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# LETROZOLE ROLE IN BREAST CANCER AND INFERTILITY: A REVIEW OF LITERATURE.

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**Abstract**

Letrozole is being considered as potential prophylactic agent for breast cancer after discontinuation of 5-year tamoxifen therapy for steroid HR-positive breast cancer in postmenopausal women with breast cancer letrozole effect along with RT in aromatase expressing breast tumour cell showed efficacy as oral administration along with favourable toxicities when taken orally. Letrozole improves disease free survival in metastatic breast cancer Therapy with zoledonic acid is required as long-term use of aromatase inhibitior results in bone loss Letrozole is potent competitive aromatase inhibitor, a nonsteroidal Benzhydroltriazole derivative, highly selective. Women who had taken tamoxifen for 5 years after discontinuation have taken letrozole and chances of recurrence were less depending upon tumour characteristics. Therapy with letrozole lasts usually 3-4 months and has been extended up to 12 months. Aromatase inhibitors are now a days used worldwide as adjuvant therapy, particularly letrozole significantly improves disease free survival and time to distant recurrence In contrast to tamoxifen, letrozole cause decrease in circulating estrogen levels. Letrozole is better considered for disease free survival in postmenopausal women for preventing metastatic breast cancer in contrast to tamoxifen. Letrozole for its ovulatory effect is proved to be better with many respects as compared to clomiphene citrate. Though with some respects and in some research patterns clomiphene citrate came out to be a better ovulation stimulator but still letrozole has fewer side effects as compared to clomiphene citrate and more thickening of endometrial layer which is certainly a supportive factor for clinical pregnancy. Furthermore letrozole when used with combination of FSH and GnRH for ovulation stimulation, it decreases the dose required for fertility when either of both (FSH, GnRH) used alone. In women undergoing IUI and IVF it also plays a supportive role by improving the endocrine environment of the women.

**Key words:** postmenopausal women, Letrozole, Aromatase inhibitors, controlled ovarian hyperstimulation, Clomiphene, Tamoxifen.

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## INTRODUCTION

### Aromatase inhibitors

In common practice aromatase inhibitors (AIs) are used in adjuvant and palliative settings. These agents inhibit the enzyme aromatase, and cause interruption of estrogen synthesis which converts androgens into estrogens by a process called aromatization and ultimately suppression of tumour. Aromatase inhibitors (AIs) are commonly used in practice. Two being the nonsteroidal are letrozole and anastrazole, one being steroidal exemestane. Two main approaches are

1. Irreversible steroidal inhibitors, such as exemetase (Aromasin) forms a permanent and deactivating bond with the aromatase enzyme.

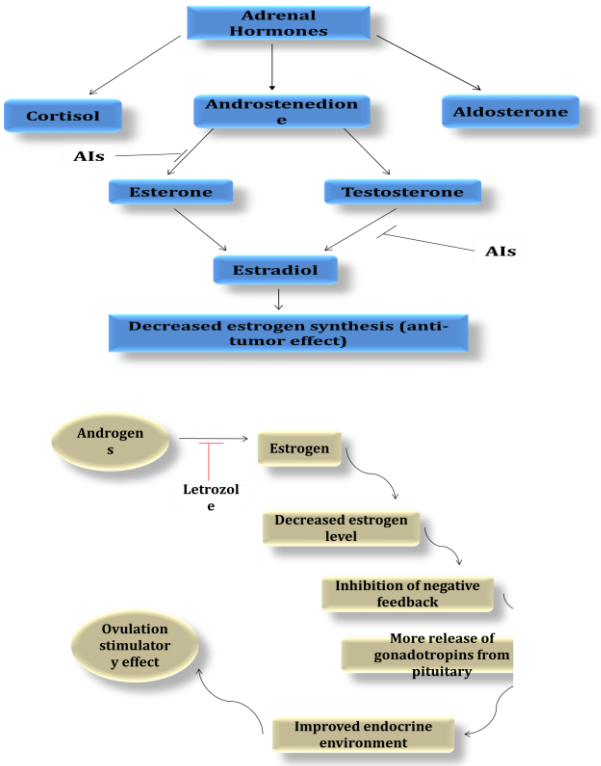
2. Nonsteroidal inhibitors, such as anastrozole (Arimidex) and letrozole (Femara), inhibit the synthesis of estrogen via reversible competition for the aromatase enzyme.

### Letrozole Vs tamoxifen:

Different therapeutic benefits of letrozole by applying different strategies have been observed as a preventive agent for breast cancer for those women entering malignant stage[1].

(Harper-Wynne et al., 2002). Post tamoxifen therapy with leterozole depends upon the fact that National cancer institute has discontinued its use after five years of therapy[2]

(Goss et al., 2003). However, high benefit to risk ratio came out with letrozole as compared to tamoxifen for postmenopausal ER+ breast cancer[3] (B. I. G.-C. Group, 2005). In some patients prior to surgery comparison was performed between letrozole and tamoxifen to check its efficacy[4] (Eiermann et al., 2001). Sensitization of RT in postmenopausal women with breast cancer post surgery was one of the notable features of letrozole. Aromatase inhibitor particularly letrozole has been found to be superior to (TAM) tamoxifen as first line treatment for metastatic breast cancer in post-menopausal women[5] (Azria et al., 2004). Esterogen triggers the cell division of breast cancer cells so they are the main mitogens for breast cells with tumour[6] (Goss et al., 2005). Tamoxifen being anti estrogen has been taken as there is a competition with E2 for the ER in the nucleus of cell with carcinoma[7] (B.-C. Group, 2009). Adrenal cortex is the primary source of estrogen in post-menopausal women or castrated women[8] (Ingle et al., 1999). Now a days, three clinically active generation of aromatase inhibitors are available; two being reversible nonsteroidal inhibitors, letrozole and anastrozole; one is irreversible exemestane[9] (Beom et al., 2017).




| Letrozole anti-tumor effect (in breast) | Letrozole ovulation stimulatory effect |
|---|---|

**Side effects Associated:**

Letrozole is found to be efficacious and safe with HR-positive early breast cancer in postmenopausal women however long term intake is associated with bone loss and may increases the future risk for fracture or may lead to osteoprosis, arthritis, joint pain and osteonecrosis of jaw and also cause bone resorption so zoledronic acid is given intravenously which is a bisphosphonate. Other side effects associated are adrenal insufficency, hair loss, aggressive behaviour and kidney failure[10] (Bundred et al., 2008). AIs are only suitable for those women whose ovaries has stopped producing oestrogen where they cause inhibition of oestrogen production in non-ovarian tissues [11](Kemp et al., 2014).

## Epidemiology of breast cancer:

Breast cancer is the leading cause of morbidity and mortality worldwide and its incidence is continuously increasing in women with age particularly above 50 years of age,80% breast cancer cases are reported[12] (Shaikh, Kumar, Raza, Mehboob, & Ishtiaq, 2012). Aromatase inhibitors have challenged the status of traditionally used tamoxifen along withadjuvant hormonal therapy[13] (Krainick-Strobel et al., 2008). In developed countrieslike Canada overall lifetime probability of developing breast cancer in present situation is about 11% and risk of death is somewhere 4.1% which is now being important to the healthcare providers that new treatment methodologies will provide care & safety along with cost-effective[14] (Nuijten, McCormick, Waibel, & Parison, 2000). In women with HR-positive breast cancer adjuvant endocrine therapy lessens the risk of recurrence and death[15] (Schiavon & Smith, 2014).

## Selectivity of letrozole:

Letrozole being selective aromatase inhibitor used in postmenopausal women the efficacy of which has been proved through clinical trial [16] (Dieudonné, Lambrechts, Wildiers, & Neven, 2013). AIs, aromatase inhibitors acts by preventing the conversion of androstenedione to estradiol either by reversibly or irreversibly inhibiting the aromatase enzyme so provide better treatment option for postmenopausal women[17] (Dent, Gaspo, Kissner, & Pritchard, 2011). All detectable cancer can be removed surgically in early stage in women but if remains undetected, develop into a clinically detectable recurrence which ultimately leads to death [18](E. B. C. T. C. Group, 1998b). Endocrine therapy is the basis of post-surgical treatment for women with hormone dependant positive breast cancer (E. B. C. T. C. Group, 1998a). The benefits with aromatase inhibitors were attained with possibly minor side effects [19](Fisher et al., 1989). It has been proven clinically that adjuvant treatment with tamoxifen for

5 years [20](Pharoah, Abraham, & Caldas, 2012) when further proceeded with letrozole reduces breast cancer recurrence. Several double blind trials were performed with placebo and letrozole which showed that letrozole markedly improves the survival period [21](Jakesz et al., 2007). Patients who switch on to letrozole from 5 year treatment with tamoxifen experienced more bone fractures, arthralgia, low grade hypercholesterolemia[22] (Colleoni et al., 2011) whereas with tamoxifen were thromboembolic, endometrial pathology, hot flashes etc[6] (Goss et al., 2005). In women receiving letrozole incidences of contralateral breast cancer were found to be lower[23] (Coates et al., 2007).

## Role of letrozole in fertility:

Letrozole being the main focus of this review is analyzed with different aspects and procedures with sometimes same results and outcomes and sometimes with slight but no significant difference. Reviewing its ovulation stimulating aspect it is found that first line therapy of infertility remained clomiphene citrate. Its mechanism of action is by competitive inhibition of estrogen receptors for estradiol in the hypothalamus, so suppressing the negative feedback effect of it and ultimate increased release of FSH from pituitary gland. Now increased FSH is responsible for enhanced growth of follicles with increased chances of ovulation.

## Letrozole Vs clomiphene citrate:

In unexplained infertility of couples, male factor infertility and other disorder where COH (controlled ovarian stimulation) is of value, CC is effective in producing multiple ovulations. But despite of its approved use In United states for more than 40 years, some considerable limitations are associated with Clomiphene due to its side effects like hot flushes and mood swings which are psychologically troublesome, also abnormal cervical secretions and impaired endometrial development being harmful to fertility. Furthermore, 25-15% of anovulatory women do not respond to this medication for appropriate follicular growth. After all these shortcomings of Clomiphene citrate a comparatively newer drug in field of fertility was introduced from class of aromatase inhibitors, which inhibits the synthesis of estradiol and has the ability to increase FSH release, one of such inhibitors letrozole being approved for breast cancer treatment in 1997 is our focus of this review. Firstly used for treatment of breast cancer, letrozole was later used in 2001 in field of fertility successfully in anovulatory women, so recently used for controlled ovarian hyperstimulation (COH) and ovulation dysfunction. Reason of its acceptance after clomiphene was half life of only 45 hours and side effects far milder and less frequent, beside all other limitations of it in different research patterns [24](Pritts, Yuen, Sharma, Genisot, & Olive, 2011).

## Letrozole with FSH in poor responders:

For researchers and clinicians during an assisted reproduction major concern is comparatively poorer response to controlled ovarian stimulation. In women who are poor responders to ovarian stimulation, a high dose of FSH can induce mild ovarian stimulation being preferable. For this purpose researchers used CC alone or in combination with FSH and letrozole alone or in combination with FSH to induce mild ovarian stimulation protocol in poor responders[25] (Eftekhar, Mohammadian, Davar, & Pourmasumi, 2014).

## Comparison of side effects:

Even clomiphene is recently a first line therapy drug for infertility remedy in polycystic ovary syndrome (PCOS), but letrozole an aromatase inhibitor may result in relatively better pregnancy outcomes. It is proved that as a whole with no significant differences in congenital anomalies letrozole group had more live births than those of clomiphene group. When seen adverse effects of both drugs,

clomiphene was found with increased hot flushes while letrozole with higher incidences of dizziness and fatigue. Some other adverse effects were almost similar in both of the treatment groups[26] (Legro et al., 2014).

## High dose trial with letrozole in no response women:

Now in another research women not responding to lower doses of letrozole, a high dose letrzole trial was done to see its effects. Although letrozole as an aromatase inhibitor showed good effectiveness in ovarian hyperstimulation as well in ovulation induction but in some women lower doses does not produce any considerable response, so there produced a need for higher doses in those women, who when given higher doses of letrozole, came out with increased follicular growth and an increased number of predicted ovulations, with a surprisingly good point of no detrimental effect on endometrial thickness[24] (Pritts, Yuen, Sharma, Genisot, & Olive, 2011).

## Letrozole and GnRH combination in poor responders:

Some women being the poor responders for controlled ovarian hyperstimulation were given many drugs through different strategies to improve their response but outcomes were not satisfactory. Those strategies were MF protocol (microdose gonadotrpin-releasing hormone (GnRH) agonist flare protocol), high dose of follicle stimulating hormone (FSH), combination of clomiphene citrate and human menopausal gonadotropin (hMG), stop GnRH-agonist protocol, addition of growth hormone, GnRH antagonists, and even a natural cycle but outcomes was near to negligible. Among all above combination MF protocol was widely used in poor responder women, while combination of letrozole and GnRH antagonists for induction of controlled ovarian hyperstimulation was expected to enhance pregnancy outcomes in assisted reproductive technology cycles [27](Davar, Oskouian, Ahmadi, & Firouzabadi, 2010).

## Birth defects observed with Letrozole:

Some other researchers for safety reasons observed the birth defect influence of letrozole. For that they compared birth defect effects of both clomiphene citrate and letrozole. It was observed that instead clomiphene citrate was associated with unwanted effects in mothers which were intrauterine growth restriction, low pregnancy rates, multiple gestations, unfavorable cervical mucus, thinning of the endometrium. While letrozole showed higher pregnancy rates, avoiding some of the unwanted effects linked with clomiphene citrate, and was not associated with an increased risk of children born with birth defects[28] (Gill, Moretti, & Koren, 2008). Although clomiphene and gonadotropin is considered standard therapy for subjects with unexplained infertility, but in one different observation letrozole inducing the ovarian stimulation was associated with reduced multiple gestations with maintenance of live birth rates[29] (Diamond et al., 2015). Again after a different research letrozole came out with better pregnancy outcomes; even clomiphene is currently considered first-line therapy for infertility problem in women[26] (Legro et al., 2014)

## Letrozole effect in women undergone IVF:

Some researchers in subjects with IVF setting tried to see facilitative effect of letrozole and clomiphene as a comparative study for production of merely one or two embryos. In that study either of the drugs was used with gonadotropins[30] (Rose, Laky, & Rose, 2015). Women with chronic anovulation were studied for increased induction of ovulation by central block of estrogen action. These anovulatory women were having sufficient levels of serum estrogen, FSH, prolactin (PRL), with or without clinical or

biochemical hyperandrogenism (WHO class II). Letrozole though does not interfere with the estrogen receptors like clomiphene but it stops the conversion of androgens to estrogen thus decreasing the estradiol level and reducing the negative feedback mechanism for estrogen thus ultimate increase in pituitary gonadotropin output, so ovarian function increases[31] (Requena et al., 2008).

## Letrozole effect when initiated on different days following menstruation:

In women who failed to respond clomiphene citrate were studied with letrozole doses with initiation on different days. Their ultrasonographic and hormonal characteristics were compared.[32] (Ghomian, Khosravi, & Mousavifar, 2015).

## Letrozole in breast cancer women and women undergone IUI:

In women with intrauterine insemination program (IUI) who were recently undergone surgery for minimal to mild endometriosis pregnancy rates were evaluated with letrozole and clomiphene alone after inducing superovulation[33] (Abu Hashim, El Rakhawy, & Abd Elaal, 2012). In breast cancer treated women during their disease- free interval undergoing embryo or oocyte cryopreservation prior to adjuvant chemotherapy, effect of controlled ovarian stimulation was determined using combination of letrozole with standard fertility ovarian stimulation (COS) [34](Azim, Costantini-Ferrando, & Oktay, 2008).

## Effect of combination of letrozole and metformin:

In women with clomiphene-resistant infertility with PCOS, efficacy of combined metformin-letrozole administration was compared to that of metformin-clomiphene [35](Sohrabvand, Ansari, & Bagheri, 2006). Now in normo-ovulatory women when endocrinological profile was investigated with letrozole versus clomiphene citrate administration from day 3 to day 7 following menstruation which showed significantly lower expectancy of estradiol concentrations and follicles in letrozole group than that of clomiphene citrate group[36] (Fatemi et al., 2003). Effect of addition of letrozole in decreasing the requirement for other accompanying drugs like gonadotrpins was determined for controlled ovarian hyperstimulation (COH) for IUI [37] (Casper, 2003).

## Level of estradiol with letrozole in breast cancer women:

Effect of letrozole combination with that of gonadotropin treatment in breast cancer women was seen for standard IVF for not increasing estradiol level in breast cancer women and no delay in the initiation of chemotherapy [38] (Oktay et al., 2006). A comparative evaluation was done for congenital malformations among offsprings of women conceiving naturally or with clomiphene or letrozole therapy (Sharma et al., 2014). When letrozole was used in combination with FSH injections it reduced the dose of FSH alone needed to induce controlled ovarian hyperstimulation (COH) [39](Casper & Mitwally, 2011).

## CONCLUSION

After all the aspects mentioned we may conclude that aromatase inhibitors particularly, Letrozole is most effective with minor side effects as compared to tamoxifen (initially used for 5 years) when used in postmenopausal women for metastatic breast cancer. While as an ovulation stimulant letrozole came out to be a more appropriate drug for monofollicular stimulation and improvement of endocrine environment with least harm to endometrium.

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**REFERENCES:**

1. Harper-Wynne C, Ross G, Sacks N, Salter J, Nasiri N, Iqbal,J. Dowsett, M. Effects of the aromatase inhibitor letrozole on normal breast epithelial cell proliferation and metabolic indices in postmenopausal women. *Cancer Epidemiology and Prevention Biomarkers,* 2002*11*(7), 614-621.
2. Goss PE, Ingle JN, Martino S, Robert N. J, Muss HB, Piccart MJ Pritchard KI. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New England Journal of Medicine*,2003;*349*(19), 1793-1802.
3. Group, BIGC. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med, 2005*(353), 2747-2757.
4. Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes, J Chaudri-Ross H. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Annals of Oncology,* 2001;*12*(11), 1527-1532.
5. Azria D, Larbouret C, Cunat S, Ozsahin M, Gourgou S, Martineau P Pèlegrin A. Letrozole sensitizes breast cancer cells to ionizing radiation. *Breast Cancer Research,* 2004;*7*(1), R156.
6. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Pritchard KI. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA. 17. *Journal of the National Cancer Institute,* 2005;*97*(17), 1262-1271.
7. Group BC. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med, 2009*(361), 766-776.
8. Ingle JN, Suman VJ, Johnson PA, Krook JE, Mailliard JA, Wheeler R H, Dowsett M. Evaluation of tamoxifen plus letrozole with assessment. (1999).
9. Beom SH. Oh J. Kim T.-Y. Lee K.-H. Yang Y. Suh K. J. . . . Han W. (). Efficacy of Letrozole as First-Line Treatment of Postmenopausal Women with Hormone Receptor–Positive Metastatic Breast Cancer in Korea. *Cancer research and treatment: official journal of Korean Cancer Association* 2017;*49*(2) 454.
10. Bundred NJ. Campbell I D. Davidson N. DeBoer RH. Eidtmann H. Monnier A. Schenk NL. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Cancer* 2008;*112*(5) 1001-1010.
11. Kemp A. Preen D. B. Saunders C. Boyle F. Bulsara M. Holman C A J. Roughead EE. Women commencing anastrozole letrozole or tamoxifen for early breast cancer: the impact of comorbidity and demographics on initial choice. *PloS one* 2014;*9*(1) e84835.
12. Shaikh AJ. Kumar S. Raza S. Mehboob M. Ishtiaq (2012). Adjuvant hormonal therapy in postmenopausal women with breast cancer: Physician's choices. *International journal of breast cancer 2012*.
13. Krainick-Strobel UE. Lichtenegger W. Wallwiener D. Tulusan A. H. Jänicke F. Bastert G. Paepke S. Neoadjuvant

letrozole in postmenopausal estrogen and/or progesterone receptor positive breast cancer: a phase IIb/III trial to investigate optimal duration of preoperative endocrine therapy. *BMC cancer* (2008). *8*(1) 62.

14. Nuijten M. McCormick J. Waibel F. & Parison D. (). Economic evaluation of letrozole in the treatment of advanced breast cancer in postmenopausal women in Canada. *Value in Health* 2000;*3*(1) 31-39.
15. Schiavon G. & Smith I. E. (). Status of adjuvant endocrine therapy for breast cancer. *Breast Cancer Research* 2014;*16*(2) 206.
16. Dieudonné A.-S. Lambrechts D. Wildiers H. & Neven P. (). Why should results from metastatic trials no longer matter for early-stage disease? *Journal of Clinical Oncology* 2013;*31*(21) 2753-2753.
17. Dent SF. Gaspo R. Kissner M. Pritchard K. I. (). Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. *Breast cancer research and treatment* 2011;*126*(2) 295-310.
18. Group E. B. C. T. C. Polychemotherapy for early breast cancer: an overview of the randomised trials. *The Lancet* (1998a). *352*(9132) 930-942.
19. Fisher B. Costantino J. Redmond C. Poisson R. Bowman D. Couture J. . . . Fisher E. R. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor–positive tumors. *New England Journal of Medicine* (1989). *320*(8) 479-484.
20. Pharoah PD. Abraham J. Caldas C. Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1-98 trial and Re: CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. *Journal of the National Cancer Institute* (2012). *104*(16) 1263-1264.
21. Jakesz R. Greil R. Gnant M. Schmid M. Kwasny W. Kubista E. . . . Hofbauer F. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *Journal of the National Cancer Institute* (2007). *99*(24) 1845-1853.
22. Colleoni M. Giobbie-Hurder A. Regan M. M. Thürlimann B. Mouridsen H. Mauriac L. . . . Smith I. Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. *Journal of Clinical Oncology* (2011). *29*(9) 1117-1124.
23. Coates AS. Keshaviah A. Thurlimann B. Mouridsen H. Mauriac L. Forbes J. FColleoni M Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *Journal of Clinical Oncology* .(2007). *25*(5) 486-492.
24. Pritts EA. Yuen AK. Sharma S. Genisot R. & Olive D. L. (2011). The use of high dose letrozole in ovulation induction and controlled ovarian hyperstimulation. *ISRN obstetrics and gynecology 2011*.
25. Eftekhar M. Mohammadian F. Davar R. & Pourmasumi S. Comparison of pregnancy outcome after letrozole versus clomiphene treatment for mild ovarian stimulation protocol in poor responders. *Iranian journal of reproductive medicine* (2014). *12*(11) 725.
26. Legro R. S. Brzyski R. G. Diamond M. P. Coutifaris C. Schlaff W. D. Casson P. Alvero R. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *New England Journal of Medicine* (2014). *371*(2) 119-129.
27. Davar R. Oskouian H. Ahmadi S. & Firouzabadi R. D. GnRH

antagonist/letrozole versus microdose GnRH agonist flare protocol in poor responders undergoing in vitro fertilization. *Taiwanese Journal of Obstetrics and Gynecology* (2010). *49*(3) 297-301.

28. Gill S. K. Moretti M. & Koren G. Is the use of letrozole to induce ovulation teratogenic? *Canadian Family Physician* (2008). *54*(3) 353-354.
29. Diamond M. P. Legro R. S. Coutifaris C. Alvero R. Robinson R. D. Casson P. . . . Hansen K. R. Letrozole gonadotropin or clomiphene for unexplained infertility. *New England Journal of Medicine* (2015). *373*(13) 1230-1240.
30. Rose B. Laky D. & Rose S. A comparison of the use of clomiphene citrate and letrozole in patients undergoing IVF with the objective of producing only one or two embryos. *Facts views & vision in ObGyn* (2015). *7*(2) 119.
31. Requena A. Herrero J. Landeras J. Navarro E. Neyro J. L. Salvador C. . . . Farré M. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. *Human reproduction update* (2008). *14*(6) 571-582.
32. Ghomian N. Khosravi A. & Mousavifar N. A randomized clinical trial on comparing the cycle characteristics of two different initiation days of letrozole treatment in clomiphene citrate resistant PCOS patients in IUI cycles. *International journal of fertility & sterility* (2015). *9*(1) 17.
33. Abu Hashim H. El Rakhawy M. & Abd Elaal I. Randomized comparison of superovulation with letrozole vs. clomiphene citrate in an IUI program for women with recently surgically treated minimal to mild endometriosis. *Acta obstetricia et gynecologica Scandinavica* (2012). *91*(3) 338-345.
34. Azim A. A. Costantini-Ferrando M. & Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *Journal of Clinical Oncology* (2008). *26*(16) 2630-2635.
35. Sohrabvand F. Ansari S. & Bagheri M. Efficacy of combined metformin–letrozole in comparison with metformin–clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. *Human Reproduction* (2006). *21*(6) 1432-1435.
36. Fatemi H. M. Kolibianakis E. Tournaye H. Camus M. Van Steirteghem A. & Devroey P. Clomiphene citrate versus letrozole for ovarian stimulation: a pilot study. *Reproductive biomedicine online* (2003). *7*(5) 543-546.
37. Casper R. F. Letrozole: ovulation or superovulation? *Fertility and sterility* (2003). *80*(6) 1335-1337.
38. Oktay K. Hourvitz A. Sahin G. Oktem O. Safro B. Cil A. & Bang H. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. *The Journal of Clinical Endocrinology & Metabolism* (2006). *91*(10) 3885-3890.