Impact of Letrozole Starting Dose on Endometrial Thickness in Ovulation Induction for PCOS

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ABSTRACT

Background: PCOS is a common cause of anovulatory subfertility, and letrozole is widely used as first-line ovulation induction. Beyond ovulation, adequate endometrial thickness is important for implantation, and dose-related effects on endometrial development remain uncertain across protocols. **Methods & Materials:** This comparative prospective study was conducted at the Department of Obstetrics and Gynecology, BIRDEM General Hospital, from June 2023 to January 2025. Data were recorded in a structured CRF and analyzed using IBM SPSS Statistics; $p<0.05$ was considered significant. **Results:** Baseline characteristics did not differ significantly between groups in terms of age, body mass index (BMI), subfertility type, or duration. On cycle day 12, endometrial thickness was significantly greater in the letrozole 7.5 mg group compared to the 5 mg group, with mean values of 8.20 ± 1.99 mm and 6.45 ± 2.40 mm, respectively ($p=0.001$). The proportion of participants with endometrial thickness ≥8 mm was also higher in the 7.5 mg group (60.0%) than in the 5 mg group (37.5%; $p=0.044$). Among women with a dominant follicle, the proportion achieving ≥8 mm was similar between groups (88.9% vs 82.4%; $p=0.66$), although mean thickness remained higher with 7.5 mg (9.54 ± 0.80 mm vs 8.96 ± 0.74 mm; $p=0.038$). Both groups demonstrated significant increases in endometrial thickness from baseline to day 12 ($p<0.001$). **Conclusion:** A 7.5 mg starting dose of letrozole resulted in a thicker endometrium by day 12, with a greater proportion of women achieving an endometrial thickness (ET) of at least 8 mm compared to the 5 mg dose in polycystic ovary syndrome (PCOS) ovulation induction.

Keywords: *Polycystic ovary syndrome, Letrozole, Ovulation induction, Endometrial thickness, and Transvaginal ultrasonography*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine and metabolic disorder characterized by oligo- or anovulation, hyperandrogenism, and polycystic ovarian morphology. It is among the most common causes of anovulatory subfertility and is a frequent indication for ovulation induction in infertility practice [1,2]. Global estimates of PCOS prevalence vary substantially due to differences in diagnostic criteria and study populations. Contemporary evidence synthesis continues to show wide ranges across regions and case definitions, underscoring that PCOS constitutes a major reproductive health burden with significant clinical heterogeneity [3]. In Bangladesh, facility-based data from infertility services have reported a high proportion of PCOS among women evaluated for subfertility, emphasizing its local significance for service planning and protocol optimization [4]. Beyond infertility, PCOS is clinically important because it is associated with increased cardiometabolic risk, psychological burden, and adverse pregnancy outcomes. These factors make effective and safe fertility treatment a priority that aligns reproductive goals with broader health considerations [2].

Ovulation induction is a central component of fertility management in PCOS. International evidence-based guidelines recommend aromatase inhibitors, particularly letrozole, as the preferred first-line pharmacologic option for anovulatory infertility due to PCOS. This recommendation is supported by improved reproductive outcomes compared with clomiphene citrate in many clinical settings and an acceptable safety profile [1,5]. However, in clinical practice, success is determined by more than follicular growth or ovulation alone. Endometrial development is clinically significant, as inadequate late follicular endometrial thickness may indicate suboptimal endometrial proliferation and receptivity. Clomiphene citrate can exert anti-estrogenic effects on the endometrium, with mechanistic and clinical data demonstrating impaired endometrial receptivity markers and reduced endometrial thickness in some stimulated cycles [6,7]. Several South Asian studies comparing letrozole with clomiphene have reported more favorable endometrial thickness with letrozole during monitored cycles, supporting the hypothesis that aromatase inhibition may be more beneficial for endometrial development in ovulation induction [8-10].

Although letrozole is widely accepted, the optimal starting dose remains uncertain, and clinical practice varies among centers. Many protocols initiate treatment with 2.5 to 5 mg for 5 days, while some clinicians use higher doses to enhance early cycle response, particularly in settings where minimizing prolonged step-up cycles and intensive monitoring is important. Evidence comparing different letrozole regimens indicates that starting at 5 mg or using extended courses can improve ovulation efficiency and reduce time to ovulation and pregnancy without a clear increase in multifollicular development. However, the effects of higher starting doses on endometrial thickness are less consistently characterized in studies focused on PCOS [11]. In this context, the present study aimed to evaluate the impact of letrozole starting dose, 5 mg versus 7.5 mg, on endometrial thickness among subfertile women with PCOS.

METHODS & MATERIALS

This comparative prospective study was conducted in the Department of Obstetrics and Gynecology, BIRDEM General Hospital, Dhaka, Bangladesh, from June 2023 to January 2025. Subfertile women with polycystic ovary syndrome (PCOS) undergoing ovulation induction were enrolled by consecutive sampling. A total of 80 women were allocated into two treatment arms according to the starting dose of letrozole:

- **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.

Women with contraindications to letrozole, other major causes of infertility requiring alternate management, endocrine disorders likely to affect ovulation (e.g., thyroid dysfunction or hyperprolactinemia), uterine pathology known to distort the cavity, or incomplete follow-up were excluded.

At baseline (cycle day 2), transvaginal ultrasonography was performed to document endometrial thickness and exclude ovarian cysts or other abnormalities. Follicular monitoring was done by ultrasonography and repeated until approximately day 12 to assess follicular response and endometrial development. The primary outcome was endometrial thickness on day 12, analyzed both as a continuous variable (mean ± SD, mm) and as a categorical outcome using a clinically meaningful threshold (≥8 mm vs <8 mm). A secondary analysis was performed among women who developed a dominant follicle by day 12.

Data were recorded in a structured case record form and analyzed in SPSS (V-26.0). Between-group comparisons were performed using appropriate inferential tests. Within-group changes from day 2 to day 12 were assessed using paired t-tests. A p-value <0.05 was considered statistically significant. Ethical approval was obtained from the institutional review committee, and written informed consent was taken from all participants.

RESULTS

The two groups were well matched. Most women were aged 18–24 years, 45.0% in the 5 mg group versus 35.0% in the 7.5 mg group, with similar mean age, 25.55±4.82 vs 26.53±4.38 years (p=0.35). BMI distribution was also comparable, normal BMI 45.0% vs 42.5%, obesity 22.5% vs 27.5%, and mean BMI 23.14±1.87 vs 23.46±1.89 kg/m² (p=0.45). Primary subfertility predominated in both arms, 95.0% vs 97.5% (p=1.0). Duration of subfertility was mostly under 5 years, 62.5% vs 55.0%, and mean duration showed no significant difference, 4.05±2.65 vs 5.17±2.61 years (p=0.06) *Table I.*

Table I

Baseline comparability of the study groups (*n*=80).

Variable	Letrozole 5 mg (n=40) n (%)	Letrozole 7.5 mg (n=40) n (%)	p value
Age group (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 category			
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)	1.0 (ns)
Secondary	2 (5.0)	1 (2.5)	
Duration of subfertility			
<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

The 7.5 mg group achieved a thicker endometrium by Day 12. Endometrial thickness ≥8 mm occurred in 60.0% (24/40) with 7.5 mg compared with 37.5% (15/40) with 5 mg (p=0.044). Mean endometrial thickness was significantly higher with 7.5 mg, 8.20±1.99 mm versus 6.45 ± 2.40 mm (p=0.001) *Table II.*

Table II

Endometrial thickness on Day 12 (primary outcome focus).

Endometrial thickness on Day-12	Letrozole 5 mg (n=40) n (%)	Letrozole 7.5 mg (n=40) n (%)	p value
<8 mm	25 (62.5)	16 (40.0)	0.044 (s)
≥8 mm	15 (37.5)	24 (60.0)	
Mean ± SD (mm)	6.45 ± 2.40	8.20 ± 1.99	0.001 (s)

Among responders with dominant follicles, the proportion achieving endometrial thickness ≥8 mm was high in both groups and not significantly different, 82.4% in the 5 mg group (14/17) versus 88.9% in the 7.5 mg group (24/27), p=0.66. However, mean endometrial thickness remained higher in the 7.5 mg group, 9.54 ± 0.80 mm versus 8.96 ± 0.74 mm (p=0.038) *Table III.*

Table III

Endometrial thickness among women with dominant follicles on Day 12 (*n*=44).

Endometrial thickness on Day-12	Letrozole 5 mg (n=40) n (%)	Letrozole 7.5 mg (n=40) n (%)	p value
<8 mm	3 (17.6)	3 (11.1)	0.66 (ns)
≥8 mm	14 (82.4)	24 (88.9)	
Mean ± SD (mm)	8.96 ± 0.74	9.54 ± 0.80	0.038 (s)

Both regimens produced significant endometrial growth from baseline to Day 12. In the 5 mg group, thickness increased from 4.75±1.6 mm to 6.45±2.40 mm ($p<0.001$). In the 7.5 mg group, it increased from 4.9±1.5 mm to 8.20±1.99 mm ($p<0.001$), showing a larger absolute gain by follow-up (*Table IV*).

Table IV
Within-group change in endometrial thickness, Basal (Day-2) to Follow-up (Day-12).

Group	Basal scan Day-2 (mm)	Follow-up scan Day-12 (mm)	p value
	Mean ± SD	Mean ± SD	
Letrozole 5 mg (n=40)	4.75 ± 1.6	6.45 ± 2.40	<0.001 (s)
Letrozole 7.5 mg (n=40)	4.9 ± 1.5	8.20 ± 1.99	<0.001 (s)

DISCUSSION

In this prospective comparison among subfertile women with PCOS undergoing ovulation induction, a higher letrozole starting dose, 7.5 mg/day from cycle day 2–6, was associated with greater endometrial development by day 12 than 5 mg/day. Clinically, the proportion reaching an endometrial thickness (ET) ≥8 mm increased from 37.5% with 5 mg to 60.0% with 7.5 mg, alongside a higher mean ET, 8.20 mm versus 6.45 mm. Although ET cut-offs are imperfect surrogates for receptivity, thinner endometrium is generally linked to lower implantation probability in fertility care, so the observed shift toward ≥8 mm is pragmatically relevant for cycle management and counseling [12]. The dose effect also remained detectable among day 12 responders: despite similar proportions achieving ET ≥8 mm (82.4% vs 88.9%), mean ET was still modestly higher with 7.5 mg (9.54 vs 8.96 mm), suggesting that the overall between-group difference was partly mediated by improved follicular response, yet not entirely eliminated when restricting to dominant-follicle cycles. Most comparative literature positions letrozole as endometrium-friendly relative to clomiphene citrate (CC), a consistency that supports biological plausibility for using a higher starting dose without compromising endometrial growth. Multiple clinical trials have reported thicker or less frequently "thin" endometrium with letrozole than with CC, attributable to letrozole's shorter half-life and lack of peripheral anti-estrogenic effects on endometrium and cervical mucus [13-17]. The multicenter PPCOS II trial (Legro et al.) established superior ovulation and live-birth outcomes with letrozole versus CC, a shift that has reinforced letrozole as first-line therapy in PCOS, and these benefits have commonly been accompanied by acceptable endometrial development [16]. Findings from regional trials in South Asia similarly describe better endometrial response with letrozole-based induction, aligning with the present Bangladeshi cohort in which both regimens produced significant within-group endometrial growth, but the higher starting dose produced a larger absolute gain [13,15,16]. Evidence syntheses echo these patterns. A meta-analysis of randomized trials found higher ovulation, pregnancy, and live-birth rates with letrozole compared with CC, without consistent signals of endometrial harm [18]. Cochrane evidence likewise supports aromatase inhibitors as effective options for anovulatory PCOS, again without suggesting deterioration of endometrial parameters as a limiting issue [19]. More recent meta-analytic work continues to favor letrozole over CC for key reproductive outcomes, strengthening the argument that optimizing the letrozole regimen is a rational lever in routine practice [20]. Direct evidence specifically interrogating "starting dose" is less abundant than head-to-head comparisons with CC, yet regimen-focused work indicates that beginning at higher doses can improve ovulation efficiency and shorten time to ovulation, a pathway that plausibly increases late-follicular estradiol exposure and supports thicker endometrium by mid-cycle, consistent with the present day 12 measurements [21]. Clinically, these findings suggest that a 7.5 mg starting dose may be particularly useful where thin endometrium at trigger timing is a recurring barrier, or where early cycle efficiency matters, provided ultrasound monitoring is available.

LIMITATIONS

Single-center, small sample, non-randomized allocation; limits generalizability and leaves residual confounding. Endometrial thickness is a surrogate outcome, pregnancy and live-birth outcomes were not assessed.

CONCLUSION

In subfertile women with PCOS undergoing ovulation induction, a 7.5 mg starting dose of letrozole produced significantly greater endometrial thickness by cycle day 12, and a higher proportion achieved ET ≥8 mm, compared with 5 mg. Among women who developed a dominant follicle, endometrial thickness remained slightly higher with 7.5 mg, suggesting a potential advantage when optimizing endometrial development under ultrasound monitoring.

RECOMMENDATIONS

Letrozole 7.5 mg can be considered as a starting dose for ovulation induction in PCOS, especially when achieving adequate mid-cycle endometrial thickness is a concern, with routine ultrasound monitoring to individualize response and minimize multifollicular risk. Larger, multicenter randomized trials in similar settings should compare starting-dose strategies and include endometrial pattern, hormonal profiles, and clinical outcomes, including ovulation, pregnancy, and live birth, to guide standardized dosing protocols.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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