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GLIMPSE ON SPLENDID AROMATASE INHIBITOR – LETROZOLE - A PRAGMATIC REVIEW

Akash Gajjar[1], Narendra Gajjar[2], Neerjesh*[3], Dhvani Gajjar[4], Shrish Raut[5] and Bhavna B.[6]

[1]Ex-Senior Resident, Department of Obstetrics and Gynecology, GMERS, Valsad.

[2]Gynecologist, Private Practitioner, Ashirwad Hospital, Chikhli.

[3]Associate Professor and Head, Department of Pharmacology, Narsinhbhai Patel Dental College & Hospital, Visnagar (Gujarat), India.

[4]Gynecologist, Private Practitioner, Ashirwad Hospital, Chikhli.

[5]Assistant Professor, Bharti Vidyapeeth, Pune.

[6]Embryologist, Radhey Hospital, Surat.

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***Corresponding Author**
Dr. Neerjesh
Associate Professor and Head, Department of Pharmacology, Narsinhbhai Patel Dental College & Hospital, Visnagar (Gujarat), India.

ABSTRACT

Letrozole is the third-generation aromatase inhibitor (AI) most commonly used in assisted reproduction. It brings ovulation by inhibiting estrogen production; the consequent hypoestrogenic state enhances GnRH release and pituitary follicle-stimulating hormone (FSH) synthesis. 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 effective 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 reveal situations where it is more efficacious than gonadotropin treatment. A conclusion established was letrozole is as effective as other methods of ovulation induction. Further randomized-controlled studies are warranted to define more clearly the efficacy and safety of letrozole in human reproduction.

KEYWORDS: Letrozole, unexplained infertility, diminished ovarian reserve.

INTRODUCTION

Earlier Clomiphene was the current first-line infertility treatment in women with the polycystic ovary syndrome, but aromatase inhibitors, including letrozole, might result in better pregnancy outcomes. In women treated for anovulation, the aim 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 higher no. of follicles than a single mature follicle to increase number of 'targets' for the sperm.[1]

Since that time, many researchers have been investigating the function of this drug in the treatment of infertility. An edifying review emphasizes on role of letrozole, its safety, efficacy and comparative value in such treatment.

History

Clomiphene citrate was first approved for its indication in women with anovulation by the FDA in 1967. It was originally approved at 50mg daily, taken on days 5–9 of the cycle. Its primary mechanism of action is by competitively preventing the binding of estradiol to its receptor in the hypothalamus, thereby releasing the hypothalamus from negative feedback and allowing augmented release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. This rise in FSH is thought to enhance follicular stimulation, leads to greater chance of follicular growth and ovulation.

Although there are some negative effects of clomiphene citrate, as it has both agonistic and antagonistic activity at target tissue specific level. At endometrial and cervical mucus, it has antagonistic activity. For anovulatory women, clomiphene citrate will confer ovulation in 75–80% of cycles.[2] Within 4-6 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 includes the use of injectable gonadotropins, with their risks of high order multiple pregnancies, ovarian hyperstimulation syndrome, painful injection sites, and demands extensive and invasive monitoring during treatment and higher cost of therapy.

Letrozole was originally approved from the FDA in 1997 for the treatment of breast cancer in postmenopausal women. Its first use was in the treatment of anovulatory infertility in 2001.

Patients who failed to ovulate with clomiphene citrate (used in doses up to 100mg for 5 days) were treated with 2.5mg 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 8mm.[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 2.5mg 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 acts 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 increases intrafollicular androgens[10] which is turn is thought to upregulate and sensitize FSH receptors in the ovary[11,13] as well as increase active secretion, which further increases the secretion of FSH from the pituitary gland. Letrozole, unlike clomiphene citrate, does not have adverse effect on the endometrial lining.[6,7] In fact, the decrease in serum estrogen is thought to upregulate FSH receptors. Letrozole is having short half-life (44 h) ensures no adverse effects on implantation because its clearance by the body before implantation occurs, unlike clomiphene citrate.[7]

Therapeutic Uses

Letrozole is usually 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 2.5mg was inferred from several studies carried out on postmenopausal women using the drug to treat breast cancer.[14,15] This, nevertheless, 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 suitable 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 using Letrozole at 2.5 mg daily for 5 days demonstrates 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 many unsuccessful cycles might wish for maturation of three or four follicles.[19]

Various studies reveal 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 5mg 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 5mg dose group as well (5.9% versus 26.3%).

In 2004, the first investigators had demonstrated that the dose of 7.5mg letrozole given daily for 5 days in women and it was compared with clomiphene citrate outcomes at 100mg daily.[21] This group found 1.4 ovulations in women using this dose compared with 1.1 ovulations with 100mg 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 by Badawy et al.[16] had utilized either 2.5, 5, or 7.5mg 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 7.5mg daily versus 5 or 2.5mg (3.4, 1.4, or 1.0, respectively).

In a recent study, 218 patients who had previously failed clomiphene citrate at 100mg for 5 days were randomized to receive 5mg of letrozole for 5 days or 2.5mg for 10 days, both are starting on day 1 of the menstrual cycle. Ovulation rates were equal at 65.7% for the long course versus 61.8% for the short course. Although, in the short regimen, an average of 1.8 follicles more than 18mm were measured at the day of HCG administration, while a mean of three follicles more than 18mm were seen in the long regimen. Pregnancy rates were 12.4% with the short and 17.4% with the long protocol.[22]

In previous case report, women were allocated in 2 groups, one with a single dose of 20mg letrozole and another group with 2.5mg from day 3–7 of the cycle. Number of ovulations (1.9 versus 1.7) and pregnancy rates (15% versus 18%) were no statistically different.[23]

Some studies suggested that using higher doses of letrozole might antagonize the growth of the endometrium during the follicular phase of the cycle, thus diminishing 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 7.5mg 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 indices are favorable in women undergoing letrozole treatment.[27] Optimal dose or length of treatment by letrozole is yet to be defined.

Unexplained infertility

In women with unexplained infertility when we compare letrozole with clomiphene citrate, the results of various randomized controlled trials are consistent. The previous studies utilized letrozole in the dose from 2.5 to 7.5mg 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, the various randomized controlled trials are again consistent in women with unexplained infertility utilizing letrozole versus gonadotropins in form of similar pregnancy rates but with significantly reduced costs in the letrozole group.

In one randomized trial, letrozole 5mg 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 5mg 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, 5mg 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 9.7mm versus 7.8mm 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 more advantageous than hybrid treatment with clomiphene citrate and gonadotropins.

Chronic anovulation

In patients with chronic anovulation, the goal is simply one to two ovulations per cycle; 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 V et al., when utilizing 2.5mg of letrozole versus 100mg 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 5mg on days 3–7 of the cycle, but a higher pregnancy rate at 19% versus 12.5%.[27]

In women who failed to ovulate with lower doses of clomiphene citrate or letrozole, 7.5mg letrozole versus 150mg 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 reviewed this issue.[37] By adding metformin to either letrozole at 2.5mg or clomiphene citrate at 100mg, both given days 3–7 of the cycle and showed significantly higher pregnancy rates in the letrozole group (34.5% versus 16.7%).

Ganesh et al. showed a higher pregnancy rate in women taking letrozole 5mg 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 17mm (18%). Cases were included in this study who had 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 resistant anovulatory women, confers higher 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.

Poor ovarian reserve

In women with poor ovarian reserve, there is a diminished response to ovulation induction medications. In some cases it is due to lack of oocytes and in others it is due to a decrease in follicular FSH receptors. With the use of letrozole, an increase level of androgen augments these receptors expression. Thus in theory, letrozole could be a unique and valuable treatment for a subset of women with diminished or poor 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 given letrozole at 2.5mg on days 3–7, followed by gonadotropins at 50–250 IU until lead follicles measured more than 18mm. The subjects then underwent intrauterine insemination. In the previous cycles, the total number of mature follicles had been 1.9; with letrozole and gonadotropins group 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 2.5mg 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 15mm were noted, then the letrozole in a subsequent cycle was increased to 5mg 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 both 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 2.5mg letrozole to produce 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 in both groups.[38]

Reproductive endocrinology Aspect

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 guidelines of Letrozole

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 has failed to demonstrate 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, 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]

In 2008 study reviewed occurrence of congenital anomalies following the usage of clomiphene citrate, letrozole and injectable gonadotropins. Clomiphene citrate had a slightly increased risk of neural tube defects and severe hypospadias than the other medications.[43]

CONCLUSION

Letrozole is an excellent alternative to either clomiphene citrate or injectable gonadotropins in women undergoing ovulation induction in the case of anovulatory infertility or controlled ovarian hyperstimulation. It has minimal side effects, no proven teratogenicity when used for ovulation induction, and it 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 12.5mg per day for 5 days maintains endometrial integrity while producing a dose-dependent increase in the number of mature follicles (Yuen 2010, personal communication). In addition, the long-term health effects of this medication on both mother and child need further investigation.

In women with PCOS, the percentage of monofollicular cycles obtained in patients treated with AIs is higher than in those treated with CC, as a result of which a lower rate of multiple pregnancies is specific advantage.

When endometrial thickness was examined, most studies showed the negative impact of CC compared with AIs. However, results of the meta-analysis showed that letrozole was not significantly superior to CC in the following variables like ovulatory cycles, pregnancy cycle rate and pregnancy patient rate. The recommended regimen in ovarian stimulation for IUI includes the use of letrozole 2.5 mg/day (from Day 3 to Day 7 of the cycle) plus FSH (usually 100 IU/day, although doses can vary depending on the characteristics of the patients) starting on Day 8. This schedule favors lower consumption of FSH injections and more moderate ovarian responses are obtained (lesser mature follicles and lower levels of estradiol), minimizing the effect of letrozole on the endometrium.

In fact, letrozole is a very hopeful addition to the armamentarium of ovulation enhancing drugs available to the Reproductive Endocrinologist.

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