A comparison of letrozole regimens for ovulation induction in women with polycystic ovary syndrome

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Objective: To determine the optimal letrozole regimen for ovulation induction (OI) in women with polycystic ovary syndrome (PCOS)
Design: Retrospective cohort study.
Setting: Single academic fertility clinic from 2015–2022.
Patient(s): A total of 189 OI cycles in 52 patients with PCOS
Intervention(s): Patients were prescribed 1 of 4 letrozole regimens (group 1: 2.5 mg for 5 days, group 2: 2.5 mg for 10 days, group 3: 5 mg for 5 days, and group 4: 5 mg for 10 days).
Main outcome measure(s): The primary outcome was ovulation, and secondary outcomes included multifollicular development, and clinical pregnancy rate, which were analyzed with binary logistic regression. Kaplan-Meier cumulative response curves and a Cox proportional hazard regression model were used for time-dependent analyses.
Results: Mean age was 30.9 years (standard deviation [SD], 3.6) and body mass index was 32.1 kg/m^2 (SD, 4.0). Group 2 (odds ratio [OR], 9.12; 95% confidence interval [CI], 1.92–43.25), group 3 (OR, 3.40; 95% CI, 1.57-7.37), and group 4 (OR, 5.94; 95% CI, 2.48–14.23) had improved ovulation rates after the starting regimen as compared with group 1. Cumulative ovulation rates exceeded 84% in all groups, yet those who received 5 mg and/or 10 days achieved ovulation significantly sooner. Multifollicular development was not increased in groups 2–4 as compared with group 1. Groups 2–4 also demonstrated improved time to pregnancy.
Conclusions: Ovulation rates are improved when starting with letrozole at 5 mg and/or a 10-day extended course as compared with the frequently-used 2.5 mg for 5 days. This may shorten time to ovulation and pregnancy. (F S Rep® 2024;5:170–5. ©2024 by American Society for Reproductive Medicine.)
Key Words: ovulation induction, letrozole, ovulation, polycystic ovary syndrome

Letrozole is a selective, reversible, competitive inhibitor of the aromatase enzyme developed initially in the early 1990s for the treatment of postmenopausal women with estrogen-sensitive breast cancer (1). Initial phase I and II studies of letrozole in postmenopausal women found that estrogen levels correlated with letrozole dose but that in this population doses >0.5 mg led to extremely low-estrogen levels below assay limits (2–5). Subsequent randomized controlled trials suggested that 2.5 mg was the optimal dose in terms of breast cancer survival (5–8).

Mitwally and Casper (9) first described the off-label use of letrozole for ovulation induction in women with polycystic ovary syndrome (PCOS) who had failed treatment with clomiphene citrate. They used the Food and Drug Administration–approved 2.5 mg dose, extrapolated from the treatment of postmenopausal women with hormone-sensitive breast cancer, and administered letrozole between days 3–7 of the menstrual cycle as is typical with the clomiphene citrate regimen. Since then, multiple high-quality studies have suggested that letrozole indeed may be superior to clomid for ovulation induction in women with PCOS, in increasing ovulation and live birth rates and decreasing risk of multiple gestation (10–14).

However, despite favorable data supporting the use of letrozole for ovulation induction in women with PCOS, the ideal letrozole regimen remains unknown and warrants evaluation. Pharmacodynamic data in postmenopausal women that underpin the commonly used 2.5 mg dose may not be valid in premenopausal

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reproductive-aged women who have active ovarian estrogen production, particularly women with PCOS who often have elevated body mass and chronic estrogen exposure. It is possible that higher doses may be beneficial in fertility patients for a greater degree of suppression of estrogen production and resultant follicle-stimulating hormone rise. Additionally, while usually administered for 5 days as with clomiphene citrate, letrozole differs from clomiphene citrate in its mechanism of action and half-life. Letrozole is an aromatase inhibitor with a shorter half-life of 2 days, whereas clomiphene is an estrogen receptor antagonist with a half-life more than twice that. Thus, a 5-day course of letrozole may not be the ideal duration to support follicular growth.

The objective of this study was to compare 4 different starting doses of letrozole for ovulation induction in women with PCOS.

MATERIALS AND METHODS

Study participants and protocol

This was a retrospective study of patients diagnosed with PCOS by Rotterdam criteria between 2015 and 2022 in the Los Angeles General Hospital Reproductive Endocrinology and Infertility Clinic. The study protocol was approved by the University of Southern California institutional review board (HS-22-00197). The study clinic is a county-based fertility clinic that serves a predominantly Hispanic population.

Patients were prescribed a regimen of letrozole beginning on day 2–3 of a spontaneous menstrual cycle or after a progestin withdrawal. Anovulatory patients confirmed to have low-serum estradiol and progesterone levels were allowed to "random start" letrozole. Baseline ultrasound in all patients confirmed early follicular phase and no significant ovarian pathology. Patients were prescribed 1 of 4 different letrozole regimens based on provider preference: 2.5 mg for 5 days, 2.5 mg for 10 days, 5 mg for 5 days, or 5 mg for 10 days. Patients were excluded if they received clomiphene or if they were prescribed a different letrozole regimen because of low numbers of patients in these groups.

Patients were scheduled an appointment for an ultrasound to determine response to letrozole around cycle days 10–12. Response to the initial letrozole regimen was determined by the presence of a follicle $\geq$ 14 mm on ultrasound. Patients were instructed to begin ovulation predictor kits on day 10 of their cycle. Ovulation was triggered either with 10,000 IU subcutaneous human chorionic gonadotropin injection when $\geq$1 follicles were $\geq$ 17–18 mm or was allowed to proceed spontaneously with endogenous luteinizing hormone surge based on patient and provider preference. If the patient did not present for the scheduled ultrasound, response was determined by an ovulation predictor kit, midluteal progesterone $\geq$ 3 ng/dL around cycle day 21, an appropriately timed menses, or if the patient had a positive pregnancy test. If no method to determine response was available, the patient was determined as lost to follow-up and excluded from the analysis. If there was no response to the initial letrozole regimen, letrozole was represcribed per provider preference typically at a higher dose or for longer duration in attempts to catalyze follicular development and ovulation; however, original grouping was unchanged in the analysis. Cycles were considered separate events if they were separated by a menstrual period or if >1 month time elapsed without intervention in anovulatory patients with confirmation of ovarian quiescence based on hormone levels and ultrasound before the next cycle.

Primary outcomes

The primary outcome of the study was response to the starting letrozole regimen in that particular ovulation induction cycle, i.e., whether or not ovulation occurred. Secondary outcomes were the rate of multifollicular development and clinical pregnancy rate. Clinical pregnancy rate was determined by a positive pregnancy test followed by the presence of fetal cardiac motion on ultrasound.

Statistical analysis

Patient baseline characteristics and demographics were analyzed with χ^2 test for categorical variables or analysis of variance for continuous variables. Binary logistic regression was used to assess differences in ovulation rates, pregnancy rates, and multifollicular development among the 4 groups. For these analyses, group 1 was designated as the referent group; however, pairwise comparisons also were performed to detect any differences between other groups. Results were confirmed with a generalized estimating equation controlling for repeated measures, as patients underwent multiple cycles of ovulation induction in attempts to achieve pregnancy.

Given time to reach ovulation is relevant clinically for patients with PCOS and patients may require redosing of medication to achieve response in the same cycle, a time-dependent analysis was performed to assess letrozole response. The Kaplan-Meier method was used to assess cumulative response curves with the log-rank test. A Cox proportional hazard regression model then was used to analyze differences in letrozole response among the 4 groups controlling for age, parity, body mass index, anti-müllerian hormone levels, diabetes status, hypertension, hyperlipidemia, and metformin use. The effect size of statistical significance was expressed with hazard ratios and 95% confidence interval (CI).

All statistical analyses were based on 2-tailed hypotheses, and P value of $<.05$ was considered statistical significant. Statistical Package for Social Sciences (IBM SPSS, version 27.0, Armonk, NY) was used for the analysis. The STROBE guidelines were consulted for the performance of this observational cohort study.

RESULTS

Of 144 patients with PCOS who presented for fertility treatment during the study period, 52 underwent 189 ovulation induction cycles and were included in the study (Supplemental Fig. 1, available online). There were 62 cycles (32.8%) in group 1 (letrozole 2.5 mg for 5 days), 17 cycles (9.0%) in group 2 (letrozole 2.5 mg for 10 days), 57 (30.2%) in group 3 (letrozole 5 mg for 5 days), and 53 (28.0%) in group 4 (letrozole 5 mg for 10 days). Patient demographic variables are shown in Table 1

TABLE 1

Patient demographics

Variable	Group 1 2.5 mg, 5 d	Group 2 2.5 mg, 10 d	Group 3 5 mg, 5 d	Group 4 5 mg, 10 d	*P* value
Age, y (mean, SD)	30.6 (3.6)	29.9 (3.7)	32.0 (3.8)	30.2 (3.1)	.03
Hispanic (%)	96.8	100	100	96.2	445
Body mass index, kg/m^2 (mean, SD)	32.1 (3.7)	30.2 (16)	31.2 (4.4)	32.5 (4.1)	.09
Antimulterian hormone (mean, SD)	8.4 (5.8)	7.2 (4.3)	7.9 (38)	10.6 (5.6)	.021[a]
Day 2-3 folicle-stimulating hormone (mean, SD)	-1.3	4.9 (16)	6.0 (1.0)	6.0 (16)	.007[a]
Nuligravid (%)	64.5	82.4	36.8	71.7	.002[a]
Multiparity (%)	18.8	16.7	50.8	7.4	<.001[a]
Oligomenorrhea (%)	98.4	100	100	100	.560
Hyperandrogenism (%)	75.8	70.6	82.5	90.6	.133
Polycystic ovarian morphology (%)	88.7	100	94.7	96.2	.221
Prediabetes or diabetes mellitus (%)	40.3	5.9	47.4	41.5	.035[a]
Metformin use (%)	33.9	5.9	45.6	39.6	.025[a]
Hypertension (%)	97	0	12.3	1.9	.104
Hyperlipidemia (%)	32.3	29.4	43.9	17	.26

Mean (standard deviation) or percentage per column for each group is shown. Analysis of variance (ANOVA) was used for *P* value for continuous variables, and X^2 test for categorical variables.
[a] Significant *P values*.

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per group. Mean age of the entire cohort was 30.6 years (standard deviation [SD], 4.0) and body mass index was 32.0 kg/m^2 (SD, 4.1). The vast majority of patients were Hispanic, nulligravid, and obese. Antimüllerian hormone values were elevated across all groups consistent with PCOS. Most patients met all 3 Rotterdam criteria for PCOS diagnosis. Group 2 patients had lower rates of prediabetes or diabetes mellitus. The mean number of cycles per patient was 3.8 (SD, 3.0). Of the patients in the data set 29% underwent only 1 cycle, whereas 60% underwent ≥3, and 23% underwent ≥6 cycles. The mean number of days between ovulation induction cycles in this study was 117 days (SD, 208). A new cycle was defined in this study as a menstrual period if the patient was ovulatory the prior cycle, or in anovulatory patients, if at least 1 month time elapsed without intervention and there was confirmation of early follicular phase based on serum hormone values and ultrasound findings. These data reflect that many times patients had nonconsecutive cycles because of either lapses in treatment or returning to treatment after pregnancy (either birth or miscarriage) in attempts to conceive again. There was no significant difference in time between ovulation induction cycles between groups.

Outcomes after starting the letrozole regimen for ovulation induction cycles are shown in Table 2. Group 1 had a statistically significantly lower ovulation rate after the starting letrozole regimen than groups 2, 3, or 4. There was no statistical difference in pairwise comparisons between groups 2, 3, and 4. Rates of multifollicular development did not increase with increased dose or duration of letrozole. Finally, the clinical pregnancy rate was highest in group 3 (22%) and lowest in group 2 (6.7%); however, differences in clinical pregnancy rates were not statistically significant with group 1 as the referent group nor with additional pairwise comparisons (*P*>.05, all). There were no multiple gestations in the cohort.

If a patient did not respond to the initial letrozole dose, the dose was increased sequentially in a stair-step method until ovulation was achieved. Overall response after "stair-stepping" the dose did not significantly differ among the 4 groups (*P*>.05, all), and >84% of patients eventually ovulated in all groups. However, time to ovulation was statistically significantly longer for patients in group 1 as compared with the other 3 groups after adjusting for preselected covariates (Fig. 1, *P*<.001). Mean time to ovulation was 22.4 (SD, 11.0) days for group 1 as compared with 12.0 (SD, 3.8), 12.9 (SD, 5.9), and 14.3 (SD, 3.6) for groups 2, 3, and 4, respectively. In a time-dependent multivariable model, ovulation was >3 times more likely for patients in groups 2, 3, or 4 as compared with group 1 (Table 3). Increasing body mass index also was associated with lower likelihood of response.

Based on these results, a time-dependent analysis of cumulative pregnancy rate was performed (Supplemental Fig. 2 and Supplemental Table 1, available online). Patients were censored if there was no follow-up or a lapse in treatment. Groups 2–4 were combined given low numbers of total events and no difference between the groups in the primary endpoint. Indeed, there was a significant difference in cumulative pregnancy rates between groups 2–4 and group 1 (*P*=.005), and in the multivariable Cox regression model, there was an increased hazard of pregnancy in groups 2–4 as compared with group 1 (*P*=.006; Supplemental Table 1).

DISCUSSION

Results of this study suggest that a starting dose of letrozole 2.5 for 5 days is associated with lower ovulation rates and a longer time interval to reach ovulation as compared with starting at a 5 mg dose or for an extended 10-day course. There was no increased likelihood of multifollicular recruitment with a higher dose or longer duration in this study.

Most studies evaluating letrozole for ovulation induction in PCOS have used a starting regimen identical to that as reported by Casper and Mitwally (9) in 2001 with sequential increases in dose if there was no response (10, 15, 16). The 2014 randomized controlled trial by Legro

TABLE 2

Letrozole outcomes by group

Groups	Ovulation rate	Multifollicular development	Clinical pregnancy rate
Group 1 2.5 mg, 5 d	45.2% Ref	23.8% Ref	14.8% Ref
Group 2 2.5 mg, 10 d	88.2% OR, 9.12 [95% CI, 1.92–43.25] *P*=.005[a]	20.0% OR, 0.80 [95% CI, 0.13–5.07] *P*=.813	6.7% OR, 0.41 [95% CI, 0.04–4.06] *P*=.446
Group 3 5 mg, 5 d	73.7% OR, 3.40 [95% CI, 1.57–7.37] *P*=. 002	21.9% OR, 0.90 [95% CI, 0.24–3.31] *P*=.869	22.0% OR, 1.62 [95% CI, 0.44–5.90] *P*=.467
Group 4 5 mg, 10 d	83.0% OR, 5.94 [95% CI, 2.48–14.23] *P*<.001[a]	32.0% OR, 1.51 [95% CI, 0.41–5.58] *P*=.540	13.6% OR, 0.91 [95% CI, 0.23–3.56] *P*=.890

Binary logistic regression models were used for analysis between groups with group 1 as the referent group.
95% CI = confidence interval; OR = odds ratios.
[a] Significant *P values*.

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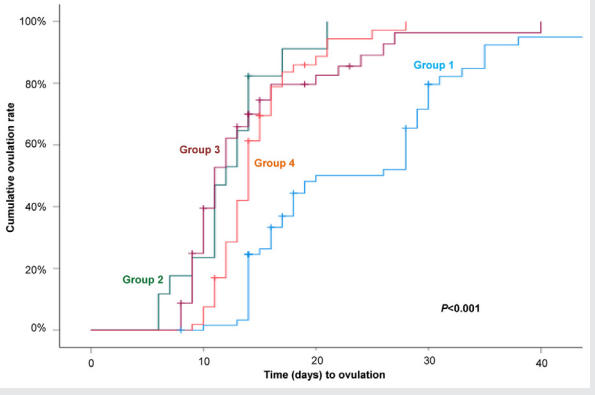
et al. (10) comparing clomiphene 50 mg to letrozole 2.5 mg for ovulation induction in 750 patients with PCOS is perhaps the most widely-cited evidence for letrozole use. In that study, the dose was increased if no response was observed. Interestingly, after letrozole 2.5 mg for 5 days only, 28.6% of patients ovulated; the majority required dose increases to achieve response. Legro et al. (10) reported time from study randomization to live birth, and they found that letrozole had a cumulative higher birth rate, but time to pregnancy did not differ between the 2 groups. Our study suggests that time to pregnancy theoretically could be improved with higher starting doses of letrozole or extended duration.

FIGURE 1



Ovulation by starting letrozole group.
Kaplan-Meier survival analysis with log-rank test for *P value*. X-axis represents time to ovulation in days. Y-axis represents cumulative ovulation rate.

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There is sparse high-quality literature examining higher doses and extended regimens of letrozole, but the studies that do exist report conflicting results. In terms of dose, higher starting doses of letrozole have been studied with varying success in the PCOS and unexplained infertility populations. Al-Fadhli, et al. (17) randomized patients with unexplained infertility to letrozole 2.5 or 5 mg on days 3–7 of the menstrual cycle and found that the 5 mg dose led to significantly increased number of periovulatory follicles and pregnancy rates. In contrast, a randomized controlled trial in patients with PCOS undergoing ovulation induction that compared a 5 mg to a 7.5 mg dose did not find any statistical difference in outcomes (18). Similarly, another randomized trial comparing 3 doses of letrozole (2.5, 5, and 7.5 mg) found that a higher doses led to an increase in the number of periovulatory follicles but that this did not translate to higher pregnancy rates (19). It appears that dose increases to even as high as 12.5 mg may increase number of follicles but may not translate to significantly improved pregnancy rates (20).

The first study to examine longer durations of letrozole was in 2009 and found that women with PCOS who were randomized to letrozole 2.5 mg for 10 days had an increased number of follicles and a higher pregnancy rate per cycle compared with those who received 5 mg for 5 days (21). There was no significant difference, however, in the number of patients who achieved ovulation after the starting regimen (65.7% vs. 61.8%, respectively). Another very recent study also reported on a method to increase duration of letrozole treatment sequentially at a 5 mg dose from 5 to 7 to 10 days should no response occur with a 5-day course (22). This study reported that 70% of patients ovulated after a 7-day cycle, which is similar to but slightly lower than the response rates in groups 2–4 in our study after the first starting letrozole course. The referenced study only considered a subset of patients who were resistant to letrozole 5 mg for 5 days however, it validates the idea that a more aggressive starting letrozole regimen may be an appropriate strategy.

TABLE 3

Multivariable model for cumulative ovulation

Study groups	Adjusted HR [95% CI]	*P* value
Age, y	1.04 [0.9–1.11]	.165
Body mass index, kg/m^2	0.92 [0.87–0.97]	.001[a]
Antimullerian hormone	0.99 [0.95–1.03]	.522
Multiparity	1.24 [0.65–2.36]	.524
Prediabetes/diabetes mellitus	1.12 [0.70–1.80]	.627
Hypertension	1.36 [0.69–2.68]	.380
Hyperlipidemia	1.32 [0.81–2.14]	.268
Letrozole group Group 1	Referent	
Group 2	4.60 [2.35–9.00]	<.001[a]
Group 3	3.69 [2.35–5.77]	<.001[a]
Group 4	3.84 [2.41–6.14]	<.001[a]

Cox proportional hazard regression model for analysis for *P* value adjusted for preselected covariates as shown. Adjusted hazard ratios with 95% confidence intervals are reported. Significant *P values* are italicized and in bold font. Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Significant *P* values.

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Of course, the concern with higher doses or duration of ovulation induction medication is that of multifollicular development resulting in multiple gestation or adverse effects. This is, indeed, true with clomiphene citrate when used at high doses or for repeated cycles; its long half-life leads to drug accumulation and high rates of multiple ovulation as well as antiestrogenic effects on the endometrium (23). Unlike clomiphene, letrozole has a short half-life, which reduces the possibility of drug accumulation and does not have active metabolites (24). Our study did not show increased rates of multifollicular development with higher letrozole doses or extended regimens. There were no cases of multiple gestation, although larger scale studies are needed to assess this further given low numbers of patients who achieved pregnancy in this cohort. Other studies also have shown that letrozole is associated with reduced or similar rates of multiple pregnancy as compared with clomiphene and that increased doses do not seem to increase the risk of multiple gestation (10, 11, 17, 25). Endometrial thickness also does not to appear to be affected detrimentally with letrozole even at high doses (20). Finally, studies also have shown no increase in the incidence of congenital anomalies with letrozole (26–28).

Strengths of the current study include the analysis of several different combinations of letrozole regimens, in dose and duration. Existing studies have compared either increasing dose or duration but not both. Homogeneity of the population minimizes confounding variables but also limits generalizability of findings to other populations because this population consists predominantly of Hispanic nulligravid women of low socioeconomic status who experience significant barriers in access to fertility treatments. Other limitations include the possibility for selection bias because providers chose the letrozole regimen, and possible patient factors may have influenced this choice that were not known. There also was heterogeneity in clinical practice patterns given aforementioned health care barriers in this patient population to additional medications, laboratory tests, or visits; e.g., some patients received trigger injections or had additional monitoring ultrasounds while others preferred spontaneous ovulation and at-home testing. Furthermore, individual patients underwent multiple cycles in this analysis. Although we accounted for repeated measures, patients' history undoubtedly impacted prescribing practices in subsequent cycles. There also were low numbers of patients particularly in group 2 and for pregnancy data, which limits further analysis among individual groups 2–4. A small number of patients also were lost to follow-up, and the outcomes of these cycles (i.e., whether they ovulated) are unknown but may have influenced results.

CONCLUSION

Based on this study, it appears that a starting dose of 2.5 mg for 5 days may lead to inferior response rates for ovulation induction, and consideration should be given to starting patients with PCOS undergoing ovulation induction at a higher dose or administering letrozole for an extended duration. Ultimately, after patients who did not respond to the initial letrozole regimen were re-dosed or "stair-stepped," ovulation and pregnancy rates did not differ between groups in this study, but patients who started their cycle at the 2.5 mg dose for 5 days required more time to reach those endpoints. This study also shows that reducing time to ovulation may translate to reduced time to pregnancy, and this may be because patients can complete more cycles within a given time period.

CRediT Authorship Contribution Statement

Rachel S. Mandelbaum: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ravi Agarwal:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Samuel Melville:** Writing – original draft, Data curation. **Caroline J. Violette:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Sharon Winer:** Writing – review & editing, Methodology, Conceptualization. **Donna Shoupe:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Koji Matsuo:** Writing – review & editing, Formal analysis, Conceptualization. **Richard J. Paulson:** Writing – review & editing, Supervision, Conceptualization. **Molly M. Quinn:** Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of Interests

R.S.M. has nothing to disclose. R.A. has nothing to disclose. S.M. has nothing to disclose. C.J.V. has nothing to disclose. S.W. has nothing to disclose. D.S. has nothing to disclose. K.M. has nothing to disclose. R.J.P. has nothing to disclose. M.M.Q. has nothing to disclose.

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