Novel letrozole dosing: is a single dose of letrozole equivalent to traditional 5-day dosing?

The novel use of an aromatase inhibitor, letrozole, for ovulation induction was first published by Mitwally and Casper (1) in a landmark proof-of-concept paper almost 20 years ago. The authors described using letrozole for ovulation induction in women with polycystic ovarian syndrome (PCOS) who were refractory to clomiphene citrate and for women who either failed to ovulate with clomiphene citrate or only developed thin endometrial linings. That succinct paper with a total of 12 patients with PCOS and 10 patients with thin linings catalyzed a change in our field regarding oral infertility treatments. Although letrozole for ovulation induction in PCOS took time to become widely adapted, a large randomized controlled trial showed improved ovulation and live birth rates with letrozole over clomiphene citrate in women with body mass index $>$ 30 (2). Letrozole is still not approved by the Federal Drug Administration for ovulation induction, although letrozole has become the standard of care for ovulation induction over clomiphene citrate in patients with PCOS.

In this issue of *F&S Reports*, a paper by McGrail et al. (3), suggests using a single dose of letrozole 25 mg on cycle day 3 may be equivalent to traditional administration on cycle days 3 to 7 with regard to pregnancy, live birth, and miscarriage rates (3). The study also had a cohort that received gonadotropins. The authors did not break down the results by infertility diagnosis. They cite a single paper from 2005 as the rationale behind using a single dose, also from Mitwally and Casper (4). The 2005 paper compares using a one-time, 20 mg dose of letrozole on cycle day 3 to typical 5-day dosing on cycle days 3 to 7 and found that the two regimens were equivalent in terms of peak estradiol levels, number of follicles recruited, and pregnancy rates (4). Mitwally and Casper suggest that the single-dose regimen may be preferable because letrozole would be fully metabolized by the time ovulation occurred given the 45-hour half-life (4). Differing from Mitwally and Casper (4), McGrail et al. (3) use 25 mg instead of 20 mg.

Could McGrail et al. (3) be presenting the next big treatment shift in oral ovulation induction? Although taking medication for 5 days out of the cycle is not typically considered a high burden, taking a medication just one time instead of 5 days in a row would likely be preferable for most patients. Additionally, the idea that letrozole would be metabolized by the time of ovulation is appealing. Although there is no evidence that children conceived with letrozole have a higher incidence of birth defects compared with the general population, less chemical manipulation is generally preferable in medicine.

Given the retrospective nature of the study, the authors were unable to ascertain whether there were more side effects experienced by one cohort versus the other. For a single-dose regimen of letrozole to be adapted, a couple of clear steps are needed. One would be a study examining the lowest doses of medication associated with ovulation. Ideally, the lowest dose of letrozole would be used. McGrail et al. (3) used 25 mg, while Mitwally and Casper used 20 mg (4). Perhaps an even lower dose, such as 15 mg, may work. A study such as this would also help to elaborate on the side effect profile of a single dose compared with the 5-day dosing. Although letrozole is tolerated well, perhaps a large one-time dose would contribute to more side effects than a 5-day regimen. It would also be helpful to evaluate whether there is a higher likelihood of multifollicular development depending on particular doses. Although McGrail et al. (3) did not see a higher likelihood of multiples in the single 25 mg dose versus the 5-day dosing, it is possible that this may be an inadvertent result of treatment. An additional necessary next step would be to perform a randomized controlled trial comparing the efficacy and outcomes of a higher single dose of letrozole compared with the 5-day dosing. This could be done either with a PCOS cohort alone or additionally with a cohort of unexplained infertility. It may be best to prioritize a PCOS group alone since there are more data supporting letrozole use in patients with PCOS compared with clomiphene citrate. It would also be important to omit gonadotropins from the protocol.

The innovative nature of the McGrail et al. (3) paper is exciting and could truly, if further investigated, shift our practice. The study was possible given varying practice patterns among physicians in the same practice. Retrospective or prospective examination of specific variations in practice patterns between providers treating similar cohorts of patients could inform the field of other possible changes in practice that could benefit our patients.

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https://doi.org/10.1016/j.xfre.2020.08.003

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