Single-dose administration of an aromatase inhibitor for ovarian stimulation

Recently, the success of a 5-day administration of an aromatase inhibitor for ovarian stimulation has been shown. In this report, a convenient simple regimen of administering an aromatase inhibitor as a single dose has been found to have comparable success to a 5-day regimen for ovarian stimulation. (Fertil Steril® 2005; 83:229–31. ©2005 by American Society for Reproductive Medicine.)

The two main medications used for induction of ovulation include an oral antiestrogen, such as clomiphene citrate (CC), and injectable gonadotropins, predominantly recombinant FSH. The use of CC and gonadotropins for induction of ovulation is associated with several drawbacks, including a lower pregnancy rate, despite a high ovulatory rate (especially for CC), multiple gestation, the risk of life-threatening ovarian hyperstimulation syndrome, the need for intensive monitoring, and the increased cost of treatment and parenteral administration (mainly with gonadotropin injections) (1–4). We have recently reported the successful use of an aromatase inhibitor as a new low-cost oral method for ovulation induction that could eliminate many of the problems listed above (5–9). In all our studies reported so far, the aromatase inhibitor letrozole was administered as a 5-day regimen, usually from day 3 to 7 of the menstrual cycle, at a dose of 2.5–7.5 mg/day (5–9).

In this clinical trial, we explored a new approach of administering an aromatase inhibitor for ovarian stimulation, namely, a single dose on the third day of the menstrual cycle. This idea stemmed from the elimination half-life of about 45 hours for the new third generation aromatase inhibitors, such as letrozole and anastrazole, which should allow therapeutic levels of estrogen suppression between 4 and 6 days and complete clearance of the drugs by 10 days after a single-dose administration. The outcome of this new protocol was compared with the 5-day regimen of letrozole administration, which has been reported elsewhere (5–10).

We obtained approval from the Institutional Research Board for using an aromatase inhibitor for ovarian stimulation. The study was conducted in two tertiary referral academic centers: the Reproductive Biology Unit of Mount Sinai Hospital and the Toronto Center for Advanced Reproductive Technology. These clinics are affiliated with the Division of Reproductive Sciences, University of Toronto, Canada. Patients were enrolled from January 2000 until July 2001.

Patients who had at least 2 years of infertility with patent fallopian tubes and who presented for infertility treatment with ovarian stimulation and cycle monitoring for timed intercourse or intrauterine insemination (IUI) were offered the option of trying the single-dose regimen of the aromatase inhibitor letrozole for ovarian stimulation. Patients who opted to participate in the study received letrozole at a single dose of 20 mg on day 3 of the menstrual cycle, either alone or in conjunction with FSH injections that started on day 7 of the menstrual cycle.

The 20-mg dose was selected by calculations based on previous pharmacodynamic studies of letrozole, demonstrating 100% bioavailability of the drug by mouth and a half time of drug disappearance of 45 hours (11, 12). Using these parameters, we estimated that the therapeutic level of aromatase inhibition after a single dose administration should last about 5 days and that clearance of all drug from the body should occur by day 13. The total dose in the 5-day regimen is 12.5 mg, which is about 62.5% of the single dose (20 mg). To our current knowledge, there are no published studies comparing different regimens of aromatase inhibitor administration for ovarian stimulation.

This was a nonrandomized study in which patients who received the aromatase inhibitor letrozole at a single dose (alone or in conjunction with FSH) were compared with those who received a 5-day regimen of letrozole (alone or in conjunction with FSH). Letrozole (Femara; Novartis, East Hanover, NJ) was used in a single dose of 20 mg (eight tablets) on the third day of the menstrual cycle or at a dose of 2.5 mg/day from day 3 to 7 of the menstrual cycle.

When FSH was given in conjunction with the aromatase inhibitor, FSH injection started at a dose of 50–150 IU/day beginning on cycle day 7 until the day of hCG administration. The dose of FSH was adjusted according to patient response to achieve 2–3 mature follicles (>16 mm) on the

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TABLE 1

Various characteristics of the letrozole single-dose regimen (alone or plus FSH) compared with the 5-day regimen (alone or plus FSH) treatment cycles.

	Letrozole only			Letrozole plus FSH		
	Single dose	*P*	5-Day regimen	Single dose	*P*	5-Day regimen
Day of hCG administration	11.9 ± 2.2	.26	11 ± 4.3	12.6 ± 2.7	.61	12 ± 3.4
Endometrial thickness (mm)	8.5 ± 2.4	.77	8.8 ± 1.9	0.84 ± 0.1	.14	9.2 ± 1.6
Follicles >1.5 cm	1.7 ± 0.7	.35	1.9 ± 0.8	2.8 ± 2.5	.97	2.8 ± 1.5
E_2 level (pmol/L)	642 ± 425	.30	784 ± 398	904 ± 430	.25	1,338 ± 976
FSH dose (unit/cycle)	NA	NA	NA	784 ± 532	.19	490 ± 330
Clinical pregnancy rate per cycle	15%	.27	18%	20%	.21	16.7%

Note: Data are presented as mean ± SD on the day of hCG administration (except pregnancy rate, which is presented as clinical pregnancy rate per cycle). $P < .05$ was considered statistically significant. NA = not available.

Mitwally. Single-dose aromatase inhibitor for ovarian stimulation. Fertil Steril 2005.

day of hCG administration. The choice of the FSH dose was mainly based on the clinical profile of the patient, including age, weight, and duration of infertility as well as prior response to FSH. All patients received recombinant (Gonal-F Serono, Oakville, Ontario, Canada; or Puregon, Organon, Scarborough, Ontario, Canada) or highly purified FSH (Fertinorm, Serono). There was no significant difference between the study groups regarding the use of recombinant or highly purified FSH. Human chorionic gonadotropin (Profasi, Serono; or Pregnyl, Organon) was given as a single injection of 10,000 IU to trigger ovulation when the mean diameter of at least two ovarian follicles was >18 mm.

The development of ovarian follicles was monitored by both transvaginal ultrasound measurement of the mean follicular diameter as well as serial assays of E_2 and LH levels every 1–3 days during the follicular phase. Intercourse was advised (in timed intercourse cycles) or insemination was performed (in IUI cycles) 40 hours after hCG administration if no endogenous LH surge occurred. If an endogenous LH surge was detected on the day of hCG administration, intercourse was advised or IUI was performed on each of the following 2 days. An LH surge was defined as an increase in LH level >100% over the mean of the preceding 2 days. There was no statistically significant difference in the number of cycles in which an endogenous LH surge occurred or the number of inseminations in IUI cycles among the study groups. The same two infertility nurses did IUIs in all patients. Pregnancy was diagnosed by quantitative βhCG 2 weeks after the insemination. Clinical pregnancy was confirmed by observing fetal cardiac pulsation by transvaginal ultrasound 4 weeks after a positive pregnancy test.

The various outcome measures were expressed as mean ± SD. The Student's *t*-test and the χ^2 test were used to compare between the various outcome measures presented in Table 1. The statistical tests were performed with SigmaStat for Windows Version 1.0 software (SigmaStat Software, HighEdit Professional, MicroHelp, and HeilerSoftware, San Rafael, CA).

Table 1 compares various characteristics of a letrozole single-dose regimen (alone or plus FSH) compared with a 5-day regimen (alone or plus FSH), respectively. There was no significant difference in any of the studied cycle characteristics between the single and 5-day regimens of letrozole administration (alone or in conjunction with FSH). Clinical pregnancy rates per cycle were comparable among the single and 5-day letrozole groups.

Single-dose administration of the aromatase inhibitor letrozole seems to be comparable to the 5-day regimen for ovarian stimulation with the potential advantage of increased safety due to rapid clearance from the body. The new single-dose regimen was not significantly different from the 5-day regimen in any of the studied cycle characteristics with achievement of comparable clinical pregnancy rates per cycle.

Administering an aromatase inhibitor as a single dose on day 3 of the menstrual cycle has the advantage of providing higher concentrations to achieve more potent aromatase inhibition when it is needed (early in the follicular phase), while allowing rapid clearance of the aromatase inhibitor from the body due to its short half-life (around 2 days) (11, 12). This will lead to negligible levels of the aromatase inhibitor in the body around ovulation and an early embryogenesis period resulting in enhanced safety. Besides the increased safety of the single-dose administration, it is more convenient and may improve patient compliance by avoiding the need to remember to take five daily doses.

To conclude, the new approach of a single-dose regimen of an aromatase inhibitor for ovarian stimulation seems to be as effective as the previously reported 5-day regimen. The current report carries several limitations, including the nonrandomized design of the study, the small numbers in the single-dose regimen groups, and the retrospective analysis of the data. However, these preliminary observations seem convincing enough to warrant further research to discover the optimal regimen of administering an aromatase inhibitor for ovarian stimulation.

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