Review / Derleme

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The letrozole use in reproductive medicine: Beyond aromatase inhibition - a comprehensive review

Üreme tıbbında letrozol kullanımı: Aromataz inhibisyonunun ötesi - kapsamlı derleme

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Abstract

Letrozole and other aromatase inhibitors are increasingly recognized as first-line ovulation induction (OI) medications, offering an efficient and physiologic approach to ovarian stimulation that enhances outcomes in reproductive medicine. By selectively inhibiting aromatase and maintaining lower peripheral estrogen levels, letrozole supports mono- or bi-follicular development while reducing the risk of supraphysiologic estradiol exposure seen with traditional gonadotropin regimens. These pharmacological characteristics have contributed to its expanding use not only in OI but also in various assisted reproductive technologies. To evaluate the clinical benefits, effectiveness, and safety of using letrozole in in vitro fertilization (IVF), in vitro maturation (IVM), and OI, with particular attention to reproductive outcomes, ovarian response, endometrial effects, cycle characteristics, and treatment-related adverse events. A comprehensive systematic search covering the period from December 2000 to November 2025 was conducted across major electronic databases including PubMed, Embase, the Cochrane Library, and Google Scholar. The search strategy incorporated predefined keywords related to letrozole, aromatase inhibition, OI, IVF, and IVM. Studies involving randomized controlled trials, observational cohorts, and meta-analyses were included, while non-clinical and non-reproductive data were excluded. Relevant outcomes were extracted and synthesized qualitatively. Letrozole demonstrates broad clinical utility in reproductive medicine, spanning assisted reproductive techniques, ovarian stimulation strategies, and the management of ovarian hyperstimulation syndrome risk, ectopic pregnancy, and endometriosis-related infertility. Its targeted estrogen suppression, cost-effectiveness, and favorable safety profile make it a valuable component of individualized treatment protocols. Nonetheless, further high-quality research is required to refine optimal dosing strategies, identify ideal patient populations, and clarify long-term reproductive and obstetric safety.

Keywords: Letrozole, assisted reproductive medicine, infertility, in vitro fertilization, in vitro maturation

Öz

Letrozol ve diğer aromataz inhibitörleri, giderek artan biçimde birinci basamak ovülasyon indüksiyonu (Oİ) ajanları olarak kabul edilmekte olup, üreme tıbbında sonuçları iyileştiren etkili ve fizyolojik bir over stimülasyon yaklaşımı sunmaktadır. Aromatazı selektif olarak inhibe ederek periferal östrojen düzeylerini düşürmesi, geleneksel gonadotropin protokollerinde görülen suprafizyolojik östradiol maruziyetini azaltırken, mono- veya bifolliküler gelişimi desteklemektedir. Bu farmakolojik özellikler, letrozolün yalnızca Oİ'de değil, çeşitli yardımcı üreme tekniklerinde de kullanım alanının genişlemesine katkı sağlamıştır. Letrozolün in vitro fertilizasyon (IVF), in vitro maturasyon (IVM) ve Oİ'deki klinik faydalarını, etkinliğini ve güvenlilik profilini değerlendirmek; özellikle üreme sonuçları, over yanıtı, endometriyal etkiler, siklus karakteristikleri ve tedaviye bağlı advers olaylara odaklanmak. Aralık 2000 ile Kasım 2025 dönemini kapsayan kapsamlı bir sistematik tarama, PubMed, Embase, Cochrane Library ve Google Scholar gibi temel elektronik veri tabanlarında gerçekleştirilmiştir. Arama stratejisinde letrozol, aromataz inhibisyonu, Oİ, IVF ve IVM ile ilgili önceden belirlenmiş anahtar kelimeler kullanılmıştır. Randomize kontrollü çalışmalar, gözlemsel kohortlar ve meta-analizler dahil edilmiş; klinik dışı ve üreme tıbbıyla ilişkili olmayan veriler dışlanmıştır. İlgili sonuçlar çıkarılmış ve niteliksel olarak sentezlenmiştir. Letrozol, yardımcı üreme tedavileri, over stimülasyon stratejileri ve yumurtalık hiperstimülasyon sendromu risk yönetiminden ektopik gebelik ve endometriozis ilişkili infertiliteye kadar geniş bir klinik kullanım yelpazesi göstermektedir. Hedefe yönelik östrojen baskılanması, maliyet etkinliği ve olumlu güvenlilik profili ile bireyselleştirilmiş tedavi protokollerinin değerli bir bileşenidir. Bununla birlikte, optimal dozlama stratejilerinin netleştirilmesi, ideal hasta gruplarının belirlenmesi ve uzun dönem üreme ile obstetrik güvenliğin aydınlatılması için daha yüksek kaliteli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Letrozol, yardımcı üreme tıbbı, infertilite, in vitro fertilizasyon, in vitro maturasyon

Introduction

Despite remarkable advancements in reproductive medicine, many conditions continue to limit treatment success and patients' quality of life. As the field increasingly moves toward individualized, physiology-based therapies, agents that modulate estrogen pathways while maintaining favorable safety profiles have gained renewed clinical relevance.

Targeted blockade of estrogen production is a cornerstone treatment strategy for estrogen-sensitive tumors; aromatase inhibitors have been used for this purpose[1]. It was then discovered, coincidentally, that a decrease in estrogen produces a feedback-driven increase in endogenous follicle-stimulating hormone (FSH) secretion, and that aromatase inhibitors were found to be strong ovulation inducers nearly two decades ago[2].

Letrozole, a non-steroidal oral third-generation aromatase inhibitor (AI), reversibly blocks the cytochrome P450 aromatase enzyme, a key enzyme in the biosynthesis of estrogens from androgens[1,3].

Legro et al.[2] published the first article on the use of letrozole as a sole ovulation-induction agent in 2004, and since then, letrozole has been used worldwide, even in the USA, where the Food and Drug Administration (FDA) disapproved the use of letrozole as an agent for infertility.

Although decades have passed since aromatase inhibitors were introduced in reproductive endocrinology, data remain fragmented across heterogeneous populations and diverse clinical scenarios. To accurately define the present role of letrozole and to anticipate its future place in reproductive practice, a comprehensive synthesis of current insights, clinical applications, and safety considerations is essential. In this review, we aimed to consolidate existing knowledge across all major domains of the use of letrozole, clarify areas of controversy, and provide clinicians with an updated, evidence-based framework for its responsible and informed application.

Methods

A comprehensive systematic search from 2000 to November 2025 was conducted in the databases PubMed, Embase, the Cochrane Library, and Google Scholar, using the following keywords: "in vitro fertilization" or "IVF", "in vitro maturation" or "IVM", "letrozole", "clomiphene citrate", "ovulation induction" or "OI", "ovarian hyperstimulation

syndrome" or "ovarian hyperstimulation syndrome (OHSS)", "ectopic pregnancy", "complications". The search strategy involved combining keywords using the Boolean operator 'AND'. After retrieving the related articles, the authors also evaluated the reference lists and citations for additional eligible data. All relevant articles were available in full text and English.

Inclusion Criteria

Regardless of study design, we included studies of letrozole for IVF, IVM, and OI. Articles comparing letrozole with clomiphene citrate, discussing letrozole-related complications, and addressing letrozole use for ectopic pregnancy were also retrieved.

Exclusion Criteria

Articles published before 2000 were excluded, except for selective references, to capture more recent data. Non-systematic reviews were excluded because of the risk of selection bias. Expert opinions and opinion-based papers were also excluded.

Data Collection and Analysis

Three review authors (MHD, AT and SH) independently checked for overlaps (duplications) among selected studies, assessed risk of bias, and extracted data.

Two Cell Two Gonadotropin Theory

Estrogen biosynthesis in the ovary is governed by the coordinated actions of theca and granulosa cells, as outlined in the "two-cell, two-gonadotropin theory." Ovarian steroidogenesis requires cooperative interactions between theca and granulosa cells, which are mainly controlled by luteinizing hormone (LH) and FSH. Falck first demonstrated the ovary as the site of estrogen production in rat microtransplantation studies[4]. Short[5] later proposed that theca cells convert progesterone to estrogens, further supporting this model.

According to this theory, LH stimulates theca cells to produce androgens, while FSH promotes aromatization of these androgens into estrogens within granulosa cells. Aromatase (CYP19), localized predominantly in granulosa cells, catalyzes this conversion, whereas 17α-hydroxylase (CYP17A1) is confined to the theca compartment, confirming functional specialization[6,7].

During follicular development, theca cells express LH receptors, P450scc (CYP11A1), and 3β-HSD, enabling cholesterol transport and conversion to pregnenolone. Androgen synthesis progresses via CYP17A1, and these androgens diffuse into granulosa cells, where FSH-dependent aromatase converts them into estrone and estradiol[7,8]. Rising estradiol exerts negative feedback on pituitary gonadotropin release.

FSH remains essential for early folliculogenesis, whereas LH supports terminal follicle maturation by increasing androgen substrate availability, enhancing dominant follicle selection, and promoting atresia of smaller follicles[9].

Aromatase Enzyme Activity; Both Sides of Reaction and Implications of Inhibition

Aromatase, an enzyme that catalyzes the demethylation of carbon-19 from androgens to produce phenolic 18-carbon estrogens, is a member of the cytochrome P450 superfamily. This superfamily includes more than 480 members and is the product of the *CYP19* gene. This reaction, catalyzed by aromatase, occurs mainly in the ovary[10]. Its expression in granulosa cells is regulated by cAMP and gonadotropins[11].

Letrozole competitively binds to aromatase due to structural similarity to androgen substrates, suppressing estrogen synthesis by up to 99%[12,13]. Reduced estradiol relieves negative feedback on gonadotropin-releasing hormone (GnRH), increasing FSH secretion and enhancing follicular recruitment[14].

Inhibition of aromatization increases intraovarian androgens, which support early follicular growth by stimulating granulosa-cell mitosis and FSH-receptor expression[15,16]. While moderate androgen exposure promotes folliculogenesis, excessive androgen levels in late follicular stages may induce atresia[17].

Aromatase is also expressed in extragonadal tissues, including adipose tissue, bone, brain, and vascular endothelium, contributing to systemic estrogen production[18]. Consequently, aromatase inhibition has therapeutic applications beyond reproductive medicine.

Third-generation aromatase inhibitors such as letrozole, anastrozole, and exemestane suppress systemic estrogen levels by over 95%[19,20].

Clinical Applications Beyond Infertility

Hormone-sensitive Breast Cancer

Aromatase inhibitors are cornerstone therapies for postmenopausal women with estrogen receptor (ER)-positive breast cancer. By depriving cancer cells of estrogen, AIs reduce tumor proliferation and recurrence, and thus offer superior outcomes compared with selective ER modulators like tamoxifen[21].

Endometriosis Management

Endometriosis, the expression and growth of endometrial tissue (both glands and stroma) outside the uterus, is associated with greatly increased aromatase activity compared with eutopic endometrium. Estrogen dependence in endometriotic lesions makes aromatase inhibition a promising approach. Studies have reported reduced lesion size and symptomatic relief in women treated with letrozole or other agents. This is particularly the case when combined with GnRH agonist suppression of ovarian estradiol production[22,23].

Bone Health: While the reduction in systemic estrogen levels seen with long-term AI use, commonly prescribed

for ER-positive cancers, poses a risk of loss of bone mineral density, concurrent use of bisphosphonates or selective ER modulators can mitigate this side effect[24].

Research into the combination of aromatase inhibitors with other therapeutic agents holds promise for enhancing efficacy and reducing resistance. For instance, combining AIs with selective ER degraders or targeted molecular therapies is under investigation for advanced breast cancer[25].

In reproductive medicine, tailoring AI protocols based on individual ovarian reserve markers and genetic predispositions could optimize outcomes and minimize adverse effects[26]. Large doses of letrozole, up to 20 mg daily, have been used to induce multifollicular development in women with decreased ovarian reserve undergoing IVF, resulting in significant cost savings compared with gonadotropins[27].

Although aromatase inhibitors are generally well-tolerated, clinicians must remain vigilant regarding potential adverse effects, including musculoskeletal pain, hot flashes, and lipid profile alterations[28]. Monitoring and individualized patient management are essential to balance therapeutic benefits against risks.

Aromatase Inhibitors and Their Clinical Use

The development of AIs began with first-generation agents such as aminoglutethimide, which inhibited not only aromatase but also enzymes involved in the synthesis of cortisol, aldosterone, and thyroid hormones[29]. Fadrazole, a more potent and selective inhibitor than aminoglutethimide, was approved in Japan for estrogen-dependent postmenopausal breast cancer, but was never marketed in the United States[30]. Formestane, a steroidal aromatase inhibitor, significantly reduces circulating estrogen levels and demonstrates antitumor activity in postmenopausal women with breast cancer. Its side-effect profile is more favorable than that of aminoglutethimide[31,32]. Currently, three third-generation oral aromatase inhibitors—anastrozole, letrozole, and exemestane—are FDA-approved for the treatment of hormone-receptor-positive breast cancer in postmenopausal women. Large clinical trials have shown that AIs are generally more effective and better tolerated than tamoxifen, with superior response rates and longer time to progression[33,34]. These third-generation agents exhibit high selectivity for aromatase with minimal cross-reactivity[35].

Exemestane, the only steroidal oral AI, is widely used, particularly in combination with everolimus, for human epidermal growth factor receptor 2-negative, hormone-receptor-positive advanced breast cancer[36]. Exemestane is an active, well-tolerated third-line hormonal therapy for postmenopausal patients with advanced breast cancer who do not respond to standard first- and second-line hormonal therapies[37]. Comparative studies among exemestane, anastrozole, and letrozole have shown comparable efficacy[38,39]. Notably, all three AIs demonstrated superior efficacy to the ER antagonist tamoxifen in large head-to-head clinical trials for the treatment of postmenopausal estrogen-dependent breast cancer[34]. Vorozole was evaluated in Europe and Canada, but never received FDA approval[39].

Letrozole, an oral non-steroidal aromatase inhibitor, lowers estrogen levels in postmenopausal women by inhibiting cytochrome P450 aromatase, the enzyme that converts testosterone to estrogen. It does not stop the production of estrogen in the ovaries. It decreases the growth of hormone-receptor-positive breast cancer cells by reducing the amount of estrogen[40,41].

Letrozole: Molecular Structure and Mechanism of Action

Letrozole (code name: CGS-20267), a non-steroidal type II AI with a triazole ring, enables high-affinity, reversible binding at the aromatase substrate site[42]. With each successive generation, AIs have become increasingly powerful and specialized. Letrozole has the chemical formula C17H11N5 (illustrated in Figure 1) and a molecular weight of 285.31 g/mol[43]. Due to its favorable pharmacokinetic profile, letrozole can inactivate more than 98% of peripheral aromatase even at low daily doses of 0.5-2.5 mg[44]. It is rapidly absorbed with nearly 100% bioavailability, is 60% protein-bound (primarily to albumin), has a 42-hour half-life, and is hepatically metabolized to an inactive carbinol derivative that is excreted renally.

Letrozole competitively inhibits the aromatization of androstenedione and testosterone into estrone and estradiol,

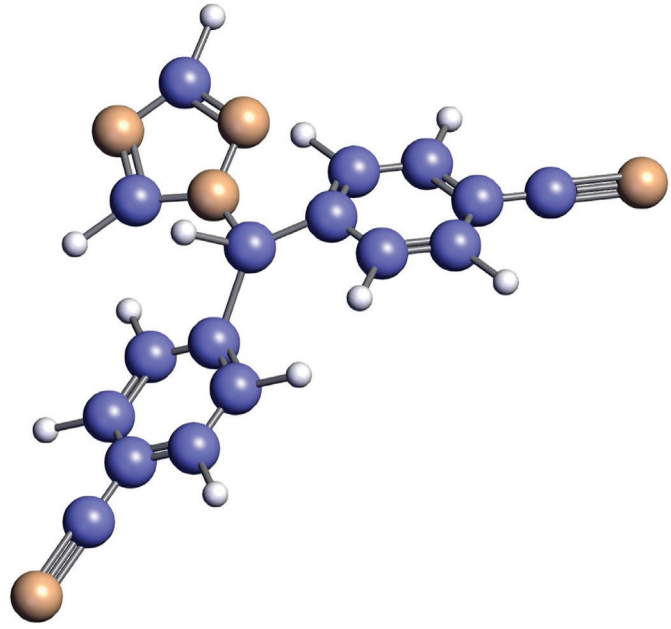

Figure 1. Chemical formula of letrozole (C17H11N5)

This figure illustrates the 3D ball-and-stick representation of letrozole, a non-steroidal aromatase inhibitor characterized by a triazole ring and substituted benzene moieties. The spatial configuration highlights key functional groups responsible for its high-affinity, reversible binding to the aromatase enzyme, underpinning its potent estrogen-suppressive activity

respectively. This inhibition creates a biochemical shift toward increased androgens and decreased estrogens. Its triazole structure coordinates to the heme iron of aromatase, effectively blocking hydroxylation reactions essential for aromatization and thereby achieving high potency and specificity[45].

Reduced estrogen levels remove negative feedback on the hypothalamic-pituitary axis, resulting in increased FSH secretion and stimulation of follicular development[46]. Increased intraovarian androgens further enhance follicular sensitivity to FSH and insulin-like growth factor-1 signaling. Because letrozole does not antagonize ERs in the brain, normal endocrine feedback resumes once the drug is cleared, promoting monofollicular development and reducing the risk of multifollicular development[47].

Decreased estrogen levels in the circulation and peripheral tissues, resulting from potent aromatase inhibition by letrozole, cause upregulation of ERs in the endometrium. Therefore, when estrogen secretion is restored, rapid endometrial growth is observed[48]. This is necessary for healthy implantation.

Letrozole Versus Clomiphene Citrate

Letrozole has been widely used for OI since 2001[43]. It suppresses estrogen synthesis, leading to compensatory increases in FSH, without exerting anti-estrogenic effects on the endometrium or the cervical mucus. Its short half-life (~48 hours) ensures rapid clearance letrozole also has proven reversible effects in postmenopausal breast cancer therapy[44]. Clomiphene citrate (CC), a selective ER modulator introduced in 1961, has long been used for OI in polycystic ovary syndrome (PCOS) and in intrauterine insemination (IUI) and IVF treatments[49]. By competitively binding to ERs, CC removes estrogen's negative feedback, thereby increasing gonadotropin secretion and follicular growth. However, CC exerts anti-estrogenic effects on endometrial development and cervical mucus, contributing to lower pregnancy rates despite adequate ovulation[50]. ER depletion in the endometrium leads to endometrial thinning in 15-50% of patients on CC treatment[51,52].

Many studies—including meta-analyses—show higher pregnancy and live-birth rates with letrozole. Fixed-dose study designs, however, limit some analyses. Letrozole has also been evaluated in normo-ovulatory women, showing favorable outcomes[53,54].

Letrozole's advantages include rapid elimination, the absence of endometrial ER depletion, and lower estradiol levels, despite similar numbers of preovulatory follicles. Letrozole-stimulated cycles typically avoid the supraphysiological E2 levels seen with CC[55]. Mitwally et al.[56] reported that pregnancies conceived after letrozole had miscarriage and ectopic rates similar to those in other stimulation groups, and that patients treated with letrozole had lower multiple gestation rates. Formun AltıMultifollicular development is common during CC treatment, and the risk of multiple gestation is increased to approximately 10-20% overall, compared with natural cycles.

Letrozole also appears to preserve endometrial receptivity better than CC. Experimental studies show that CC—but not letrozole—reduces key implantation markers, such as HOXA10 and integrin αvβ3[57]. Molecular studies further suggest that letrozole improves endometrial gene expression in PCOS, thereby making letrozole an alternative to CC[58].

Some evidence suggests increased aromatase activity in PCOS, potentially enhancing responsiveness to letrozole[59,60]. In unexplained infertility, letrozole improves endometrial thickness compared with CC, but results in similar pregnancy and miscarriage rates[61]. Additional studies indicate superior endometrial receptivity markers in PCOS treated with letrozole[62,63]. Letrozole is consistently associated with higher pregnancy rates, shorter time to conception, and a lower risk of multiple pregnancy due to monofollicular development.

Letrozole is also recommended for CC-resistant PCOS[64]. and may offer an effective alternative to CC-gonadotropin combinations in controlled ovarian hyperstimulation[65]. Mejia et al.[66] showed that the combination of letrozole and CC was associated with a higher ovulation rate than letrozole alone in women with infertility and PCOS. This therapy may be an alternative low-risk, low-cost infertility treatment that improves ovulation rates.

For unexplained infertility, heterogeneity across studies and patient populations limits the ability to draw firm conclusions; meta-analyses show no consistent difference between letrozole and CC[67].

Letrozole Use in Ovulation Induction

Letrozole has been widely used as an OI agent for over two decades. As an aromatase inhibitor, it blocks the conversion of androgens to estrogens, thereby relieving the hypothalamic-pituitary axis of estrogen-mediated negative feedback. This mechanism increases endogenous gonadotropin secretion while preserving endometrial receptivity, thereby distinguishing letrozole from traditional agents such as CC. The ability of letrozole to avoid antiestrogenic effects on the endometrium confers a significant clinical advantage over CC.

Its efficacy has been demonstrated in multiple randomized controlled trials and meta-analyses, which report superiority, or at least non-inferiority, to CC with respect to ovulation and pregnancy outcomes, as well as reduced multiple pregnancy rates and improved live birth rates[66].

Letrozole is now considered the first-line OI agent for women with PCOS, following the pivotal multicenter randomized controlled trial by Eskew et al.[67], which demonstrated significantly higher live birth rates than CC. In unexplained infertility, the combination of letrozole with IUI yields pregnancy rates comparable to CC but with fewer adverse effects.

Letrozole has also shown benefit in women with minimal-to-mild endometriosis by reducing estrogen-driven endometriotic activity and enhancing ovarian response[68]. In addition, recent evidence suggests potential utility in women with diminished ovarian reserve, in whom its ability to stimulate follicular recruitment without excessive estrogen exposure may offer a more physiological and tailored approach[69,70].

Letrozole Use in In Vitro Fertilization

Modified natural IVF (Mona-IVF) is a form of natural IVF in which follicle growth is augmented either with oral agents alone or together with parenteral drugs. Spontaneous ovulation can be suppressed or serum LH monitored without suppression, then final oocyte maturation is usually triggered by human chorionic gonadotropins.

CC and letrozole can only be used in a modified natural manner or as an adjunct to gonadotropin therapy for OI as a co-treatment in ovulatory and anovulatory patients in IVF protocols when ovarian function is present[71]. Advantages of Mona-IVF include fewer injections, reduced treatment burden, fewer side effects, reduced stress, and substantially decreased OHSS risk[13].

Letrozole promotes follicular development via aromatase inhibition, increasing intraovarian androgens that may upregulate FSH receptors and improve ovarian responsiveness-an effect particularly relevant for poor responders[72-74]. Its ability to maintain physiologic estradiol levels also makes it suitable for breast cancer patients who require controlled estrogen exposure during the IVF process.

Letrozole has also been used for endometrial preparation, resulting in physiologic serum estradiol levels and favorable endometrial morphology[75,76]. As proposed in a recent publication of Aydin et al.[77], letrozole may, due to its mechanism of action and its ability to enable formation of a corpus luteum, even be considered a first choice compared with natural and programmed cycles in various clinical scenarios. These features make letrozole useful for assisted reproductive techniques (ART).

Letrozole can be effectively used for OI in IVF cycles across different infertile populations, including patients with a poor ovarian response[71,78-80], patients with PCOS[81,82], patients with unexplained infertility[83], and women with contraindications to stimulation drugs. A recently published meta-analysis reported no difference in the number of oocytes retrieved [p=0.72, 95% confidence interval (CI): -0.41 to 0.60] or in the clinical pregnancy rate (CPR) (p=0.39, 95% CI: -0.02 to 0.06) between letrozole co-treatment and conventional IVF. However, subgroup analysis of five studies (n=526) involving patients with poor ovarian reserve revealed significantly higher live birth rates favoring letrozole, with a risk difference of 0.07 (p=0.03, 95% CI: 0.01 to 0.13)[84].

Letrozole can also be added to gonadotropins continuously throughout the ovarian stimulation period, with the aim of normalizing the disrupted endocrine milieu and reducing excessive estradiol levels resulting from multiple follicular development, particularly in patients with hormone-dependent breast cancer[85].

Letrozole Use in Modified Natural Fet Cycles (Mona-FET)

Freeze-all strategies are beneficial for patients at high-risk of OHSS, particularly patients with PCOS, and permit optimization of embryo transfer timing while maximizing cumulative live birth rates[86]. Endometrial preparation for FET can be performed via full natural cycle, modified natural cycle, or artificial cycle with hormone-replacement therapy (HRT)[87,88].

Although HRT cycles were previously dominant, natural[89] and modified natural approaches have gained preference due to more physiological hormonal profiles and reduced thromboembolic and hypertensive risks[90].

Full natural cycles require detection of the LH peak and have limited scheduling flexibility. Modified natural cycles address this by triggering ovulation with human chorionic gonadotropin (hCG), thereby providing improved timing control and a reduced monitoring burden.

Letrozole may be used alone or with gonadotropins in Mona-FET cycles, achieving adequate endometrial thickness (>7 mm) and preserving endometrial receptivity[75,76]. Letrozole-induced cycles have shown improved clinical pregnancy rates and live-birth rates compared with artificial cycles and gonadotropin-based preparations[82]. Several studies report that letrozole priming achieves outcomes comparable to natural cycles without adverse maternal or perinatal effects[91]. Tatsumi et al.[92] reported improved CPR and live birth rate (LBR) following frozen blastocyst transfers using letrozole compared with natural cycles.

In patients with PCOS, observational and propensity-score-matched analyses show that letrozole-FET improves CPR and LBR, reduces miscarriage rates, and lowers the incidence of hypertensive disorders and gestational diabetes compared with HRT. Endometrial thickness and morphology appear comparable to those in natural cycles, with potentially increased integrin expression[93].

Letrozole Use for Fertility Preservation

Letrozole is widely used in cancer patients undergoing oocyte cryopreservation due to its ability to suppress estradiol levels during controlled ovarian stimulation (COS). Studies have shown that adding letrozole to COS protocols reduces luteal-phase progesterone and estradiol levels, which is desirable in ER-positive breast cancer[94,95].

A French study reported comparable numbers of cryopreserved oocytes in COS with and without letrozole, and significantly lower luteal progesterone and estradiol levels in the letrozole group[96].

The letrozole-triggered decrease in the post-ovulatory peak serum concentration of estradiol is the desired effect in

women with breast cancer undergoing fertility preservation to diminish the risk of cancer recurrence. Whether to choose a COS protocol with letrozole in such patients depends on the growing evidence regarding the long-term safety of estrogen modulation and its benefits for cancer patients in terms of cancer recurrence rates[97].

An Italian study showed that letrozole significantly altered follicular steroid profiles; however, insufficient pregnancy outcome data prevented definitive conclusions regarding oocyte competence[98].

Use of letrozole for cryopreservation does not limit the risk of OHSS, and caution should be exercised, especially in cancer patients, to avoid delaying chemotherapy. The role of letrozole in fertility preservation in patients with gynecological malignancies remains unknown, but its efficacy for ovarian stimulation in patients with ovarian cancer has been described in case reports[99,100].

Letrozole Use in In Vitro Maturation

Compared to other uses mentioned above, the use of letrozole in IVM is a relatively recent approach, and the results of letrozole-primed IVM are promising. Rose[101] published the first paper on the use of letrozole-primed IVM. In their retrospective non-inferiority study, they compared letrozole-primed IVM with FSH-hCG-primed IVM and reported that letrozole-primed IVM can be used for IVM cycles in a more patient-friendly manner.

Hatırnaz et al.[102] reported a second paper on letrozole priming in IVM; in their study, they used letrozole-primed IVM in women with PCOS cancer phobia, and oocyte maturation abnormalities (OMAS). Their work led to the first live births following letrozole-primed IVM in patients with OMAS[103]. In the review by Rose and Brown[13] in 2020, the authors questioned whether letrozole use is optimal. In that paper, the benefits of letrozole use were extended.

Emerging observations suggest that IVM may serve as a dynamic platform for exploring maturation competence in women with OMAS-related mutations. These insights have driven the development of two innovative therapeutic concepts. The first involves letrozole-primed IVM combined with growth hormone supplementation, which is applied both *in vivo* and in the culture environment to support maturation in individuals with empty follicle syndrome, reactive oxygen species, mixed ovarian endometrioma (OMA), or poor embryo development. The second approach is designed for patients who demonstrate maturation only under stimulated conditions: a stimulated IVF cycle with adjunctive growth hormone is followed by an IVM-based laboratory protocol, where the addition of growth hormone to the culture medium appears essential. This letrozole-growth hormone strategy aims to recapitulate physiologic follicular signaling. Early experience indicates that the strategy is potentially applicable even to PCOS patients and yields high-quality blastocysts suitable for cryopreservation.

Letrozole Use for OHSS Prevention

OHSS is a potentially serious iatrogenic complication in ART cycles[104].

It typically arises after hCG administration for final oocyte maturation and is associated with substantial morbidity[105]. The clinical manifestations of OHSS, regardless of trigger type[106], include ascites, pleural effusion, electrolyte imbalance, venous thromboembolism, and significantly enlarged ovaries driven by cytokine-mediated vascular permeability changes, primarily mediated by vascular endothelial growth factor (VEGF)[107].

Based on symptom severity, the American Society for Reproductive Medicine classifies OHSS as mild, moderate, or severe[108]. Although treatment strategies exist, prevention remains the cornerstone of clinical management[109].

Elevated estradiol levels correlate strongly with OHSS risk; when E2 exceeds 6.000 pg/mL, the OHSS rate may reach 38%[110,111]. Because letrozole lowers circulating estrogen by inhibiting aromatase, it has been explored as a prophylactic agent in high-risk cycles.

Multiple studies evaluated letrozole at varying doses during the luteal phase. Fatemi et al.[112] demonstrated significant suppression of estrogen levels with 5 mg daily, whereas others observed similar reductions with 2.5 mg daily[113]. He et al.[114] found that higher doses (7.5 mg) more effectively reduced E2 and VEGF levels and lowered the incidence of early-onset OHSS compared with lower doses. However, contradictory findings exist: Haas et al.[115] reported elevated intrafollicular VEGF in letrozole cycles.

A systematic review concluded that letrozole reduces total and moderate-to-severe but does not significantly prevent individual categories of OHSS[116]. A recent Cochrane review found OHSS rates similar between letrozole and selective ER modulators[54].

While promising, letrozole has not yet been incorporated into major guidelines and is not considered first-line for OHSS prevention[117].

Letrozole Use for Ectopic Pregnancy

Laganà et al.[118] conducted a nonrandomized trial in 42 women with tubal ectopic pregnancies, comparing letrozole, methotrexate (MTX), and salpingectomy. Letrozole (5 mg/day for 10 days) demonstrated a success rate of 86%, equivalent to that of MTX. The decline in β-hCG appeared faster with letrozole, but the difference was not statistically significant. Unlike MTX, letrozole did not affect hematologic parameters and had minimal systemic adverse effects.

Additional small studies have similarly reported that β-hCG decline with letrozole is comparable to, or faster than, that with MTX, with no significant pre-treatment differences in β-hCG among groups[118-120].

Alabiad et al.[121] compared 5 mg for 5 days, 10 mg for 10 days, and laparoscopic salpingectomy. The 10 mg/10-day

regimen was significantly more effective in resolving ectopic pregnancy.

In a randomized controlled study, MTX plus letrozole for 5 days was compared with letrozole for 10 days. It was observed that 10-day use resulted in a greater reduction in β-hCG levels, but no difference in treatment success was observed between MTX and letrozole[122].

A systematic review and meta-analysis by Tarafdari et al.[123] concluded that letrozole is an effective and potentially safer alternative to MTX in the medical management of ectopic pregnancy.

Letrozole Use for Endometriosis

Endometriosis is a chronic, neuro-inflammatory disorder affecting approximately 10% of reproductive-aged women and is associated with dysmenorrhea, chronic pelvic pain, dyspareunia, irregular bleeding, and infertility[124]. Despite a variety of medical and surgical treatment options, recurrence rates remain high[125]. Because the disease is estrogen-dependent, aromatase inhibitors such as letrozole have emerged as potential therapeutic alternatives capable of reducing both systemic and lesion-derived estrogen production[126]. This approach offers an additional therapeutic avenue for patients who do not achieve adequate symptom control with standard hormonal regimens.

Clinical evidence indicates that letrozole substantially reduces endometriosis-associated pain, particularly when combined with progestins. Early work demonstrated that the combination of letrozole and norethindrone acetate produced meaningful reductions in pelvic pain and regression of visible lesions[127]. Subsequent data confirmed that letrozole combined with norethisterone acetate is superior to norethisterone acetate alone in alleviating pain[128], and a systematic review found that administering 2.5 mg of letrozole daily for six months effectively reduced pain severity in most patients[129]. While the overall impact on lesion volume has been variable across studies[129], more focused investigations suggest benefits in particular subgroups. For instance, a randomized trial reported that letrozole, administered in combination with either GnRH agonists or progestogens, significantly reduced the size of rectovaginal nodules[130]. Additional biological support for lesion modulation was provided by studies demonstrating that the combination of letrozole and dydrogesterone decreases expression of angiogenic and growth factors[131].

In the context of endometriosis-associated infertility, letrozole is a well-established OI agent and, alongside clomiphene citrate, is considered a first-line option in patients with minimal-to-mild disease prior to IVF[132,133]. Multiple studies suggest that letrozole may offer superior reproductive outcomes compared with clomiphene in this population, contributing to a growing expert consensus in its favor. Letrozole-based ovarian stimulation protocols have also demonstrated advantages in IVF cycles. Kim et al.[134] showed that letrozole combined with gonadotropins maintained lower estradiol levels while producing similar oocyte and embryo yields compared with conventional stimulation, and a double-blind randomized trial reported that adding letrozole reduced gonadotropin requirements and estradiol levels without compromising pregnancy rates[135]. Further, combining letrozole with GnRH agonists may provide enhanced reproductive outcomes in more advanced disease stages. For example, co-treatment with letrozole and leuprolide acetate improved clinical pregnancy and live-birth rates in women with OMAs[23]; similar benefits were observed in stage I-II endometriosis[136]. Collectively, these findings suggest that integrating peripheral aromatase inhibition with central ovarian suppression may offer a synergistic benefit for selected patients undergoing fertility treatment.

Complications Related to the Use of Letrozole

Letrozole is generally considered a well-tolerated and patient-friendly medication. Commonly reported adverse effects include mild headaches, fatigue, cramps, and dizziness, which are typically less severe than those associated with clomiphene citrate[2].

Like other OI agents, letrozole remains associated with multiple pregnancy, a major complication in OI cycles. Although twin pregnancies are the most common, triplet and higher-order gestations are also reported[137]. Close cycle monitoring and cycle cancellations to avoid extreme gestations would be mandatory, especially for patients with a history of multifollicular development or unresponsiveness to the standard dosage (5 mg/day)[138]. Supporting this, reports indicate that letrozole dosage correlates with complications. The Best results are obtained with 5 mg/day. When the dosage is 2.5 mg/day, fewer complications and no cyst formation are reported. When the dose is 7.5 mg/day (administered because of no response to lower doses), it helps induce ovulation and conception but is associated with increased cyst formation in 3.7% of cycles[139].

Letrozole is not associated with an increased risk of OHSS compared with CC[140]. Estradiol >3.500 pg/mL indicates elevated OHSS risk[141]; however, high estradiol alone does not induce OHSS[142,143]. Meta-analysis shows no significant OHSS reduction with letrozole alone, therefore, it should not be considered as the first-line treatment for prevention[116]. Letrozole promises benefits in combination regimens[144].

Another issue to be taken in to consideration for drug safety is teratogenicity Although aromatase inhibitors—particularly letrozole—are approved for breast cancer treatment and prevention, they are widely used off-label for OI. In 2005, a study comparing 150 infants conceived with letrozole to 36,005 controls reported methodological limitations, yet suggested increased cardiac and skeletal anomalies[145], prompting the manufacturer to advise against letrozole use in premenopausal women. However, a 2006 Canadian study of 911 newborns conceived after letrozole or CC found

no difference in the rates of major or minor congenital malformations[146]. More recent data evaluating infertility drugs similarly found no association between letrozole and teratogenicity[147]. Thus, despite its oncological origin, letrozole continues to be considered safe for use in infertile patients.

Conclusion

Letrozole has evolved from a breast cancer therapy into a versatile agent with broad applications in reproductive medicine. Its unique ability to selectively inhibit aromatase and modulate estrogen-dependent pathways provides therapeutic advantages in diverse clinical scenarios, ranging from OI and COS to endometrial preparation, fertility preservation, and the management of complex reproductive conditions. Evidence supports its efficacy as a first-line OI agent, particularly in women with polycystic ovary syndrome, and a growing body of evidence demonstrates its usefulness in IVF protocols by reducing gonadotropin requirements, maintaining physiologic estradiol levels, and improving outcomes in selected patient populations. Its estrogen-suppressive capacity also offers potential benefits for reducing the risk of OHSS, treating ectopic pregnancy, and managing endometriosis-related pain and infertility, especially in combination regimens.

Across indications, letrozole is generally well tolerated, with a favorable side-effect profile compared with other hypoestrogenic therapies. However, optimal dosing strategies, ideal treatment combinations, and the long-term consequences of extended aromatase inhibition remain areas of active investigation. Future research should aim to refine individualized treatment algorithms, identify patient subgroups most likely to benefit from letrozole-based approaches, and clarify long-term safety, particularly regarding bone health and metabolic effects.

In summary, letrozole represents a safe, adaptable, and clinically valuable tool within reproductive medicine. As mechanistic insights deepen and evidence from large-scale randomized trials continues to accumulate, letrozole is poised to become an increasingly integral component of personalized treatment strategies, ultimately improving reproductive outcomes and quality of life for a wide range of patients.

Footnotes

Authorship Contributions

Concept: G.A., Ş.H., M.D., Design: G.A., Ş.H., M.D., Data Collection or Processing: G.A., Ş.H., E.S.H., M.B.Ç., M.C., S.L.T., Analysis or Interpretation: Ş.H., M.B.Ç., M.C., S.L.T., A.U., M.D., Literature Search: G.A., Ş.H., E.S.H., M.B.Ç., M.A., N.D.G., O.G., M.A.M., A.U., S.E., Ö.T., A.B., E.Y., B.K., H.G., N.G., P.K., Z.Y., G.M.B., A.İ.T., R.S., N.T., A.T., M.C., S.L.T., O.H., M.D., Writing: G.A., Ş.H., E.S.H., M.B.Ç., M.A., N.D.G., O.G., M.A.M., A.U., S.E., Ö.T., A.B., E.Y., B.K., H.G., N.G., P.K., Z.Y., G.M.B., A.İ.T., R.S., N.T., A.T., M.C., S.L.T., O.H., M.D.

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