# Letrozole for ovulation induction and controlled ovarian hyperstimulation

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**Purpose of review**

Letrozole, an aromatase inhibitor, is the newest addition to our armamentarium in the treatment of infertility. It is utilized in much the same way as clomiphene citrate, but with some additional benefits. In this review, the latest studies will be summarized with emphasis on dose, duration of use, safety, number of mature follicles, and pregnancy outcomes.

**Recent findings**

Letrozole has fewer side effects, and a shorter half-life than clomiphene citrate, and no demonstrable effect upon the receptivity of the endometrium. It is efficacious in treating women with chronic anovulation, unexplained infertility and diminished ovarian reserve. Its safety is superior to clomiphene citrate. Utilizing bio-equivalent doses, letrozole pregnancy rates are equal or superior to clomiphene citrate. Several studies suggest situations where it is more efficacious than gonadotropin treatment.

**Summary**

With further study, this drug could replace clomiphene citrate as the primary medication for chronic anovulation and/or unexplained infertility. It could augment or even obviate the use in gonadotropins in the treatment of women who have been unsuccessful in achieving pregnancy with clomiphene citrate. This may also be an adjunct to women with diminished ovarian reserve. Further studies are needed to determine optimal dosing and long term safety for women treated with the drug.

**Keywords**

diminished ovarian reserve, letrozole, PCOS, unexplained infertility

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## Introduction

Until recently, clomiphene citrate was the only oral ovulation induction or superovulation agent available to women trying to increase their fecundity. In women treated for anovulation, the goal is to allow the maturation of a single follicle during their treatment cycle. For those undergoing treatment for male factor, tubal factor or unexplained infertility, the goal may be to grow more than a single mature follicle to increase number of 'targets' for the sperm. In 2000, a case series of women utilizing the aromatase inhibitor letrozole as an ovulation induction agent was reported [1]. Since that time, many researchers have been investigating the role of this drug in the treatment of infertility. This review will focus on letrozole, its safety, efficacy and comparative value in such treatment. Future areas for study will also be addressed.

## History

Clomiphene citrate was first approved for use in women with anovulation by the FDA in 1967. It was initially approved at 50 mg daily, taken on days 5–9 of the cycle. The medication works primarily by competitively inhibiting the binding of estradiol to its receptor in the hypothalamus, thereby releasing the hypothalamus from negative inhibition and allowing increased release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. This increase in FSH is thought to enhance follicular stimulation, resulting in a greater chance of follicular growth and ovulation. However, there are also negative effects of clomiphene citrate, as it has both agonistic and antagonistic activity that is target tissue specific. In particular, the endometrium and cervical mucus may be adversely affected by its use.

For anovulatory women, clomiphene citrate will confer ovulation in 75–80% of cycles [2]. Within 6–9 cycles, the cumulative pregnancy rates are approximately 70–75% [3]. Using the best evidence, it seems that the pregnancy rates are approximately 22% per month for women who ovulate using clomiphene citrate [4]. However, studies have demonstrated that many anovulatory women are

resistant to clomiphene citrate, failing to ovulate while utilizing the drug [5••,6–8]. In patients resistant to clomiphene citrate, a common next step in treatment usually involves the use of injectable gonadotropins, with their known risks of high order multiple pregnancies, ovarian hyperstimulation syndrome, painful injection sites, and the need for extensive and invasive monitoring during treatment, not to mention the increased costs associated with its use.

Letrozole gained its original approval from the FDA in 1997 for the treatment of breast cancer in postmenopausal women.

It was first used for infertility treatment in anovulatory women in 2001. Patients who failed to ovulate with clomiphene citrate (used in doses up to 100 mg for 5 days) were given 2.5 mg of letrozole days 3–7 of the menstrual cycle. With letrozole use, 9/12 ovulated and 25% became pregnant. The mean number of ovulations per patient was 2.3 and the average endometrial thickness was 8 mm [1].

The first randomized controlled trial comparing clomiphene citrate with letrozole for women with unexplained infertility was presented at the American Society for Reproductive Medicine in 2001 [9]. The participants were given 2.5 mg letrozole or 100 mg of clomiphene citrate for 5 days beginning on day 3 of the cycle. On the day of human chorionic gonadotropin (hCG) administration, the number of follicles was greater with clomiphene citrate at 2 versus 1 for letrozole, but the endometrial thickness was greater with letrozole at 8.6 versus 6.9 mm. The pregnancy rates were 16.7% for the letrozole group and 5.9% for the clomiphene citrate group.

## Mechanism of action

Letrozole is a third-generation aromatase inhibitor that works by inhibiting estrogen biosynthesis, thereby releasing the hypothalamus/pituitary from negative feedback and increasing the secretion of FSH by the pituitary. As a result, the ovary receives increased FSH stimulation, allowing for greater follicular development [6]. It also is known to increase intrafollicular androgens [10] which is turn is thought to upregulate and sensitize FSH receptors in the ovary [11–13], as well as increase activin secretion, which further increases the secretion of FSH from the pituitary gland. Letrozole, unlike clomiphene citrate, does not decrease the estrogen receptor density or thin the endometrial lining [6,7]. In fact, the decrease in serum estrogen is thought to upregulate FSH receptors. Letrozole's short half-life (44 h) ensures clearance by the body before implantation occurs, unlike clomiphene citrate [7].

## Dosing

Letrozole is typically administered on days 3–7 of the menstrual cycle at doses of 2.5–7.5 mg/day in 2.5 mg increments. The choice of original dosing of letrozole at 2.5 mg was extrapolated from several studies performed on postmenopausal women utilizing the drug to treat breast cancer [14,15]. This, however, is problematic in that the ovarian suppression of estrogen in the postmenopausal woman is more easily accomplished than in the reproductive age female. Unfortunately, little investigation has been attempted to define optimal dosing in infertile women desiring conception.

It is unlikely that a single dose, or even dose range, is appropriate for all infertile women. An example would be for women with anovulatory infertility, in which only one or two ovulations are desired per month. Most studies utilizing Letrozole at 2.5 mg daily for 5 days show between one and two mature follicles grown at this dose [1,16,17,18•]. Conversely, couples being treated for male factor or unexplained infertility with multiple unsuccessful cycles might wish for maturation of three or four follicles [19].

Available evidence suggests a dose–response with letrozole, with higher doses producing more mature follicles and higher ovulation rates. In 2006, randomized patients received either 2.5 or 5 mg of letrozole followed by intrauterine insemination [20]. With a higher dose of letrozole came a higher number of ovulations (1.1 versus 1.3). Pregnancy rates were higher in the 5 mg dose group as well (5.9% versus 26.3%).

In 2004, the first investigators reported outcomes with a dose of 7.5 mg letrozole given daily for 5 days in women and compared it with clomiphene citrate outcomes at 100 mg daily [21]. This group found 1.4 ovulations in women using this dose compared with 1.1 ovulations with 100 mg of clomiphene citrate. Although pregnancy rates were not different at 11.5% versus 8.9%, the miscarriage rates were significantly higher using clomiphene citrate.

The first randomized controlled trial addressing letrozole dosing was performed in 2007 [16]. Badawy *et al.* utilized either 2.5, 5, or 7.5 mg for couples with unexplained infertility. Although they found no differences in pregnancy or miscarriage rates, the number of mature follicles was significantly higher in the group of women receiving 7.5 mg daily versus 5 or 2.5 mg (3.4, 1.4, or 1.0, respectively).

The optimum length of treatment in a cycle is also unknown at this time. In a recent study, 218 patients who had previously failed clomiphene citrate at 100 mg for 5 days were randomized to receive 5 mg of letrozole

for 5 days or 2.5 mg for 10 days, both starting on day 1 of the menstrual cycle. Ovulation rates were similar at 65.7% for the long course versus 61.8% for the short course. However, in the short regimen, an average of 1.8 follicles more than 18 mm were measured at the day of hCG administration, while a mean of three follicles more than 18 mm were seen in the long regimen. Pregnancy rates were 12.4% with the short and 17.4% with the long protocol [22••].

In an earlier case report, women were given either a single dose of 20 mg letrozole or 2.5 mg days 3–7 of the cycle. Number of ovulations (1.9 versus 1.7) and pregnancy rates (15% versus 18%) were no different [23].

Some authors have theorized that utilizing higher doses of letrozole might antagonize the growth of the endometrium during the follicular phase of the cycle, thus negating the positive effects of multiple ovulations upon treatment outcomes [24]. However, subsequent data have not born this out. The endometrial thickness does not seem to be negatively affected even with doses up to 7.5 mg and when used as long as 10 days into a menstrual cycle [22••,25••]. Furthermore, when looking at pinopod expression and endometrial histology, the use of letrozole resulted in a similar profile to that found during the natural menstrual cycle in ovulatory patients [26]. In addition, uterine artery Doppler resistive indices and pulsatility indices are favorable in women undergoing letrozole treatment [27•].

Other indicators of endometrial receptivity seem to be conserved as well, at least in rat endometrium, with expression of HOXA10, and integrin alpha V beta 3 being decreased in rat uterine epithelium during clomiphene citrate administration but not being affected with letrozole or saline administration [28•].

In summary, we currently do not know the optimal dose or length of treatment for letrozole. It does appear that higher doses of the drug and longer intervals confer higher number of ovulations. This might translate into letrozole being an even more effective therapy than it currently appears.

## Use of the drug

As stated above, the therapeutic goal of letrozole will vary depending upon the infertile couple's diagnosis. For example, with anovulatory women, the goal is to produce one or possibly two ovulations. However, in patients with unexplained, male factor, or even tubal factor infertility, superovulation with anywhere from 2 to 4 ovulations per month may be the goal. Predicted ovulations can be calculated from follicular size and number at the time of hCG administration [29]. As goals differ by diagnosis, it is imperative that treatment regimens be compared within diagnostic categories.

### Unexplained infertility

When comparing letrozole with clomiphene citrate in women with unexplained infertility, the randomized controlled trials are consistent. They utilize anywhere from 2.5 to 7.5 mg for 5 days in the early follicular phase of the cycle. The clomiphene citrate dose is always 100 mg. In a recent meta-analysis of these trials, the pregnancy rates were no different, even though the number of mature follicles was less in women utilizing letrozole [30].

In theory, the hypoestrogenic state created by letrozole should not last late into the follicular phase of the menstrual cycle due to its short half-life, creating a higher likelihood of monofollicular growth [30]. This brings to bear the argument yet again, that the optimum dose and length of letrozole are unknown. If a low dose of letrozole with a brief bioavailability does not often produce multiple ovulations, perhaps higher doses or longer treatment times would induce multifollicular growth.

When looking at women with unexplained infertility utilizing letrozole versus gonadotropins, the randomized controlled trials are again consistent, showing similar pregnancy rates but with significantly reduced costs in the letrozole group. In one randomized trial, letrozole 5 mg daily for 5 days was compared to 150 IU daily of gonadotropins, beginning at day 3 of the cycle, with later adjustment based on monitoring results. Pregnancy rates were not significantly different (8.9% for letrozole, 14% for gonadotropins), and there was no difference in mature follicle number (1.3 versus 1.8) [31].

A second randomized controlled trial compared letrozole at 5 mg on days 3–7 of cycle with human menopausal gonadotropins at 75–150 IU beginning on day 3 of the cycle. Pregnancy rates were again not statistically different at 18.4% for letrozole versus 15.7% for gonadotropins, with the cost being much higher for the injectable group [32].

Letrozole has also been compared with a combination of clomiphene citrate and gonadotropin treatment. In a randomized trial examining these two protocols for unexplained infertility, 5 mg of letrozole for 5 days produced two mature follicles while the clomiphene citrate/gonadotropin combination produced the same. The endometrial thickness was greater with letrozole at 9.7 mm versus 7.8 mm with the hybrid treatment. The pregnancy rates, however, were 32.8% with letrozole and 14.3% with the hybrid cycle [33].

Thus, it appears that for couples with unexplained infertility, when considering ovulation, endometrial thickness,

and pregnancy rates, letrozole has similar efficacy to clomiphene citrate or injectable gonadotropins, and outperforms hybrid treatment with clomiphene citrate and gonadotropins.

## Chronic anovulation

In contrast to women with unexplained infertility, in patients with chronic anovulation, the goal is simply one to two ovulations per cycle; more may be potentially dangerous. In such patients, the initial choice of treatment could either be clomiphene citrate or letrozole.

Four randomized trials have addressed this issue [27•,34,35,36••]. Two of the studies showed no differences in pregnancy rates [35,36••]. However Atay, when utilizing 2.5 mg of letrozole versus 100 mg of clomiphene for 5 days in the early follicular phase, found fewer mature follicles (1.2 versus 2.4) but higher pregnancy rates with letrozole use (22% versus 9%) [34]. Baruah and his group found no differences in number of mature follicles (1.62 versus 1.63) for letrozole at 2.5 or 5 mg on days 3–7 of the cycle, but a higher pregnancy rate at 19% versus 12.5% [27•].

In patients who have failed previous clomiphene citrate treatment, the option is to treat with a higher dose of clomiphene citrate, or switch to letrozole. Only one randomized trial addresses this question. In women who failed to ovulate with lower doses of clomiphene citrate or letrozole, 7.5 mg letrozole versus 150 mg of clomiphene citrate was utilized. With the higher doses of letrozole, the ovulation rate was 62.5% ovulation with letrozole treatment and 37.5% rate with clomiphene citrate. Pregnancy rates were quite high at 41% for the letrozole group and 19% for the clomiphene citrate group [25••].

The addition of metformin to these two drugs may alter the relative value of these medications. One study has examined this issue [37]. By adding metformin to either letrozole at 2.5 mg or clomiphene citrate at 100 mg, both given days 3–7 of the cycle, pregnancy rates were significantly higher in the letrozole group (34.5% versus 16.7%).

It may also be reasonable to ask if letrozole can outperform gonadotropin therapy in the patient with chronic anovulation. Ganesh *et al.* showed a higher pregnancy rate in women taking letrozole 5 mg on days 3–7 (24%) than in women taking gonadotropins beginning day 2 of the cycle and continuing until the lead follicle measure at least 17 mm (18%). To gain entrance into the study, the patients needed to fail six cycles of clomiphene citrate up to 100 mg on days 3–7 of the cycle, or have a suboptimal endometrial thickness (<0.7 cm) on day of hCG administration. The number of mature follicles at hCG administration was not commented upon [5••].

It appears that letrozole, when used for clomiphene citrate naive or resistant anovulatory women, confers superior pregnancy rates with lower miscarriage rates. This seems to occur even when the total number of mature follicles is lower than with clomiphene citrate. Letrozole also performs as well, if not better than, gonadotropin therapy in women with clomiphene-resistant anovulation; and at a fraction of the cost.

## Diminished ovarian reserve

In women with diminished ovarian reserve, there is a poor response to ovulation induction medications. In some, it is due to lack of oocytes; in others however, it is due to a decrease in follicular FSH receptors. With the use of letrozole, an increase of androgen is known to increase these receptors. Thus in theory, letrozole could be a unique and valuable treatment for a subset of women with diminished ovarian reserve [11,38].

In 2002, Mitwally studied women with poor response to gonadotropins in previous stimulation cycles (less than three dominant follicles). They were subsequently given letrozole at 2.5 mg on days 3–7, followed by gonadotropins at 50–250 IU until lead follicles measured more than 18 mm. The subjects then underwent intrauterine insemination. In the previous cycles, the total number of mature follicles had been 1.9; with letrozole and gonadotropins, 3.3 mature follicles developed. The pregnancy rate was 21% in these patients [39].

A recent retrospective study by Bedaiwy looked at letrozole/gonadotropins versus gonadotropins alone for women 40 years and older during intrauterine insemination (IUI) cycles. The investigators used 2.5 mg letrozole on days 3–7 of the cycle, followed by FSH injections on day 7 of the cycle through hCG administration. If less than two follicles greater than 15 mm were noted, then the letrozole in a subsequent cycle was increased to 5 mg daily. In the group of women receiving only gonadotropins, the dosing began at 50–100 IU daily and was adjusted based upon follicular response. FSH injections produced more mature oocytes (3.8 versus 2.9) and a higher estradiol level, but pregnancy rates between the groups were no different (9.3% versus 10.2%). The cost per pregnancy was twice as high for FSH than with the letrozole/hybrid cycles [40••].

In an observational cohort IVF study addressing the treatment of low responders, Garcia-Velasco *et al.* compared rFSH and highly purified hMG along with antagonist in one group, then added 2.5 mg letrozole to create a second group for comparison. The implantation rate was higher in the letrozole group at 25% versus 9.4% for gonadotropins alone, and the pregnancy rate was higher (41.6% versus 28.9%), although not statistically significant [38].

Thus, it appears that letrozole does indeed represent a viable treatment option for many women with diminished ovarian reserve. Future studies should focus upon high quality randomized trials to confirm these findings, as well as attempting to determine which women with diminished ovarian reserve are a priori good candidates for this treatment.

## Safety

Initially, there was concern that letrozole treatment for infertility would be associated with teratogenic effects. In 2005 data were presented suggesting an increased rate of bone and cardiac anomalies in fetuses born to women after letrozole treatment. However, more extensive examination of this issue has failed to substantiate these findings [41]. In fact, letrozole may well be teratogenically safer than clomiphene citrate. The shorter half-life virtually assures elimination from the body prior to implantation, whereas this is not the case with the relatively slowly eliminated clomiphene citrate.

Recently, 911 newborns were evaluated for the incidence of congenital malformations among children born to women after clomiphene citrate or letrozole treatment. Overall the rate of chromosomal abnormalities and congenital malformations was 2.4% with letrozole and 4.8% with clomiphene citrate. With letrozole, the major malformation rate was 1.2% and a single infant was born with a cardiac malformation. With clomiphene citrate, the major malformation rate was 4.8% with four ventral septal defects in this group. The overall rate of cardiac anomalies was 1.8% with clomiphene citrate and 0.2% with letrozole [42].

A review published in 2008 also looked at congenital anomalies following the use of clomiphene citrate, letrozole, and injectable gonadotropins. Clomiphene citrate had a slightly higher risk of neural tube defects and severe hypospadias than the other medications [43].

## Summary

In women undergoing ovulation induction in the case of anovulatory infertility, or women undergoing controlled ovarian hyperstimulation, letrozole is an excellent alternative to either clomiphene citrate or injectable gonadotropins. It has minimal side effects, no proven teratogenicity when used for ovulation induction, and is more cost-effective than other available therapies.

Further studies are needed to evaluate the optimum dose and length of treatment. We have recently noted that letrozole in doses up to 12.5 mg per day for 5 days maintains endometrial integrity while producing a dose-dependent increase in the number of mature follicles (Yuen 2010, personal communication). Lengthier administration remains virtually uninvestigated. In addition, the long-term health effects of this medication on both mother and child need further investigation. Nonetheless, it appears that letrozole is a very promising addition to the armamentarium of ovulation enhancing drugs available to the Reproductive Endocrinologist.

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