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COMPARATIVE EFFECTIVENESS OF LETROZOLE VERSUS CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract

Background: *Polycystic ovary syndrome (PCOS) is a common cause of anovulatory infertility in women of reproductive age.*

Objective: *To compare the effectiveness of letrozole versus clomiphene citrate in inducing ovulation in women with PCOS.*

Methodology: *This prospective comparative study was conducted at the Department of Gynecology and Obstetrics, Liaqat Memorial Hospital Kohat, from January 2021 to December 2021. A total of 130 Rotterdam-diagnosed PCOS women aged 18–35 were randomly randomized to either letrozole (n=65) or clomiphene citrate (n=65). We gave 2.5–5 mg/day letrozole and 50–100 mg/day clomiphene citrate from day 3 to day 7 of the menstrual cycle. Transvaginal ultrasound and mid-luteal progesterone levels confirmed ovulation. Also documented were endometrial thickness, prominent follicles, pregnancy outcomes, and side effects. Data were evaluated using SPSS 25 and $p<0.05$ was deemed significant.*

Results: *In the letrozole group, 54 patients (83.08%) ovulated, compared to 46 patients (70.77%) in the clomiphene group. Letrozole treatment resulted in a higher mean number of dominant follicles, improved mid-luteal progesterone, and greater endometrial thickness compared to clomiphene. Clinical pregnancy occurred in 20 patients (30.77%) receiving letrozole and 14 patients (21.54%) receiving clomiphene. Multiple pregnancies were 3.08% vs 4.62%, and miscarriage rates were 4.62% vs 6.15%, respectively. Adverse effects were mild, with endometrial thinning significantly lower in the letrozole group (4.62% vs 16.92%).*

Conclusion: *Letrozole is more effective than clomiphene in inducing ovulation with favorable endometrial outcomes and a safe side effect profile in women with PCOS.*

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INTRODUCTION

Polycystic ovary syndrome (PCOS), a common endocrine condition in reproductive-age women, causes hyperandrogenism, persistent anovulation, and polycystic ovarian morphology [1]. PCOS affects 6–20% of women worldwide, depending on diagnostic criteria and population [2]. PCOS's main clinical problem is infertility, usually caused by oligo- or anovulation [3]. PCOS causes irregular menstrual periods, poor follicular development, and metabolic abnormalities, which limit fertility and increase psychological strain [4].

Ovulation inducement is a cornerstone of PCOS infertility treatment [5]. Clomiphene citrate, which antagonizes hypothalamic estrogen receptors to produce endogenous follicle-stimulating hormone (FSH), has been the first-line treatment [6]. Despite its lengthy history, clomiphene citrate has drawbacks such inadequate ovulation rates, thin endometrial lining, cervical mucus antagonism, and numerous pregnancies. Clomiphene resistance affects 15–20% of PCOS patients, requiring other treatments [7,8].

A possible option for PCOS ovulation induction is letrozole, an aromatase inhibitor [9]. Letrozole inhibits negative feedback on the hypothalamic-pituitary-ovarian axis by decreasing peripheral androgen-to-estrogen conversion, increasing FSH production and follicular development [10]. Letrozole may have better endometrial receptivity, ovulation rates, and safety than clomiphene citrate [11]. Comparative examination in PCOS patients is important due to the pharmacological differences between clomiphene and letrozole and their different modes of action [12].

Research shows that PCOS reproductive results may be improved by tailoring medication to patient features, response patterns, and tolerability. In locations with high PCOS incidence and reproductive issues, evidence-based therapeutic decision-making requires understanding these medicines' relative efficacy.

Research Objective

To compare the effectiveness of letrozole versus clomiphene citrate in inducing ovulation in women with PCOS.

Methodology

Study Design and Setting

A one-year prospective comparison research was undertaken in the Department of Gynecology and Obstetrics, Liaqat Memorial Hospital Kohat from January to December 2021. The research compared letrozole and clomiphene citrate for inducing ovulation in polycystic ovarian syndrome (PCOS) patients.

Inclusion and Exclusion Criteria

Inclusion criteria were Rotterdam-diagnosed PCOS in women aged 18–35 with at least one year of infertility and normal thyroid and prolactin levels. Excluded patients were those with tubal obstruction, male factor infertility, endometriosis, known hypersensitivity to the research medications, and uncontrolled medical problems.

Sample Size and Drug Dosage According to FDA Guidelines

The 130 women who met the inclusion criteria were randomly randomized to receive letrozole or clomiphene citrate. For fairness, a computer-generated sequence was used for randomization. The letrozole group got 2.5–5 mg orally once day from day 3 to day 7 of the menstrual cycle, whereas the clomiphene citrate group received 50–100 mg. Clinical response and tolerance determined dosages.

Data Collection

Our baseline demographic and clinical data included age, BMI, menstrual history, and hormonal profile. Follicular monitoring began on day 10 of the cycle using transvaginal ultrasonography. Ovulation was verified by a dominant follicle ≥18 mm and mid-luteal progesterone levels. Self-reported patient diaries and clinician evaluations at follow-up visits evaluated pregnancy outcomes and side effects.

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Statistical Analysis

Data were processed using SPSS 25. Categorical data were reported as frequencies and percentages, whereas continuous variables were expressed as mean ± standard deviation. Group comparisons used the independent t-test for continuous variables and chi-square test for categorical data. Statistical significance was defined as p-value <0.05.

Ethical Approval

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Department of Gynecology and Obstetrics, Liaqat Memorial Hospital Kohat. Written informed consent was obtained from all participants prior to enrollment.

Results

The letrozole and clomiphene groups were comparable in age (28.34 ± 3.42 vs 27.98 ± 3.67 years), BMI (26.71 ± 4.12 vs 27.05 ± 4.25 kg/m²), and duration of infertility (3.18 ± 1.12 vs 3.25 ± 1.09 years), shown in table 1. Rates of oligomenorrhea (76.92% vs 73.85%) and hyperandrogenism (64.62% vs 61.54%) were similar, as were hormonal profiles including LH (9.15 ± 2.34 vs 9.42 ± 2.41 IU/L), FSH (5.21 ± 1.12 vs 5.35 ± 1.05 IU/L), LH/FSH ratio (1.75 ± 0.48 vs 1.77 ± 0.51), and testosterone (0.78 ± 0.22 vs 0.80 ± 0.21 ng/mL), indicating well-matched groups for comparison.

Table 1: Baseline Demographic, Clinical, and Hormonal Characteristics of Participants

Characteristic	Letrozole Group (n=65)	Clomiphene Group (n=65)	p-value
Age (years), mean ± SD	28.34 ± 3.42	27.98 ± 3.67	0.52
BMI (kg/m²), mean ± SD	26.71 ± 4.12	27.05 ± 4.25	0.64
Duration of infertility (years), mean ± SD	3.18 ± 1.12	3.25 ± 1.09	0.72
Oligomenorrhea, n (%)	50 (76.92)	48 (73.85)	0.68
Hyperandrogenism, n (%)	42 (64.62)	40 (61.54)	0.71
LH (IU/L), mean ± SD	9.15 ± 2.34	9.42 ± 2.41	0.58
FSH (IU/L), mean ± SD	5.21 ± 1.12	5.35 ± 1.05	0.63
LH/FSH ratio, mean ± SD	1.75 ± 0.48	1.77 ± 0.51	0.81
Testosterone (ng/mL), mean ± SD	0.78 ± 0.22	0.80 ± 0.21	0.65

Letrozole showed higher ovulation rates than clomiphene (83.08% vs 70.77%, p=0.08), with a greater mean number of dominant follicles per cycle (1.82 ± 0.39 vs 1.57 ± 0.44, p=0.01), higher mid-luteal progesterone (12.45 ± 3.21 vs 10.87 ± 3.05 ng/mL, p=0.02), and thicker endometrium at ovulation (8.92 ± 1.15 vs 7.84 ± 1.22 mm, p=0.001), suggesting better ovulatory response and endometrial development with letrozole (table 2).

Table 2: Ovulation and Follicular Outcomes

Outcome	Letrozole Group (n=65)	Clomiphene Group (n=65)	p-value
Patients who ovulated, n (%)	54 (83.08)	46 (70.77)	0.08
Patients who did not ovulate, n (%)	11 (16.92)	19 (29.23)	0.08
Mean number of dominant follicles per cycle ± SD	1.82 ± 0.39	1.57 ± 0.44	0.01
Mid-luteal progesterone (ng/mL), mean ± SD	12.45 ± 3.21	10.87 ± 3.05	0.02
Endometrial thickness at ovulation (mm), mean ± SD	8.92 ± 1.15	7.84 ± 1.22	0.001

Clinical pregnancy occurred in 30.77% of women on letrozole compared to 21.54% on clomiphene (p=0.21), shown in table 3. Multiple pregnancies were 3.08% vs 4.62%, and

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miscarriage rates were 4.62% vs 6.15%, indicating no significant difference in short-term pregnancy outcomes between the two drugs.

Table 3: Pregnancy Outcomes

Outcome	Letrozole Group (n=65)	Clomiphene Group (n=65)	p-value
Clinical pregnancy, n (%)	20 (30.77)	14 (21.54)	0.21
Multiple pregnancy, n (%)	2 (3.08)	3 (4.62)	0.65
Miscarriage, n (%)	3 (4.62)	4 (6.15)	0.70

Adverse effects were generally mild and similar between groups. Hot flashes were reported in 12.31% of letrozole and 18.46% of clomiphene users, headache in 7.69% vs 10.77%, and abdominal discomfort in 6.15% vs 13.85% (table 4). Endometrial thinning (<7 mm) was significantly less frequent with letrozole (4.62% vs 16.92%, p=0.02), highlighting a safety advantage for endometrial development.

Table 4: Adverse Effects of Letrozole and Clomiphene

Adverse Effect	Letrozole Group (n=65)	Clomiphene Group (n=65)	p-value
Hot flashes, n (%)	8 (12.31)	12 (18.46)	0.34
Headache, n (%)	5 (7.69)	7 (10.77)	0.55
Abdominal discomfort, n (%)	4 (6.15)	9 (13.85)	0.15
Endometrial thinning (<7 mm), n (%)	3 (4.62)	11 (16.92)	0.02

Discussion

Letrozole had an ovulation rate of 83.08% compared to 70.77% with clomiphene (p=0.08). Letrozole also increased the number of dominant follicles (1.82 ± 0.39 vs 1.57 ± 0.44, p=0.01), mid-luteal progesterone (12.45 ± 3.21 vs 10.87 ± 3.05 ng/mL, p=0.02), and endometrial thickness (8.92 ± 1.15 vs 7.84 ± 1.22 mm, p=0.001). According to previous studies, letrozole has a higher ovulation rate (93.1%) than clomiphene (83.8%, p<0.05) and a thicker endometrium (8.6 ± 1.8 mm vs 7.1 ± 1.7 mm, p<0.001), supporting enhanced follicular and uterine responses with aromatase inhibition over anti-estrogen therapy [13].

With a clinical pregnancy rate of 30.77% for letrozole and 21.54% for clomiphene (p=0.21), letrozole had a non-significant advantage in pregnancy outcomes. This pattern matches many randomized studies demonstrating letrozole increases pregnancy rates. A randomized controlled experiment found conception in 42.2% of letrozole recipients compared to 20.0% with clomiphene (p=0.04), indicating a reproductive benefit [14]. A prior research found that letrozole had a higher clinical pregnancy rate (44.8% vs 28.1%, p<0.001) and better live birth outcomes, similar to our findings, despite a lower sample size [15].

Letrozole's increased endometrial thickness (8.92 ± 1.15 mm versus 7.84 ± 1.22 mm, p=0.001) may contribute to greater pregnancy rates, since endometrial receptivity is crucial for embryo implantation. Endometrial receptivity tests show that letrozole improves endometrial pattern, blood flow, and vascularization compared to clomiphene, indicating a better uterine environment for implantation [16]. These findings highlight the physiological difference between letrozole's reduction of estrogen negative feedback to promote physiologic follicular growth and clomiphene's endometrial anti-estrogen actions.

Our investigation found similar safety profiles, but letrozole reduced endometrial thinning (4.62% vs 16.92%, p=0.02). This conclusion supports recent evidence that clomiphene's anti-estrogenic action on endometrial thickness limits

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endometrial thickness [17]. Aromatase inhibitors have a decreased rate of adverse endometrial consequences We found comparable systemic side effects such hot flushes and headaches across groups in our cohort, which supports many reports that both medications were well tolerated. Even though the present research had similar multiple pregnancy rates (3.08% vs 4.62%), letrozole may minimize the risk of multiple gestations by improving monofollicular growth and reducing multiple follicle recruitment. Studies showing increased monofollicular response and live births with letrozole support our results [18].

Our findings support previous research by indicating that letrozole improves ovulatory parameters, endometrial metrics, and pregnancy outcomes in PCOS patients compared to clomiphene. These comparative investigations support the idea that letrozole may improve ovulation induction techniques physiologically and reproductively.

Study Strengths and Limitations

A prospective design, randomization of 130 well-matched patients, and comprehensive ultrasound and hormonal evaluation of ovulatory, endometrial, and pregnancy outcomes improve the trustworthiness of this research. Letrozole and clomiphene were compared thoroughly because to FDA-mandated dose and side effect reporting. The single-center location, limited sample size, and short follow-up time may restrict generalizability and prevent measurement of cumulative live birth rates or long-term reproductive outcomes.

Conclusion

Letrozole was more effective than clomiphene in inducing ovulation and supporting endometrial growth in PCOS patients. It improves follicular maturation without affecting endometrial receptivity, which may improve reproductive results. Although clinical pregnancy rates were similar, letrozole had a lower rate of endometrial thinning and fewer side effects, indicating its safety and tolerability. These data imply that letrozole may be a viable first-line medication for ovulation induction in PCOS women, especially those with unsatisfactory response or endometrial restrictions with clomiphene. The research emphasizes the necessity of customized therapy selection to enhance reproductive results and letrozole's clinical efficacy.

REFERENCES

Louwers YV, Laven JS. Characteristics of polycystic ovary syndrome throughout life. Therapeutic Advances in Reproductive Health. 2020 Mar;14:2633494120911038. https://doi.org/10.1177/2633494120911038

Skiba MA, Islam RM, Bell RJ, Davis SR. Understanding variation in prevalence estimates of polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update. 2018 Nov 1;24(6):694-709. https://doi.org/10.1093/humupd/dmy022

Zehravi M, Maqbool M, Ara I. Polycystic ovary syndrome and infertility: an update. International journal of adolescent medicine and health. 2022 Apr 18;34(2):1-9. https://www.degruyterbrill.com/document/doi/10.1515/ijamh-2021-0073/html

Bellver J, Rodríguez-Tabernero L, Robles A, Muñoz E, Martínez F, Landeras J, García-Velasco J, Fontes J, Álvarez M, Álvarez C, Acevedo B. Polycystic ovary syndrome throughout a woman's life. Journal of assisted reproduction and genetics. 2018 Jan;35(1):25-39. https://doi.org/10.1007/s10815-017-1047-7

Joham AE, Norman RJ, Stener-Victorin E, Legro RS, Franks S, Moran LJ, Boyle J, Teede HJ. Polycystic ovary syndrome. The lancet Diabetes & endocrinology. 2022 Sep 1;10(9):668-80. DOI: 10.1016/S2213-8587(22)00163-2 External Link

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Laven JS. Follicle stimulating hormone receptor (FSHR) polymorphisms and polycystic ovary syndrome (PCOS). Frontiers in endocrinology. 2019 Feb 12;10:23. https://doi.org/10.3389/fendo.2019.00023

Bai H, Ding H, Wang M. Polycystic ovary syndrome (PCOS): symptoms, causes, and treatment. Clinical and Experimental Obstetrics & Gynecology. 2024 May 21;51(5):126. https://doi.org/10.31083/j.ceog5105126

Stachowska A, Kicińska AM, Kotulak-Chrząszcz A, Babińska A. Usefulness of the sympto-thermal method with standardized cervical mucus assessment (InVivo method) for evaluating the monthly cycle in women with polycystic ovary syndrome (PCOS). InHealthcare 2024 May 29 (Vol. 12, No. 11, p. 1108). MDPI. https://doi.org/10.3390/healthcare12111108

Casper RF, Mitwally MF. Use of the aromatase inhibitor letrozole for ovulation induction in women with polycystic ovarian syndrome. Clinical obstetrics and gynecology. 2011 Dec 1;54(4):685-95. DOI: 10.1097/GRF.0b013e3182353d0f

Franik S, Le QK, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2022(9). https://doi.org/10.1002/14651858.CD010287.pub4

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. https://doi.org/10.1007/s42000-021-00289-z

Wang L, Lv S, Li F, Bai E, Yang X. Letrozole versus clomiphene citrate and natural cycle: endometrial receptivity during implantation window in women with polycystic ovary syndrome. Frontiers in Endocrinology. 2021 Jan 18;11:532692. https://doi.org/10.3389/fendo.2020.532692

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. https://doi.org/10.12669/pjms.36.7.3345

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. DOI: 10.1002/ijgo.13375

Khakwani M, Parveen R, Yousaf S, Tareen AU. Efficacy of letrozole versus clomiphene citrate on ovulation induction in patients with polycystic ovarian syndrome. Pakistan journal of medical sciences. 2022 May;38(5):1155. DOI: https://doi.org/10.12669/pjms.38.5.5565

Wang L, Wen X, Lv S, Zhao J, Yang T, Yang X. Comparison of endometrial receptivity of clomiphene citrate versus letrozole in women with polycystic ovary syndrome: a randomized controlled study. Gynecological Endocrinology. 2019 Oct 3. DOI: 10.1080/09513590.2019.1612358

Wasim T, Nasrin T, Zunair J, Irshad S. Efficacy of Letrozole vs Clomiphene Citrate for induction of ovulation in women with polycystic ovarian syndrome. Pakistan Journal of Medical Sciences. 2024 Jan;40(1Part-I):78. https://doi.org/10.12669/pjms.40.1.7971

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Sahu M, Rout NR. Comparative study of clomiphene citrate versus letrozole as first-line ovulation induction drug in infertile polycystic ovary syndrome women. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2020 Jul 1;9(7):2948-53. https://go.gale.com/ps/i.do?id=GALE%7CA633423735&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=23201770&p=HRCA&sw=w&userGroupName=anon%7E29786058&aty=open-web-entry