Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/ck164369

CLINICAL OUTCOMES OF LETROZOLE VERSUS CLOMIPHENE CITRATE IN OVULATION INDUCTION THERAPY

Humaira Alam*[1], Sayeba Akhter[2], Nigar Sultana[3], Kazi Farhana Begum[4]

[1*]Assistant Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Former Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Assistant Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[4]Medical Officer, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

***Corresponding Author:** Humaira Alam
*Assistant Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

Background: Clomiphene citrate has long been the standard treatment for ovulation induction in women with polycystic ovarian syndrome (PCOS); however, its antiestrogenic effects and resistance issues limit its efficacy. Letrozole, an aromatase inhibitor, has emerged as a promising alternative treatment. This study aimed to compare the clinical outcomes of letrozole versus clomiphene citrate in ovulation induction therapy among infertile women with PCOS in a Bangladeshi tertiary care setting.

Methods: This randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from January 2009 to December 2010. A total of 500 women (250 per group) with anovulatory infertility received either 2.5 mg letrozole or 50 mg Clomiphene citrate from days 2 to 6 of their menstrual cycle. The primary outcomes included ovulation rate, endometrial thickness, clinical pregnancy rate, and live birth rate.

Results: Letrozole showed a significantly higher ovulation rate (76.8% vs. 61.2%, p=0.001), thicker endometrium (8.9 mm vs. 7.4 mm, p<0.001), and improved clinical pregnancy (29.2% vs. 19.6%, p=0.01) and live birth rates (24.8% vs. 16.0%, p=0.02) than Clomiphene citrate. Adverse effects were more common in the Clomiphene citrate group.

Conclusion: Letrozole is more effective and better tolerated than clomiphene citrate for ovulation induction and should be considered a first-line option for the treatment of anovulatory infertility in similar clinical settings.

Keywords: Letrozole, Clomiphene Citrate, Ovulation Induction, PCOS, Infertility.

INTRODUCTION

Infertility is a major public health issue affecting 10–15% of reproductive-aged couples worldwide, with anovulatory disorders representing a leading cause, particularly in women with polycystic

ovary syndrome (PCOS) [1,2]. In South Asia, including Bangladesh, the prevalence of PCOS-related infertility is rising, attributed to changing lifestyle factors and increasing rates of metabolic disorders [3.4]. These challenges highlight the pressing need for effective, affordable, and safe ovulation induction therapies tailored to the regional population.

Clomiphene citrate (CC) has historically been the first-line treatment for ovulation induction. As a selective estrogen receptor modulator, CC acts at the hypothalamic level to increase gonadotropin release and stimulate follicular growth [5]. However, approximately 20–25% of women exhibit clomiphene resistance, and CC's anti-estrogenic effects on the endometrium and cervical mucus may impair implantation and reduce pregnancy success [6].

Letrozole, a third-generation aromatase inhibitor, has emerged as a promising alternative. By suppressing estrogen synthesis, letrozole induces a transient rise in follicle-stimulating hormone (FSH), promoting mono-follicular development while avoiding the peripheral anti-estrogenic effects seen with CC [7,8]. Mitwally and Casper first demonstrated its effectiveness in women who had inadequate responses to CC [8], and subsequent randomized controlled trials confirmed its potential in both CC-resistant and treatment-naïve women.

Clinical studies, including those by Zeinalzadeh et al. and El Bigawy et al., showed that letrozole not only improves ovulation rates but also results in better endometrial thickness compared to CC, enhancing implantation potential [9,10]. Moreover, Al-Fozan et al. demonstrated that letrozole is associated with a reduced risk of multiple follicular development, thereby lowering the likelihood of multiple pregnancies [11]. These advantages are particularly important in low-resource settings where minimizing complications is critical.

Evidence from South Asian studies further supports these findings. Ivy et al. reported significantly improved ovulation and pregnancy outcomes with letrozole among Bangladeshi women, while Begum et al. demonstrated its utility in women who previously failed CC therapy [12,13]. In addition, Zegers-Hochschild et al. emphasized that effective ovulation induction agents should be evaluated not only by ovulation rates but also by their impact on live births, safety, and patient tolerability [1].

This study was designed to compare the clinical outcomes of letrozole and clomiphene citrate in ovulation induction among women treated at a tertiary care center in Bangladesh. By focusing on ovulation, pregnancy, and safety profiles, this research aims to generate evidence relevant to both clinical decision-making and reproductive health policy in low- and middle-income settings.

METHODOLOGY & MATERIALS

This randomized controlled trial study was conducted at the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2009 to December 2010. A total of 500 participants were enrolled, with 250 randomly assigned to the letrozole group and 250 to the clomiphene citrate group. The study population included women aged 20–35 years who presented with primary or secondary infertility attributed to anovulatory polycystic ovarian syndrome (PCOS).

Inclusion criteria:

1. Women diagnosed with anovulatory infertility based on the Rotterdam criteria for PCOS
2. Normal thyroid and prolactin levels
3. Patent fallopian tubes confirmed by hysterosalpingography (HSG) or laparoscopy

Exclusion criteria:

1. Known hypersensitivity to letrozole or clomiphene
2. History of ovarian surgery or malignancy
3. Hyperprolactinemia or thyroid dysfunction
4. Uterine abnormalities such as fibroids or synechiae
5. Male factor infertility

Data Collection and Study Procedure:
Written informed consent was obtained from all participants before inclusion. A structured data collection form was used to record the baseline characteristics, hormonal profiles, ultrasound findings, and treatment responses. Participants in the letrozole group received 2.5 mg daily from days 2 to 6 of the menstrual cycle, while those in the CC group received 50 mg daily during the same period. Ovulation was monitored via transvaginal sonography, and endometrial thickness was measured on days 12–14 of the cycle. Pregnancy was confirmed by serum β-hCG levels 14 days after ovulation and transvaginal ultrasound at 6 weeks. All data were anonymized to ensure participant confidentiality and were analyzed using SPSS version 17.0. Statistical tests included chi-square for categorical variables and t-test for continuous variables, with $p < 0.05$ considered significant.

RESULTS

Table 1: Baseline characteristics of the study participants (n=250)

Characteristic	Letrozole Group (n=250)	CC Group (n=250)	p-value
Mean Age (years)	26.8 ± 3.4	27.1 ± 3.6	0.41
BMI (kg/m²)	25.2 ± 2.9	25.5 ± 3.1	0.35
Duration of Infertility (yrs)	3.6 ± 1.8	3.5 ± 1.9	0.78
Serum FSH (mIU/mL)	6.2 ± 1.1	6.4 ± 1.0	0.15
Serum LH (mIU/mL)	9.3 ± 2.3	9.5 ± 2.1	0.45
Hirsutism	56 (22.4)	54 (21.6)	0.82
Oligomenorrhea	172 (68.8)	175 (70.0)	0.77

Table 1 describes the baseline characteristics of the study population. The mean age of participants in both groups was similar (Letrozole: 26.8 ± 3.4 years; CC: 27.1 ± 3.6 years). Body mass index (BMI), duration of infertility, and hormonal parameters (FSH, LH) showed no statistically significant differences. Hirsutism was observed in 56 (22.4%) participants in the letrozole group and 54 (21.6%) in the CC group, while oligomenorrhea was noted in 172 (68.8%) and 175 (70.0%), respectively.

Table 2: Ovulation and Pregnancy Outcomes

Outcome	Letrozole (n=250)	Clomiphene Citrate (n=250)	p-value
Ovulation Rate	192 (76.8)	153 (61.2)	0.001
Monofollicular Ovulation	149 (59.6)	103 (41.2)	0.002
Bi-/Multifollicular	33 (13.2)	70 (28.0)	0.001
Endometrial Thickness (≥ 8 mm)	180 (72.0)	130 (52.0)	<0.001
Cycle Cancellation	11 (4.4)	24 (9.6)	0.02

Table 2 presents ovulation and endometrial findings. The ovulation rate was significantly higher in the letrozole group (192, 76.8%) than in the CC group (153, 61.2%). Monofollicular ovulation occurred in 149 (59.6%) women treated with letrozole compared to 103 (41.2%) with CC, whereas multifollicular ovulation was more frequent in the CC group (70, 28.0%) versus letrozole (33, 13.2%). Endometrial thickness ≥ 8 mm was observed in 180 (72.0%) of the letrozole group compared to 130 (52.0%) in the CC group ($p < 0.001$). Cycle cancellation was significantly lower in the letrozole group (11, 4.4%) versus CC (24, 9.6%).

Table 3: Pregnancy and Live Birth Outcomes

Outcome	Letrozole (n=250)	Clomiphene Citrate (n=250)	p-value
Clinical Pregnancy	73 (29.2)	49 (19.6)	0.01
Live Birth	62 (24.8)	40 (16.0)	0.02
Multiple Pregnancy	6 (2.4)	14 (5.6)	0.06
Miscarriage	11 (4.4)	14 (5.6)	0.53

Table 3 outlines pregnancy-related outcomes. Clinical pregnancy and live birth rates were significantly higher in the letrozole group (29.2% and 24.8%, respectively) than in the CC group (19.6% and 16.0%). Although the miscarriage rate was marginally lower in the letrozole group (4.4% vs. 5.6%), this difference was not statistically significant. Notably, the incidence of multiple pregnancies was lower in the letrozole group (2.4%) than in the CC group (5.6%).

Table 4: Adverse Effects and Tolerability

Side Effects	Letrozole (n=250)	Clomiphene Citrate (n=250)	p-value
Headache	16 (6.4)	27 (10.8)	0.08
Hot Flashes	9 (3.6)	28 (11.2)	0.001
Nausea	13 (5.2)	12 (4.8)	0.83
Abdominal Discomfort	18 (7.2)	23 (9.2)	0.41
Patient-reported Tolerance	231 (92.4)	212 (84.8)	0.01

Table 4 highlights adverse effects and patient-reported tolerability. Headaches and hot flashes were significantly more prevalent in the CC group (10.8% and 11.2%, respectively) compared to the letrozole group (6.4% and 3.6%). Nausea and abdominal discomfort occurred at similar frequencies in both groups. Overall patient-reported tolerance was higher in the letrozole group (92.4%) than in the CC group (84.8%).

DISCUSSION

The present study demonstrates that letrozole offers superior ovulation induction outcomes compared to clomiphene citrate (CC) in Bangladeshi women with anovulatory infertility, which aligns with several regional and international trials. Ivy et al. reported a significantly higher ovulation rate and improved endometrial thickness with letrozole in a Bangladeshi cohort, findings that mirror our results [12]. Similarly, Ray et al. observed higher pregnancy rates with letrozole in Indian women, highlighting its relevance in South Asian populations [14].

The superior ovulation rate in our study (76.8% for letrozole vs. 61.2% for CC) is comparable to the outcomes in the randomized trial by Atay et al., which demonstrated enhanced monofollicular ovulation with letrozole [15]. This is clinically significant because monofollicular ovulation reduces the risk of multiple pregnancies while maintaining conception potential. Fisher et al. further supported these findings, showing that letrozole preserves normal hypothalamic-pituitary feedback, facilitating more physiological ovulation [16].

Endometrial thickness is another critical determinant of implantation. Our findings of greater endometrial thickness in the letrozole group are supported by studies from Sammour et al. and Gonen & Casper, which emphasized that CC's anti-estrogenic effects can lead to a thinner, less receptive endometrium [17,18]. By contrast, letrozole's aromatase inhibition avoids receptor depletion, allowing favorable endometrial development and better receptivity.

Pregnancy outcomes in this study were also consistent with prior evidence. Hussain et al. in Malaysia and Aletebi & Alaa in a randomized controlled trial found significantly higher clinical pregnancy rates with letrozole compared to CC [19,20]. Hajishafiha et al. also reported higher pregnancy rates in women receiving letrozole during intrauterine insemination cycles [21]. These findings reinforce letrozole's superiority in improving conception outcomes.

Adverse effects in our trial were less frequent in the letrozole group, aligning with reports from Casper and Begum et al., who noted that CC is associated with vasomotor symptoms such as hot flashes due to its anti-estrogenic action [7,13]. Better tolerability enhances compliance and may improve long-term success rates, particularly in resource-limited settings.

From a physiological perspective, Mitwally & Casper demonstrated that letrozole induces ovulation by transient estrogen suppression, which increases FSH secretion without the peripheral anti-

estrogenic effects associated with CC [8]. This mechanism, combined with the favorable endometrial environment reported by Cortinez et al., may explain the improved live birth rates seen in our study [22].

Although our findings strongly favor letrozole, it is worth noting that some studies, such as Bayar et al., reported similar pregnancy outcomes between the two agents [23]. These discrepancies may be attributed to variations in study design, dosing regimens, and population characteristics. Nevertheless, the weight of evidence from South Asian studies including Ivy et al. and Ray et al. supports the preferential use of letrozole in our context [12,14].

In summary, the collective evidence underscores that letrozole not only improves ovulatory and pregnancy outcomes but also enhances patient tolerability compared to CC. These findings support its use as a first-line therapy for ovulation induction in PCOS patients within Bangladesh and similar settings.

Limitations of the study

Despite study strengths, several limitations existed.

1. Follow-up was limited to one ovulatory cycle per patient, preventing evaluation of cumulative pregnancy or birth rates.
2. The study lacked hormonal monitoring, which could have provided insights into physiological mechanisms.
3. Blinding was not feasible due to distinct drug dosing protocols, introducing potential observer bias.
4. Findings from this tertiary care setting may not fully generalize to rural or community healthcare contexts with limited monitoring resources.

CONCLUSION

This study demonstrated that letrozole is superior to clomiphene citrate in inducing ovulation and achieving higher clinical pregnancy and live birth rates in women with anovulatory infertility, particularly in the Bangladeshi population. Letrozole also exhibited better endometrial outcomes and tolerability than anastrozole. Based on these findings, letrozole should be considered a first-line agent for ovulation induction, especially in low-resource settings.

Acknowledgment

I would like to express my sincere gratitude for the invaluable support and cooperation provided by the staff, participants, and my co-authors/colleagues who contributed to this study.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Zegers-Hochschild F, Adamson GD, De Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Van der Poel S. The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. Human reproduction. 2009 Nov 1;24(11):2683-7.
2. Balen AH, Tan SL, Jacobs HS. Hypersecretion of luteinising hormone: a significant cause of infertility and miscarriage. BJOG: An International Journal of Obstetrics & Gynaecology. 1993 Dec;100(12):1082-9.
3. Saxena P, Prakash A, Nigam A, Mishra A. Polycystic ovary syndrome: Is obesity a sine qua non? A clinical, hormonal, and metabolic assessment in relation to body mass index. Indian journal of endocrinology and metabolism. 2012 Nov 1;16(6):996-9.
4. FRANKS S, ADAMS J, MASON H, POLSON D. Ovulatory disorders in women with polycystic ovary syndrome. Clinics in obstetrics and gynaecology. 1985 Sep 1;12(3):605-32.

5. Kistner RW. Induction of ovulation with clomiphene citrate (clomid). Obstet Gynecol Surv. 1965 Dec;20(6):873-900.
6. 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. Fertility and sterility. 1993 Apr 1;59(4):756-60.
7. Casper RF. Letrozole versus clomiphene citrate: which is better for ovulation induction? Fertility and sterility. 2009 Sep 1;92(3):858-9.
8. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertility and sterility. 2001 Feb 1;75(2):305-9.
9. El Bigawy AF, Fouda UM, Wahab HA. A randomized trial of letrazole versus clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome (PCOS).
10. Zeinalzadeh M, Basirat Z, Esmailpour M. Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. The Journal of reproductive medicine. 2010 Jan 1;55(1-2):36-40.
11. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertility and sterility. 2004 Dec 1;82(6):1561-3.
12. Ivy R, Chowdhury A, Haque K, Ara H. Aromatase Inhibitor for Ovulation Induction: A Comparative Study Between Letrozole and Clomiphen Citrate in Anovulatory Infertile Women. Bangladesh Journal of Physiology and Pharmacology. 2009:10-2.
13. Begum MR, Quadir E, Begum A, Begum RA, Begum M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. Journal of Obstetrics and Gynaecology Research. 2006 Oct;32(5):502-6.
14. 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. Archives of gynecology and obstetrics. 2012 Mar;285(3):873-7.
15. Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. Journal of international medical research. 2006 Jan;34(1):73-6.
16. 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. Fertility and sterility. 2002 Aug 1;78(2):280-5.
17. Sammour A, Biljan MM, Tan SL, Tulandi T. Prospective randomized trial comparing the effects of letrazole (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 Sep 1;76(3): S110.
18. Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Human Reproduction. 1990 Aug 1;5(6):670-4.
19. Hussain NH, Ismail M, Zain MM, Yeu PC, Ramli R, Mohammad WM. Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience.
20. Aletebi F, Alaa N. The effect of letrozole versus clomiphene citrate on ovulation induction in polycystic ovarian syndrome patients: RCT. Journal of Evidence-Based Women's Health Journal Society. 2013 May 1;3(2):51-3.
21. Hajishafieiha M, Poorfarzan L, Kiarang N. Comparing the clinical effects of letrozol vs clomifene in infertile ovulator women (borderline male factor infertility, and unexplained infertility) undergoing intrauterine in semination. Studies in Medical Sciences. 2009 Jun 10;20(1):8-12.

22. Cortínez A, De Carvalho I, Vantman D, Gabler F, Iñiguez G, Vega M. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. Fertility and sterility. 2005 Jan 1;83(1):110-5.
23. Bayar Ü, Tanrıverdi HA, Barut A, Ayoğlu F, Özcan O, Kaya E. Letrozole vs. clomiphene citrate in patients with ovulatory infertility. Fertility and sterility. 2006 Apr 1;85(4):1045-8.