Letrozole: an emerging array of hope for infertile women

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ABSTRACT

Ovulation induction has been a major breakthrough in the management of female infertility since many decades. Letrozole, an aromatase inhibitor has been used as a potential therapy for ovulation induction. A large number of clinical evidences have been emerging which cite the beneficial role of Letrozole in conditions like anovulatory infertility, polycystic ovary syndrome (PCOS), unexplained infertility and an incipient role in endometriosis- related infertility with regards to higher live-birth rates. Letrozole is a superior alternative to Clomiphene citrate (CC) which has been used conventionally as ovulation inducer. Clomiphene citrate has certain well-defined disadvantages, whereas Letrozole overcomes these limitations to a reasonable extent. The peripheral anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus. Persistent blockade of estrogen receptor leads to CC resistance and is associated with reduced ovulation and pregnancy rates. Available evidences suggest Letrozole is superior to CC owing to the lack of persistent anti-estrogenic action due to its short half-life and lack of action on estrogen receptors. This typically leads to monofollicular growth and also higher live birth rates. The current evidences suggest that Letrozole can be placed as first line therapy for the management of infertility due to PCOS and unexplained infertility.

Keywords: Anti-estrogenic effects, Anovulation, Aromatase inhibitors, Clomiphene citrate resistance, Infertility, Oral ovulation inducers, Polycystic ovary syndrome, Unexplained infertility

INTRODUCTION

A basic paradox surrounding human reproduction is that even though reproduction is critical for the survival, the process is highly inefficient in some individuals.1

Infertility, one of the major health issues, is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.2 In women greater than 35 years of age, an earlier evaluation is necessary after 6 months of regular unprotected sexual intercourse.3 Worldwide, the prevalence of infertility is around 8-12%.4 In India, an estimated 13-19 million couples are expected to be infertile at a given point of time.5 Infertility can be diagnosed as primary or secondary infertility. Primary infertility refers to a condition when a woman in the age group of 15-49 years is unable to deliver a live birth after being exposed to unprotected sexual intercourse. Secondary infertility is a condition in which a woman after having successful...
previous pregnancy and live-birth is unable to bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth.

**Female infertility - a rising concern**

Around 25-40% of females suffer from infertility. Advancing age significantly increases the risk of infertility as the fecundity of women tends to decline after the age of 35 years. Lifestyle diseases like obesity, diabetes, stress and anxiety have also been compromising the chances of conception. One of the major contributors of female infertility is ovulatory disorders, others being tubal pathology (like blocked fallopian tubes), uterine fibroids and cervical pathology (cervicitis). Ovulatory disorders result from asynchronous functioning of hypothalamus, pituitary and ovarian axis; subsequently leading to anovulation, oligo-ovulation and irregular menstrual cycles. Diseases of female reproductive tract such as PCOS, endometriosis drastically alter the functioning of female reproductive system eventually causing infertility. Pelvic surgery can induce structural changes in female reproductive tract and further affect the fecundity, ovulation and implantation.

The most widely used treatment for ovulatory disorders is ovarian stimulation which includes ovulation induction, superovulation and controlled ovarian hyperstimulation (COH). This approach is used for treatment of anovulation or oligo-ovulation. Ovulation induction can be achieved by administration of exogenous gonadotropins alone or in combination with Clomiphene citrate or aromatase inhibitor (AI).

**Review of literature**

This is a review of the evidences published in the literature. The review was conducted via searching the articles in the databases of Pub Med, Cochrane Database of Systematic Reviews, MEDLINE, Science Direct, Embase, Scopus and Google scholar using key words. All the relevant articles on the topic were reviewed. Amongst which, 43 articles were fully accessed and referenced.

**Clomiphene citrate therapy for ovulation induction**

Clomiphene citrate was introduced more than 50 years ago and gained popularity based on the fact that it was highly affordable and possessed various advantages over its injectable and expensive competitors like gonadotropin analogues. Clomiphene citrate as an ovulation inducer was first of its kind that was capable of bringing about a revolution in infertility management.

Clomiphene citrate is structurally similar to estrogen which allows it to bind to estrogen receptors and blocks it. The blockade of estrogen receptors on the hypothalamus prevents the accurate interpretation of circulating estrogen levels. The reduced interpretation of estrogen increases the pulsatile release of gonadotropin releasing hormone (GnRH) which in turn stimulates the release of follicle stimulating hormone (FSH) from pituitary thereby setting the ovarian follicular activity in motion as shown in Figure 1.

**Clomiphene citrate isomers - more than meets the eye**

**Effect on ovulation rate**

In spite of being used as a conventional ovulation inducer, it is difficult to predict the success rate with Clomiphene citrate regarding ovulation and pregnancy. The reason being, Clomiphene citrate acts as a Selective Estrogen Receptor Modulator (SERM) and contains an unequal mixture of two isomers as their citrate salts, Enclomiphene (62%) and Zuclomiphene (38%) displaying mixed agonist and antagonistic properties. Enclomiphene is estrogen antagonist while Zuclomiphene has got mixed estrogenic and anti-estrogenic properties depending upon the target tissue. For e.g.; Zuclomiphene exhibits estrogenic effects in pituitary whereas in cervix and endometrium, it is anti-estrogenic. Due to this property of Zuclomiphene at pituitary level, there is a mid-follicular peak in estrogen levels thereby exerting a positive feedback on GnRH. This is turn leads to luteinizing hormone (LH) surge and reduction in FSH release, arresting the growth and maturation of oocytes. This greatly hampers the ovulation process leading to reduction in ovulation rate by Clomiphene citrate.

Moreover, Clomiphene citrate is cleared slowly from the body and is detectable in blood for more than a month due to long half-life of approximately 2 weeks. As a consequence, it remains bound to the estrogen receptors leading to desensitization of the receptors. Clomiphene citrate fails to act on these desensitized receptors in the subsequent treatment cycles (if the treatment cycle needs to be repeated) leading to variability in ovulation rates as shown in Figure 1.

**Effect on pregnancy rate**

Clomiphene citrate blocks estrogen receptors on cervix and alters the permeability properties of cervical mucus which hinders the smooth passage of sperm through it to reach the oocyte. This can be explained by the reduction in the peripheral availability of estrogen which is required for increasing the hydration of mucus via water transudation along with small electrolytes thereby resulting in cervical mucus secretion which is watery in nature with low viscosity.

Further, blockade of endometrial estrogen receptors by Clomiphene citrate reduces the availability of estrogen which otherwise directly influences the uterine blood flow by activating endothelial cells. This in turn causes release of endogenous nitric oxide, a potent vasodilator that mediates the uterine blood flow. Uterine blood flow ensures optimum uterine receptivity which is extremely crucial for embryo nidation. As per a study carried out by
Omran E et al, endometrial perfusion was significantly lower in Clomiphene citrate-stimulated cycles during peri-implantation when compared to natural ones in patients with unexplained infertility. Other unfavorable clinical implications of Clomiphene citrate have been summarized in Table 1.

**Aromatase inhibitors - a potential alternative as ovulation inducer**

Estrogen is one of the primary steroid hormones for normal female physiology and reproduction. Aromatase, an enzyme containing cytochrome P450 hemoprotein, catalyzes the rate limiting step in the conversion of androstenedione and testosterone to estrogen. The ovarian aromatase is produced in abundance in women during reproductive phase since ovaries are the major site for the production of estrogen. Hence, aromatase can be a good target for selective inhibition of estrogen production thereby correcting ovulatory disorders.

### Journey of Letrozole as ovulation inducer

Over the last 30 years, a large number of aromatase inhibitors have been developed with third generation aromatase inhibitors being licensed for use in hormone receptor-positive breast cancer in post-menopausal women. Following the clinical failure of first- and second-generation aromatase inhibitors owing to significant side effects and below par potency in inhibiting aromatase enzyme, the third-generation aromatase inhibitors like Letrozole and Anastra唑ole became commercially available for management of breast cancer in post-menopausal women. They were highly potent with 97-99% reduction of estrogen levels as detected by most sensitive immunoassays.

### Table 1: Clomiphene citrate: other unfavorable clinical implications.

<table>
<thead>
<tr>
<th>Implications</th>
<th>Possible reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifollicular growth and increased risk of pregnancy complications</td>
<td>Due to continual blockade of estrogen receptors for ~ 2 weeks, there is an unhampered release of FSH which leads to growth and maturation of more than one follicle.</td>
</tr>
<tr>
<td>Clomiphene citrate resistance</td>
<td>Factors like insulin resistance, hyperandrogenemia, and obesity prevents follicular growth and maturation in response to increased levels of FSH. Moreover, due to the long half-life of Clomiphene citrate (~ 2 weeks), there are high chances of desensitization of estrogen receptors, thereby hampering the ovulation process.</td>
</tr>
<tr>
<td>Delayed time to pregnancy</td>
<td>Presence of Clomiphene citrate resistance or Clomiphene failure (poor quality cervical mucus and thin endometrial lining) can delay pregnancy.</td>
</tr>
</tbody>
</table>

### Table 2: Letrozole - favorable clinical implications over Clomiphene citrate.

<table>
<thead>
<tr>
<th>Clinical implication</th>
<th>Possible reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher ovulation rate</td>
<td>Letrozole has no effect on estrogen receptors; it blocks the aromatase enzyme for 5 days after which the drug is eliminated from the body. Hence normal physiological process is resumed leading to higher ovulation rate as compared to Clomiphene citrate.</td>
</tr>
<tr>
<td>Higher pregnancy rate</td>
<td>Lack of action on estrogen receptors in cervix and endometrium leads to better conception and implantation resulting in higher pregnancy rates.</td>
</tr>
<tr>
<td>Monofollicular growth and singleton pregnancy</td>
<td>Letrozole does not exert anti-estrogenic action at the level of estrogen receptors. Hence, no desensitization of estrogen receptors is observed thereby maintaining the normal physiological ovulation process.</td>
</tr>
<tr>
<td>Lesser time to pregnancy</td>
<td>No action on estrogen receptors and with short half-life of ~45 hours leads to rapid restoration of normal physiological ovulation process leading to lesser time to achieve pregnancy.</td>
</tr>
</tbody>
</table>

In the purview of preventing estrogen feedback on FSH by blocking aromatase enzyme, Letrozole 2.5 mg was tested for ovulation induction in ten women with polycystic ovary syndrome (PCOS). It was reported that two women had clinical pregnancies. In one more study involving patients with Clomiphene citrate resistance with a thin endometrium, use of Letrozole led to normal endometrial thickness along with estrogen triple line pattern clearly seen. These favorable clinical experiences led to addition of Letrozole in the armamentarium of infertility management as a potent oral ovulation inducer.

### Letrozole in ovulation induction

a. Central mechanism

Letrozole inhibits the aromatization of androgen to estrogen by blocking the aromatase enzyme. This inhibition of aromatization releases the
hypothalamic/pituitary axis from estrogenic negative feedback. The resultant increase in gonadotropin secretion stimulates the growth of ovarian follicles. Since, Letrozole has a short half-life of (~ 45 hours); it is rapidly eliminated from the body. Hence, the blockade on the aromatization is removed and hypothalamic-pituitary axis is again able to detect the presence of endogenous circulating estrogen and leads to gradual stoppage of FSH. This results in normal follicle growth, selection of dominant follicle and atresia of other growing follicles. The detection of endogenous circulating estrogen by hypothalamic-pituitary axis also leads to timely release of LH from pituitary gland and finally leads to ovulation as shown in Figure 2.

![Figure 1: Different actions of Clomiphene citrate isomers in pituitary gland, cervix and endometrium.](image)

**Figure 1: Different actions of Clomiphene citrate isomers in pituitary gland, cervix and endometrium.**

**DISCUSSION**

**Efficacy of Letrozole in overcoming infertility in various population**

a. In patients with PCOS (Table 3)

Wang L et al studied 160 patients with PCOS and randomized them to receive 50 mg/day Clomiphene citrate and 2.5 mg/day Letrozole for ovulation induction. The endometrial thickness with Letrozole was found to be 10.8 mm in comparison to 7.8 mm with Clomiphene citrate. Due to improved endometrial thickness, pregnancy rates were also found to be higher with Letrozole i.e. 22.5% as compared to 10% with Clomiphene citrate as shown in Figure 4.23

The efficacy of Letrozole versus Clomiphene citrate for infertility treatment in patients with anovulatory infertility caused by PCOS was evaluated in 200 patients. The biochemical pregnancy rate in Letrozole was found to be 35.5% along with higher live birth rate i.e. 28%. With Clomiphene citrate, the biochemical pregnancy was found to be 28.8% with live birth rate 18% as shown in Figure 5.26 Chakravorty et al randomized 127 patients of infertility with PCOS receiving either (2.5-5 mg) of Letrozole daily or 50-100 mg of Clomiphene citrate daily for 5 days starting on day 3 of menses. Ovulation in 37.87% in Letrozole group was observed as compared to 19.67% in Clomiphene citrate group. Endometrial thickness was found to be 9.82 mm in Letrozole and 9.13 mm in Clomiphene citrate. As shown in Figure 5, Legro et al studied 750 women with PCOS by randomizing them to receive Letrozole or Clomiphene citrate. In comparison to Clomiphene citrate, the ovulation rate was found to be higher in Letrozole group i.e. 61.7% as compared to 48.3% with Letrozole.

The favorable clinical implications of Letrozole are mentioned in Table 2.

**b. Peripheral mechanism**

The blockade of aromatization in the early follicular phase can lead to increase in intra-ovarian androgen. Intra-ovarian androgen has an important effect on early follicular growth. Androgens increase the number of preantral and small antral follicles as androgens stimulate theca and granulosa cell proliferation and inhibit apoptosis of the follicles. This effect is mediated by androgen receptors which are found to be 4.2-fold higher in granulosa cells from immature follicles than in preovulatory follicles as shown in Figure 3.23,24
Letrozole was also associated with higher live-birth i.e. 27.5% as compared to 19.1% with Clomiphene citrate. As shown in Figure 4, Roy et al randomized 204 patients with PCOS to receive 2.5-5 mg of Letrozole and 50-100 mg of Clomiphene citrate. The pregnancy rate with Letrozole was significantly higher i.e. 43.8% as compared to 26.4% with Clomiphene citrate.

![Figure 4: Pregnancy rates (%) comparing Letrozole and Clomiphene citrate in patients with PCOS.](image)

![Figure 5: Live birth rate (%) comparing Letrozole and Clomiphene citrate in patients with PCOS.](image)

**Table 3: Summary of Letrozole trials in PCOS patients.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient/condition</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang L&lt;sup&gt;25&lt;/sup&gt;</td>
<td>160 patients with PCOS</td>
<td>Letrozole 2.5 mg/day (for 1 cycle) versus Clomiphene citrate 50 mg/day (for 1 cycle)</td>
<td><strong>Ongoing pregnancy rate (%)</strong>&lt;br&gt;Letrozole: 22.5%&lt;br&gt;Clomiphene citrate: 10%&lt;br&gt;<strong>Endometrial thickness (mm)</strong>&lt;br&gt;Letrozole: 10.8 mm&lt;br&gt;Clomiphene citrate: 7.8 mm</td>
</tr>
<tr>
<td>Radjenovic RS&lt;sup&gt;26&lt;/sup&gt;</td>
<td>200 infertile women with PCOS</td>
<td>Letrozole 5 mg/day (for 1 cycle) versus Clomiphene citrate 100 mg/ day (for 1 cycle)</td>
<td><strong>Live birth rate (%)</strong>&lt;br&gt;Letrozole: 28&lt;br&gt;Clomiphene citrate: 18</td>
</tr>
<tr>
<td>Chakravorty R&lt;sup&gt;27&lt;/sup&gt;</td>
<td>127 infertile women having anovulation due to PCOS</td>
<td>Letrozole 2.5 mg/day (for 1 cycle) and 5 mg (for 2&lt;sup&gt;nd&lt;/sup&gt; cycle) versus Clomiphene citrate 50 mg/day (for 1&lt;sup&gt;st&lt;/sup&gt; cycle)</td>
<td><strong>Endometrial thickness (mm)</strong>&lt;br&gt;Letrozole: 9.82 mm&lt;br&gt;Clomiphene citrate: 8.13 mm <strong>Ovulation (%)</strong></td>
</tr>
</tbody>
</table>

b. In patients with unexplained infertility (Table 4)

Harira randomized 172 women with unexplained infertility with improper endometrial response to Clomiphene citrate were randomized to receive 100 mg Clomiphene citrate and 4 mg Estradiol Valerate on the 8<sup>th</sup> day of menstruation until 14<sup>th</sup> day and 5 mg Letrozole from day 3 to 7 of menstruation. The endometrial thickness in Letrozole group was significantly higher i.e. 9.2 mm as compared to Clomiphene citrate i.e. 8.28 mm. The pregnancy rate was similar in Letrozole and Clomiphene citrate group i.e. 16.2% versus 12.7% respectively as shown in Figure 6. Fouda et al randomized 214 patients with unexplained infertility were treated by either Letrozole 2.5 mg/day from cycle day 1 to 9 (extended protocol) or Clomiphene citrate 100 mg/day from cycle day 3 to 7. Endometrial thickness in extended protocol of Letrozole was significantly greater i.e. 9.10 mm as compared to Clomiphene citrate i.e. 8.18 mm. The cumulative pregnancy rate in Letrozole was observed to be 37.73% as compared to 22.86% in Clomiphene citrate group as shown in Figure 6.1<sup>31</sup> <sup>32</sup>
### Table 4: Summary of Letrozole trials in patients with unexplained infertility.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient/condition</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legro RS</td>
<td>750 infertile women with PCOS</td>
<td>Letrozole 2.5 mg daily (for up to five menstrual cycles.)</td>
<td><strong>Ovulation rate (%)</strong> Letrozole: 61.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Letrozene citrate: 48.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Live births (%)</strong> Letrozole: 27.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Letrozene citrate: 19.1</td>
</tr>
<tr>
<td>Roy KK</td>
<td>204 patients of anovulatory PCOS.</td>
<td>Letrozole: 2.5 mg (for 1 cycle) versus Clomiphene citrate: 50 mg (for 1 cycle)</td>
<td><strong>Endometrial thickness (mm)</strong> Letrozole: 9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 6.3</td>
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<td></td>
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<td></td>
<td><strong>Pregnancy Rates (%)</strong> Letrozole: 43.8</td>
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<td></td>
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<td>Clomiphene citrate: 26.4</td>
</tr>
</tbody>
</table>

### Table 5: Summary of Letrozole trials in patients with Clomiphene resistance.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient/condition</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harira M</td>
<td>172 patients with unexplained infertility for one to three years</td>
<td>Letrozole 5 mg daily from cycle day 3 to day 7. versus Clomiphene citrate 100 mg and Estradiol 4 mg</td>
<td><strong>Endometrial thickness (mm)</strong> Letrozole: 9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 8.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Pregnancy rate (%)</strong> Letrozole: 16.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 12.7</td>
</tr>
<tr>
<td>Fouda MU</td>
<td>214 patients with unexplained infertility</td>
<td>Letrozole: 2.5 mg/day for 10 days (from day 1 to day 9) versus Clomiphene citrate: 100 mg/day (for 1 cycle)</td>
<td><strong>Endometrial thickness (mm)</strong> Letrozole: 9.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 8.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Cumulative pregnancy rate (%)</strong> Letrozole: 37.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 22.86</td>
</tr>
<tr>
<td>Barroso G</td>
<td>41 patients with unexplained infertility</td>
<td>Letrozole: 2.5 mg/d for 5 days (for 1 cycle) versus Clomiphene citrate: 100 mg/d (for 1 cycle)</td>
<td><strong>Endometrial thickness (mm)</strong> Letrozole: 9.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Clinical pregnancy rate (%)</strong> Letrozole: 23.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 20</td>
</tr>
<tr>
<td>Mitwally MFM</td>
<td>110 women with unexplained infertility</td>
<td>Letrozole (2.5 mg/day from day 3 to day 7) + FSH 50±150 IU/day versus Clomiphene citrate 100 mg from day 5 to day 9 of the menstrual cycle + FSH injection 50±150 IU/day</td>
<td><strong>Total FSH dose/cycle (IU)</strong> Letrozole + FSH: 465</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene Citrate + FSH: 619</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Clinical pregnancy rate (%)</strong> Letrozole: 22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clomiphene citrate: 11.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient/condition</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim MH</td>
<td>80 women with Clomiphene citrate-resistant PCOS</td>
<td>Letrozole 2.5 mg/day (for up to six cycles.) versus Laparoscopic drilling (LOD)</td>
<td><strong>Ovulation rate (%)</strong> Letrozole: 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOD: 57.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Pregnancy rate (%)</strong> Letrozole: 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOD: 27.5</td>
</tr>
<tr>
<td>Nabih EL-Gharib</td>
<td>60 infertile women with Clomiphene resistant PCOS</td>
<td>Letrozole 2.5 mg/day (for 5 days) versus Tamoxifen 20 mg/day (for 5 days)</td>
<td><strong>Endometrial thickness (mm)</strong> Letrozole: 10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tamoxifen: 9.1</td>
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<td></td>
<td></td>
<td></td>
<td><strong>Ovulation (%)</strong> Letrozole: 23.33</td>
</tr>
</tbody>
</table>
Barroso G et al randomized 41 patients with unexplained infertility undergoing intrauterine insemination (IUI) therapy to receive either Letrozole or Clomiphene citrate along with rFSH. Endometrial thickness observed in Letrozole group was 9.5 mm as compared 7.3 mm with Clomiphene citrate. The clinical pregnancy rate was in Letrozole group was 9.5 mm as compared to rFSH. Endometrial thickness observed in Letrozole group was 9.5 mm as compared to Clomiphene citrate i.e. 23.8% versus 20% as shown in Figure 6.

c. In patients with Clomiphene resistance (Table 5)

Ibrahim MH et al studied 80 women with PCOS who were randomly allocated to undergo laparoscopic ovarian drilling (LOD) or receive 2.5 mg Letrozole from days 3 to 7 of menses for up to six cycles. A higher ovulation rate was found in Letrozole group i.e. 70% as compared to patients who underwent LOD i.e. 57.5% as shown in Figure 7. Pregnancy rate in Letrozole group was 35% as compared to in LOD group which was found to be 27.5%. Gharib NE et al studied 60 infertile women with PCOS and Clomiphene citrate resistance who were randomized to receive 2.5 mg/day of Letrozole or 20 mg/day of Tamoxifen daily for 5 days from day 5 of menses. The endometrial thickness and ovulation rate was found to be higher in Letrozole i.e. 10.2 mm and 23.3% respectively as compared to 9.1 mm and 8.89% in Clomiphene citrate group as shown in Figure 7. Rahman E et al observed 44 clomiphene-resistant infertile patients who were randomly allocated to receive 2.5 mg, 5 mg, and 7.5 mg of Letrozole. The ovulation and pregnancy rate were found to be 44.24% and 23.89% respectively. Elnashar A et al studied 44 infertile women with Clomiphene citrate resistance who received Letrozole 2.5 mg/day for 5 days. The ovulation rate and pregnancy rate was found to be 54.6% and 25% respectively.

**Letrozole - the road ahead**

a. Potential role in endometriosis associated infertility

Endometriosis-associated infertility represents a therapeutic dilemma because of ovulatory dysfunction related to altered folliculogenesis as well as impaired steroidogenesis of granulosa cells, impaired fertilization, low quality embryos, defective implantation, sperm phagocytosis, embryo-toxic environment and pelvic adhesions in advanced stages. Standard medical treatments aim either at inducing hypoestrogenism or at antagonizing estrogen action since estrogen is released aberrantly in endometriosis. Estrogen is a potent stimulator of cyclooxygenase 2 (COX-2) in uterine endothelial cells which in turn forms prostaglandin E2 from arachidonic acid which leads to painful stimuli in patients with endometriosis.

![Figure 7: Comparative ovulation rate (%).](image)

The molecular basis for the use of aromatase inhibitors is that they suppress estrogen production in peripheral tissues to decrease circulating estrogen levels considerably thereby reducing further proliferation of endometriotic lesions and painful stimuli. Letrozole has a significant reduction in total body estrogen (97-99%) and hence shown high efficacy in symptomatic management of endometriosis. Mitra et al studied the effects of Letrozole and Leuprolide, a GnRH agonist in women from 18-45 years of age with symptomatic (pain) endometriosis. The results showed that mean decrease of visual analogue score (VAS) before and after 3 months of treatment with Letrozole was highly significant and comparable to Leuprolide. However, it was observed that the safety profile of Letrozole was better as compared to Leuprolide.
b. Potential role in male infertility

Fifty percent of infertility cases is attributed to multiple causes including abnormalities in sperm parameters like sperm concentration, count, motility, vitality and morphology.\(^2\) In Males, aromatase is present in testis (particularly in Leydig and Sertoli cells), liver and brain.

This enzyme is responsible for the conversion of testosterone to estradiol and androstenedione to estrone. Aromatase inhibitors have found its role in increasing endogenous testosterone production by inhibiting the conversion of testosterone to estradiol and androstenedione to estrone leading to an increase in spermatogenesis.\(^4\)

**Letrozole - addressing key issues**

A significant proportion of success rate in inducing ovulation and achieving pregnancy in women with anovulatory infertility i.e. PCOS and unexplained infertility has been achieved with Letrozole which is one of the third-generation aromatase inhibitors (AIs). The major standout point for Letrozole is its lack of anti-estrogenic effects due to its shorter half-life thereby preserving the feedback mechanism of hypothalamic-pituitary-ovarian axis. This ensures monofollicular growth leading to singleton pregnancies thereby avoiding the co-morbidities associated with multiple pregnancies. Letrozole used in higher doses can enhance the follicular growth without detrimental effects on the endometrium thereby allowing more and more patients to retain on oral therapy without shifting to expensive gonadotropin therapy or in vitro-fertilization.

The clinical evidences wherein Letrozole has been used as first line therapy for ovulation induction is ever increasing making Letrozole an important tool in the infertility treatment armamentarium.

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