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AROMATASE INHIBITOR VERSUS CLOMIPHENE CITRATE FOR INDUCTION OF OVULATION IN UNEXPLAINED INFERTILITY

By

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ABSTRACT

Background: Infertility is the inability of a sexually active couple with no contraception to achieve natural pregnancy within one year. Unexplained female infertility should be a term used when the female reproductive system has been evaluated according to current agreed standards, and no abnormalities are detected. Clomiphene citrate (CC) has been used as a first-line ovulation induction agent. Aromatase inhibitors are new groups of drugs for fertility treatment. Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction.

Objective: This study compared the effect of clomiphene citrate and letrozole in induction of ovulation in the treatment of infertility.

Patients and methods: This prospective randomized controlled study was conducted at Obstetrics and Gynecology Department, Al-Azhar University Hospitals and Al-Ahrar Hospital (ministry of health) on 100 women between 20 - 35 years old having unexplained infertility. Patients were divided into two equal groups: Letrozole group received 5 mg of letrozole orally daily from day 3 to day 7 of menses, and CC group, women received 100 mg of clomiphene citrate orally once daily from day 3 to day 7 of the menses and for up to three menstrual cycles.

Results: There was a significant increase of positive pregnancy test in letrozole group compared to clomiphene group.There was a significant difference in multiple pregnancy rate and high significant differences in Doppler flow indices between letrozole group and clomiphene group. Conclusion:Letrozole has a better ovulation rate with better follicular development and higher pregnancy rate, CC group has less effect on the endometrial thickness and side effects.

Keywords: Unexplained infertility, induction of ovulation, clomiphene citrate, letrozole (aromatase inhibitor).

INTRODUCTION

Infertility is customarily defined as failure of a couple to conceive after 12 months of unprotected regular intercourse *(Esteves et al., 2015).*

Infertility causes, according to the current consensus, include anovulation, male factor, tubal factor, cervical factor, endometriosis, and unexplained infertility (UI) *(National Institute for Clinical Excellence, 2013).*

Unexplained female infertility is a term used when the female reproductive system has been evaluated according to current

agreed standards, and no abnormalities are detected *(Hamada et al., 2011).*

Clomiphene citrate is widely accepted as first line of ovulation-inducing agent *(Angel et al., 2014).*The starting dose of clomiphene citrate is 50 mg per day for 5 days, commencing between day 2 and 5 of menses *(Vause et al., 2010).*

Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme and catalyzes the rate-limiting step in the production of estrogens *(Prasad and Sharma, 2018).*

Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. It has no adverse effect on endometrium and cervical mucus *(Kar, 2012).*

Letrozole, in contrast to CC, increases endometrial thickness by upregulation of estrogen receptors. So, it increases pregnancy rate and decreases incidence of multiple pregnancy *(Mitwallyet al., 2012).*

The aim of this prospective study was to compare results of letrozole with clomiphene citrate in infertile patients with unexpaind infertility.

PATIENTS AND METHODS

This prospective randomized controlled study was performed at Obstetrics and Gynecology Department, Al-Azhar University Hospitals and Al-Ahrar Hospital (Ministry of Health) during the period from August 2018 to August 2019.

All patients involved in the current study were informed about the nature and details of the current work and a written consent was obtained for each one.

One hundred patients diagnosed as unexplained infertility were included in the work. They were divided into 2 equal groups:

•**Group (A)** taking letrozole 5 mg tablet (Femara, Novartis, East Hanover, NJ) orally once daily started in day 3 to day 7 of menstrual cycle.

•**Group (B)** taking clomiphene citrate (Clomid-Aventis) 100 mg tablet orally once daily started day 3 to day 7 of menstrual cycle to be repeated for 3 cycles.

Inclusion criteria:

1. Patients with age 20 to 35 years.
2. Patients with infertility lasting ≥one year.
3. Patents assigned as having unexplained infertility.

Exclusion criteria:

1. Tubal factor infertility.
2. Hypothalamic amenorrhea.
3. Any hormonal abnormalities; elevated serum PRL >26 ng/mL, and basal day F.S.H > 10 m IU/ml.
4. Patients with irregular cycles.
5. Patients with Ovarian cysts >20mm in mean diameter in the second or third day of the menstrual cycle.
6. Patients with endometriosis.

All patients were subjected to:

1. Detailed history taking including full personal, menstrual and medical history.
2. General, abdominal and local examinations.

3. Pelvic ultrasound, hormonal profile, semen analysis and laparoscopic free.
4. Basal transvaginal ultrasound examination.
5. Folliculometry by transvaginal ultrasound starting from day 9 of the menstrual cycle then every other day.
6. Sexual intercourse on the day of HCG injection and every other day for 4 days after HCG injection.
7. Pregnancy test done two day after next missed period.
8. Transvaginal ultrasound examination was performed 5 weeks after last menstrual period.
9. Transabdominal ultrasoune examination was performed 7 weeks after last menstrual period.

Outcome measures:

1. Primary outcome:
   - Number and size of mature follicles in each group.
   - Endometrial thickness on day of HCG administration (mm).
2. Secondary outcome measures were pregnancy rate per cycle and multiple pregnancies.

Statistical analysis:

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare continuous quantitative data of two groups, Mann whitney test (for non-normally distributed data) and independent sample t test (for normally distributed data) were used. The level statistical significance was set at 5% ($P<0.05$).

RESULTS

There was no significant difference between both groups as regards demographic characteristics and serum E2 levels, FSH levels and LH levels at the second day of cycle between both groups **(Table 1)**.

Table (1): Comparison between the studied groups regarding demographic characteristics, serum E2 levels, FSH levels and LH levels at the second day of cycle

Groups / Parameters	**Letrozole group (n = 50)**	**Clomiphene group (n = 50)**	**p**
Age (years)			
Mean ± SD	33.72 ± 3.9	33.06 ±2.53	0.318¥
Range	20-40	29-39	
Duration of infertility (years)			
Mean ± SD	7.84 ± 2.49	7.1 ± 3.47	0.058#
Range	2-14	3-15	
BMI (kg/m^2)			
Mean ± SD	25.8 ± 4.6	27.2 ± 3.8	0.09¥
Range	18-36	22-35	
Type of infertility			
Primary	20 (40%)	18 (36%)	0.68∞
Secondary	30 (60%)	32 (64%)	
Serum E_2at 2nd day of cycle			
Mean ± SD	28.14 ± 9.07	29.26 ± 10.2	0.114#
Range	12-54	10-53	
FSHat 2nd day of cycle			
Mean ± SD	4.87 ± 1.69	5.1 ± 2.07	0.181#
Range	1.1-9.9	1.6-10.9	
LH at 2nd day of cycle			
Mean ± SD	8.25 ± 4.51	8.99 ± 5.49	0.574#
Range	1.2-15.7	0.6-21	

¥ Independent sample t test # Mann Whitney test ∞Chi square test

There was statistically significant difference as regard to number of mature follicles, and endometrial thickness and positive pregnancy test and multiple pregnancy rates with no deference according to ectopic pregnancy **(Table 2)**.

Table (2): Comparison between studied groups as regard to number of mature follicles,endometrial thickness,clinical pregnancy rate and secondary pregnancy outcome

Groups / Parameters	**Letrozole (n = 50)**	**Clomiphene (n = 50)**	**P**
Number of mature follicles			
Mean ± SD	1.84±0.58	2.3 ± 0.76	0.001
Range	1-3	1-3	
Endometrial thickness on hCG day (mm)			
Mean ± SD	9.6 ± 0.9	7.2 ± 0.3	< 0.0001
Range	(8-11)	(6-9)	
Clinical pregnancy rate			
No	29 (58%)	39 (78%)	0.03
Yes	21(42%)	11(22%)	
Secondary pregnancy outcome in studied groups			
	(n = 21)	**(n = 11)**	
Multiple pregnancy rate	1 (4.8%)	4 (36.4%)	4 (36.4%)
Ectopic pregnancy rate	0	0	

There were statistically high significant differences in Doppler flow indices including of uterine artery, pulsatility index and resistance index between letrozole group and clomiphene group **(Table 3)**.

Table (3): Doppler flow indices of uterine and subendometrial vessels on the day of LH surge

Groups / Parameters	Letrozole group (n = 50)	Clomiphene group (n = 50)	P
Uterine artery			
P1	2.3 ± 0.11	2.9 ± 0.2	< 0.001
P2	0.4 ± 0.11	1.2 ± 0.13	< 0.001
Subendometrial artery			
PI	1.31 ± 0.5	1.75 ± 0.6	< 0.001
RI	0.69 ± 0.1	0.78 ± 0.12	< 0.001

PI = Pulsatility Index, RI = Resistance Index

DISCUSSION

The present study aimed to compare the effect of clomiphene citrate and letrozole in induction of ovulation in the treatment of infertile women with unexplained infertility.

About 60% of letrozole group and 64% of CC group had secondary infertility. Statistically, there was no significant difference between both groups.

Ibrahim et al. (2012) stated that there were no significant differences between

women of both groups concerning age, BMI, duration and types of infertility.

Mosammat et al. (2009) reported that there war a significant difference in follicular development in both groups.

An aromatase inhibitor, letrozole, decreases estrogen concentration, which in turn results in an increase in FSH secretion from the pituitary gland. Letrozole causes temporary accumulation of androgens in the ovarian follicles which increase the sensitivity of the growing follicles to FSH by increasing the expression of FSH receptors *(Veltman-Verhulst et al., 2012).*

With a half-life of 45 h, administration of letrozole in drug levels extremely decreased during the late follicular phase and, therefore, estradiol produced by growing follicles increases, which suppress the release of FSH, and those follicles that are smaller than the dominant follicle undergo atresia (degeneration), leading to mono-ovulation in most cycles *(Ramezanzadeh et al., 2011).*

On the other hand, CC induces prolonged estrogen receptor depletion in the brain. So, the central suppression of FSH release is not put into effect by the increased estradiol. Therefore it produces development of multiple follicles, which do not yield oocytes but facilitated the estrogen concentration and risk of multiple pregnancies *(Casper and Mitwally, 2010).*

Liu et al. (2014) found that the concentration of serum E2 on hCG day was lower for women treated with letrozole than for those treated with clomiphene. Significant heterogeneity existed in this comparison.

On the day of hCG triggering, ultrasonography assessment for the endometrial thickness demonstrated that the mean endometrial thickness on the day of hCG administration (measured by transvaginal ultrasonography) was higher in letrozole group comparing with CC group. Thus, the endometrium was of adequate thickness to allow implantation.

Kar (2012) reported that the mean endometrial thickness was slightly higher in Letrozole group, compared to CC group. *Ibrahim et al. (2012)* discovered that, in patients stimulated with CC for IUI, no pregnancy was observed when the endometrial thickness was 6 mm on the day of hCG administration, and all preclinical abortions emerged when endometrial thickness was 6–8 mm.

However, *Ramezanzadeh et al. (2011)* have announced decreased endometrial thickness at 7.5 mg letrozole. Probably, the higher dose of letrozole leads to greater inhibition of E2 and thus decreases endometrial thickness, which brings about a lower pregnancy rate. This seems to indicate that 2.5 mg letrozole over 5 days or extended treatment may produce a higher rate of clinical pregnancy than clomiphene.

In our study, there was a significant increase of positive pregnancy test in letrozole group in comparison to clomiphene group However; there was a non-significant difference in abortion rate between both studied groups.

Pregnancy rate per cycle was astonishingly high with Letrozole in the study of *Kar (2012)* comparing with the results of *Badawy et al. (2009)* who presented the pregnancy and neonatal outcomes following the use of aromatase

inhibitors and clomiphene citrate (CC) for ovulation induction in comparison with the outcome after spontaneous (non-stimulated) pregnancy. They reported that pregnancy rate was slightly better pregnancy rate in CC group than Letrozole group.

Zeinalzadeh et al. (2010) reported slightly better pregnancy rates with letrozole. However, no statistically significant difference between the two groups.

In our study, there was a significant difference in multiple pregnancy rate between letrozole group and clomiphene group, but there were no significant differences as regard to ectopic pregnancy rate and OHSS.

Badawy et al. (2009) detected one molar pregnancy and two congenital anomalies in the letrozole group, and one ectopic pregnancy and one congenital anomaly in the clomiphene group. They reported that both aromatase inhibitors and CC are equally effective in inducing and augmenting ovulation in many situations. Both drugs resulted in favorable pregnancy outcomes and average miscarriage rates. The use of least effective doses will result in a lower incidence of multiple pregnancies and usually avoid ovarian hyper stimulation syndrome.

In our study, there were statistically high significant differences in Doppler flow indices including indices of uterine artery, pulsatility index and resistance index between letrozole group and clomiphene group. *Ibrahim et al. (2012)* found that there were statistical significant differences in Doppler flow indices of uterine and subendometrial vessels between the two groups.

CONCLUSION

In women with unexplained infertility, induction of ovulation using letrozole have a better ovulation rate with better follicular development and higher pregnancy rate that using CC beside less effect on the endometrial thickness and side effects.

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المقارنة بين فاعلية مثبط إنزيم الأروماتيز و سترات الكلوميفين فى الحث على التبويض فى حالات العقم غير المبرر

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خلفيـــة البحـــث: العقـــم هـــو محاولـــة حـــدوث الحمـــل بواســـطة محـــاولات الإتصـــال المتكـــرر لمـــدة ســـنة علـــى الأقـــل دون نجـــاح وتعتبرالحالـــة غيـــر مبـــررة الســـبب بعـــد عمـــل الفحوصـــات اللازمـــة والتـــى تثبـــت أنـــة لا يوجـــد أى خلـــل فـــى هورمونـــات الغـــدة النخاميـــة ولا تعـــانى المـــراة مـــن متلازمـــة المبـــيض متعـــددة التكيســـات ولا يوجـــد أى تلـــف أو انســـداد فـــى قنـــاتى فـــالوب ولا يوجـــد مـــا يـــدل علـــى فشـــل المبـــايض المبكـــر أو تشـــوهات فـــى الـــرحم او عنـــق الـــرحم او المهبـــل أو حـــدوث التهابـــات فـــى الحـــوض أو وجـــود بطانـــة الـــرحم المهـــاجرة ولا يوجـــد أيضـــا أى خلـــل لـــدى الـــزوج والتأكـــد مـــن صـــحة الحيوانات المنوية.

الهـــدف مـــن الدراســـة: المقارنـــة بـــين عقـــار الليتريـــزول وعقـــار ســـترات الكلـــوميفين فـــى النســـاء اللاتـــى يعـــانون مـــن ضـــعف الخصـــوبة عـــن طريـــق تحديد معدل حدث الإباضة وسمك بطانة الرحم ومعدل حدوث الحمل.

المرضـــى وطـــرق البحـــث: تمـــت هـــذه الدراســـة بقســـم التوليـــد وأمـــراض النســـاء بمستشـــفيات جامعـــة الأزهـــر ومستشـــفى الأحـــرار التعليمـــى (وزارة الصـــحة والســـكان) علـــى ١٠٠ مـــريض مـــن حـــالات تـــاخر الإنجـــاب للدراســـة، مقســـمون إلـــى مجمـــوعتين متســـاويتين: المجموعـــة الأولـــى تتنـــاول عقـــار اليتريـــزول بجرعـــة ٥مجـــم يوميـــا مـــن اليـــوم الثالـــث إلـــي اليـــوم الســـابع مـــن الحـــيض، والمجموعـــة الثانيـــة تتنـــاول عقارســـترات الكلـــوميفين بجرعـــة ١٠٠ مجم يوميا من اليوم الثالث الي اليوم السابع من الحيض.

نتـــائج البحـــث: معـــدلات التبـــويض وحـــدوث الحمـــل وزيـــادة فـــى ســـمك بطانـــة الرحم أعلى مع عقار البيتريزول مقارنة بعقار سترات الكلوميفين.

الاســـتنتاج: ينصـــح باســـتخدام عقـــار الليتريـــزول نظـــرا لتـــأثيرة الأفضـــل علـــى التبـــويض وحـــدوث معـــدلات الحمـــل مـــع وجـــود أعـــراض جانبيـــة أقـــل ولا يوجـــد فـــرق بينهمـــا فـــى معـــدلات الأجهـــاض وحـــدوث تشـــوهات الأجنـــة وحدوث الحمل خارج الرحم.