A: 4.1 ± 1.5 years; Group B: 3.9 ± 2.2 years; p>0.05).

Table I: Basic Socio-Demographic Profile of the Study Cases

Socio-Demographic Profile	Letrozole(n=80)	Clomiphene Citrate(n=80)	p-value
Age (Years)	28.3± 2.8	27.6±.3.2	0.45
Age Of Marriage	21.5±2.1	20.8±2.7	0.45

Table II reveals a statistically significant association between follicular development and group assignment (p = 0.002). In Group A, 70% (56 cases) exhibited monofollicular development, compared to 55% (40 cases) in Group B. Conversely, multi-follicular development was observed in 32.5% (26 cases) of Group A compared to 45% (36 cases) of Group B. Endometrial thickness did not differ significantly between the groups (p > 0.05). The average thickness in Group A was 9.51 mm (standard deviation: 2.13 mm), while Group B averaged 8.34 mm (standard deviation: 2.09 mm).

Table II: Outcome of treatment

Development	Group A	Group B	p-value
Mono follicular development	56(70%)	40(55%)	0.002
Multi follicular development	26(32.5%)	36(45%)	
Endometrial thickness	9.51±2.13	8.34±2.09	>0.05

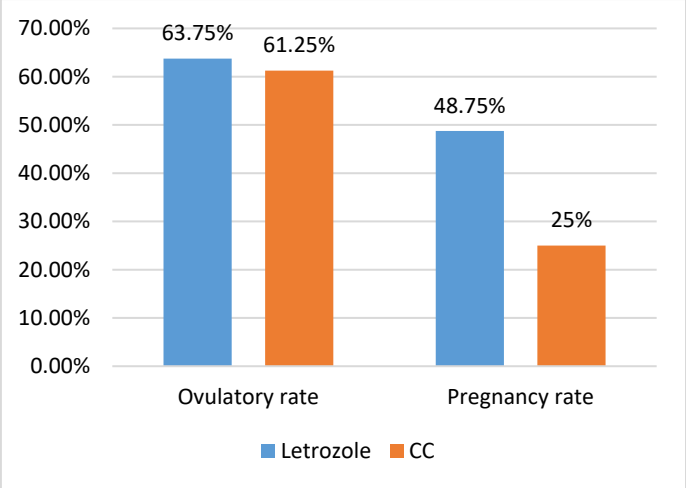

Figure 1: Pregnancy Rate of our Study Cases

Figure 1 presents a comparison of ovulation and pregnancy rates between groups A and B. The ovulation rate was similar in both groups, with no significant difference observed (p = 0.796). However, a significant disparity in pregnancy rates was found between the two groups (p = 0.000961). Specifically, group A exhibited a notably higher pregnancy rate than group B.

DISCUSSION

Our study undertakes a comprehensive comparative analysis of the socio-demographic characteristics of Group A and Group B participants. The results demonstrate that there were no significant differences between the two groups regarding the mean age of participants, with Group A having an average age of 28.3 ± 2.8 years and Group B having an average age of 27.6 ± 3.2 years (p > 0.05). Similarly, the mean age at marriage did not differ significantly between the groups, with Group A participants marrying at an average age of 21.5 ± 2.1 years and Group B at 20.8 ± 2.7 years (p > 0.05). These findings suggest that age and age at marriage do not appear to be distinguishing factors between the two groups[14].

Additionally, no significant differences were identified in the duration of infertility between the groups, with Group A having a mean duration of 4.1 ± 1.5 years and Group B 3.9 ± 2.2 years (p > 0.05). This finding suggests that the duration of infertility is relatively similar between the two populations[15].

Our findings further indicate a significant association between the type of follicular development and group assignment (p = 0.002). In Group A, mono follicular development was observed in 70% of participants (56 cases), while in Group B, it was present in 55% (40 cases). Conversely, multi-follicular development was more prevalent in Group B, with 45% (36 cases) exhibiting this condition, compared to 32.5% (26 cases) in Group A. These findings suggest that Group B may have a higher tendency towards

multi-follicular development. Despite these differences in follicular development, there was no significant difference in endometrial thickness between the groups (p>0.05) [16]. Group A exhibited an average endometrial thickness of 9.51 mm (standard deviation: 2.13 mm), while Group B had an average thickness of 8.34 mm (standard deviation: 2.09 mm), indicating similar endometrial characteristics.

Additionally, the study explored the ovulation and pregnancy rates in Groups A and B. The ovulation rates were comparable, with no statistically significant difference between the groups (p=0.796), suggesting that both groups had similar ovulatory responses[17]. However, a notable disparity was observed in pregnancy rates, with Group A demonstrating a significantly higher rate compared to Group B (p = 0.000961). This significant difference in pregnancy rates highlights a potential area for further investigation into factors contributing to the higher success rate in Group A[18]. Overall, our study provides valuable insights into the demographic and clinical characteristics of the two groups, revealing key areas of similarity and difference that may inform future research and clinical practice in reproductive health. Overall outcome Ovulation rate and pregnancy rate were found consistent with other studies[19].

Conclusion

Letrozole is better than clomiphene citrate in patients with PCOS with subfertility where letrozole users demonstrated significantly higher pregnancy rates than clomiphene citrate users. So letrozole should be considered as first line treatment option for ovulation induction in patients with PCOS with subfertility.

REFERENCE

1. *Baker P, Balen A, Poston L, Sattar N. Obesity and reproductive health. London: RCOG Press; 2007.*
2. *Hamilton-Fairley D, Taylor A. Anovulation. BMJ. 2003;327:546-9.*
3. *Tsikouras P, Spyros L, Manav B, Zervoudis S, Poiana C, Nikolaos T, et al. Features of polycystic ovary syndrome in adolescence. J Med Life. 2015;8(3):291.*
4. *Buggs C, Rosenfield RL. Polycystic ovary syndrome in adolescence. Endocrinol Metab Clin North Am. 2005;34(3):677-705.*
5. *Hassan A, Gordon CM. Polycystic ovary syndrome update in adolescence. Curr Opin Pediatr. 2007;19(4):389-97.*
6. *Yun JH, Choi JW, Lee KJ, Shin JS, Baek KH. The promoter-1031 (T/C) polymorphism in tumor necrosis factor-alpha associated with polycystic ovary syndrome. Reprod Biol Endocrinol. 2011;9:1-6.*
7. *Deligeoroglou E, Vrachnis N, Athanasopoulos N, Iliodromiti Z, Sifakis S, Iliodromiti S, et al. Mediators of chronic inflammation in polycystic ovarian syndrome. Gynecol Endocrinol. 2012;28(12):974-8.*
8. *Lakhani K, Prelevic GM, Seifalian AM, Atiomo WU, Hardiman P. Polycystic ovary syndrome, diabetes and cardiovascular disease: risks and risk factors. J Obstet Gynaecol. 2004;24(6):613-21.*
9. *Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011;3:25-35.*
10. *Mitwally MF, Casper RF. Aromatase inhibition: a novel method of ovulation induction in women with polycystic ovary syndrome. Reprod Technol. 2001;10(5):244.*
11. *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;75(2):305-9.*

12. *Homburg R. Clomiphene citrate—end of an era? A mini-review. Hum Reprod. 2005;20(8):2043-51.*
13. *Ramezanzadeh F, Nasiri R, Sarafraz Yazdi M, Baghrei M. A randomized trial of ovulation induction with two different doses of Letrozole in women with PCOS. Arch Gynecol Obstet. 2011;284:1029-34.*
14. *Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. Arch Gynecol Obstet. 2009;279:311-4.*
15. *Begum MR, Ferdous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertil Steril. 2009;92(3):853-7*
16. *Sohrabvand F, Ansari SH, Bagheri M. Efficacy of combined metformin–letrozole in comparison with metformin–clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Hum Reprod. 2006;21(6):1432-5.*
17. *Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. J Int Med Res. 2006;34(1):73-6.*
18. *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.*
19. *Zeba D, Biswas R, Fatema K, Khair MA, Zesmin F, Sharifa J. Letrozole or clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome: a prospective randomized trial. Faridpur Med Coll J. 2018;13(2):78-81.*