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ORIGINAL ARTICLE

Comparison of Extended Dose Letrozole Versus Letrozole Short Protocol for Ovulation Induction in Infertile Female with Polycystic Ovary Syndrome Receiving Metformin

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ABSTRACT

Background: *Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility. Letrozole is widely used for ovulation induction, while metformin is recommended for insulin resistance in PCOS. However, comparative evidence on short- versus extended-course letrozole combined with metformin remains limited.* ***Methods & Materials:*** *This quasi-experimental study included 100 infertile women with PCOS at Dhaka Medical College Hospital, aged 18–35 years with BMI 25–29.9 kg/m². All received metformin (1500 mg/day) for 3 months, followed by either extended-course letrozole (2.5 mg twice daily, days 2–11) or short-course letrozole (5 mg twice daily, days 2–6). Follicular development was assessed by transvaginal sonography, with ovulation confirmed by mid-luteal serum progesterone (≥3 ng/mL). Outcomes included follicular response, endometrial thickness, ovulation, and biochemical pregnancy rates over three cycles.* ***Results:*** *The mean age was 25.9 ± 4.4 years, with BMI 25–29.9 kg/m², and baseline characteristics and hormone profiles were comparable between groups. After three cycles, Group A showed significantly higher mean follicle number (2.36 ± 1.03 vs. 1.87 ± 1.09; p = 0.024) and follicle size (18.05 ± 1.82 vs. 17.62 ± 1.91 mm; p = 0.041) in the third cycle. Overall, follicle number was also higher in Group A (1.87 ± 1.18 vs. 1.66 ± 1.16; p = 0.048), while differences in follicle size and endometrial thickness were not significant. Ovulation (82% vs. 71%) and cumulative biochemical pregnancy rates (24% vs. 18%) were higher in Group A, although not significantly. Side effects were minimal in both groups.* ***Conclusion:*** *Extended-course letrozole with metformin improved follicular development and ovulation compared with the short course, with a non-significant trend toward higher biochemical pregnancy rates.*

Keywords: *Polycystic ovary syndrome, Infertility, Letrozole, Metformin, Ovulation induction, Follicular development, Endometrial thickness, Biochemical pregnancy.*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age and is associated with reproductive, metabolic, and psychological consequences [1]. PCOS is a heterogeneous disorder characterized by menstrual irregularity, anovulation, hyperandrogenism, infertility, and metabolic abnormalities such as insulin resistance and metabolic syndrome [2,3]. Its pathophysiology involves complex interactions between genetic and environmental factors, with hyperandrogenism and insulin resistance contributing to impaired folliculogenesis and anovulation [4]. Insulin resistance occurs in both obese and non-obese women with PCOS and promotes hyperinsulinemia, increased ovarian androgen production, and disrupted follicular development [5].

Management of anovulatory infertility includes lifestyle modification, ovulation induction, surgery, and assisted reproductive techniques [6]. Letrozole, an aromatase inhibitor, is currently recommended as the first-line pharmacological treatment for anovulatory women with PCOS without other infertility factors [1]. By inhibiting estrogen synthesis, letrozole increases follicle-stimulating hormone (FSH) secretion and promotes follicular development, with advantages including monofollicular ovulation and a lower risk of multiple pregnancy compared with clomiphene citrate [7].

However, the short half-life of letrozole may allow estrogen-mediated suppression of FSH during the late follicular phase, limiting continued development of smaller follicles [8,9]. Extended letrozole regimens may prolong the FSH window and support continued follicular growth, potentially improving ovulation and pregnancy outcomes [2]. Such protocols have shown promising results in women with inadequate response to conventional ovulation induction and may reduce the need for exogenous gonadotropins [10,11].

Metformin, an insulin-sensitizing agent, improves insulin sensitivity and may reduce circulating insulin and androgen levels, thereby supporting ovulatory function [12]. It is particularly beneficial in women with PCOS and higher body mass index and may enhance reproductive outcomes when combined with ovulation-inducing agents [13].

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Despite these advances, evidence remains limited regarding the comparative effectiveness of extended versus short-course letrozole in women with PCOS receiving metformin. Therefore, this study aims to compare the efficacy of extended versus short-course letrozole protocols for ovulation induction in women with PCOS receiving metformin, focusing on ovulatory response and reproductive outcomes.

METHODS & MATERIALS

Study design: This quasi-experimental study was conducted in the Department of Reproductive Endocrinology and Infertility and IVF Centre, Dhaka Medical College Hospital, over a period of one year.

Study population: The study population consisted of infertile women of reproductive age diagnosed with polycystic ovary syndrome (PCOS) who attended the study centre for evaluation and ovulation induction.

Sample size: Purposive sampling was used. Participants were selected according to the predefined inclusion and exclusion criteria. The sample size was calculated as 50 participants per group, resulting in a total of 100 infertile women with PCOS included in the study.

Selection criteria:

Inclusion criteria:

1. Infertile female with PCOS, diagnosed according to Rotterdam Criteria, aged 18 to 35 years.
2. Infertile female with PCOS, under optimisation with Metformin (insulin sensitizer) in last three months, having BMI (25 to 29.9) kg/m2.
3. Patient with patent fallopian tube proved by HSG or SIS.
4. Husband semen analysis is normal.

Exclusion criteria:

1. Size of follicle > 10 mm in baseline scan.
2. Patients with other causes of female infertility (endometriosis, bilateral tubal block).
3. History of taking ovulation-inducing drugs in last three months
4. History of taking other insulin sensitizer, like inositols, within last three months.

Study procedure: The study was conducted in the Department of Reproductive Endocrinology and Infertility, Dhaka Medical College Hospital, Dhaka. Infertile women with PCOS who fulfilled the inclusion and exclusion criteria were enrolled after obtaining ethical approval from the Ethical Review Committee of DMCH and written informed consent. Detailed history, including age, sociodemographic characteristics, and duration of infertility, was recorded, followed by general and systemic examinations. Baseline investigations, including hormonal analysis and Day-2 transvaginal ultrasonography (TVS), were performed, and male-factor infertility was excluded based on previous reports.

Participants were allocated into two groups. Group A received letrozole 2.5 mg twice daily for 10 days (Day 2–11), while Group B received letrozole 5 mg twice daily for 5 days (Day 2–6). Both groups received metformin 500 mg as concomitant therapy, and treatment was continued for a maximum of three cycles. Ovarian response was monitored by serial TVS from Day 12/13 until follicular maturation. A preovulatory follicle was defined as a mean diameter ≥18 mm with endometrial thickness ≥7 mm, while follicles ≥10 mm were considered growing follicles. The total number of growing follicles in both ovaries was recorded. Serum progesterone was measured on Days 21–23, and ovulation was confirmed by a mid-luteal progesterone level ≥3 ng/mL. Biochemical pregnancy was also recorded.

Statistical analysis: Data were recorded and analysed using SPSS version 27. Quantitative variables such as the number of growing follicles, follicular size, endometrial thickness, and serum progesterone levels were expressed as mean ± standard deviation. Qualitative variables like ovulation and pregnancy rates were expressed as frequencies and percentages. Independent sample t-test and Mann-Whitney U test were used to compare means between the two groups. Categorical variables were compared using the Chi-square or Fisher's exact test where appropriate. A p-value of <0.05 was considered statistically significant.

Ethical considerations: The study protocol was submitted to the Ethical Review Committee and Research Review Committee of Dhaka Medical College Hospital. After registration, patients meeting the inclusion criteria were thoroughly evaluated by the researcher. The study objectives, procedures, and relevant information were explained in the local language using a printed handout. Written informed consent was obtained from all participants. They were informed that their confidentiality would be maintained, there would be no monetary benefit for participation, participation was voluntary, and they could withdraw at any time without affecting their treatment. It was also explained that the study involved no invasive procedures.

RESULTS

Table I shows that the baseline characteristics and clinical profiles of the participants were comparable between the two groups. The mean age was 25.9 ± 4.5 years in Group A and 26.2 ± 4.1 years in Group B, with most participants aged 25–29 years. The mean height, weight, and BMI were also similar between the groups ($p>0.05$). Primary infertility was predominant in both Group A (74.0%) and Group B (78.0%), while most participants had infertility for ≤5 years (70.0% vs. 78.0%). No statistically significant differences were observed in the type or duration of infertility between the groups ($p=0.614$ and $p=0.362$, respectively). Overall, the two groups were well matched at baseline.

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Table I: Baseline Characteristics and Clinical Profile of Study Participants (*n* = 100)

Variable	Category	Group A: Extended (n=50), n (%)	Group B: Short (n=50), n (%)	Total (n=100), n (%)	p-value
Age (years)	18–24	18 (36.0)	20 (40.0)	38 (38.0)	NS
	25–29	22 (44.0)	18 (36.0)	40 (40.0)	
	30–35	10 (20.0)	12 (24.0)	22 (22.0)	
	Mean ± SD	25.9 ± 4.5	26.2 ± 4.1	25.9 ± 4.4	
Height (m)	Mean ± SD	1.57 ± 0.03	1.56 ± 0.06	—	0.381
Weight (kg)	Mean ± SD	69.93 ± 4.98	69.53 ± 6.13	—	0.717
BMI (kg/m^2)	Mean ± SD	28.26 ± 1.51	28.37 ± 1.55	—	0.698
Type of infertility	Primary	37 (74.0)	39 (78.0)	76 (76.0)	0.614*
	Secondary	13 (26.0)	11 (22.0)	24 (24.0)	
Duration of infertility (years)	≤5	35 (70.0)	39 (78.0)	74 (74.0)	0.362*
	>5	15 (30.0)	11 (22.0)	26 (26.0)	

Table II shows that the pre-treatment hormonal profiles were comparable between the two groups. The mean FSH, LH, TSH, and prolactin levels were similar in Group A and Group B, with no statistically significant differences observed for any hormonal parameter (p>0.05). Thus, both groups had comparable baseline hormonal characteristics before initiation of ovulation induction.

Table II: Pre-treatment Hormonal Profile of Study Participants (*n* = 100)

Hormonal profile	Group A: Extended (n=50) Mean ± SD	Group B: Short (n=50) Mean ± SD	p-value*
FSH (mIU/mL)	5.35 ± 1.10	5.60 ± 1.00	0.138
LH (mIU/mL)	6.00 ± 1.10	6.20 ± 1.20	0.410
TSH (mIU/mL)	2.50 ± 0.50	2.60 ± 0.50	0.384
Prolactin (ng/mL)	15.90 ± 2.50	15.70 ± 2.40	0.564

Table III shows that follicular development was comparable between Groups A and B during the first and second treatment cycles (p>0.05). In the third cycle, Group A showed a significantly higher proportion of participants with ≥3 growing follicles compared with Group B (61.4% vs. 31.1%, p=0.024). Similarly, the proportion developing a follicle ≥18 mm was significantly higher in Group A than in Group B (75.6% vs. 66.7%, p=0.041). These findings indicate a greater follicular response with the extended letrozole regimen, particularly by the third treatment cycle.

Table III: Cycle-wise Follicular Development in Groups A and B

Cycle	Follicular outcome	Group A (Extended) n (%)	Group B (Short) n (%)	p-value
1st cycle	≥3 growing follicles	17 (34.0)	15 (30.0)	0.630
	Follicle ≥18 mm	17 (42.5)	19 (48.7)	0.712
2nd cycle	≥3 growing follicles	19 (39.5)	16 (33.4)	0.410
	Follicle ≥18 mm	27 (67.5)	23 (59.0)	0.128
3rd cycle	≥3 growing follicles	27 (61.4)	14 (31.1)	0.024†
	Follicle ≥18 mm	31 (75.6)	26 (66.7)	0.041†

Table IV shows that endometrial thickness was comparable between Groups A and B across all three treatment cycles, with no statistically significant differences (p>0.05). The cumulative mean endometrial thickness was 7.69 ± 0.63 mm in Group A and 7.51 ± 0.69 mm in Group B (p=0.103). However, the mean number of growing follicles was significantly higher in Group A than in Group B (1.87 ± 1.18 vs. 1.66 ± 1.16, p=0.048). The mean follicle size was also slightly higher in Group A, although the difference was not statistically significant (17.70 ± 2.74 vs. 17.39 ± 2.82 mm, p=0.214).

Table IV: Comparison of Endometrial Thickness and Overall Ovarian Response

Outcome	Group A (Extended)	Group B (Short)	p-value
Endometrial thickness (mm)			
1st cycle	7.60 ± 0.66	7.34 ± 0.73	0.128
2nd cycle	7.75 ± 0.62	7.56 ± 0.69	0.214
3rd cycle	7.75 ± 0.60	7.64 ± 0.66	0.427
Cumulative mean	7.69 ± 0.63	7.51 ± 0.69	0.103
Number of growing follicles	1.87 ± 1.18	1.66 ± 1.16	0.048†
Mean follicle size (mm)	17.70 ± 2.74	17.39 ± 2.82	0.214

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Table V shows that ovulation rates increased progressively across treatment cycles in both groups. Although Group A had higher ovulation rates in the second and third cycles, the differences were not statistically significant (p>0.05). The cumulative ovulation rate was higher in Group A than Group B (82.0% vs. 71.0%), but this difference did not reach statistical significance (p=0.067). Mid-luteal progesterone levels were comparable between the groups (14.3 ± 4.1 vs. 14.1 ± 4.4 ng/mL, p=0.611). Similarly, cumulative biochemical pregnancy was higher in Group A (24.0% vs. 18.0%), but the difference was not statistically significant (p=0.469).

Table V: Comparison of Ovulation and Biochemical Pregnancy Outcomes

Outcome	Group A (Extended), n (%)	Group B (Short), n (%)	p-value
Ovulation rate			
1st cycle	22 (44.0)	22 (44.0)	1.000
2nd cycle	31 (64.0)	28 (56.0)	0.542
3rd cycle	36 (81.9)	30 (66.6)	0.205
Cumulative ovulation	82 (82.0)	71 (71.0)	0.067
Mid-luteal progesterone (ng/mL)	14.3 ± 4.1	14.1 ± 4.4	0.611
Cumulative biochemical pregnancy	12 (24.0)	9 (18.0)	0.469

Table VI shows that most participants in both groups experienced no adverse effects. Headache, cramp, hot flush, and abdominal pain/nausea/GIT upset were reported in both groups, but none of these adverse effects differed significantly between the groups (all p>0.05). Thus, the extended and short-course letrozole regimens demonstrated comparable tolerability.

Table VI: Comparison of Adverse Effects Between the Groups

Adverse effect	Group A (Extended) n (%)	Group B (Short) n (%)	p-value
No effect	44 (86.3)	40 (71.7)	0.123
Headache	3 (5.9)	3 (5.7)	1.000
Cramp	1 (2.0)	2 (3.8)	1.000
Hot flush	2 (3.9)	5 (9.4)	0.495
Abdominal pain/nausea/GIT upset	1 (2.0)	5 (9.4)	0.465

DISCUSSION

A total of 100 participants were enrolled, with 50 in each group, and all completed three treatment cycles. Baseline characteristics were comparable between the groups. The mean age was 25.9 ± 4.5 years in Group A and 26.2 ± 4.1 years in Group B, while BMI was similar. Primary infertility and infertility duration ≤5 years were predominant in both groups. Baseline FSH, LH, TSH, and prolactin levels were also comparable. Similar baseline characteristics and hormonal profiles have been reported in previous studies of women with PCOS undergoing ovulation induction [2,9,14,15].

The extended letrozole regimen produced a greater follicular response, particularly in the third cycle. In our study, ≥3 growing follicles developed significantly more often in Group A than Group B, and the overall mean number of growing follicles was also higher. Similarly, follicles ≥18 mm were more frequent in Group A in the third cycle. Greater follicular development with extended letrozole regimens has also been reported in previous studies, including improved follicular and ovulatory responses [2,9,10,16].

Endometrial thickness and mean follicle size were comparable between the groups. Cumulative ovulation was higher with extended letrozole, although the difference was not statistically significant. Biochemical pregnancy was also higher in Group A, but the difference was not significant. Similar findings, showing a numerical advantage in ovulation but no significant difference between extended and short regimens, have been reported previously. Other studies also found greater follicular development without significant differences in dominant follicle size, endometrial thickness, ovulation, or pregnancy rates [15,17].

Both groups received metformin, with cumulative ovulation rates of 82.0% and 71.0% in the extended and short-course groups, respectively. These rates were higher than those reported with comparable regimens in another study, where ovulation rates were 60% and 53%, respectively [18]. Combined metformin and letrozole therapy have also been associated with improved ovulation and pregnancy outcomes, although a significant benefit in live birth may not be observed [19]. Therefore, concomitant metformin may have contributed to the overall ovulatory response in both groups.

Both regimens were well tolerated in our study, with no significant differences in headache, cramps, hot flushes, or abdominal pain, nausea, or gastrointestinal symptoms. Similar minimal and comparable adverse effects have been reported with different letrozole regimens [14]. Overall, the findings suggest that extended letrozole may provide a greater follicular response, particularly with repeated cycles, while maintaining comparable endometrial thickness, pregnancy outcomes, and tolerability.

CONCLUSION

The present study demonstrated that extended letrozole regimen, when combined with metformin, results in significantly better follicular development compared to the short course. Ovulation rate and biochemical pregnancy rate were also successively better in extended protocol, although not statistically significant. While both courses achieved favourable results, the extended regimen produced a higher proportion of follicular responses and improved ovulation in later cycles, with a non-significant trend toward higher biochemical pregnancy rates. These findings support the clinical utility of extended letrozole regimens as an improved approach to ovulation induction in PCOS women receiving metformin.

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