

Pregnancy rates from intrauterine insemination are equivalent following 1- versus 5-day letrozole administration for ovulation induction: a retrospective study

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Objective: To compare the efficacy of single-dose letrozole (25 mg) with a 5-day course (5 mg/day) for ovulation induction (OI).

Design: Retrospective cohort study.

Setting: Hospital.

Patient(s): Patients undergoing first round of OI and intrauterine insemination with letrozole from January 2015 through December 2017.

Intervention(s): Patients received letrozole as either a single 25 mg dose for 1 day (1D) versus 5 mg daily for 5 days (5D). A secondary analysis was performed on patients also receiving gonadotropins (GND).

Main Outcome Measure(s): Pregnancy rate (PR) determined by positive human chorionic GND.

Result(s): There were 847 patients included in the study, 302 in the 1D group and 284 in the 5D group; 261 patients had concurrent GND administration, 162 1D+GND and 99 5D+GND. There was no difference in smoking status, primary versus secondary infertility, or total motile sperm concentration. Comparing 1D with 5D, there was a statistically significant, although not clinically relevant, difference in both age and body mass index (31 vs. 31.8 years; 26.2 vs. 27.4, respectively). Similarly, comparing 1D+GND with 5D+GND, there was statistically significant difference in body mass index (27.19 vs. 29.1). Secondary outcomes included live birth rate (LBR), multiple gestation rate (MG), and miscarriage rate (SAB). There were no differences between 1D and 5D in the primary outcome of PR (14.2% vs. 11.6%), LBR (9.6% vs. 7%), MG (16.2% vs. 13.8%), or SAB (16.22% vs. 13.8%). In looking at the GND groups alone, there was no difference in PR (18.3% vs. 23.8%), LBR (11.72% vs. 17.86%), MG (8.7% vs. 5.56%), or SAB (13.64% vs. 5.56%). There was a significant difference in cycle cancellation rate in the 1D versus 5D groups (3.9% vs. 9.6%); however, this was not seen in the 1D+GND versus 5D+GND groups.

Conclusion(s): A single-dose protocol with letrozole in an OI/intrauterine insemination cycle may be considered an alternative to standard 5D dosing protocols with the potential for improved compliance and similar reproductive outcomes. (*Fertil Steril Rep*® 2020;1:202-5. ©2020 by American Society for Reproductive Medicine.)

Key Words: Ovulation induction, letrozole, IUI

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Infertility affects approximately 15% of the reproductive-age population, and the first-line standard of care for many of these couples is ovulation induction (OI) followed by insemination (1). Traditionally, the agent of choice was clomiphene citrate; however, in recent years, the aromatase inhibitor letrozole has increasingly been used. Letrozole reduces serum concentration of estradiol in vivo by blocking conversion from androgens via aromatase, promoting a release of gonadotropins (GND) from the anterior pituitary by release of negative feedback (2). In fact, letrozole has become the treatment of choice for OI in patients with hyperandrogenemia, such as in polycystic ovary syndrome (3, 4). Moreover, it has been shown to be equivocal to clomiphene in other populations, with a better side effect profile (5, 6).

Similar to the dosing protocol for clomiphene, letrozole is given in daily doses of 2.5 to 7.5 mg daily over 5 days in the early follicular phase (7, 8). Mitwally and Casper (8) published a study in 2005 comparing the administration of a 5-day course of letrozole to a single dose protocol for OI (8). Patients either received a single dose of 20 mg letrozole on cycle day 3 or a 5-day dose of 2.5 mg per day. Investigators reported no difference in pregnancy rates between these two groups. Importantly, this study did not describe its sample size or any randomization methodology, limiting the ability to interpret these results.

Therefore, we designed a study to critically evaluate these two protocols in a well-established homogenous population. We hypothesized that the pregnancy rate would not differ between women undergoing intrauterine insemination (IUI) after a single dose or 5-day dose of letrozole.

MATERIALS AND METHODS

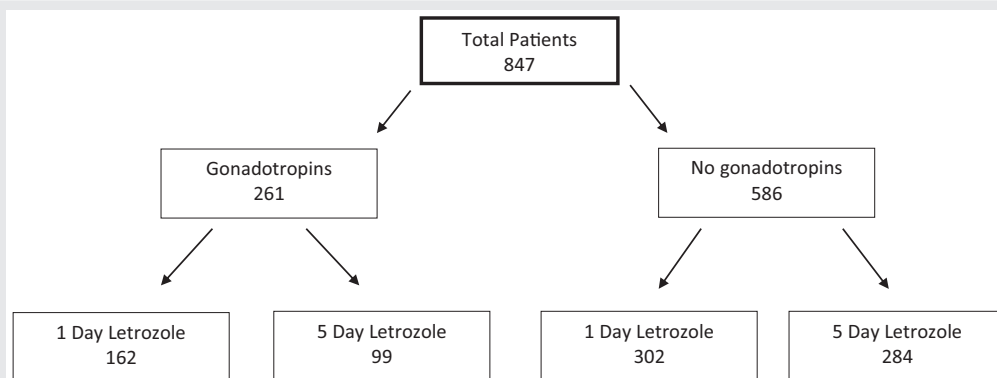
We conducted a retrospective cohort study of patients undergoing OI with letrozole at a private practice fertility clinic. The study was composed of women undergoing their first OI cycle with letrozole (either 1- or 5-day administration) with planned IUI between January 1, 2015, and December 31, 2017 (n = 586). The indication for treatment was either

ovulatory dysfunction, male factor infertility, or unexplained infertility. There was no difference in the diagnoses among the study groups. Given the retrospective nature of the study, there was limited information available on the duration of infertility of some couples, and therefore this information was not included in the analysis. A secondary analysis was conducted in patients who received injectable GNDs after the administration of letrozole in the late follicular phase (n = 261). This study was deemed exempt from Institutional Review Board review as all study data were deidentified.

All patients undergoing OI/IUI during the time frame of the study were included. Patients were treated with either received a single dose of 25 mg letrozole on cycle day 3 (1D) or a dose of 5 mg daily for 5 days from cycle days 3–7 (5D). Patients were not prospectively randomized to any particular protocol but rather were treated based on individual physician practice. All patients underwent ultrasound monitoring for the treatment cycle, starting with a baseline ultrasound between cycle days 1 and 5 followed by an ultrasound between cycle days 10 and 12 to determine response to the protocol and timing of trigger as indicated. All patients were triggered using 10,000 IU of human chorionic GND followed by single IUI; no further evaluation was performed via ultrasound or laboratory monitoring, such as progesterone levels, after triggering. The addition of GND injections in the late follicular phase after administration of letrozole was determined by the physician based on ultrasound and laboratory evaluation of follicular response.

Primary and secondary outcomes were identified by medical record review. The primary outcome of the study was pregnancy rate, defined as positive serum beta human chorionic GND (>20 mIU/mL). Secondary outcomes included live birth, miscarriage, multiple gestation, and cycle cancellation rates. Live birth was defined as a live birth after 24 weeks' gestation. Miscarriage was defined as a pregnancy loss before 20 weeks' gestation. Reasons for cycle cancellation included either low ovarian response (lack of development of lead follicle at least >14 mm), multifollicular response, response from

FIGURE 1



Final study cohort from first cycle ovulation induction with letrozole (January 2015–December 2017).

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TABLE 1**Patient demographics**

Characteristic	Without GND			With GND		
	1-Day	5-Day	P value	1-Day	5-Day	P value
n	302	284		162	99	
Age, y	31	31.8	.03	30.98	31.94	.14
BMI, kg/m ²	26.2	27.4	.02	27.19	29.1	.048
Smoker (yes), %	7.9	9.2	.60	8.72	6.45	.553
Gravid (yes), %	37.7	39.1	.74	60.39	65	.98
Total motile count, millions	80.3	76.1	.68	80.79	89.65	.478

Note: Data presented as total number of patients; unless stated otherwise. BMI = body mass index; GND = gonadotropins.

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side of known tubal occlusion, low total motile count on semen prep of <10 million, premature ovulation, or noncompliance. Statistical analysis was performed with GraphPad Prism using Student's *t* test, χ^2 test, and Fisher's exact test where appropriate. Data are expressed as mean or percentage where appropriate, and $P < .05$ was considered statistically significant.

RESULTS

In total, 847 individual first cycles of OI were analyzed during the study period. Of these, 302 received the 1D protocol and 283 received the 5D (Fig. 1). The remaining 261 patients received subsequent GND after the letrozole and were analyzed in a secondary analysis, 162 received 1-day dosing (1D+GND), and 99 received 5 day dosing (5D+GND). In the primary cohort, there were no differences regarding smoking status, gravidity, and total motile count. There was a significant, although not clinically relevant, difference between both age (31.0 vs. 31.8, $P = .03$) and body mass index (26.2 vs. 27.4, $P = .02$) when comparing the 1D versus 5D, respectively (Table 1). In the secondary cohort, there were also no differences in smoking status, gravidity, and total motile count, nor were there any differences in age. However, there was a slight difference in body mass index (27.19 vs. 29.1, $P = .048$) comparing 1D+GND versus 5D+GND, respectively.

Examination of the primary outcome revealed no significant difference observed in pregnancy rates between 1D and 5D (14.2% vs. 11.6%, $P = .35$). Moreover, no difference was observed in live birth rate (9.6% vs. 7%, $P = .26$), miscarriage

rate (13.9% vs. 12.12%, $P = 1$), or multiple gestation (13.9% vs. 12.12%, $P = 1$). Interestingly, there was a significant lower cancellation rate in 1D compared with 5D (3.9% vs. 9.6%, $P = .007$). However, when subdivided into reason for cancellation, there was no difference seen between the two groups (Table 2).

Similar to the primary cohort, there was no significant difference in the secondary cohort in pregnancy rates between 1D+GND and 5D+GND (18.25% vs. 23.75%, $P = .43$; Table 3). Additionally, there was no difference observed in live birth (10.5% vs. 15.15%, $P = .27$), miscarriage (12% vs. 5.3%, $P = .62$), multiple gestation (8% vs. 5.3%, $P = 1$), or cycle cancellation rates (14.81% vs. 19.2%, $P = .36$; Table 3).

DISCUSSION

Our results are consistent with the earlier findings of Mitwally and Casper (8) that pregnancy rates after a single dosing protocol of letrozole in OI are not different from those after a standard dosing protocol administered over a 5-day period in the early follicular phase. Moreover, miscarriage, multiple gestation, and live birth rates were not different between these groups. Overall, the populations compared were very similar, with statistical differences only noted in age and body mass index. These differences between the two populations with these demographics were very slight and likely a result of the small variance in the populations and arguably not clinically relevant. Furthermore, while cancellation rate appeared to be significantly lower after the single dosing protocol, when further subdivided by reason of cancellation, there was no significant difference seen between the groups. Further, the main reason for cancellation in the 5D group was ovulation on the wrong side, which is not a sign of treatment failure but rather a result of chance requiring cancellation in this cohort.

With similar pregnancy rates, the single dosing protocol can provide simpler administration with the potential for improved compliance. In the earlier study by Mitwally and Casper (8), patients received letrozole either alone or in combination with GND, similar to our study. However, the investigators did not separate these patients into subgroups. By separating those who received GND and those who did not into separate cohorts, we were able to show there was still

TABLE 2**Comparison of cancellation reasons between 1-day and 5-day letrozole groups.**

Reason for cancellation	1-Day	5-Day	P value
Dominant follicle on wrong side	2	11	.26
Low ovarian response	1	4	1.00
Multifollicular response	0	2	1.00
Premature ovulation	4	4	.20
Premature ovulation	2	0	.08
Low total motile count	1	5	.65
Noncompliance	1	0	.30

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TABLE 3

Comparison of outcomes between 1-day and 5-day letrozole groups, with and without gonadotropins.

Variable	Without GND			With GND		
	1-Day, %	5-Day, %	P value	1-Day, %	5-Day, %	P value
Pregnancy rate	14.2	11.6	.030	18.3	23.8	.430
Live birth rate	9.6	7	.263	11.72	17.86	.266
Miscarriage rate	16.22	13.79	1.000	13.64	5.56	.622
Twins	16.22	13.79	1.000	8.7	5.56	1.000
Cycle cancelled	3.9	9.6	.007	17.39	23.75	.355

Note: GND = gonadotropins.

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no difference seen in outcomes between the protocols whether GND were added or not.

Although patients were not specifically asked about side effects of single-dose letrozole at the time of administration, there did not appear to be any significant side effects reported by patients receiving this larger dose. Future prospective studies could explore this further by asking patients to report any symptoms during their cycle.

This study had both strengths and limitations. One strength of the study is that it included a large, contemporary cohort. We also examined only first-cycle IUI data to decrease confounding variables. One limitation of the study is that we did not exclude any patients based on infertility diagnosis. Future research could examine whether results would differ in patients with ovulatory defects such as polycystic ovary syndrome versus other fertility diagnoses.

Letrozole with or without GND administration has been shown to be an effective form of OI, particularly in patients with ovulatory dysfunction, such as seen in polycystic ovary syndrome (2). With no difference in pregnancy outcomes, single dosing of letrozole appears to be equivalent to 5-day dosing for OI and may be considered a reasonable alternative administration regimen. However, future, prospective studies that would preferably be randomized and blinded are needed to draw a meaningful conclusion. Until such time, any changes to the standard dosing protocol on a large basis are not yet warranted but may be considered on an experimental basis. Based on these retrospective data, the single dosing

protocol may provide simpler administration with potential for improved compliance, without any difference in pregnancy outcomes.

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