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2nd Edition

Practical Guide to Ovulation Induction



Chaitanya Nagori
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4 CHAPTER

Letrozole

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INTRODUCTION

Letrozole is an aromatase inhibitor used for ovulation induction. It is the third generation of aromatase inhibitor. The first and second generations of aromatase inhibitors are not used in clinical practice. The main advantage of letrozole is that it is a reversible enzyme inhibitor. It was for the first time used in 2001 for ovulation induction.[1]

MECHANISM OF INDUCTION OF OVULATION

- *Central mechanism:* Estrogen withdrawal centrally causes an increase in activins produced from the pituitary and several other tissues.[2] This stimulates the synthesis of follicle-stimulating hormone (FSH) by a direct action on gonadotropes.[3]
- *Peripheral mechanism:* Androgens have a stimulatory role in early follicular growth[4] mediated directly through testosterone augmentation of follicular FSH receptor expression[5,6] and directly through androgen stimulation by insulin-like growth factor 1 (IGF-1), which may synergize with FSH to promote folliculogenesis.[7,8]

Aromatase, a cytochrome P450-dependent enzyme, acts as the ultimate step in the synthesis of estrogen, catalyzing the conversion of androgen to estrogen. This conversion occurs at peripheral sites such as muscle, fat, and liver. Letrozole inhibits aromatase enzyme by completely binding to the heme of cytochrome P450 subunits of enzyme so that androgen is not converted to estrogen.

The end result is low estrogen causing negative feedback at hypothalamus and pituitary releasing FSH and luteinizing hormone (LH) releasing factors resulting in high FSH and LH causing folliculogenesis.

As androgen is not converted into estrogen, there is a slightly higher level of androgen which also helps folliculogenesis. Letrozole has no effect on estrogen receptors and acts on hypothalamus. So, it has no deleterious effect on LH surge, cervical mucus, and endometrium.

As FSH and LH stimulate folliculogenesis, estrogen will rise and will cause negative feedback on FSH release so that FSH will decrease. This decrease in FSH is responsible for monofollicular development as other follicles will not grow. This is not the case with clomiphene citrate (CC), which binds to estrogen receptors and FSH will go on rising in spite of high estrogen, leading to multifollicular development. Another important advantage is that along with FSH, LH will not increase and so the quality of ova is not disturbed and does not affect implantation. This is another advantage over CC which causes persistent high LH along with FSH.

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The possible explanation for higher pregnancy rate in letrozole group is because of higher ovulation rate and lower mid-secretory estradiol level that favors implantation. Higher progesterone levels in secretory phase is due to sustained effect of letrozole in luteal phase causing aromatase inhibition and favors implantation.

INDICATIONS

- *CC-resistant cases:* When 100–150 mg of CC fails to induce ovulation, letrozole should be tried.
- *Polycystic ovary syndrome (PCOS):* In these patients, baseline estradiol (E2) is elevated which blocks the hypothalamus causing anovulation. Letrozole will reduce estrogen and stimulate hypothalamus to release luteinizing hormone-releasing hormone (LHRH) to secrete more FSH and induce folliculogenesis.
- It is useful in cases where CC induces cervical dysmenorrhea and poor endometrium. Letrozole is devoid of antiestrogenic effect as it does not bind to estrogen receptors.
- When LH is elevated on Day 8 or 9 after CC, letrozole should be tried.
- It is useful in poor responders along with gonadotropins.
- Endometriosis.
- Breast carcinoma.

CHARACTERISTICS

- It causes total suppression of estrogen (up to 97–99%) with doses up to 5 mg/day. Maximum suppression occurs between Day 5 and 7.
- After Day 7, the estrogen level will rise due to folliculogenesis because of increasing FSH after negative feedback of estrogen due to letrozole.
- This rise of estrogen will continue for 5–7 days. This E2 peak will cause LH surge for ovulation. So LH surge occurs after 2 days unlike CC when it occurs early.
- High estrogen rise after 7 days will decrease FSH, which is responsible for monofollicular development.
- It has no antiestrogenic effect on cervical mucus or endometrium.
- Temporary rise of androgen improves the sensitivity of follicle to gonadotropin. The patient, therefore, requires a lower dose of gonadotropins when it is combined with letrozole.
- The half-life of letrozole is 48 hours. So it requires a once daily dose.
- It improves endometrial receptivity.

ADVANTAGES

These may be divided under the following heads:

A. Ovulation
B. Implantation
C. Fetal outcome
D. Maternal complications.

A. Ovulation

- It is almost free from side effects and is well-tolerated.
- Monofollicular development.
- No antiestrogenic effect leading to higher pregnancy rates.
- Low multiple pregnancy rate due to monofollicular development.
- Higher androgen stimulates follicle and so lower doses of gonadotropins are required.

There is a transient accumulation of androgens in the ovary when letrozole is given for ovulation induction. This creates an androgenic microenvironment in the maturing follicle that enhances

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the follicular sensitivity to FSH for a short duration (half-life of letrozole is approximately 45 hours). This action is of help to poor responders in whom ovarian aging has already reduced ovarian androgens. It is useful in patients with a high body mass index (BMI).[9]

B. Implantation

- It has a low abortion rate because of no effect on endometrium.
- It improves the level of a marker of endometrial receptivity better than CC.[10]
- Aromatase inhibition may potentially improve endometrial receptivity, especially in patients with endometriosis.[11]
- Concomitant use of aromatase inhibitors with gonadotropins reduces the doses of gonadotropins required[12] and improves the response of gonadotropins in poor responders.[13] It also reduces the supraphysiological levels of estrogen seen with the development of multiple ovarian follicles and improves treatment outcome. Low estrogen levels decrease ubiquitination to allow upregulation of estrogen receptors and increase sensitivity to subsequent estrogen rise.[14] This, in turn, leads to improved endometrial blood flow and faster proliferation of the endometrium, which might have a positive impact on implantation.[15]
- The endometrium of PCOS females is dysfunctional.[16] Estrogen receptors in the endometrium, which should normally reduce in the midsecretory phase,[17] are not reduced, with the altered status of other receptors also. This functional derangement leads to progesterone resistance. This is why antiestrogenic agents for ovulation induction may be beneficial in PCOS patients. Moreover, these agents would also improve endometrial receptivity by suppressing the action of ERα and also has a positive impact on the endometrial expression of αvβ3.[18]

C. Fetal Outcome

The incidence of cardiac anomalies in the letrozole group was slightly lower than the 1 in 400 rates quoted in the general population,[19] whereas the cardiac anomaly rate in fetuses of mothers with CC stimulation was about seven times higher.

D. Maternal Complications

Letrozole also leads to the reduction in the secretion of estrogen from granulosa cells leading to less circulating estrogens; therefore, there are less chances of thrombosis in hyperestrogenic states during controlled ovarian hyperstimulation (COH) and also an additional safety for women with hormone-dependent cancers undergoing fertility therapy.[11]

DOSES

- The recommended dose is 2.5 mg from Day 3 to 7.
- Some workers suggest a 5-mg dose. The disadvantage of a 5-mg dose routinely is not justified as 2.5 mg can suppress 97–99% of the estrogen. A 5-mg dose may suppress more estrogen causing more FSH to be secreted. So, it may not cause monofollicular development. As it is a chemotherapeutic agent, it may be toxic to the ovum and embryo. High doses have no advantage in terms of pregnancy rate.[20]
- *20 mg on Day 3:* It has the advantage of having a short half-life and reduces the embryotoxic effect. But symptoms of hypoestrogenism may develop.

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- Anastrozole 1 mg from Day 3 to 7 or anastrozole 5-mg single dose may give poorer results. Anastrozole is weak and less effective for follicular growth.[21]

New Regimes

- *Extended letrozole therapy:* 2.5 mg letrozole is given from Day 1 for 10 days in CC-resistant PCOS patients. It may produce more follicles and may give better pregnancy rates.[22]
- *Letrozole step-up protocol:* One, two, three, and four tablets of 2.5 mg of letrozole are given, respectively, on Day 2, 3, 4, and 5. This gives multifollicular development and a higher pregnancy rate. The mechanism of action in this regime is a longer duration of FSH exposure and prevention of estrogen secretion from granulosa cells, so estrogen does not rise and FSH does not get suppressed.[23] But in both these cases, the actual advantages of letrozole, unnecessary exposure of ovum to LH, and monofollicular development are lost as both lead to a longer duration of FSH and LH secretion and also lead to multifollicular development. Therefore, larger and more robust studies are required to accept these protocols in routine practice.

Recently Zhu X et al. have published a two-step extended regimen.[24]

2.5 mg for 5 days:

- If anovulation, 5 mg is given for 5 days in next cycle.
- If anovulation 5 mg for 7 days in subsequent cycle.
- If anovulation, 5 mg for 10 days is given.

It has been reported as a feasible treatment with LE resistance in PCOS. In both the groups ovulation occurred with follicular size >18–25 mm between 11 and 24 days without trigger. When letrozole was given in this extended regime, LH was significantly higher on 10–12 days and so this may be detrimental to oocyte quality. Here there is gradual increase in endometrial thickness that was initially thin due to hypoestrinism. The authors claim that the higher dose is better than extending 2.5 mg for 10 days as number of follicles are more and multiple pregnancy rate and OHSS rate is high when 2.5 mg is given for 10 days. Extended regime is given to the resistant PCOS subgroup. Strategy of waiting for spontaneous rupture gives better endometrial growth. But this is a retrospective study and requires further validation. Besides 7.5 mg, trial is not tested. Effect of high LH has not been emphasized and premature LH surge was also common.

SIDE EFFECTS (DRAWBACKS)

- It increases intrafollicular androgen which may arrest the growth of the follicle. But the optimum level of androgen is not yet decided.
- As it is a chemotherapeutic agent for carcinoma of breast, it may be teratogenic to ovum and embryo. But it is not proved.
- A multicentric study of 911 newborns conceived after CC27 and letrozole and another recent study[25] have shown that there was no increase in congenital malformations following the use of letrozole. In a recent randomized control study of letrozole for ovulation induction in 900 patients with unexplained infertility, no increase was found in congenital malformations than CC or gonadotropins.[26]

FUTURE USES

- Letrozole helps to improve implantation in IVF (in vitro fertilization). Some women have high levels of aromatase P450 in the endometrium and are related to poor IVF results. It can be useful to them.

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- Decreased supraphysiological estrogen and decreased aromatase will improve implantation.
- It stimulates follicles for in vitro maturation (IVM) in PCOS.
- Letrozole may reduce the chronic pelvic pain of endometriosis.[27]
- Letrozole may be used to reduce the risk of ovarian hyperstimulation syndrome (OHSS) and thrombosis due to hyperestrogenism—when given on Day 4–7 and 10 after human chorionic gonadotropin (hCG) trigger in an IVF patient, it reduces estrogen levels and thus reduce the risk of OHSS.[28]
- Letrozole challenge test may be used for predicting the ovarian response to gonadotropin stimulation. This test is done by evaluating FSH on Day 3 and 7 of a letrozole cycle. The ratio of Day 7 and 3 FSH is >1.5 which predicts poor response to gonadotropins.[29] Aromatase inhibitors are also used to treat male subfertility.
- Anastrozole 1 mg/day or letrozole 2.5 mg/day is the recommended dose for patients with high aromatase activity and increased testosterone to estrogen ratio in nonobstructive azoospermic patients. Therefore, in patients with low testosterone levels, the use of aromatase inhibitors is justified.[30]
- Letrozole can be used for treatment of pregnancy of unknown location (PUL) or ectopic pregnancy. Dose is 5 mg every day for 10 days. As it decreases estrogen, it disturbs progesterone receptors and pregnancy does not proceed further.[31]

AUTHOR'S VIEW

Should letrozole replace CC: I strongly believe that letrozole should be used as the first line of the drug. The argument is that it has a comparable pregnancy rate with CC and it does not increase congenital malformations. The main advantage is that it has no antiestrogenic effect on cervical mucus and endometrium and so it will cut down superfluous cycles of treatment. No antiestrogenic effect is the single most important benefit of letrozole that prevents the use of CC. Efficacy-wise, letrozole gives better ovulation and pregnancy rate compared to CC. The results of the trial by Amer et al. are consistent with the recent Cochrane review indicating that letrozole is better as a primary ovulating agent in PCOS with a 40% increase in pregnancy rates and with a shorter time to pregnancy.[32]

LETROZOLE + GONADOTROPINS

We have found letrozole + recombinant FSH (rFSH), a very useful combination for giving equivalent pregnancy rates like gonadotropins with the advantage that a lower number of ampoules are required. Apart from this, it gives a lower rate of multiple births. It sensitizes the ovary by rise in androgen level, which is an added advantage that reduces the number of gonadotropin ampoules. We have used this combination routinely in superovulation with intrauterine insemination (IUI).

Hence, letrozole is superior to CC in PCOS and poor responders.

Other aromatase inhibitors, especially anastrozole, were also tried for ovulation induction. It appears from clinical studies that anastrozole is less effective than letrozole for ovulation induction.[33,34]

LETROZOLE + CLOMIPHENE CITRATE

As letrozole and CC have different mechanisms of action, the combination of both may improve the ovulation rate than letrozole alone. Mejia et al. gave letrozole 2.5 mg and CC 50 mg from Day 3 to 7 in PCOS

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patients. Patients who received both the drugs had a higher ovulation rate. But there was no difference in pregnancy rate, multiple pregnancy rate, or abortion rate.

Patients who ovulated showed no difference in endometrial thickness, size of the follicle, or serum progesterone levels. But an absolute difference of 34% in ovulation was noted.[35]

Hajisafi et al. used 100 mg of CC and 5 mg of letrozole in resistant cases of CC and letrozole.[36] This observation requires further studies. LH, which is already high in PCOS, will be increased further when both the drugs are used. This LH will not come down because of receptors occupied by CC even after high estrogen after follicular development. This may reach the "ceiling level of LH." This is the only reason that like CC, the ovulation rate is high with this combination but the pregnancy rate is not increased and perhaps it may decrease instead than when giving only letrozole. Instead, letrozole + FSH is a better combination.

For Ovulation Induction in IVF (Low Responders)

With aging, significant androgen reduction is observed. Letrozole improves intraovarian androgen and sensitizes the follicle to FSH with a relatively short duration of action of 45 hours. Patients treated with letrozole + gonadotropins, both started from Day 2, and letrozole given for 5 days got a higher number of oocytes and higher implantation rates in low responders.[11]

Risk of Ovarian Hyperstimulation Syndrome

Whenever a long protocol is used, there is no option to hCG trigger. E2 reduction by letrozole after ovum pick up is tried by Fatemi et al. as 5 mg dose. They did not observe any change in progesterone and LH in 10 days.[28,37]

But we must keep in mind that E2 reduction does not necessarily mean that the risk of severe OHSS is lessened. However, it definitely reduces the risk of thromboembolism.

Endometriosis

Aromatase is expressed in women with endometriosis. Letrozole will prevent the production of E2. When letrozole or anastrozole is given with GnRHa depot preparation, there is a marked reduction in endometrioma volume and also in CA-125 levels.

Miller et al. confirmed that the use of aromatase inhibitors might improve the IVF success rate in a subset of women with endometriosis and implantation failure.[38]

Letrozole 5 mg is given from day 2 to 6 along with gonadotropins in ovulation induction in IVF cycles. This is more effective when integrin is very low or absent in endometrial biopsy in patients with recurrent implantation failure or recurrent IVF failure.

CARRY HOME MESSAGE

- Letrozole causes monofollicular development.
- It has no antiestrogenic effect.
- It is a drug of choice in PCOS and poor responders.
- Letrozole + gonadotropins is an excellent combination.
- Letrozole may replace CC as the first line of treatment in the future.

REFERENCES

1. Mitwally MFM, Casper RF. Use of aromatase inhibitor for ovulation induction in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001;75:2-8.
2. Roberts V, Meunier H, Vaughan J, Rivier J, Rivier C, Vale W, et al. Production

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and regulation of inhibin subunits in pituitary gonadotropes. Endocrinology. 1989;124:552-4.
3. Weil SJ, Vendola K, Zhou J, Adesanya OO, Wang J, Okafor J, et al. Androgen receptor gene expression in the primate ovary: cellular localization, regulation and functional correlations. J Clin Endocrinol Metab. 1989; 837:2479-85.
4. Mason AJ, Berkemeier LM, Schmelzer CH, Schwall RH. Activin B: precursor sequences, genomic structure and in vitro activities. Mol Endocrinol. 1989;3:1352-8.
5. Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. J Clin Endocrinol Metab. 1999;84:2951-6.
6. Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest. 1998;101:2622-9.
7. Vendola K, Zhou J, Wang J, Famuyiwa OA, Bievre M, Bondy CA, et al. Androgens promote oocyte insulin-like growth factor I expression and initiation of follicle development in the primate ovary. Biol Reprod. 1999;61:353-7.
8. Giudice LC. Insulin like growth factors and ovarian follicular development. Endocr Rev. 1992;13:641-69.
9. McKnight KK, Nodler JL, Cooper JA, Chapman VR, Cliver SP, Bates GW Jr. Body mass index-associated differences in response to ovulation induction with letrozole. Fertil Steril. 2011;96(5):1206-8.
10. Wallace KL, Johnson V, Sopelak V, Hines R. Clomiphene citrate versus letrozole: molecular analysis of the endometrium in women with polycystic ovary syndrome. Fertil Steril. 2011;96(4):1051-6.
11. Garcia-Valesco JA. The use of aromatase inhibitors in in vitro fertilization. Fertil Steril. 2012;98(6):1356-8.
12. Mitwally MF, Casper RF. Aromatase inhibition reduces the dose of gonadotropin required for controlled ovarian hyperstimulation. J Soc Gynecol Investig. 2004;11:406-15.
13. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle stimulating hormone in poor responders. Fertile Steril. 2002;77:776-80.
14. Mitwally MF, Witchel SF, Casper RF. Troglitazone: a possible modulator of ovarian steroidogenesis. J Soc Gynecol Investig. 2002;9:163-7.
15. Nirmala PB, Thampan RV. Ubiquitination of the rat uterine oestrogen receptor: dependence on oestradiol. Biochem Biophys Res Commun. 1995;213:24-31.
16. Giudicel C. Endometrium in PCOS: implantation and predisposition to endocrine CA. Best Pract Res Clin Endocrinol Metab. 2006;20:235-44.
17. Lessey BA, Killam AP, Metzger DA, Haney AF, Greene GL, McCarty KS Jr. Immunohistochemical analysis of human uterine estrogen and progesterone receptors through the menstrual cycle. J Clin Endocrinol Metab. 1988;67:334-40.
18. Lessey BA, Palomino WA, Apparao KBC, Young SL, Lininger RA. Estrogen receptor-alpha (ER-alpha) and defects in uterine receptivity in women. Repro Biol Endocrinol. 2006;4(1):S9.
19. Hoffman JI. Incidence of congenital heart disease: I. Postnatal incidence. Pediatr Cardiol. 1995;16:103-13.
20. Badawy A, Metwally M, Fawzy M. Randomised controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reprod Biomed Online. 2007;14:559-62.
21. Griesinger G, von Otte S, Schultze-Mosgau A, Diedrich K, Schröer A. Follicular and endocrine response to anastrozole versus clomiphene citrate administered in follicular phase to normo-ovulatory women: a randomised comparison. Fertil Steril. 2009;91:1831-6.
22. Badawy A, Mosbah A, Tharwat A, Eid M. Extended letrozole therapy for induction of ovulation in CC resistant PCOS patients: a novel protocol. Fertil Steril. 2009;92:236-9.
23. Mitwally MF, Said T, Galal A. Letrozole step-up protocol: a successful superovulation protocol. Fertil Steril. 2008;89:523-4.
24. Zhu X, Fu Y. Extending letrozole treatment duration is effective in inducing ovulation

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in women with polycystic ovary syndrome and letrozole resistance. Fertil Steril. 2023;119(1):107-13.
25. Hull MGR. The causes of infertility and relative effectiveness of treatment. In: Templeton AA, Drife JO (Eds). Infertility. London: Springer-Verlag; 1992. pp. 33-62.
26. Legro DM, Raivero CC, Robinson R, Zhung H. Letrozole, clomiphene or gonadotropin for unexplained infertility. N Engl J Med. 2015;373:1230-40.
27. Pavone ME, Bulun SE. Aromatase inhibitors for treatment of endometriosis. Fertil Steril. 2012;98(6):1370-9.
28. Fatemi HM, Popovic-Todorovic B, Donoso P, Papanikolau E, Smitz J, Devreoy P. Luteal phase oestradiol suppression by letrozole: a pilot study in oocyte donors. Reprod Biomed Online. 2008;17:307-11.
29. Bentov Y, Burstein E, Esfandiari N, Casper R. Use of letrozole challenge test to adjust gonadotropin dose in non-downregulated cycles. Fertil Steril. 2011;95(8):2492-3.
30. Schlegel PN. Aromatase inhibitors for male infertility. Fertil Steril. 2012;98(6):1359-62.
31. Mitwally MF, Hozayen WG, Hassanin KMA, Abdalla KA, Abdalla NK. The aromatase inhibitor, letrozole: a novel treatment for ectopic pregnancy. Fertil Steril. 2020;114:361-5.
32. Amer SA, Smith J, Mahran A, Fox P, Fakis A. Double blind randomised controlled trial of letrozole versus clomiphene citrate in subfertile women with PCOS. Hum Reprod. 2017;32:1631-8.
33. Tredway D, Schettz JC, Bock D, Hemsey G, Diamond MP. Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II randomized, dose-finding study. Fertil Steril. 2011;95:1720-4.
34. Tredway D, Schettz JC, Bock D, Hemsey G, Diamond MP. Anastrozole single dose protocol in women with oligo- or anovulatory infertility: results of a randomized phase II dose-response study. Fertil Steril. 2011;95:1724-8.
35. Mejia RB, Summers KM, Kresowik JD, Van Voorhis BJ. A randomized controlled trial of combination of letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with PCOS. Fertil Steril. 2019;111(3):571-8.
36. Hajisafi M, Dehgan M, Kiarang N, Sadegh-Asadi N, Shayegh SN, Ghasemi-Rad M. Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug Des Devel Ther. 2013;7:1427-31.
37. Gracia-Valesco JA, Oyea G, Piro M, Mayoral M, Ruiz M, Toribio M, et al. Letrozole administration during the luteal phase after ovarian stimulation impacts corpus luteum function: a randomized, placebo controlled trial. Fertil Steril. 2009;92:222-5.
38. Miller PB, Parnell BA, Bushnell G, Talliman N, Forstein DA, Higdon HL 3rd, et al. Endometrial receptivity defects during IVF cycles with and without letrozole. Hum Reprod. 2012;27:881-8.

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