



Role of Letrozole in Management of Female Infertility; Review Article

Maha Fouad Messawa^{1*}, Salma Yousef Omar² and Reem Ahmed Babagi³

¹Heraa General Hospital (HGH), Makkah, KSA.

²Maternity & Children Hospital (MCH), Makkah, KSA.

³King Abdullah Medical Complex (KAMC), Jeddah, KSA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/V33i48A33249

Editor(s):

(1) P. Veera Muthumari, V.V.Vanniaperumal College for Women, India.

Reviewers:

(1) Anup Pradhan, Sikkim Manipal University, India.

(2) Sasmita Kumari Acharjya, Roland Institute of Pharmaceutical Sciences, India.

(3) Katarzyna Rygiel, Medical University of Silesia, Poland.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/75357>

Received 20 August 2021

Accepted 30 October 2021

Published 08 November 2021

Systematic Review

ABSTRACT

Background: Letrozole is a highly steroidal and selective oral aromatase inhibitor (AI). Several studies show that Co-treatment with letrozole significantly reduced gonadotropin consumption and the incidence of Ovarian Hyperstimulation Syndrome in normal/high responders, with pregnancy outcomes comparable to or better than the other groups. In this article we will be looking at role of letrozole in treatment of infertility

Methodology: A simple systematic review was carried out, searching databases PubMed, Google Scholar, and EBSCO. The authors extracted qualitative data, and then the author's names, year, study type, methodology, and the result were reported.

Results and Conclusion: Letrozole has effectiveness which is near the usage of the Human Menopausal Gonadotrophin in the numbers of pregnancies per cycle but have much less cost which indicates cost effectiveness of the drug. Furthermore, studies show that administration of the drug is effective in inducing pregnancy, with higher dose more than 5mg and 7.5mg more effective.

¹Consultant of Obstetrics and gynae oncology;

²Consultant of Obstetrics and Gynecology;

³Consultant Obstetrics and Gynecology;

Keywords: Letrozole; femara; infertility; oral aromatase inhibitor; pregnancy; systematic.

ABBREVIATIONS

AI	: aromatase inhibitor;
WHO	: World Health Organization;
FSH	: Follicle Stimulating Hormone;
HPO	: hypothalamic-pituitary-gonad;
CC	: clomiphene citrate;
IUI	: Intercourse or intrauterine insemination;
COS	: controlled ovarian stimulation;
Ohss	: Ovarian Hyperstimulation Syndrome;
ART	: assisted reproductive technology;
AMH	: Anti-Mullerian Hormone;
HRT	: hormone-replacement therapy.

1. INTRODUCTION

Infertility is a medical condition that can cause psychological, physical, mental, spiritual, and medical detriments to the patient. The World Health Organization (WHO) reported that 37% of infertile couples were regarded for female infertility as the cause [1].

Letrozole, an aromatase inhibitor that blocks estrogen synthesis by inhibiting the final step of the estrogen biosynthetic pathway, has been used in the applications of a wide range of infertility settings. It has been more than 20 years since the initial clinical trial of letrozole for ovulation induction. Letrozole is also used for fertility preservation in women with estrogen-sensitive cancers. Also, studies showed the effectiveness of letrozole in endometrium preparation for frozen-thawed embryo transfer (FET) [2-4].

Letrozole is a highly steroidal and selective oral aromatase inhibitor (AI) that can be reversed in the route of oestrogen manufacture by binding the rate limiting enzyme P450 to prevent testosterone transformation into estradiol and androstenedione into estrone [5]. Down-regulated oestrogen increases Follicle Stimulating Hormone (FSH) release as feedback to encourage ovulation. Now, in anovulatory infertile patients and for ovulatory women, letrozole is often used to induce ovulation. In addition, letrozole is an intrauterine [6] and IVF (IVF)/intracytoplasmic injection sperm supplement.

The molecular structure of Letrozole is 4,40 to benzene nitric methylene [(1H-1,2,4-triazole-1-yl) [7]. It has been shown to be a very powerful

aromatase inhibitor in in vitro, in vivo animals and humans [7]. Letrozole kinetics were characterised by a quick and complete absorption ($t_{max}=1h$). A very slow elimination, and a plasma half-life (2.5 mg once daily) is 41, ~48 hours after oral treatment. Plasma half-lives are 41,08 mg once daily [8]. Intake of food did not affect the degree of letrozole absorption [8]. Metabolism into an inactive metabolite of carbinol through CYP450 isoenzymes [2].

Letrozole suppresses aromatase activity by over 95% and endogenous oestrogen production by 97-99% [9]. Letrozole's mechanism of action for OI is unknown. It has been suggested, however, that it may function through both central and peripheral pathways [10]. Letrozole decreases oestrogen levels considerably in the brain, preventing negative feedback on the hypothalamic-pituitary-gonad (HPO) axis [11]. The brief buildup of intraovarian androgens may boost follicular sensitivity by amplifying of FSH receptor gene expression [11] when the conversion of androgen substrates to oestrogen is blocked.

Letrozole can be administered alone or combined with exogenous FSH to treat OI, however the best dose and regimen are still unknown [12]. The use of letrozole for OI is similar to that of clomiphene citrate (CC). Letrozole is typically administered in doses of 2.5 to 7.5 mg per day for a 5-day regimen, which corresponds to the availability of a 60.8 mm follicle. Increased androgen levels at this stage encourage granulosa cell mitosis and induction of FSH receptors [13]. The 6mm follicle is endowed with a high amount of androgen receptors.

Letrozole is also often given to help ovulatory patients boost their chances of becoming pregnant. Mild male factor, endometriosis, pelvic factor, and advanced maternal age are common diagnoses [14,15]. Despite letrozole's benefit in PCOS patients, infertile women with moderate oligoasthenospermia, early-stage endometriosis, and unexplained infertility who underwent time intercourse or intrauterine insemination (IUI) had equivalent success with letrozole and CC [16]. In women with infertility and PCOS, an RCT published in 2019 found that the combination of letrozole and CC was associated with a greater ovulation rate than letrozole alone [17]. However, further research is required in this check.

Despite extensive screening of both male and female partners, the aetiology of unexplained infertility may remain unknown [18]. It is found in ten percent to thirty percent of couples seeking infertility therapy [19]. In 2019, a systematic review and meta-analysis found no difference between letrozole and CC for unexplained infertility in terms of clinical pregnancy, live birth, spontaneous miscarriage, or twin gestation [20]. In 2020, a multicenterrandomised controlled experiment found that gonadotropin, clomiphene, and letrozole resulted in the same pregnancy outcomes [21]. However, according to a research by Usama M Fouda et al, the extended letrozole regimen had a much higher pregnancies rate.

Letrozole would accomplish mono-follicular development in the majority of cycles, reducing multiple gestation pregnancy and OHSS, and with a pregnancy success rate comparable to gonadotropins or CC, it might become the first line of treatment for unexplained infertility [18].

Letrozole medication in the early follicular phase during controlled ovarian stimulation (COS) enhanced testosterone and androstenedione levels in follicular fluid, which improved follicular sensitivity to FSH stimulation. Some preliminary data showed that letrozole could increase ovarian responsiveness to FSH and reduce the number of gonadotropin doses while enhancing pregnancy outcomes in poor responders [22].

Co-treatment with letrozole significantly reduced gonadotropin consumption and the incidence of OHSS in normal/high responders, with pregnancy outcomes comparable to or better than the other groups [23]. Adjunctive use of letrozole, especially in ICSI cycles, may be an effective low-cost IVF treatment option. In addition, co-treatment with letrozole has been

shown to improve pregnancy outcomes by reverting the expression of v3 integrin in the endometrium [24]. In IVM cycles, letrozole priming did not outperform low-dose FSH priming in terms of pregnancy rate [25], but there are few researches on this topic [26].

2. METHODOLOGY

A simple systematic review was carried out, searching databases PubMed, Google Scholar, and EBSCO using the following terms in different combinations: Letrozole, Femara, infertility along with other keywords. We included all full texts [randomized controlled trials, observational, review articles and experimental studies in making up of this study. The authors extracted qualitative data, and then the author's names, year, study type, methodology, and the result were reported (Table 1). Inclusion criteria included all relevant studies with similar objectives as our study. Time and language restrictions were made to 20 years and English language due to lack of translation sources. Exclusion criteria included all studies irrelevant to our topic and papers published 20 years ago or more.

2.1 Statistical Analysis

No software has been utilized to analyze the data. The data was extracted based on specific form that contains (Author's name, publication year, country, methodology and results). These data were reviewed by the group members to determine the initial findings, and the modalities of performing the surgical procedure. Double revision of each member's outcomes was applied to ensure the validity and minimize the mistakes.

3. RESULTS

The search of the mentioned databases returned a total of 367 studies that were included for title screening. 368 of them were included for abstract screening, which led to the exclusion of 266 articles. The remaining 102 publications full-texts were reviewed. The full-text revision led to the exclusion of 25 studies, and 9 were enrolled for final data extraction (Table 1).

Baysoy A, Serdaroglu H, et al. discovered that Letrozole has effectiveness of almost the same as the HMG (18.4 versus 15.7%). in the numbers of pregnancies per cycle but have much less cost [27].

Steiner N, Shrem G, et al. observed Effect of GnRH agonist and letrozole treatment in women with recurrent implantation failure. Age, antral follicle count, baseline FSH levels, infertility length, previous pregnancies, and full-term births were all comparable. Compared to women who got GnRH agonist only or women who did not receive pretreatment, clinical pregnancy rates were greater in women who received GnRH agonist with letrozole (63 percent, 42 percent, and 40 percent, respectively;). When compared to the other groups, women who took GnRH agonist plus letrozole had more live births (56 percent, 36 percent, and 34 percent ;). There were no differences in pregnancy outcomes between patients who did not get pretreatment

and those who just received a GnRH agonist. Treatment with a GnRH agonist and letrozole in RIF patients may enhance live birth rates in following cycles [28].

Legro RS, Brzyski RG, Diamond MP, et al. found that Without significant differences in total congenital abnormalities, Letrozole had a greater cumulative ovulation rate than clomiphene (834 of 1352 treatment cycles [61.7 percent] vs. 688 of 1425 treatment cycles [48.3 percent]). Clomiphene was linked to a higher rate of hot flushes, while letrozole was linked to a higher rate of weariness and dizziness. Other adverse events occurred at similar rates in both treatment groups [29].

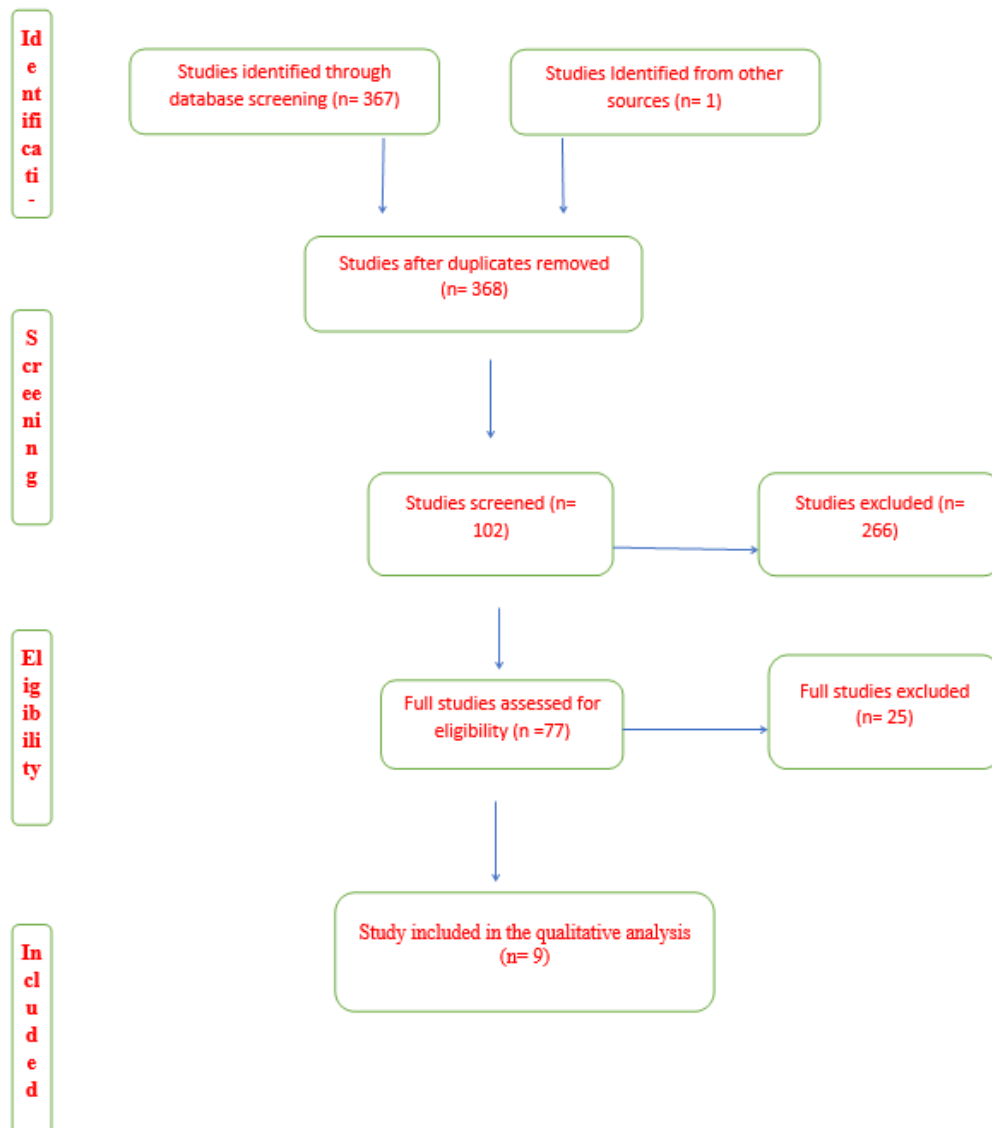


Fig. 1. Studies Included
Table 1. Review of search methods used in systematic reviews

Author, year, country	Study type	Method	Outcomes
Baysoy A, Serdaroglu H, et al. [26]	Pilot study	Eighty women aged 20 to 35 years old with unexplained infertility for at least two years were randomly assigned to the letrozole or HMG groups using a computer-generated randomization list.	Letrozole has effectiveness of almost the same as the HMG in the numbers of pregnancies per cycle but have much less cost
Legro RS, Brzyski RG, Diamond MP, et al. [28]	double-blind, multicenter trial	750 women were randomly assigned to receive letrozole or clomiphene in a 1:1 ratio for up to five treatment cycles, including visits to determine ovulation and pregnancy, followed by pregnancy tracking.	significant differences in overall congenital anomalies.
Steiner N, Shrem Get, al. [27]	Retrospective cohort study.	A total of 523 infertile women had a third frozen blastocyst transfer after two failed blastocyst transfers. Women with endometriosis were not allowed to participate.	Compared to women who got GnRH agonist only or women who did not receive pretreatment, clinical pregnancy rates were greater in women who received GnRH agonist with letrozole (63 percent , 42 percent , and 40 percent , respectively), treatment with a GnRH agonist plus letrozole may improve live birth rates in subsequent cycles..
Kar S. [30]	Review Article	Poor responders were studied in five randomized trials with a total of 265 patients. They were given either letrozole plus gonadotropins or gonadotropins alone in an antagonist or agonist strategy.	Letrozole is at least as successful as CC for ovulation, and its live birth rates are comparable. In addition, it has certain advantages over CC. Letrozole has been found in numerous studies to be equally successful as gonadotropins, with the added benefit of being less expensive and having a lower multiple pregnancy rate.
Noriega-Portella L, Noriega-Hoces L et al. [29]	Retrospective study.	Recombinant FSH alone administered from day 3 or combined with letrozole, 2.5 or 5.0 mg/day, on days 3 to 7, and gonadotropins starting on day 7 of the menstrual cycle. Ovulation was triggered with 10,000 IU of human chorionic gonadotropin (hCG), and IU performed 30 to 40 hours later.	Women treated with FSH and 5.0 mg/day of letrozole required a lower dose of FSH than the group cotreated with 2.5 mg/day of letrozole or with FSH alone
Pritts EA, Yuen AK, et	retrospective cohort	900 treatment cycles using letrozole in doses as high as 12.5 mg per day.	Patients benefit from higher doses of the

Author, year, country	Study type	Method	Outcomes
al. [31]	analysis		medicine because they experience increased follicular expansion and a higher number of anticipated ovulations. Increasing doses, on the other hand, has no negative impact on endometrial thickness. Women who may not respond well to lower dosages of letrozole may benefit from high-dose letrozole.
Pritts EA, Yuen AK, Sharma S, Genisot R, Olive DL 2011 Nov	900 treatment cycles using	insert these things in the tabular form. Table 1 Pritts EA, Yuen AK et al. observed that; 900 treatment cycles using letrozole in doses as high as 12.5 mg per day. Patients benefit from higher doses of the medicine because they experience increased follicular expansion and a higher number of anticipated ovulations. Increasing doses, on the other hand, has no negative impact on endometrial thickness. Women who may not respond well to lower	dosages of letrozole may benefit from high-dose letrozole

Noriega-Portella L, Noriega-Hoces L, et al. reported that; Women who received FSH and 5.0 mg/day of letrozole required a lower dose of FSH than those who received FSH alone or 2.5 mg/day of letrozole. The endometrial thickness was statistically substantially lower in both letrozolecotreatment groups than in the FSH control group over the majority of the follicular phase. The endometrial thickness of all the groups was comparable on the day of hCG treatment. Recombinant FSH alone or in combination with letrozole had the same pregnancy rates [30].

Kar S.et al.reported that; Letrozole is at least as successful as CC for ovulation, and its live birth rates are comparable. In addition, it has certain advantages over CC. Letrozole has been found in numerous studies to be equally successful as gonadotropins, with the added benefit of being less expensive and having a lower multiple pregnancy rate. However, the medical evidence supporting aromatase inhibitors for OI is insufficient, with a small sample size and an ineffective design. [31].

Pritts EA, Yuen AK et al.observed that; 900 treatment cycles using letrozole in doses as high as 12.5 mg per day. Patients benefit from higher doses of the medicine because they experience increased follicular expansion and a higher number of anticipated ovulations. Increasing doses, on the other hand, has no negative impact on endometrial thickness. Women who may not respond well to lower dosages of letrozole may benefit from high-dose letrozole [32].

4. DISCUSSION

Letrozole appears to have a dose-response effect, with larger doses resulting in more developed follicles and greater ovulation rates. In the first study of its kind, 5mg daily resulted in more ovulations than 2.5mg. A second study comparing 2.5 mg, 5 mg, and 7.5 mg indicated that as the dose increased, the number of mature follicles increased considerably (1.0, 1.4, and 3.4, resp.) [32].

The idea that dosages of 2.5–7.5 mg lower estradiol levels by 88–98% has been used to justify not exceeding these amounts. These findings, which come from postmenopausal breast cancer patients, may not be applicable to reproductive-age women, particularly those with high oestrogen levels due to persistent anovulation and a high BMI. Furthermore, at a daily dose of 2.5 mg, maximum suppression takes 2–4 days to develop. For as long as two months, steady-state plasma levels do not occur [32].

4.1 Letrozole in the Prevention and Treatment of Ovarian Hyperstimulation Syndrome

OHSS is a potentially fatal consequence of ovarian stimulation during assisted reproductive technology procedures (ART). Letrozole reduces VEGF levels while increasing PEDF levels in the rat OHSS model, which should contribute to a reduction in the incidence of OHSS [33].

Co-administration with letrozole reduces the risk of OHSS in PCOS patients with exceptionally high Anti-Mullerian Hormone (AMH) levels, according to a prospective randomised controlled pilot research [34]. However, a research by Wang et al. found that while letrozole reduced serum E2 levels in patients undergoing the freeze-all embryo technique during the luteal phase, it had no effect on the rate of severe OHSS when compared to the control group [35]. Despite the fact that E2 levels are positively connected with the prevalence of OHSS, the authors contend that it is still unclear whether E2 is the source or the effect of OHSS. As a result, exogenous AI therapy is a viable option.

4.2 Letrozole in Preparation of Endometrium for Fet

The key to FET's effectiveness is improving the endometrium's receptivity and synchronising endometrial and embryo development. Although Letrozole has been found to be superior than natural or hormone-replacement therapy (HRT) in terms of clinical pregnancy, live birth [35], and miscarriage [36] in some investigations. There is no consistent benefit of any endometrial preparation, according to high-quality studies [37]. Furthermore, in 2020, a major meta-analysis study with a total of 31 RCTs (5426 women) failed to reveal a conclusive best endometrial preparation approach [38]. Letrozole, on the other hand, is inexpensive, patient-friendly, and produces at least similar pregnancy rates when compared to other drugs.

4.3 Letrozole in the Treatment of Endometriosis-Associated Infertility

Letrozole is an appealing therapy for endometriosis because AIs decrease the locally generated E2 by endometriotic deposits [39]. Few studies have looked into the use of AIs, particularly letrozole, to treat endometriosis-related infertility. In a prospective RCT, letrozole 2.5 mg/day for two months had no effect on the pregnancy rate or disease recurrence rate in laparoscopic and histological diagnosis of endometriosis compared to triptorelin and control [40]. Another RCT found no difference in pregnancy rates each cycle and cumulative pregnancy rates between superovulation with letrozole + IUI versus CC + IUI in stage I-II endometriosis.

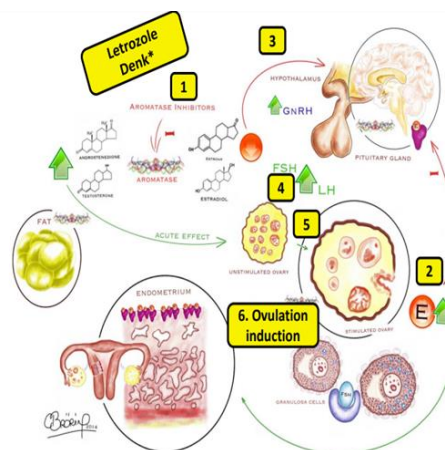


Fig . 1.

In conclusion, there is limited evidence for utilising letrozole in endometriosis-related infertility patients. Letrozole's efficacy is likely to differ depending on the stage of endometriosis. More trials are needed to offer evidence to help us manage endometriosis-related infertility with letrozole in the clinic.

4.4 Letrozole for Fertility Preservation

With advancements in cancer early detection technology, improved projected survival times, and the postponement of reproductive age, fertility preservation for young gynaecological cancer patients has become a pressing necessity [41]. Oocyte and embryo cryopreservation have become common methods for fertility preservation in recent decades [42]. The conventional COS regimen, on the other hand, can cause plasma levels of estradiol and E2 to spike up to 10 times faster than the natural cycle, thereby triggering the return of hormone-sensitive malignancies. Letrozole combined with FSH in COS (LE-FSH-COS) significantly reduced plasma E2 peak consensus compared to the normal COS regimen.

Letrozole has been shown to be effective in IVF cycles in breast cancer patients receiving fertility preservation treatment in a growing number of trials [43]. The efficiency and safety of the LE-FSH-COS regimen in terms of clinical pregnancy outcomes were further verified in a study by Oktay K et al. on fertility preservation in breast cancer patients [44]. The FET cycle had a 45 percent live birth rate in this study, and there was no statistical difference between the average live birth rate (38.2%) of IVF-ET for infertile women of the same age in the United States ($P = 0.2$). There were no prenatal or neonatal malformations reported [44]. Progesterone levels, on the other hand, were quite high [44].

Several trials have also demonstrated the benefit of letrozole in patients with other hormone-sensitive cancer types. In a mouse model, Kawahara et al. demonstrated that letrozole given during ovarian stimulation inhibited the progression of uterine endometrial cancer [45]. Six obese endometrial cancer patients who wanted to keep their fertility were enrolled in a pilot study. They were given a GnRH agonist and letrozole treatment regimen, and after a median follow-up of 4.0 years (range, 1.3-7.0 years), none of the patients had recurrences, and the pregnancy rate and live birth rate were 50.0 percent and 75.0 percent, respectively [46]. In

four women with endometrial cancer, the LE-FSH-COS regimen was employed.

Because the effect of COS on ovarian cancers has yet to be confirmed, clinical research of LE-FSH-COS in patients with borderline or invasive ovarian tumours is inadequate. Because letrozole can reduce the likelihood of recurrence in individuals with borderline ovarian cancers by inhibiting oestrogen levels during the COS process, it may be useful in minimising the chance of tumour recurrence [47]. Clinical study, however, is needed to confirm this notion.

4.5 Safety

At first, there was worry that letrozole for OI could cause teratogenic consequences in newborns [14]. However, following high-quality studies found that the rate of total chromosomal abnormalities, congenital malformations, or unfavourable pregnancy and neonatal outcomes in the letrozole group was not higher than in the CC group [48] or the general population [49]. After five years of letrozole medication, postmenopausal women with breast cancer experienced more low-grade hot flashes, arthritis, arthralgia, and myalgia than the placebo. The length of OI with letrozole is substantially less than that of breast cancer treatment, according to the study.

Letrozole may well be teratogenically safer because its half-life virtually assures elimination from the body before implantation. But before letrozole or CC administration, pregnancy should always be ruled out [49]. Further studies are needed to determine optimal dosing and long-term safety for women treated with the drug. In addition, the long-term health effects of letrozole on children need further investigation as well.

5. CONCLUSION

Letrozole has effectiveness in inducing pregnancy, with higher dose more than 5mg and 7.5mg more effective. Letrozole's application as a novel type of OI medicine is not confined to the clinical treatment of OI for timed intercourse, but also encompasses many elements of infertility treatment. Furthermore, letrozole is more readily available, has less negative side effects, and is less expensive than injectable gonadotropins. High-quality clinical and fundamental investigations have demonstrated its superiority for OI in WHO group II anovulation patients. Letrozole's actual mechanism of OI is unknown,

clinical applications are still in the early stages of development, and researchers have yet to agree on a uniform strategy. Large clinical samples from RCTs and mechanism studies are recommended.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bhatnagar AS. The Early Days of Letrozole. *Breast Cancer Res Treat.* 2007;105(Suppl 1):3–5. DOI: 10.1007/s10549-007-9699-0
2. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A Randomized Trial of Letrozole in Postmenopausal Women After Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer. *N Engl J Med.* 2003;349:1793–802. DOI: 10.1056/NEJMoa032312
3. Bhatnagar AS, Batzl C, Häusler A, Nogués V. The Role of Estrogen in the Feedback Regulation of Follicle-Stimulating Hormone Secretion in the Female Rat. *J Steroid Biochem Mol Biol.* 1993;47:161–6. DOI: 10.1016/0960-0760(93)90070-D
4. Mitwally MFM, Casper RF. Aromatase Inhibition A Novel Method of Ovulation Induction in Women With Polycystic Ovary Syndrome. *Reprod Technol.* 2000;10:244–7.
5. Rajan RK, Kumar M SS, Balaji B. Soy Isoflavones Exert Beneficial Effects on Letrozole-Induced Rat Polycystic Ovary Syndrome (PCOS) Model Through Anti-Androgenic Mechanism. *Pharm Biol.* 2017;55:242–51. DOI: 10.1080/13880209.2016.1258425
6. Huang S, Wang R, Li R, Wang H, Qiao J, Mol BWJ. Ovarian Stimulation in Infertile Women Treated with the Use of Intrauterine Insemination: A Cohort Study from China. *Fertil Steril.* 2018;109:872–8. DOI: 10.1016/j.fertnstert.2018.01.008
7. Dellapasqua S, Colleoni M. Letrozole. *Expert Opin Drug Metab Toxicol.* 2010;6:251–9. DOI: 10.1517/17425250903540246
8. Buzdar AU, Robertson JF, Eiermann W, Nabholz JM. An Overview of the Pharmacology and Pharmacokinetics of the Newer Generation Aromatase Inhibitors Anastrozole, Letrozole, and Exemestane. *Cancer.* 2002;95:2006–16. DOI: 10.1002/cncr.10908[8]
9. Yding Andersen C. Inhibin-B Secretion and FSH Isoform Distribution may Play an Integral Part of Follicular Selection in the Natural Menstrual Cycle. *Mol Hum Reprod.* 2017;23:16–24. DOI: 10.1093/molehr/gaw070
10. Mitwally MF, Casper RF. Aromatase Inhibition Improves Ovarian Response to Follicle-Stimulating Hormone in Poor Responders. *Fertil Steril.* 2002;77:776–80. DOI: 10.1016/S0015-0282(01)03280-0
11. Holzer H, Casper R, Tulandi T. A New Era in Ovulation Induction. *Fertil Steril.* 2006;85:277–84. DOI: 10.1016/j.fertnstert.2005.05.078
12. Lønning P, Pfister C, Martoni A, Zamagni C. Pharmacokinetics of Third-Generation Aromatase Inhibitors. *Semin Oncol.* 2003;30:23–32. DOI: 10.1016/S0093-7754(03)00305-1
13. Randall JM, Templeton A. Cervical Mucus Score and In Vitro Sperm Mucus Interaction in Spontaneous and Clomiphene Citrate Cycles. *Fertil Steril.* 1991;56:465–8. DOI: 10.1016/S0015-0282(16)54541-5
14. Casper RF, Mitwally MF. Use of the Aromatase Inhibitor Letrozole for Ovulation Induction in Women With Polycystic Ovarian Syndrome. *Clin Obstetrics Gynecol.* 2011;54:685–95. DOI: 10.1097/GRF.0b013e3182353d0f

15. Zadehmodares S, Niyakan M, Sharafy SA, Yazdi MH, Jahed F. Comparison of Treatment Outcomes of Infertile Women by Clomiphene Citrate and Letrozole With Gonadotropins Underwent Intrauterine Insemination. *Acta Med Iran.* 2012;50:18–20. DOI: 10.22074/ijfs.2020.5608
16. Mejia RB, Summers KM, Kresowik JD, Van Voorhis BJ. A Randomized Controlled Trial of Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Women With Polycystic Ovary Syndrome. *Fertil Steril.* 2019;111:571–578.e571. DOI: 10.1016/j.fertnstert.2018.11.030
17. Diamond MP, Mitwally M, Casper R, Ager J, Legro RS, Brzyski R, et al. Estimating Rates of Multiple Gestation Pregnancies: Sample Size Calculation From the Assessment of Multiple Intrauterine Gestations From Ovarian Stimulation (AMIGOS) Trial. *ContempClin Trials.* 2011;32:902–8. DOI: 10.1016/j.cct.2011.07.009
18. Fouda UM, Sayed AM. Extended Letrozole Regimen Versus Clomiphene Citrate for Superovulation in Patients With Unexplained Infertility Undergoing Intrauterine Insemination: A Randomized Controlled Trial. *Reprod Biol Endocrinol.* 2011;9:84. DOI: 10.1186/1477-7827-9-84
19. Eskew AM, Bedrick BS, Hardi A, Stoll CRT, Colditz GA, Tuuli MG, et al. Letrozole Compared With Clomiphene Citrate for Unexplained Infertility: A Systematic Review and Meta-Analysis. *Obstetrics Gynecol.* 2019;133:437–44. DOI: 10.1097/AOG.0000000000003105
20. Quaas AM, Gavrizi SZ, Peck JD, Diamond MP, Legro RS, Robinson RD, et al. Endometrial Thickness After Ovarian Stimulation With Gonadotropin, Clomiphene, or Letrozole for Unexplained Infertility, and Association With Treatment Outcomes. *Fertil Steril.* 2021;115:213–20. DOI: 10.1016/j.fertnstert.2020.07.030
21. Garcia-Velasco JA, Moreno L, Pacheco A, Guillen A, Duque L, Requena A, et al. The Aromatase Inhibitor Letrozole Increases the Concentration of Intraovarian Androgens and Improves In Vitro Fertilization Outcome in Low Responder Patients: A Pilot Study. *Fertil Steril.* 2005;84:82–7. DOI: 10.1016/j.fertnstert.2005.01.117
22. Shapira M, Orvieto R, Lebovitz O, Nahum R, Aizer A, Segev-Zahav A, et al. Does Daily Co Administration of Gonadotropins and Letrozole During the Ovarian Stimulation Improve IVF Outcome for Poor and Sub Optimal Responders? *J Ovarian Res.* 2020;13:66. DOI: 10.1186/s13048-020-00666-z
23. Miller PB, Parnell BA, Bushnell G, Tallman N, Forstein DA, Higdon HL 3rd, et al. Endometrial Receptivity Defects During IVF Cycles With and Without Letrozole. *Hum Reprod.* 2012;27:881–8. DOI: 10.1093/humrep/der452PubMed Abstract | CrossRef Full Text | Google Scholar
24. Rose BI. The Potential of Letrozole Use for Priming In Vitro Maturation Cycles. *Facts Views Vision ObGyn.* 2014;6:150–5.
25. Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral Medications Including Clomiphene Citrate or Aromatase Inhibitors With Gonadotropins for Controlled Ovarian Stimulation in Women Undergoing In Vitro Fertilisation. *Cochrane Database Systematic Rev.* 2017;11:Cd008528. DOI: 10.1002/14651858.CD008528.pub3
26. Baysoy A, Serdaroglu H, Jamal H, Karatekeli E, Ozornek H, Attar E. Letrozole versus human menopausal gonadotrophin in women undergoing intrauterine insemination. *Reprod Biomed Online.* 2006;13(2):208-12. DOI: 10.1016/s1472-6483(10)60617-7. PMID: 16895634.
27. Steiner N, Shrem G, Tannus S, Dahan SY, Balayla J, Volodarsky-Perel A, Tan SL, Dahan MH. Effect of GnRH agonist and letrozole treatment in women with recurrent implantation failure. *FertilSteril.* 2019;112(1):98-104. DOI: 10.1016/j.fertnstert.2019.03.021. Epub 2019 May 24. PMID: 31133384.
28. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med.* 2014;371(2):119-29. DOI: 10.1056/NEJMoa1313517.

- Erratum in: N Engl J Med. 2014 Oct 9;317(15):1465.
PMID: 25006718; PMCID: PMC4175743.
29. Noriega-Portella L, Noriega-Hoces L, Delgado A, Rubio J, Gonzales-Castañeda C, Gonzales GF. Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. *FertilSteril*. 2008;90(5):1818-25.
DOI: 10.1016/j.fertnstert.2007.08.060
Epub 2008 Feb 20. PMID: 18083169.
30. Kar S. Current evidence supporting "letrozole" for ovulation induction. *J Hum Reprod Sci*. 2013 Apr;6(2):93-8. doi: 10.4103/0974-1208.117166.
PMID: 24082649; PMCID: PMC3778612
31. Pritts EA, Yuen AK, Sharma S, Genisot R, Olive DL. The use of high dose letrozole in ovulation induction and controlled ovarian hyperstimulation. *ISRN ObstetGynecol*. 2011;2011:242864. DOI: 10.5402/2011/242864.
Epub 2011 Nov 17. PMID: 22191042; PMCID: PMC3236406.
32. Sahin N, Apaydin N, Toz E, Sivrikoz ON, Genc M, Turan GA, et al. Comparison of the Effects of Letrozole and Cabergoline on Vascular Permeability, Ovarian Diameter, Ovarian Tissue VEGF Levels, and Blood PEDF Levels, in a Rat Model of Ovarian Hyperstimulation Syndrome. *Arch Gynecol Obstetrics*. 2016;293:1101-6.
DOI: 10.1007/s00404-015-3987-4
CrossRef Full Text | Google Scholar
33. Tshzmachyan R, Hambartsoumian E. The Role of Letrozole (LE) in Controlled Ovarian Stimulation (COS) in Patients at High Risk to Develop Ovarian Hyperstimulation Syndrome (OHSS). A Prospective Randomized Controlled Pilot Study. *J GynecolObstet Hum Reprod*. 2019;49:101643.
DOI: 10.1016/j.jogoh.2019.101643
34. Wang Y-Q, Luo J, Xu W-M, Xie Q-Z, Yan W-J, Wu G-X, et al. Can Steroidal Ovarian Suppression During the Luteal Phase After Oocyte Retrieval Reduce the Risk of Severe OHSS? *J Ovarian Res*. 2015;8:63.
DOI: 10.1186/s13048-015-0190-y
35. Zhang J, Liu H, Wang Y, Mao X, Chen Q, Fan Y, et al. Letrozole Use During Frozen Embryo Transfer Cycles in Women With Polycystic Ovary Syndrome. *Fertil Steril*. 2019;112:371-7.
DOI:10.1016/j.fertnstert.2019.04.014
PubMed Abstract | CrossRef Full Text | Google Scholar
36. Mackens S, Santos-Ribeiro S, van de Vijver A, Racca A, Van Landuyt L, Tournaye H, et al. Frozen Embryo Transfer: A Review on the Optimal Endometrial Preparation and Timing. *Hum Reprod*. 2017;32:2234-42.
DOI:10.1093/humrep/dex285
PubMed Abstract | CrossRef Full Text | Google Scholar
37. Glujovsky D, Pesce R, Sueldo C, QuinteroRetamar AM, Hart RJ, Ciapponi A. Endometrial Preparation for Women Undergoing Embryo Transfer With Frozen Embryos or Embryos Derived From Donor Oocytes. *Cochrane Database Systematic Rev* (2020;10:Cd006359).
DOI: 10.1002/14651858.CD006359.pub3
CrossRef Full Text | Google Scholar
38. Abu Hashim H. Potential Role of Aromatase Inhibitors in the Treatment of Endometriosis. *Int J Women's Health*. 2014;6:671-80.
DOI: 10.2147/IJWH.S34684
CrossRef Full Text | Google Scholar
39. Alborzi S, Hamed B, Omidvar A, Dehbashi S, Alborzi S, Alborzi M. A Comparison of the Effect of Short-Term Aromatase Inhibitor (Letrozole) and GnRH Agonist (Triptorelin) Versus Case Control on Pregnancy Rate and Symptom and Sign Recurrence After Laparoscopic Treatment of Endometriosis. *Arch Gynecol Obstetrics*. 2011;284:105-10.
DOI:10.1007/s00404-010-1599-6
CrossRef Full Text | Google Scholar
40. Chen C, Sun S, Yuan JP, Wang YH, Cao TZ, Zheng HM, et al. Characteristics of Breast Cancer in Central China, Literature Review and Comparison With USA. *Breast*. 2016;30:208-13.
DOI: 10.1016/j.breast.2016.01.004
PubMed Abstract | CrossRef Full Text | Google Scholar
41. Zhang Z, Huang H, Feng F, Wang J, Cheng N. A Pilot Study of Gonadotropin-Releasing Hormone Agonist Combined With Aromatase Inhibitor as Fertility-Sparing Treatment in Obese Patients With Endometrial Cancer. *J Gynecologic Oncol*. 2019;30:e61.
DOI: 10.3802/jgo.2019.30.e61
CrossRef Full Text | Google Scholar
42. Pereira N, Hancock K, Cordeiro CN, Lekovich JP, Schattman GL, Rosenwaks

- Z. Comparison of Ovarian Stimulation Response in Patients With Breast Cancer Undergoing Ovarian Stimulation With Letrozole and Gonadotropins to Patients Undergoing Ovarian Stimulation With Gonadotropins Alone for Elective Cryopreservation of Oocytes. *Gynecol Endocrinol: Off J Int Soc Gynecol Endocrinol.* 2016;32: 823–6.
DOI:10.1080/09513590.2016.1177013
CrossRef Full Text | Google Scholar
43. Oktay K, Turan V, Bedoschi G, Pacheco Fernanda S, Moy F. Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. *J Clin Oncol.* 2015;33:2424–9.
DOI: 10.1200/JCO.2014.59.3723 PubMed Abstract | CrossRef Full Text | Google Scholar
44. Kawahara T, Okamoto N, Takae S, Kashiwagi M, Nakajima M, Uekawa A, et al. Aromatase Inhibitor Use During Ovarian Stimulation Suppresses Growth of Uterine Endometrial Cancer in Xenograft Mouse Model. *Hum Reprod.* 2018;33:303–10.
DOI:10.1093/humrep/dex368PubMed Abstract | CrossRef Full Text | Google Scholar
45. Mangili G, Somigliana E, Giorgione V, Martinelli F, Filippi F, Petrella MC, et al. Fertility Preservation in Women With Borderline Ovarian Tumours. *Cancer Treat Rev.* 2016;49:13–24.
DOI: 10.1016/j.ctrv.2016.06.010PubMed Abstract | CrossRef Full Text | Google Scholar
46. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital Malformations Among 911 Newborns Conceived After Infertility Treatment With Letrozole or Clomiphene Citrate. *Fertil Steril.* 2006;85:1761–5.
DOI:10.1016/j.fertnstert.2006.03.014PubMed Abstract | CrossRef Full Text | Google Scholar
47. Hoffman JI. Incidence of Congenital Heart Disease: I. Postnatal Incidence. *Pediatr Cardiol.* 1995;16:103–13.
DOI: 10.1007/BF00801907 PubMed Abstract | CrossRef Full Text | Google Scholar
48. Palomba S. Aromatase Inhibitors for Ovulation Induction. *J Clin Endocrinol Metab.* 2015;100:1742–7.
DOI: 10.1210/jc.2014-4235PubMed Abstract | CrossRef Full Text | Google Scholar
49. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility Preservation and Post-Treatment Pregnancies in Post-Pubertal Cancer Patients: ESMO Clinical Practice Guidelines(†). *Ann Oncology: Off J Eur Soc Med Oncol.* 2020;31:1664–78.
DOI:10.1016/j.annonc.2020.09.006CrossRef Full Text | Google Scholar

© 2021 Messawa et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/75357>*