

Current evidence supporting “letrozole” for ovulation induction

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ABSTRACT

Aromatase inhibitor “letrozole” was first introduced as a potential ovulation induction (OI) drug almost a decade back. Large number of studies has been published using letrozole for OI: In polycystic ovary syndrome (PCOS) women, clomiphene citrate (CC) resistant women, for intrauterine insemination and also in various protocols of mild stimulation for *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI). Letrozole appears to be a good option, with its oral route of administration, cost, shorter half-life and negligible side effects. However, the verdict on efficacy and safety of letrozole is still uncertain. This review explores the current scientific data supporting letrozole for OI.

KEY WORDS: Aromatase inhibitor, congenital malformations, letrozole, ovulation induction

INTRODUCTION

The need for an alternative to clomiphene citrate (CC) for ovulation induction (OI) was realized since the 1990s. CC had many problems—antiestrogenic effects on the endometrium, cervical mucus, and prolonged accumulation in tissues leading to prolonged depletion of estrogen receptors. This could result in hot flushes, perimenopausal symptoms, in addition to the above side effects. Robert Casper and Mohamed F.M. Mitwally of Toronto General Hospital are credited for proposing the concept of aromatase inhibitors as an alternative to CC for OI, more than a decade ago.^[1,2] They made attempts to synthesize orally active 4-hydroxy androstenedione (4OH-A, the only known steroidal aromatase inhibitor). This did not work out and they had to abandon the idea for another decade. In 1998, the duo, learnt about ‘Femara’ (letrozole) an orally active potent aromatase inhibitor, marketed by “Novartis” for the treatment of metastatic breast cancer. Soon a pilot study was initiated to test letrozole for OI and also in women with CC failure, which was published in 2000.^[1,2]

Over the last decade, since the first few publications, letrozole was widely accepted for OI. Numerous original articles, reviews,

and meta-analysis have been published. Especially, in women with failure or resistance to CC, letrozole was shown to be very effective both in ovulation rate and live birth rate. The year 2005, saw a major setback to the use of Letrozole in infertile women. Dr. Marinko Biljan of Montreal presented an oral abstract at the 2005 American Society of Reproductive Medicine (ASRM) annual meeting, reporting congenital anomalies in 150 babies born from infertile women treated with Letrozole.^[3] Since then, larger studies with better design and multicentric, have been published comparing the safety of letrozole and CC in the infertile group and also in comparison with general population.

At this time, medical data available shows that letrozole is at least as effective as CC for ovulation and pregnancy rates in women with CC resistance or failure. Babies born to these women are at no higher risk for congenital anomalies, overall or specific (cardiac and locomotive).^[4] Yet, in no country across the globe, is letrozole approved for OI. Its use is mostly “off label” and for research purposes. In countries like India letrozole is banned for use in premenopausal infertile women.

This article is a review of available evidence

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that supports letrozole as a drug for OI. The aim is to present convincing information, that letrozole should be accepted as an OI drug.

MECHANISM OF ACTION OF LETROZOLE AND HOW IT IS VERY DIFFERENT FROM CC

The major disadvantages of CC, are that: It depletes the estrogen receptors (ER) throughout the body, has a cumulative effect, and has a long half-life. In contrast, an aromatase inhibitor blocks the conversion of androgens to estrogens in the ovarian follicles, peripheral tissues, and in the brain. This result in two things: (a) Fall in circulating and local estrogens and (b) rise in intraovarian androgens. Fall in estrogen levels, releases the hypothalamopituitary axis from the negative feedback of estrogens. Thus, there is a surge in follicle stimulating hormone (FSH) release, which results in follicular growth. Since, the feedback mechanism is intact; normal follicular growth, selection of dominant follicle, and atresia of smaller growing follicle occurs; and thereby facilitating monofollicular growth and ovulation.^[5-10]

Another likely mechanism of action of the aromatase inhibitors is by the increasing intraovarian androgens. This likely increases the follicular sensitivity to FSH. Recent data shows the role of androgens in early follicular developments^[5,11,12,13] by augmenting FSH receptors and stimulating insulin-like growth factor (IGF)-I; FSH and IGF-I act synergistically to promote follicular growth.

Thus to summarize, an aromatase inhibitor has the following advantages over CC:

1. It does not deplete ERs throughout the body
2. It keeps the hypothalamopituitary axis intact
3. It is short acting (45 min half-life).

This pharmacodynamics of letrozole ensures improved endometrial thickness, cervical mucus, monofollicular, and better folliculogenesis. Therefore, these factors may lead to higher pregnancy rates and greater likelihood of singleton pregnancy.^[14]

REVIEW OF PUBLISHED STUDIES USING LETROZOLE FOR OVULATION INDUCTION

Following the first “Proof of Principle” report by Casper and Mitwally^[4] letrozole gradually got attention of researchers and clinician, for use in various estrogen dependant conditions in gynecology. Although widespread, its use is still “off label”. Apart from OI, letrozole is being used for endometriosis and adenomyosis^[15-17] uterine fibroids,^[18] endometrial stromal sarcoma,^[19] and medical abortion.^[20] This review will focus on use of letrozole for OI. Letrozole has been used in the following three situations:

1. OI in polycystic ovary syndrome (PCOS)
2. OI in intrauterine insemination (IUI)
3. Ovarian stimulation for IVF/ICSI.

LETROZOLE IN PCOS

There is extensive literature available on this topic. Since the data is heterogeneous, they have been compared in subgroups: Letrozole versus CC; letrozole versus CC and metformin; letrozole versus ovarian drilling; and letrozole versus anastrozole.

Letrozole vs. clomiphene citrate

The results of individual randomized controlled trials (RCTs) comparing letrozole with CC have been presented in Table 1. Overall, women with PCOS who were therapy naive or CC resistant or those without clarification as to whether they were therapy naive or CC resistant, letrozole was better than CC for ovulation rate per patient ($P < 0.0001$).^[21] There was no statistical difference between them for ovulation rate per cycle ($P < 0.37$).^[21] There was no statistical difference between letrozole and CC for pregnancy rate per patient, miscarriage rate per pregnancy, live birth rate per pregnancy, or multiple pregnancy rates per patient.^[21] High heterogeneity in the pregnancy rate was likely due to the difference in quality of the RCTs, which was used to categorize the levels of bias.^[21]

Letrozole vs. CC plus metformin

Only one RCT by Abu Hashim *et al.*, which compared 250 CC resistant PCOS women, showed that there was no statistical difference between the two groups for ovulation and pregnancy rate per cycle, miscarriage rate, and multiple pregnancy rates per pregnancy.^[22,23]

Letrozole vs. LOD

Two RCTs comparing letrozole with laparoscopic ovarian drilling (LOD) over 6 months in CC resistant PCOS women found that there was no difference between the two for all outcomes except ovulation rate per cycle.^[22,24] Until further high quality studies are reported, there is insufficient evidence to recommend the use of letrozole over LOD.^[21]

Letrozole vs. anastrozole

Two RCTs were found addressing this issue in CC resistant women. Badawy *et al.*, reported no statistical difference between letrozole and anastrozole for ovulation rate, frequency or miscarriage rate.^[25] Al-Omari *et al.*, found letrozole better than anastrozole in ovulation and pregnancy rate.^[26]

Letrozole was compared to placebo in a small but high quality RCT in CC resistant women. Ovulation rate was higher in letrozole group, however no difference in pregnancy and live birth rate.^[27] No published study has compared letrozole or any aromatase inhibitor as first line therapy in PCOS women.

Table 1: Characteristics of few RCTs comparing letrozole with clomiphene citrate in PCOS women

RCT	Patient characteristics numbers	Ovulation rate	Pregnancy rate	Multiple pregnancy rate	Miscarriage rate
Atay <i>et al.</i> , (2006)	Let=51 patients CC=55 patients	82.4% 63.6% <i>P</i> =0.016	21.6% 9.1% <i>P</i> =0.037	0% 20%	
Badawy <i>et al.</i> , (2009)	Let=540 cycles CC=523 cycles	67.5% 70.9%	15.1% 17.9% <i>P</i> =0.72	0% 3.2%	12.1% 9.7% <i>P</i> =0.43
Bayer <i>et al.</i> , (2006)	Let=99 cycles CC=95 cycles	65.7% 74.7% <i>P</i> =0.17	9.1% 7.4% <i>P</i> =0.66	0% 0%	1% 0%
Begum <i>et al.</i> , (2009)	Let=32 patients CC=32 patients	62.5% 37.5% <i>P</i> <0.05	40.62% 18.72% <i>P</i> >0.05	0% 0%	6.25% 0%
Dehbasi <i>et al.</i> , (2009)	Let=50 patients CC=50 patients	60% 32% <i>P</i> =0.009	26% 14% <i>P</i> =0.21	7.7% 14.3% <i>P</i> =1	23% 14.3% <i>P</i> =1
Zeinalzadeh <i>et al.</i> , (2010)	Not reported	86% 15.5% <i>P</i> =0.07	20% 14% <i>P</i> =0.14	10% 0%	Not reported
Kar S (2012)	Let=51 patients CC=52 patients	73.08% 60.78% <i>P</i> =0.4	21.56% 7.84% <i>P</i> =0.01	0% 0%	Not reported
Roy <i>et al.</i> , (2012)	Let=294 cycles CC=318 cycles	66.6% 67.9% <i>P</i> =0.7	43.8% 26.4%	Not reported	Not reported

Let=Letrozole; RCT=Randomized control trial; PCOS=Polycystic ovary syndrome

LETROZOLE FOR OI FOR IUI

Letrozole has been used for OI or controlled ovarian stimulation for intrauterine insemination. Indication for IUI ranging from unexplained infertility, mild moderate endometriosis to male factor. Primary advantage is reduced requirement of gonadotropins and reduced chance of multiple pregnancies. In a recent study by Abu Hashim *et al.*,^[28] 136 women who recently underwent surgery for minimal to mild endometriosis, were randomized to receive either CC or letrozole followed by IUI. There was no statistical difference for clinical pregnancy rate per cycle, cumulative pregnancy rate, miscarriage, or live birth rate. Badawy *et al.*,^[29] randomized 280 women with unexplained infertility to either CC (100 mg) or letrozole 5 mg with gonadotropins and IUI. Both groups were comparable with letrozole having no advantage over CC.

In the last 10 years, about 15 such articles have been published. Almost all have shown similar outcomes for both CC and letrozole. Letrozole being as effective as CC or letrozole offering no advantage over CC.

LETROZOLE IN OVARIAN STIMULATION FOR IVF/ICSI

Letrozole has also been tried for ovarian stimulation for assisted reproduction. With the concept of mild stimulation

in IVF to improve implantation rate, letrozole is a potential agent. Very few trials, with limited number of patients are available. Letrozole has two potential uses in IVF: First, where it is used in the follicular phase usually with FSH/human menopausal gonadotropin (HMG) for OI; second, it has also been used in luteal phase of stimulated IVF cycle and to reduce circulating E2 levels; thus, potentially reducing ovarian hyperstimulation syndrome (OHSS) risk.

Through the year 2012, seven randomized controlled trials have been published on this subject [Table 2]. Only two, Verpoest *et al.*, 2006^[30] evaluated the addition of letrozole in patients with normal ovarian response undergoing IVF or ICSI. They showed higher implantation and ongoing pregnancy rates in the letrozole cotreatment group. However the results were not statistically significant, owing mainly to the small sample size. Improved endometrial thickness in the letrozole group was significant.

Five randomized trials, with a total of 265 patients, dealt with poor responders. They were randomized to receive letrozole combined with gonadotropins or gonadotropins alone, in an antagonist or agonist protocol. The gonadotropin dose used was consistently lower in the letrozole cotreatment group in all trials. Two trials, in which gonadotropin releasing hormone (GnRH) antagonist was used, for both arms, letrozole cotreatment patients showed comparable pregnancy rates.^[31,32] In another two,

Table 2: RCTs regarding use of letrozole for ovulation induction in IVF/ICSI cycles

	Down regulation protocol	Ovarian stimulation	N numbers	Clinical pregnancy rate (%)	Number al oocytes (mean)	Implantation rate (%)	Total FSH mean
Normoresponder							
Verpoest <i>et al.</i> , 2006	Antagonist	Let+rFSH	10	50	13.8	31.25	1575
	Antagonist	rFSH	10	20	9.6	12.5	1656
Mukherjee 2012	Antagonist	Let+rFSH	42	36	4.6±25		625±98
	Antagonist	rFSH	52	33	4.9±2.3		1756±75
Poor responders							
Goswami <i>et al.</i> , 2004	Agonist	Let+rFSH	13	23	1.6	NA	150
	Agonist	rFSH	23	24	201	NA	2865
Garcia-velasco <i>et al.</i> , 2005	Antagonist	Let+rFSH+HMG	71	22.4	6.1	25	3627
	Antagonist		76	15.2	4.3	9.4	3804
Ozmen <i>et al.</i> , 2009	Antagonist	Let+rFSH	35	28.6	4.9	NA	2980
	Antagonist	rFSH	35	17.1	4.8	NA	3850
Davar 2010	Antagonist	Let+rFSH+HMG	45	4.4	2.8	3.8	3158
	Agonist	rFSH/HMG	49	12.3	4.4	7.7	3458
Mohsen and EL Din 2013	Antagonist	Let+rFSH	30	13.3	Similar in		Significantly
	Microdose agonist	rFSH	30	16.6	both		less in let group

RCT=Randomized controlled trial; IVF=*In vitro* fertilization; ICSI=Intracytoplasmic sperm injection; Let=Letrozole; HMG=Human menopausal gonadotropin; rFSH=recombinant follicle stimulating hormone

different GnRH analogues were used for down regulation. The results of the two trials with respect to pregnancy rate were totally discordant. Daval (2010)^[33] had lower implantation and pregnancy rate in letrozole group, whereas Mohsen and EI Din^[34] had similar results between the two groups.

LUTEAL PHASE AROMATASE INHIBITORS

There are two randomized controlled trials that assess the effects of administration of letrozole during the luteal phase of stimulated IVF cycles in oocyte donors.^[35,36] Both provide evidence that letrozole drastically reduces estradiol (E2) levels. Thus aromatase inhibitors have potential use in egg donors and women at high risk of OHSS.

Letrozole for fertility preservation in cancer patients

Letrozole has been explored as an OI agent in cancer patients undergoing ovarian stimulation to preserve fertility before starting chemotherapy, through embryo or oocyte cryopreservation.^[37] Benefits of letrozole that have been reported are: Significantly lower estrogen exposure, lower dose trigger (GnRH agonist), lower estradiol levels, and no increase in recurrence risk of cancer.^[38-41]

To summarize, existing evidence for use of letrozole in IVF/ICSI protocol is heterogeneous, fragmented, and weak. Limited evidence supports aromatase inhibitors can be used for fertility preservation in cancer patients prior to chemotherapy. Its use in poor responders or even normoresponders requires more publications and research.

Letrozole and congenital anomaly risk

A major setback to letrozole use in OI happened in 2005.

Dr. Marinko Biljan presented an oral abstract at ASRM of 150 babies born after letrozole use.^[3] This was compared with 36,000 spontaneous conceptions of the normal population. It reported overall congenital anomaly rate of 3-4%, which was similar to general population, but cardiac and locomotor anomalies were higher in the letrozole babies. They also reported low birth weight babies in women with gestation diabetes who has taken letrozole. This abstract was later criticized on many counts. The major flaw was that pregnancy outcome of infertile older women was being compared to general fertile population comprising of much younger women. The abstract was never published in a peer reviewed journal. However, based on this report, Novartis (manufacturers of this compound "Femara") issued a letter to physicians worldwide that Femara is contraindicated in premenopausal women, during pregnancy, and/or lactation. Following this, essentially the use of letrozole for OI stopped worldwide.

Dr. Togas Tulandi and colleagues, published a multicentric Canadian study in 2006 designed to compare neonatal outcomes of 911 babies born to women conceiving with CC or letrozole;^[42] 514 letrozole babies and 397 CC babies. Overall, congenital malformations and chromosomal abnormalities were found in 14 of 514 in the letrozole group (2.4%) and in 19 of 397 in the CC group (4.8%). Major malformation rate was 1.2 and 3% in letrozole and CC groups, respectively. Congenital cardiac anomalies was significantly higher ($P = 0.02$) in the CC group (1.8%) against letrozole group (0.2%). More specifically ventricular septal defect 0.2% in letrozole and 1.8% in CC group. Thus, they concluded that there was no difference in the overall rates of major and minor congenital malformations among newborns conceived after letrozole or CC. Moreover, they

concluded that congenital cardiac defects appear less frequently in letrozole group.

A recent multicentric study for the national birth defects prevention study, published in Human Reproduction 2011, reported on association between CC use and birth defects.^[43] Data from the National Birth Defects Prevention study, a population-based study, was used. Close to 25,000 women with or without children with congenital defects were interviewed. They were specifically asked about CC use in the period from 2 months before conception to the first month of pregnancy. They concluded significantly increased adjusted odds ratio for the use of CC and cardiac anomalies, including septal heart defects, muscular ventricular septal defects, and coarctation of the aorta.

Davies *et al.*, reported birth defects with assisted reproductive technologies.^[44] They too found increased risk for birth defects in babies born to mothers using CC. After controlling many confounding factors, the odds ratio for CC use and any birth defect was 3.19 (1.32-7.69). They however did not specify types of birth defects.

In summary, the concerns raised about letrozole safety have not yet been resolved. Available data suggests similar or higher risks with CC use also. Although CC has been in use for 40 years or more. Letrozole data is scant.

Currently, two large randomized multicentric studies by the National Institute of Child Health and Human Development (NICHD) are underway, the results of which are eagerly awaited. These could provide definitive data for pregnancy outcome with CC and letrozole.

The first study, Pregnancy in Polycystic Ovary Syndrome-II (PPCOS-II), is a randomized controlled trial comparing CC with letrozole for OI in PCOS women.^[14] They propose to enroll 750 women, across 11 centers. The primary outcome measure would be cumulative live birth rate.

The second study Assessment of Multiple Intra Uterine Gestations from ovarian stimulation (AMIGOS) trial will determine multiple pregnancy rates from OI and intrauterine insemination and is double blinded for CC or aromatase use.^[45] Cumulative and multiple pregnancy rates will be calculated in a total of 240 women. It is hoped that this trial will answer the issue of whether letrozole has a lower chance of multiple pregnancies, compared to CC or gonadotropins.

CONCLUSION

To conclude, available data shows that letrozole is at least as effective as CC for ovulation and has comparable live

birth rates. Importantly, it has definite advantages over CC. Many studies have shown letrozole to be as effective as gonadotropins, with added advantage of low cost and lower multiple pregnancy rates. However, the quality of medical evidence supporting aromatase inhibitors for OI, are inadequate, small in sample size, and inappropriate design. Moreover, there is very limited data on potential teratogenic effects, oocyte, embryo quality, and any effect on implantation.

There is no doubt that the issue of teratogenicity of letrozole needs further clarification with large scale studies. Such a study would require approximately 3,500 newborns conceived with and without letrozole. This obviously implies that the same has to be shown in case of CC. No such study has ever been conducted to prove the safety of CC.

Letrozole deserves a fair trial. At least, it should be made available in a research context, so that adequate data is collected to show its efficacy and safety.

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