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Use of Letrozole in Ovarian Stimulation in Vitro Fertilization

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ABSTRACT

Background: Letrozole is a medication that alone or combined with clomiphene citrate has been used for ovarian stimulation in women undergoing IVF. The objective of this narrative review is to investigate in the recent literature what are the main findings related to the use of letrozole in ovarian induction in human reproduction.

Methods: The search strategy was to use the keywords letrozole and ovarian stimulation and in vitro fertilization in the PubMed database in the last five years in free-text articles.

- Results-62 articles were found that applying the eligibility criteria were selected for this narrative review 12 articles.
- Results-The main findings of this study include information about the author, year, country, study design, number of participants, and more findings of each of the papers selected for this narrative review.

Conclusion: Although letrozole is a low-cost and safe medication for women, widely used in ovarian stimulation with benefits in endometrial receptivity, clinical results such as pregnancy rate and a number of live births still need large randomized trial studies.

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Introduction

In 2001, the first pilot study was published with the clinical use of Letrozole for ovulation induction in humans, reporting a high ovulation rate in women with Polycystic Ovary Syndrome (PCOS) [1]. In 2014 a study published by Legro et al showed that Letrozole was a more effective drug than clomiphene citrate when applied in this population. Since then, the use of Letrozole has been increasingly popularized in human reproduction, and its clinical effects and mechanisms of action are increasingly being studied [2,3].

Better-designed studies, with a larger number of participants and more recent ones, have already shown the safety of its use, maintaining rates similar to clomiphene citrate, for example, about rates of chromosomal abnormalities, congenital malformations, or poor outcomes in pregnancy or neonatal, and also similar to the general population without any infertility treatment [4]. Another reason for peace of mind, regarding possible teratogenic effects, lies precisely in the fact that Letrozole has a short half-life, of approximately 45h, which virtually ensures that, at the time of implantation of the embryo, the drug has already been completely metabolized and cleared from the maternal organism [3].

Currently, Letrozole has been widely used to induce ovulation in anovulatory patients with infertility and to "enhance" follicles in women who habitually ovulate. In addition, Letrozole can be used as an adjunct to intrauterine insemination and In Vitro Fertilization (IVF)/ Intracytoplasmic Sperm Injection (ICSI). It has also been widely used for cycles of controlled ovarian stimulation in cases of fertility preservation in women with estrogen-sensitive tumors (especially breast cancer). In addition, studies have also shown the effectiveness of letrozole in preparing the endometrium for frozen-thawed embryo transfer [5-8].

Therefore, the objective of this article was to verify in recent literature the benefits of using letrozole in ovarian stimulation in in vitro fertilization.

Methods

Study Design

This research is characterized as an integrative, documentary review, focusing on the specialized literature on letrozole in ovarian stimulation in patients participating in IVF and its impacts on assisted reproduction. This type of study is used to synthesize clinical findings from scientific studies of a specific topic. It provides updated knowledge for possible application in medical practice. Using research databases in the case of PubMed, information is identified, selected, analyzed, and synthesized. The knowledge imparted by the general conclusion of the study

enables the enhancement of patient care and improvement in the professional routine [9].

Eligibility Criteria

For this review, articles were included if published in peer-reviewed journals in English, from January 1, 2018, to December 31, 2022, and if available as free full texts. Gray literature works were excluded, including term papers, dissertations, and theses. Sixty-two articles were identified in PubMed and the following inclusion factors already mentioned above were applied the exclusion factors at first after reading the title and abstract were as follows, the first exclusion factor was articles that were not in line with the theme of letrozole and ovarian stimulation in IVF in which n = 37 articles were excluded and a second exclusion factor was texts in PubMed that did not have access to free full text with an = 7 articles. So, there are 17 articles left for reading the full text. Then another exclusion factor was applied after reading the full text, which did not contemplate the objective of this narrative review n = 7, leaving a total of 12 articles that were included in this narrative review (Figure 1).

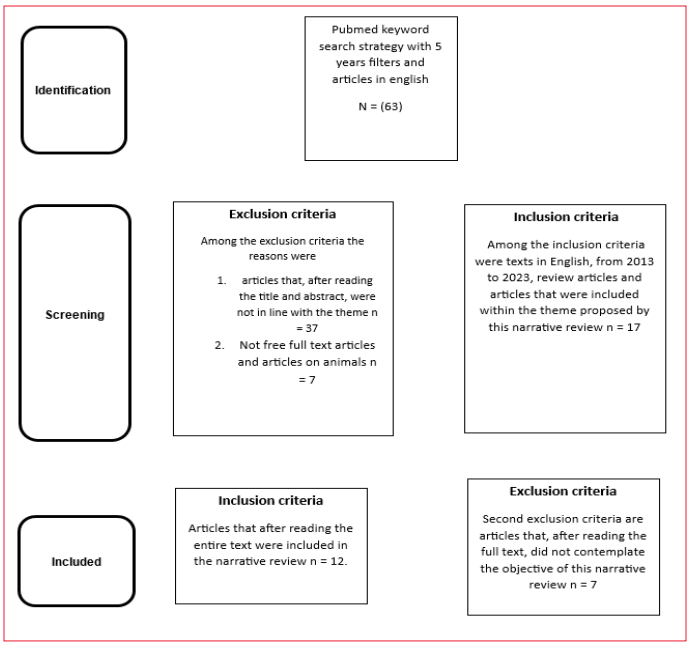

Figure 1: Flow Chart of Inclusion and Exclusion Criteria

Search Strategy

In the case of this search strategy, the keywords "letrozole" "ovarian stimulation" and "in vitro fertilization" were searched only in one database, the most important in terms of health, the PubMed Medline database. The following filters were applied, dates from 10 years ago and texts in English, Spanish, and Portuguese. The reviewers independently assessed the titles, abstracts, and full texts of the selected articles. Disagreements over article selection and data extraction were resolved by general consensus. In the end, the reviewers checked all the previously extracted information. Microsoft® Excel 2016 was used to create the data extraction form and summarize the findings. The articles selected for the narrative review were the following: A multicentre, randomized, double-blinded, placebo-controlled trial conducted in Denmark and published in the journal Human Reproduction in 2022, another work from Iran also published in 2022 and with the study design of a randomized clinical trial, an Australian work published in Fertility and Sterility from 2022 being a review article, an Italian retrospective article from 2022, another Danish study from 2022 Randomized, double-blinded placebo-controlled trial, another work done in China from 2021 which is a mini-review, a Chinese study from 2019 being a randomized parallel controlled study, another work done in China from 2021 is a retrospective study, a review from 2021 from the United States from America and another work carried out in Iran from 2019 being Randomized clinical trial and a 2022 work from Taiwan being a retrospective study, a recent work from 2023 carried out in US from 2023 being an observational, retrospective cohort study was also included in this narrative review [3, 10-20].

Results

The results are described in Table 1, which has information about author, year, country, study design, number of participants and more findings of each of the papers selected for this narrative review (Table 1).

Table 1: Containing Information on Author, Year, Country of Study, Study Design, Number of Participants and Main Findings

Authors	Year	Country	Study Design	Number of Participants	Main Findings
Eftekhar	2019	Iran	Randomized clinical trial	100	Although adding letrozole to gonadotropin in normal responders reduces the total dose of gonadotropin, it does not improve the pregnancy outcomes
Yang	2019	China	Randomized clinical trial	130	letrozole supplementation could not reduce the incidence of premature progesterone rise during the late follicular phase in stimulated in vitro fertilization cycles in expected high responders, producing a harmful effect on the pregnancy outcome
Moini	2019	Iran	Randomized clinical trial	160	Adding 5 mg of letrozole to rFSH/hMG antagonist protocol may improve the IVF/ICSI cycle outcome in POR patients.
Carson and Kallen	2021	US	Review	-	IVF with the use of also letrozole may be considered a first-line treatment strategy in women older than 38 to 40 years
Liang	2021	China	retrospective study	112	In the group with the addition of letrozole plus clomiphene citrate in women called low responders, there was a higher rate of clinical pregnancy compared with the group of control women.
Yang	2021	China	Review		letrozole is more accessible and has fewer adverse side effects and lower cost than injectable gonadotropins. The clinical applications are still in the experimental stage, and researchers have not yet reached a consensus on the standardized scheme. It is expected that large clinical samples of RCT and mechanism research will provide evidence and clear guidance for clinical application.
Bulow	2022	Denmark	Randomized, double-blinded placebo-controlled trial	129	Letrozole versus placebo decreased oestradiol levels on the ovulation trigger day by 68%. The ongoing pregnancy rate was similar between the letrozole and placebo groups (31% vs 39%).
Hart	2022	Australia	Narrative review	-	It suggests that use of clomiphene citrate and letrozole reduces gonadotrophins but with no improvement in live birth rate.
Lin	2022	Italy	retrospective study	114	Cotreatment of CC and letrozole in mild stimulation may increase the high-quality oocyte ratio and yield comparable fertilization rate and pregnancy outcomes.
Pousel	2022	Denmark	Randomized, double-blinded placebo-controlled trial	31	Letrozole cotreatment significantly suppressed oestradiol (E2) concentrations in the follicular phase (area under the curve (AUC) 58% (95% CI [70%; _43%], P<0.001))
Zhang	2022	Italy	Retrospective study	252	However, letrozole may increase the rate of embryo implantation and may reduce the requirement for exogenous gonadotrophins and, consequently, the cost of an IVF treatment cycle
Martini	2023	USA	observational, retrospective cohort study	1737	In cycles that included orals, r-hFSH-alpha starting doses were lower and dose changes were fewer than with r-hFSH-alpha alone. Smaller dose adjustments facilitate individualized treatment with the goal of reducing the risks of multiple gestation, cycle cancellation, and ovarian hyperstimulation syndrome

Discussion

Among the articles selected for this narrative review, the vast majority of articles see benefits in the use of letrozole in ovarian stimulation for in vitro fertilization.

Yang et al. also in a randomized controlled trial verified whether 130 high responders with the use of letrozole as a co-treatment reduced supraphysiological estradiol levels and impact on progesterone making the endometrium more receptive [15]. It had results that although estradiol was reduced in the group with letrozole, progesterone was increased, and as a conclusion of the work he wrote that in high-responding women this can be harmful for pregnancy results.

Moini et al. in an RCT whose objective was to investigate the effectiveness of letrozole as a co-treatment to the conventional GnRH antagonist in poor responders in IVF, had the participation of 160 infertile women and results that despite the pregnancy rate being higher in the group with letrozole was not statistically significantly and therefore concluded that letrozole 5 mg plus recombinant FSH/hMG antagonist protocol may improve fertilization in poor responder patients [18].

Liang et al. in a retrospective study, compared conventional gonadotropin treatment with a group of women who took CC plus letrozole in high, normal, and poor responders [16]. The main results were that the clinical pregnancy rate in the high

responder group was similar, in the normal responder group it was also similar between the groups, and in the poor responder women, the pregnancy rate in the CC plus letrozole group had decreased results. Coming to the conclusion CC/LE deserves more recommendations as a responsible strategy in high responders due to advantageous pregnancy outcomes. For normal responders, the strategy needs to be considered with more comprehensive factors.

In a 2021 review of North American authors, Carson and Kallen discuss the diagnoses and treatments of infertility, stating that among its main causes are ovulatory dysfunction, male factor infertility, and tubal disease [17]. The authors discuss the uses of CC, letrozole, and gonadotropins in ovarian stimulation and IVF. They cite a 2018 Cochrane review involving nearly 3000 women comparing clomiphene vs letrozole and reaching similar conclusions regarding pregnancy rate, miscarriage rates, and multiple pregnancy rates. The authors conclude that for the treatment of ovarian stimulation, the drugs clomiphene citrate, letrozole, and gonadotropins or their combination are recommended for ovarian induction.

In the mini-review by Yang et al. the work focused on the knowledge, application, and mechanism of letrozole for infertile women. The authors are emphatic in citing the effectiveness of letrozole in preparing the endometrium and in ovarian stimulation [3]. Another important issue of the work is the citation that letrozole can be used alone or in combination with Clomiphene Citrate (CC). The current recommendation is that letrozole is the first line of treatment when treating women with Polycystic Ovaries (PCOS) and also WHO group II anovulatory patients [23,24]. Another advantage of letrozole is that its use can reduce multiple pregnancies and ovarian hyperstimulation syndrome, but the authors of this work emphasize that further studies are needed to confirm this hypothesis [25]. The articles concluded that letrozole has low cost, and fewer side effects but its exact physiological mechanisms are still unclear and more large randomized clinical trial studies are needed to provide more evidence and better guide clinical applications.

Lin et al. in a retrospective study investigated the comparison of groups of women who used the combination of CC plus letrozole with conventional treatment with the use of gonadotropins. The main results were that the treatment with CC plus letrozole had less oocyte retrieval, but a higher top-quality metaphase II oocyte ratio and a similar fertilization rate, concluding that the combination of CC and letrozole can lead to higher rates of fertilization and pregnancy in these patients from group 4 of POSEIDON [19].

In the study conducted in Denmark by Poulsen et al, 2022 the study question was what were the endocrine and paracrine consequences of co-treatment with letrozole during ovarian pregnancy and whether stimulation and follicular growth and recruitment are affected by comparing the use of letrozole with the placebo [14]. This work was a randomized controlled trial with 31 healthy, normal-responding women eligible for IVF treatment. The main results were that the use of letrozole cotreatment significantly suppressed oestradiol (E2) concentrations in the follicular phase (Area Under The Curve (AUC) 58% (95% CI [70%; 43%], $P<0.001$), and also had as an important result that the Follicle-Stimulating Hormone (FSH) was increased at stimulation day 5 in the LZ group ($P<0.05$). the co-treatment with letrozole, follicular recruitment was also increased [21,22]. The authors concluded that co-treatment with letrozole in ovarian stimulation is important for obtaining better reproductive results in women.

In the work by Zhang et al. the authors state that letrozole and its co-treatment can improve clinical outcomes in high and poor responders in the GnRH antagonist protocol. This study aims of this study is to verify whether letrozole can increase the rate of normal live births responding to the GnRH antagonist treatment protocol during IVF/ICSI cycles. It is a retrospective study with 252 women. The main result was that the combination of letrozole with the GnRH antagonist did not affect the clinical pregnancy rate and cumulative live birth rate. However, the authors conclude, that letrozole may increase the implantation rate of embryos and may reduce the amount of exogenous gonadotropins and may be a safe solution for fertility preservation in estrogen-related cancer patients [13].

Bullow et al. was another study selected to be analyzed by this narrative review that aims to investigate whether co-treatment with letrozole in normal responders can decrease the proportion of women with a premature increase in progesterone [10]. Ovarine induction was performed by the following all patients received fixed-dose recombinant FSH 150 IU/day (Gonalf VR , Merck, Germany) and co-treatment with either 5mg letrozole or placebo until the day before final oocyte maturation with 250mg hCG (OvitrelleVR, Merck, Germany). GnRH antagonist 0.25mg (OrgalutranVR, MSD, USA) was administered from stimulation Day 5 until and including the day of ovulation induction, which was planned when at least two leading follicles were 17 mm. The main outcome was the ongoing pregnancy rate was similar between the letrozole and placebo groups (31% vs 39%). The authors' concluded was that the effect of letrozole on increasing androgens and reducing FSH consumption may be used in poor responders. However, the effect of letrozole on implantation and ongoing pregnancy rates should be evaluated in a meta-analysis or larger Randomized Controlled Trial (RCT).

In a narrative review by Hart he proposed to investigate poor people responding to ovarian stimulation made by Growth Hormones (GH), CC, and letrozole [12]. The main conclusions were that current knowledge does not show an increase in the rate of live births in ovarian induction by these substances and that the use of clomiphene citrate and letrozole can reduce the requirement of gonadotropins for oocyte capture (REF). Eftekhar et al. aimed to evaluate normal response IVF results after using letrozole and gonadotropins [11]. 100 women participated in the study and the main result was no difference in the clinical pregnancy rate in comparison with the use of gonadotropin plus letrozole or only gonadotropin. So the conclusion was that there was no increase in the clinical pregnancy rate when comparing the two groups.

Recently Martini et al. compared doses of gonadotropins more specifically recombinant FSH alpha with and without doses of letrozole and clomiphene citrate and concluded that with the use of these two drugs mentioned orally in cycles of ovulation induction or ovarian stimulation that included orals, r -hFSH-alpha starting doses were lower and dose changes were fewer than with r-hFSH-alpha alone [20]. Smaller dose adjustments facilitate individualized treatment to reduce the risks of multiple gestation, cycle cancellation, and ovarian hyperstimulation syndrome.

Strengths and Limitations of the Study

Among the strengths of this work are that letrozole is a low-cost drug and that it is being widely used in clinical practice by physicians in ovarian stimulation for greater oocyte capture in in vitro fertilization, another strength of the work is that only Articles published in the last 5 years were included. There is also some evidence in the literature that the use of letrozole reduces

the risk of ovarian hyperstimulation syndrome [27,28]. Among the limitations, the clearest is that because it is an article with a narrative review study design, the results are from articles already published and this study did not produce any new results. Another limitation is that in the search strategy, only free-text articles were selected due to the financial limitations of obtaining paid articles. A third limitation is that because it is a recent drug in the literature, there is still a lack of randomized studies with a high number of participants to better support the evidence and results of the use of letrozole for in vitro fertilization, as there are no differences between its use or not in the clinical pregnancy rates and live birth rates.

Conclusion

Letrozole has several benefits, among them being a low-cost and safe medication for women, widely used in ovarian stimulation with benefits in endometrial receptivity, and also improving ovulation stimulation and oocyte capture. However clinical results such as pregnancy rate and number of live births still need large randomized trial studies for further scientific evidence of its use in the main outcomes of human reproduction.

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