MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 7(12) pp. 461-465, December, 2019
Available online http://www.meritresearchjournals.org/mms/index.htm

DOI: 10.5281/zenodo.3581224

Original Research Article

Co-Administration of Tamoxifen and Letrozole: Does it Increase Endometrial Thickness and Pregnancy Rate in Cases of Ovulation Induction?

Dr. Nisreen Khaled Aref MD

Associate Professor of Obstetrics and Gynecology, Faculty of Medicine, Taif University, KSA

***Corresponding Author's Email: nisreenaref@yahoo.com**
Tel: 00966542988574

Abstract

The aim of this study was to evaluate the efficacy of co-administration of tamoxifen and letrozole as a novel protocol to increase pregnancy rates in ovulation induction. A trial conducted among 171 infertile women who were eligible for ovulation induction. Women randomized into two groups. Group A given letrozole 2.5 mg tablet daily and tamoxifen 10 mg twice daily started from the 3rd day of menstrual cycle for 5 days while for patients in group B letrozole only used. When at least one dominant follicle found, Human Chorionic Gonadotropin injection administrated intramuscularly. After 24 hours of the timed intercourse, all patients received vaginal progesterone daily. The mean number of mature follicles ≥ 18 mm was significantly higher in group A (2.6 ± 0.3) when compared to group B (1.5 ± 0.7) .Endometrial thickness was higher in group A (8.9 ± 1.4 mm versus 7.3 ± 1.2 mm in group B). As regarding pregnancy rate and ongoing pregnancy rate (21 and 19 % respectively) in-group A while (8 and 7 % respectively) in group B. Co-administration of tamoxifen with letrozole has valuable effect on increasing endometrial thickness resulted in increased pregnancy rates.

Keywords: Endometrial Thickness, Letrozole, Ovulation Induction, Tamoxifen

INTRODUCTION

One of the earlier drugs that introduced for ovulation induction is clomiphene citrate (CC). It has introduced in the early 1960s and for more than 50 years, it used widely as the most common oral agent for ovulation induction (Fisher et al., 2002; Bedaiwy et al., 2006; Sipe et al., 2006; Ganesh et al., 2009). However, due to marked discrepancy between low pregnancy rates (30-40%) which is not as high as the ovulation rate (70-80%) and relatively high resistant cases (20 – 25%) (Casper and Mitwally, 2006). In recent years an anti-estrogenic agent with close similarity to clomiphene citrate known as tamoxifen (Steiner et al., 2005; Lee and Ledger, 2011). It used for induction of ovulation and reported ovulation rates were 50 – 90% and pregnancy rates were 30 – 50% with good results in clomiphene citrate failure cases with absence of clomiphene citrate side effects as ovarian hyper stimulation and multiple pregnancies (Dhaliwal et al., 2011). Tamoxifen improves folliculogenesis process by blocking oestradiol binding sites on the hypothalamic–pituitary axis and preventing the negative feedback effect of oestradiol so increasing gonadotrophin secretion (Boostanfar et al., 2001), better functioning of the corpus luteum also seen (Fukushima et al., 1982) in association with beneficial effects on the cervical mucus (Roumen et al., 1984) with increased endometrium receptivity power (Fukushima et al., 1982). Tamoxifen used as either an alternative or a synergetic agent to increase pregnancy rates (Brown et al., 2009).

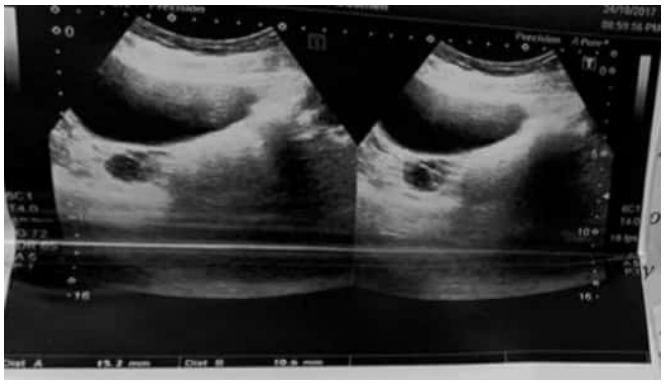
Letrozole is a third-generation aromatase inhibitor, used in ovulation induction from 2001 (Sipe et al., 2006; Banerjee et al., 2012). Aromatase inhibitor blocks the conversion of testosterone and androstenedione to oestradiol and oestrone respectively. They inhibit the oestrogen negative feedback on the hypothalamic–pituitary axis leading to increased gonadotrophin secretion, which in turn leads to ovarian follicular growth and development (Fouda and Sayed, 2011). Several evidences have supported the substitution of clomiphene citrate with letrozole due to lower incidence of side effects (Nahid and Sirous, 2012) and better effect on endometrial thickness and higher pregnancy rates (Banerjee et al., 2012).

The combined administration of tamoxifen and letrozole in cases with advanced breast cancer shown by several published studies. Tamoxifen as a selective estrogen receptor modulator (SERM) has anti estrogenic action on breast tissue with inhibition of breast tumor growth while letrozole prevents aromatization of androgens to estrogens also at breast tissues. Both drugs were accepted as first line drugs in hormonal treatment of breast cancer (Ingle et al., 1999; Oktay et al., 2005). The combination of both tamoxifen with letrozole has not been reported in the field of induction of ovulation up till now . This has triggered us to evaluate the efficacy of this new regimen on pregnancy rates in infertility cases undergoing ovulation induction.

PARTICIPANTS AND METHODS

The study carried out in accordance to the ethical principles for medical research involving human subjects included in Helsinki declaration. This randomized trial conducted at Maternity hospital, Taif city, KSA during the period from March 2018 to May 2019. Our study included cases presented to the gynecology clinic with an-ovulatory non polycystic ovarian syndrome with either with primary or secondary types of infertility. All patients had previously received clomiphene citrate and diagnosed as having clomiphene citrate failure (failure of ovulation after 6 cycles of clomiphene citrate reaching the dose of 150 mg daily) and were eligible for ovulation induction after exclusion of male factor by normal semen analysis. Inclusion criteria for our study were : Women in reproductive age (20 – 35 years) – Body Mass Index less than 30 kg/m^2 – Normal hormonal profile (follicle–stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and prolactin hormone) - Normal uterine cavity and patent fallopian tubes based on previously performed documented hysterosalpingography (HSG) - No history of induction of ovulation in the previous 3 cycles . All women fulfilling the study criteria counseled to participate in our study and received an explanation of the study then informed written consent obtained from all participants. Women who were eligible for the study (n= 188), were randomized into two groups using computer based programs. Group (A) included 94 patients received letrozole and tamoxifen while group (B) included another 94 patients received letrozole only. An explanation of the study and a signed consent sheet obtained from all participants. One hundred – seventy one patients had completed the study (86 patients in letrozole and tamoxifen group while 85 patients in letrozole group only). Cases that were poor responders (only one follicle of ≥ 16 mm size in both ovaries) or lost during follow up period excluded from the study.

Transvaginal sonar was done on the 3rd day of the menstrual cycle then induction of ovulation in group A was started with letrozole 2.5 mg tablet once daily and tamoxifen 10 mg tablet twice daily started from 3rd day to 7th day of the cycle while the same treatment protocol was used for patients in group B but without tamoxifen. Our study primary outcome measures included number of mature follicles and endometrial thickness while secondary outcome measure was pregnancy rate after one cycle of treatment protocol. In both groups , serial folliculometry done by ultrasound, which was done every other day starting from 9th day of the induced cycle. Human Chorionic Gonadotrophin (HCG) injection of 5000 I.U. was administrated intramuscularly when at least one follicle with a mean diameter ≥ 18 mm or at least two follicles 16 mm ≥ were found (Speroff et al., 2004; Aref et al., 2019). Endometrial thickness also assessed prior to HCG administration. Timed intercourse advised 24 to 36 hours after Human Chorionic Gonadotropin (HCG) injection. After 24 hours of the timed intercourse; all patients received 400 mg of micronized progesterone vaginally once a day to be continued till the end of first trimester (Aref et al., 2019). Beta human chorionic gonadotropin (B-hCG) measurement after two weeks to check for the presence of pregnancy. In cases of positive results, clinical pregnancy was defined as the detection of gestational sac by transvaginal ultrasound examination at 6th week gestation. ‘‘Ongoing pregnancy’’ was recorded when pregnancy passed to 13 weeks of gestational age (Aref et al., 2019).



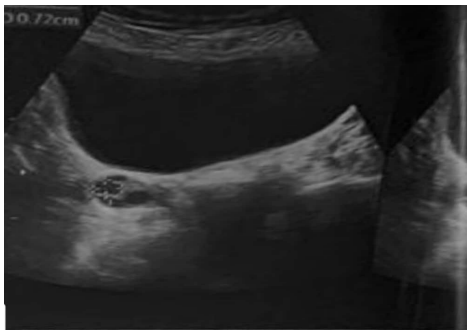


Figure 1. Ultrasound findings in study group

Table 1. Baseline characteristics between studied patients in both groups

Characteristics		Letrozole and Tamoxifen group (n=86)	Letrozole only group (n=85)	p-value
Age (Years)	Mean ± SD	27.4 ± 4.6	26.9 ± 5.2	0.2 (NS)
	Range	22 – 32	21 – 33	
BMI (kg/m^2)	Mean ± SD	26.2 ± 3.1	27.7 ± 2.4	0.3 (NS)
	Range	21 – 29	20 – 29.6	
Type of infertility	Primary	77 90%	79 93%	0.8 (NS)
	Secondary	9 10%	7 %	
Duration of infertility (Years)	Mean ± SD	4.1 ± 2.9	4.3 ± 1.8	0.6 (NS)
	Range	2 – 7	1.5 – 7.5	

NS: Not statistically significant difference (p values > 0.05)
BMI: body mass index

Table 2. Outcome measures between both groups

Characteristics		Letrozole and Tamoxifen group (n=86)	Letrozole only group (n=85)	p-value
Follicles ≥ 18 mm(N)	Mean ± SD	2.6 ± .3	1.5 ± .7	<0.01*
Endometrial thickness (mm)	Mean ± SD	8.9 ± 1.4	7.3 ± 1.2	<0.01*
Pregnancy rate	N	18 21%	7 8 %	0.03*
Ongoing pregnancy rate	N	16 19%	6 7%	0.04*

*Statistically significant difference (p values ≤ 0.05)

Statistical Analysis

Gathered data processed using SPSS version 18 (SPSS Inc., Chicago, USA). Quantitative data expressed as mean ± SD while qualitative data expressed as numbers and percentages (%). Student t test used to test significance of difference for quantitative variables and Chi Square used to test significance of Difference for qualitative variables.

RESULTS

Table 1 shows that patients of both groups matched regarding age, Body Mass Index, duration and type of infertility. Mean age was 27.4 years in group A while it was 26.9 years in group B. Our results showed that 90 % of patients in group A and 93 % of patients in group B had primary infertility and the remainder had secondary infertility (10% in group A and 7 % in group B).

The main outcome measures of our study presented in Table 2. Group A was superior to group B as regarding all studied outcomes. Mean number of mature of follicles ≥ 18 mm was statistically significantly higher in group A (2.6 ± 0.3) when compared to group B (1.5 ± 0.7) with (P-value <0.01). Endometrial thickness was significantly different between both groups; as it was higher in group A (8.9 ± 1.4 mm versus 7.3 ± 1.2 mm in

group B (P-value<0.01). It noted that there was significant statistical discrepancies between both groups regarding pregnancy rate and ongoing pregnancy rate as they were (21 and 19 % respectively) in group A while they were (8 and 7 % respectively) in group B.

DISCUSSION

In the field of reproductive medicine, co-administration of tamoxifen and clomiphene citrate as a modality for ovulation induction with proved high efficacy studied before in previous reports (Ghafourzadeh et al., 2004; Goldziehev and Axelrod, 1998; Robert et al., 2001). Co-administration of tamoxifen and letrozole as fertility preservation modality in cases of breast cancer before initiating their treatment protocols evaluated with proved efficacy and safety (Oktay et al., 2005). To the best of our knowledge, this is the first study to evaluate the combination of tamoxifen and letrozole as a novel modality for ovulation induction. The only available report that evaluated this combination studied the co-administration of letrozole and tamoxifen in the context of intrauterine insemination only (Pourmatroud et al., 2013). We found that administration of tamoxifen to letrozole appeared more advantageous than letrozole alone in ovulation induction strategy. Number of mature follicles and endometrial thickness showed marked significant difference between both studied groups as in group A, our study measures were 2.6 ± 0.8 and 8.9 ± 1.4 mm respectively to be 1.5 ± 0.9 and 7.1 ± 1.2 mm respectively in group B. Letrozole belongs to non-steroidal aromatase inhibitor that inhibits the synthesis of estrogen by blocking conversion of androgens to estrogen. Hence, reduces the negative feedback effect of estrogen at the hypothalamic pituitary axis so increasing gonadotropin secretion and stimulating ovarian follicles with locally acting in the ovary resulting in accumulation of intra ovarian androgens so increasing follicular sensitivity to FSH. Letrozole induces proper ovulation but without adverse anti estrogenic effect on the endometrium or cervical mucus. (Zeinalzadeh et al., 2010; Badaway et al., 2009). However , the situation for tamoxifen is sometimes different it is non-steroid selective oestrogen receptor modulator (SERM) which has double action as an ovarian stimulating agent and oestrogenic stimulation effect on the lower genital tract (Chia-Woei et al., 2008). It blocks oestradiol-binding sites on the hypothalamic–pituitary axis and preventing the negative feedback effect of oestradiol so increasing gonadotropin secretion and stimulating ovarian follicles hence we found a significant response regards folliculogenesis process when we co-administrated tamoxifen to letrozole in one group when compared to letrozole only group .

Our study showed significant differences in pregnancy rate observed in the treated group with tamoxifen and letrozole (21%) when compared to letrozole only group (8 %). It is postulated that endometrial thickness is one of the essential clues in determining the success in any assisted reproduction program (Chia-Woei et al., 2008). An endometrial thickness of 8 mm considered a cutoff point either for successful implantation or preclinical abortions (Dickey et al., 1993). This significant difference in pregnancy rate explained from the significant difference which found in endometrial thickness between both groups.

Tamoxifen has beneficial estrogenic stimulatory effect on the endometrium resulted in improvement of endometrial thickness in association it was found to improve of the endometrial function and receptive capacity due to increased glycogen content of the endometrial tissue at the mid luteal phase in the tamoxifen cycle as compared to endometrial tissue in the non treatment cycle (Fukushima et al., 1982). So, there was improved endometrial environment for embryo implantation could also explain higher rate of pregnancy in tamoxifen group.

The present study showed that adding tamoxifen to letrozole has valuable effect on increasing endometrial thickness with resultant increased pregnancy rates. The present study along with the previous available report [23] shows that co-administration of tamoxifen and letrozole has a potential role as co-factor during induction of ovulation for preparing the endometrium thus increasing the chances of pregnancy. However, this only available study was different to us in some points as they used this combination in association to IUI with lower endometrial thickness and pregnancy rate than our trial . We hypothesize this difference due to increased tamoxifen dose in our study 20 mg/ day when compared to 10 mg /day in that previous study.

In conclusion, our study showed promising results that co-administration of tamoxifen with letrozole in the field of reproductive medicine that could be appreciating for researchers in this field. Further multi-centered studies are required to ensure the efficacy of adding tamoxifen with letrozole as a novel regimen for induction of ovulation.

Conflicts of Interest: No conflict of interests.

REFERENCES

Aref NK, Ahmed WAS , Ahmed MR , Sedik WF (2019). A new look at low-dose aspirin: Co-administration with tamoxifen in ovulation induction in anovulatory PCOS women. J Gynecol Obstet Hum Reprod.; 48(8):673-675

Badaway A, Mosbah A, Tharwat A, Eid M (2009). Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: A Novel Protocol. *Ferti Steril*; 92(1): 352-355

Banerjee Ray P, Ray A, Chakraborti PS (2012). Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Arch Gynecol Obstet.; 285(3):873–877

Bedaiwy MA, Forman R, Mousa NA, Al Inany HG, Casper RF (2006). Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Hum Reprod . 21: 2838-2844.

Boostanfar R, Jain JK, Mishell DR, Jr., Paulson RJ (2001). A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. Fertil Steril . **75**, 1024–1026

Brown J, Farquhar C, Beek J, Boothroyd C, Hughes E (2009). Clomiphene and anti-oestrogens for ovulation induction in pcos.Cochrane Database Syst Rev 4:; CD002249

Casper RF and Mitwally MFM (2006). REVIEW . Aromatase Inhibitors for Ovulation Induction. The Journal of Clinical Endocrinology & Metabolism. 91(3): 760 – 771.

Chia-Woei W, Shang-Gwo H, Chun-Kai C, Hsin-Shih W, Hong- Yuan H, Chyi-Long L et al (2008). Ovulation induction with tamoxifen and alternate-day gonadotrophin in patients with thin endometrium. Reprod BioMed Online . 17(1):20–27

Dhaliwal LK, Suri V, Gupta KR, and Sahdev S (2011). Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome. J Hum Reprod Sci. 4(2): 76–79.

Dickey RP, Olar TT, Taylor SN *et al.* (1993). Relationship of biochemical pregnancy to pre-ovulatory endometrial thickness and pattern in *patients undergoing ovulation induction.* Human Reproduction.; 8, 327–330

Fisher SA, Reid RL, Van Vugt DA, Casper RF (2002). A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril .; 78: 280-285.

Fouda UN, Sayed AM (2011). Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized controlled trial. Reprod Biol Endocrinol. 9:84–90

Fukushima T, Choshin T, Keizo F, Masao M (1982). Tamoxifen in the treatment of infertility associated with luteal phase deficiency. Fertil Steril.;37 (6):755–61.

Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B (2009). Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. J Assist Reprod Genet. 26: 19-24.

Ghafourzadeh M, Karimi M, Karimazadeh MA, Bokai, BS (2004). Comparison between Two Methods of Ovulation Induction: Clomiphene alone and Clomiphene +Tamoxifen in PCOS Patients . Iranian Journal of Reproductive Medicine; 2. (2):74-77.

Goldziehev JW, Axelrod LR (1998). Clinical and biochemical features of polycystic ovarian disease. Fertil Steril.; 14: 631-53.

Ingle JN, Suman VJ, Johnson PA, Krook JE, Milliard JA, Wheeler RH et al (1999). Evaluation of tamoxifen plus letrozole with assessment of pharmacokinetic interaction in postmenopausal women with metastatic breast cancer. Clin Cancer Res.; 5(7):1642–1649

Lee VCY and Ledger W (2011). Aromatase inhibitors for ovulation induction and ovarian stimulation. Clinical Endocrinology.; 74, 537–546

Nahid L, Sirous K (2012). Comparison of the effects of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome. Minerva Ginecol. 64(3):253–258

Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z (2005). Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol. 23(19): 4347–4353

Pourmatroud E, Zargar M, Nikbakht R, Moramazi F (2013). A new look at tamoxifen: co-administration with letrozole in intrauterine insemination cycles. Arch Gynecol Obstet.; 287(2) :383–387

Robert Boostnfar MD, John K, Jain MD (2001). A prospective randomized trial comparing clomiphen citrate with Tamoxifen Citrate for ovulation induction. Fertil Steril. 75:(5)1024-1026

Roumen ME, Doesburg HW, Rolland R (1984). Treatment of infertile women with a deficient post-coital test with two antiestrogens: Clomiphene and tamoxifen. Fertil Steril.;41:237–43.

Sipe CS, Davis WD, Maifeld M, Van Voorhis BJ (2006). A prospective randomized trial comparing anastrozole and clomiphene citrate in an ovulation induction protocol using gonadotropins. Fertil Steril. 86: 1676-1681.

Speroff L, Glass RH, Kase NG (2004). Hormone biosynthesis, metabolism, and mechanism of action. In: Clinical gynecologic endocrinology and infertility. Baltimore, Lippincott, Williams & Wilkins, 6th ed. 31-105;488-521;1097-1132.

Steiner AZ, Terplan M, Paulson RJ (2005). Comparison of tamoxifen and clomiphene citrate for ovulation induction: a metaanalysis. Human Reproduction. 20, 1511–1515.

Zeinalzadeh M, Basirat Z, Esmailpour M (2010). Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome: *J Reprod Med*;55: 36-40.