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ISSN: 2663-9491 e-ISSN: 2789-6897

ORIGINAL ARTICLE

Comparative Effects of Letrozole 7.5 mg versus 5.0 mg on Follicular Growth in Sub-fertile Women with Polycystic Ovary Syndrome

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Received: 8 Mar 2026
Accepted: 11 Mar 2026
Published Online: 17 Mar 2026

Published by:
Gopalganj Medical College, Gopalganj, Bangladesh

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DOI: dx.doi.org

ABSTRACT

Background: *PCOS is a common cause of anovulatory subfertility in reproductive-aged women. Letrozole is a first-line ovulation induction agent, but the optimal starting dose is unclear. The study aims to compare letrozole 7.5 mg versus 5.0 mg for follicular growth in subfertile women with PCOS.* ***Methods and materials:*** *This quasi-experimental study (June 2023 to January 2025) was conducted in the Department of Obstetrics and Gynecology, BIRDEM General Hospital. Eighty subfertile women aged 18–35 years with Rotterdam-diagnosed PCOS, on metformin, were enrolled and allocated into two groups: letrozole 5 mg/day or 7.5 mg/day from cycle day 2–6. Follicular growth was measured by transvaginal ultrasound on day 2 and day 12, response was categorized by follicle size, and adverse effects were recorded.* ***Results:*** *Baseline characteristics were comparable between groups, with no significant differences in age, BMI, subfertility type, or subfertility duration. On Day 12, letrozole 7.5 mg produced a significantly larger leading follicle than 5 mg (16.81 ± 5.06 vs 13.28 ± 6.92 mm; p<0.001), with higher optimal response (67.5% vs 42.5%) and more dominant follicles (67.5% vs 42.5%; p=0.025), and fewer non-responders (12.5% vs 35.0%). Follicular size increased significantly from Day 2 to Day 12 in both arms (p<0.001 for 5 mg, p=0.003 for 7.5 mg). Adverse effects were infrequent and similar across doses, and most participants reported no side effects (90.0% vs 85.0%; p=0.74).* ***Conclusion:*** *Letrozole 7.5 mg achieved better Day 12 follicular growth and more dominant follicles than 5 mg, with similar adverse effects, supporting 7.5 mg as a more effective starting dose under ultrasound monitoring in PCOS subfertility.*

Keywords: *Polycystic ovary syndrome, Letrozole, Ovulation induction, Follicular growth, Transvaginal ultrasonography*

(The Insight 2026; 9(1): 116-119)

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and is a leading cause of anovulatory subfertility worldwide. It is characterized by hormonal imbalance, particularly excess androgen production, and is commonly associated with irregular ovulation, menstrual disturbances, acne, hirsutism, obesity, and metabolic dysfunction. Although the term "polycystic ovary" refers to the presence of multiple small ovarian follicles, not all women with PCOS demonstrate cystic ovaries on ultrasound, and conversely, polycystic ovarian morphology may be observed in women without the syndrome [1].

The pathophysiology of PCOS is complex and multifactorial. Central to its development is dysregulation of the hypothalamic-pituitary–ovarian axis, resulting in increased pulsatile secretion of gonadotropin-releasing hormone and a relative excess of luteinizing hormone over follicle-stimulating hormone. This hormonal milieu impairs normal follicular maturation and leads to follicular arrest. Additional contributing mechanisms include elevated anti-Müllerian hormone levels, increased ovarian androgen production, insulin resistance, and adipocyte dysfunction, particularly in women with central obesity. Insulin resistance not only exacerbates hyperandrogenism but also plays a key role in the metabolic manifestations of PCOS, such as dyslipidemia and type 2 diabetes mellitus [2].

Globally, PCOS affects approximately 5–10% of women of reproductive age, though prevalence varies widely depending on diagnostic criteria and population characteristics. Higher prevalence rates have been reported in Western populations, while lower rates are observed in certain African and Asian cohorts. Ultrasonographic studies indicate that a substantial proportion of women with polycystic ovarian morphology may fulfill diagnostic criteria for PCOS when clinical or biochemical features are present [3,4]. According to the Rotterdam criteria, PCOS is diagnosed when at least two of the following are present: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound [5].

Anovulation remains the principal cause of subfertility in women with PCOS [6]. Ovulation induction is therefore a cornerstone of fertility management in these patients. Letrozole, an aromatase inhibitor, has emerged as the preferred first-line agent for ovulation induction in PCOS due to its favorable ovulation and pregnancy rates and reduced

ISSN: 2663-9491 e-ISSN: 2789-6897

anti-estrogenic effects on the endometrium compared with clomiphene citrate. Since its introduction for ovulation induction in 2001, Letrozole has demonstrated advantages related to its short half-life and minimal adverse impact on estrogen-sensitive tissues [7,8]. However, clinical experience indicates that standard dosing regimens may not be uniformly effective, and a subset of women fail to achieve adequate follicular development with conventional doses [9]. This study aims to assess and compare the effects of two different starting doses of Letrozole, 7.5 mg versus 5.0 mg, on follicular growth in subfertile women with Polycystic Ovary Syndrome.

METHODS & MATERIALS

This quasi-experimental study was conducted from June 2023 to January 2025 in the Department of Obstetrics and Gynecology, BIRDEM General Hospital. The study population comprised subfertile women with Polycystic Ovary Syndrome attending the outpatient department. A total of 80 participants were enrolled through purposive sampling after obtaining written informed consent and institutional ethical approval from the relevant Research Review Committee and Ethical Review Committee.

Women aged 18–35 years, diagnosed with PCOS according to Rotterdam criteria and selected for ovulation induction, and receiving metformin therapy were included. Exclusion criteria were subfertility due to submucous uterine fibroid, Asherman's syndrome, cervical stenosis, bilateral tubal blockage, endocrine causes of anovulation (hyperprolactinaemia or thyroid dysfunction), male factor infertility, and known allergy or contraindication to letrozole.

Participants were allocated into two equal groups:

- **Group A (n=40):** received letrozole 5 mg/day orally in divided doses (2.5 mg morning and 2.5 mg night) from cycle day 2 to day 6 for 5 days,
- **Group B (n=40):** received letrozole 7.5 mg/day orally in divided doses (2.5 mg morning and 5.0 mg night) over the same schedule.

Baseline sociodemographic and clinical variables (age, education, occupation, BMI, and monthly family income) were recorded using a pre-tested structured questionnaire.Follicular growth was assessed by transvaginal ultrasonography on cycle day 2 (baseline) and day 12 (follow-up) using the same machine and observer to minimize inter-observer variability. Follicular response was categorized as non-response (<10 mm), hypo-response (10–17 mm), and optimal response (≥18 mm), and dominant follicle was defined as ≥18 mm on day 12–14. Adverse effects were recorded during follow-up.

Data were edited, coded, and analyzed using IBM SPSS version 26. Categorical variables were summarized as frequencies and percentages; continuous variables as mean ± standard deviation. Between-group comparisons used chi-square or Fisher's exact test for categorical variables and independent sample t-test for continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

Table I summarizes baseline comparability between the two groups, showing no statistically significant differences in age, BMI, subfertility type, or duration of subfertility. Most women were aged 18–29 years, and the mean age was similar between the 5 mg and 7.5 mg groups (25.55 ± 4.82 vs 26.53 ± 4.38 years; p=0.35). Mean BMI was also comparable (23.14 ± 1.87 vs 23.46 ± 1.89 kg/m^2; p=0.45), with roughly one-quarter being obese (22.5% vs 27.5%). Primary subfertility predominated in both groups (95.0% vs 97.5%; p=1.0), and the mean duration of subfertility was numerically higher in the 7.5 mg group but not statistically significant (4.05 ± 2.65 vs 5.17 ± 2.61 years; p=0.06)

Table – I: Baseline clinical characteristics of participants by group (*n*=80)

Variable	Category / Summary	Letrozole 5 mg (n=40)	Letrozole 7.5 mg (n=40)	p-value
		n (%)	n (%)	
Age (years)	18–24	18 (45.0)	14 (35.0)	0.49
	25–29	12 (30.0)	17 (42.5)	
	30–35	10 (25.0)	9 (22.5)	
	Mean ± SD	25.55 ± 4.82	26.53 ± 4.38	0.35
BMI (kg/m^2)	Normal (18.5–22.9)	18 (45.0)	17 (42.5)	0.87
	Overweight (23–24.9)	13 (32.5)	12 (30.0)	
	Obese (≥25)	9 (22.5)	11 (27.5)	
	Mean ± SD	23.14 ± 1.87	23.46 ± 1.89	0.45
Type of subfertility	Primary	38 (95.0)	39 (97.5)	1
	Secondary	2 (5.0)	1 (2.5)	
Duration of subfertility (years)	<5 years	25 (62.5)	22 (55.0)	0.65
	5–10 years	15 (37.5)	18 (45.0)	
	Mean ± SD	4.05 ± 2.65	5.17 ± 2.61	0.06

Table II presents follicular outcomes on Day 12, demonstrating a stronger follicular response with letrozole 7.5 mg. The mean leading follicular diameter was significantly larger in the 7.5 mg group compared with 5 mg (16.81 ± 5.06 vs 13.28 ± 6.92 mm; p<0.001). Optimal follicular response (≥18 mm) was more frequent with 7.5 mg (67.5%) than 5 mg (42.5%), while non-response (<10 mm) was lower (12.5% vs 35.0%). Dominant follicles were also more commonly present in the 7.5 mg group (67.5% vs 42.5%; p=0.025), supporting improved follicular maturation at the higher dose.

ISSN: 2663-9491 e-ISSN: 2789-6897

Table – II: Follicular outcomes on Day 12 (D12) by treatment group (*n*=80)

Outcome (Day-12)	Category / Summary	Letrozole 5 mg (n=40) n (%)	Letrozole 7.5 mg (n=40) n (%)	p-value
Leading follicular diameter (mm)	Mean ± SD	13.28 ± 6.92	16.81 ± 5.06	<0.001
	Median	16	18.45	
	Range	3.6–22.0	3.6–22.0	
Follicular response	Non-response (<10 mm)	14 (35.0)	5 (12.5)	-
	Hypo-response (10–17 mm)	9 (22.5)	8 (20.0)	
	Optimal (≥18 mm)	17 (42.5)	27 (67.5)	
Dominant follicle	Present	17 (42.5)	27 (67.5)	0.025
	Absent	23 (57.5)	13 (32.5)	

Table III shows a significant within-group increase in mean follicular size from Day 2 to Day 12 in both treatment arms. In the Letrozole 5 mg group (n=40), the mean increased from 6.11 ± 1.91 to 13.28 ± 6.92, indicating a statistically significant rise (p<0.001). Similarly, in the Letrozole 7.5 mg group (n=40), the mean increased from 6.19 ± 1.98 to 16.81 ± 5.06, which was also statistically significant (p<0.003).

Table – III: Within-group change from Day 2 to Day 12, follicular growth

Group	Baseline Day-2 Mean ± SD	Day-12 Mean ± SD	p-value
Letrozole 5 mg (n=40)	6.11 ± 1.91	13.28 ± 6.92	<0.001
Letrozole 7.5 mg (n=40)	6.19 ± 1.98	16.81 ± 5.06	<0.003

Table IV outlines adverse effects and shows that both regimens were generally well tolerated, with no significant between-group differences in reported side effects. Most participants experienced no adverse effect (90.0% in 5 mg vs 85.0% in 7.5 mg; p=0.74). Reported symptoms were infrequent overall, including headache (2.5% vs 7.5%; p=0.31), nausea/vomiting (5.0% vs 10.0%; p=0.68), mood change (5.0% vs 2.5%; p=1.0), and hot flashes (2.5% vs 5.0%; p=1.0), indicating a similar safety profile across doses.

Table – IV: Adverse effects by treatment group (*n*=80)

Adverse effects	Letrozole 5 mg (n=40) n (%)	Letrozole 7.5 mg (n=40) n (%)	Total (n=80) n (%)	p-value
Headache	1 (2.5)	3 (7.5)	4 (5.0)	0.31
Mood change	2 (5.0)	1 (2.5)	3 (3.8)	1
Hot flash	1 (2.5)	2 (5.0)	3 (3.8)	1
Nausea/vomiting	2 (5.0)	4 (10.0)	6 (7.5)	0.68
Dizziness	0 (0.0)	1 (2.5)	1 (1.3)	1
No adverse effect	36 (90.0)	34 (85.0)	70 (87.5)	0.74

DISCUSSION

Polycystic ovary syndrome (PCOS) is a common endocrine cause of anovulatory subfertility, and ovulation induction remains a core management step, with letrozole increasingly favored because it can achieve robust ovulatory outcomes with a generally acceptable tolerability profile [9,10]. In this study, the two dose groups were baseline comparable, with no statistically significant differences in age, BMI, type of subfertility, or subfertility duration, which strengthens internal validity because dose related differences in follicular endpoints are less likely to be explained by baseline imbalance. The mean participant age in both arms, concentrated largely in the 18–29-year range, mirrors typical PCOS infertility cohorts described previously, where most women seeking treatment are in their 20s and early 30s, a period when ovarian responsiveness is still relatively favorable [11,12]. BMI was also similar between groups, and the presence of overweight and obesity in a meaningful minority is consistent with the known metabolic phenotype of PCOS, where insulin resistance and adiposity frequently co-exist and can modulate ovarian response [13,14]. Against this balanced background, the higher starting dose of letrozole, 7.5 mg, demonstrated a clearly stronger follicular response by Day 12: the mean leading follicular diameter was significantly larger than with 5.0 mg (16.81 ± 5.06 vs 13.28 ± 6.92 mm; p<0.001), optimal response, defined as follicles ≥18 mm, occurred more often (67.5% vs 42.5%), and non-response, defined as <10 mm, was notably reduced (12.5% vs 35.0%). These findings support a practical dose-response relationship, where greater aromatase inhibition may enhance endogenous gonadotropin drive and improve dominant follicle selection in PCOS, translating into larger follicles within the same monitoring interval [9,15]. The higher proportion of dominant follicles in the 7.5 mg group (67.5% vs 42.5%; p=0.025) also aligns with reports that higher dose letrozole strategies can improve follicular maturation and reduce inadequate response in some PCOS populations [15]. Importantly, both treatment arms showed statistically significant within-group follicular growth from Day 2 to Day 12, indicating that both regimens were biologically active, but the 7.5 mg dose achieved a larger absolute gain, suggesting superior maturation kinetics rather than simply initiating growth. Similar patterns, namely improved mature follicle development with letrozole based protocols, have been reported in earlier comparative studies, supporting the plausibility of the present results [16-19]. From a safety perspective, both doses were well tolerated in the current cohort, with most participants reporting no adverse effects, and low, non-significant differences in mild symptoms such as

headache and nausea or vomiting, a pattern consistent with prior summaries indicating that letrozole adverse effects are usually infrequent and manageable during ovulation induction [10]. Overall, these findings suggest that a 7.5 mg starting dose may be more effective than 5.0 mg for achieving clinically desirable follicular size by Day 12 in subfertile women with PCOS, without evidence of increased short-term side effects, a potentially useful consideration in settings where rapid optimization of follicular response is prioritized under ultrasound monitoring [9,10,15].

LIMITATIONS

his study was conducted at a single center with a modest sample size, which may restrict the generalizability of the findings. The outcomes primarily focused on short-term follicular measures; therefore, ovulation and pregnancy outcomes were not comprehensively assessed. Additionally, unmeasured variables such as lifestyle factors or insulin resistance may have influenced the results.

CONCLUSION

Letrozole 7.5 mg produced significantly better follicular growth and a higher rate of dominant follicles by Day 12 than letrozole 5.0 mg in subfertile women with PCOS, without increasing adverse effects. These findings support 7.5 mg as a more effective starting dose under ultrasound monitoring for optimizing follicular response.

RECOMMENDATIONS

Letrozole 7.5 mg may be preferred as a starting dose for ovulation induction in subfertile women with PCOS, with ultrasound monitoring to optimize response and minimize risks. Clinicians should individualize dosing based on BMI, prior cycle response, and comorbidities, and provide lifestyle counseling alongside pharmacotherapy. Larger, multicenter studies should evaluate ovulation, pregnancy, and live-birth outcomes to confirm the clinical benefit of the higher dose.

FUNDING

No funding sources

CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

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