Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

Letrezole or clomide for ovulation induction in patients with unexplained infertility.

Dr- Nadia Saddam AL Assady / CABOG-FIBOG.

Lecturer in obstetrics and gynecology department.

College of medicine / Thiqar university.

Abstract:

Background:

The aim of our study to compare the efficacy of letrezole to clomiphene citrate in patient with unexplained infertility as empirical treatment.

Methods:

200 patients with unexplained infertility randomly divided into two groups the first group received(5mg letrezole from the day 3-7 of menstrual cycle), the second group received (100 mg clomiphene citrate from the day 2-5 of menstrual cycle), follicular development followed by serial U/S, when one or more follicles reach > 18mm in diameter ovulation trigger by hCG and timed intercourse was advise later on . Pregnancy test was performed 5 days after the miss period to confirm the pregnancy, the main outcome was the pregnancy rate and the secondary outcome was follicle development and endometrial thickness.

Result:

Both groups were comparable regarding the ovulation rate (62.5% in the group B (clomid group) and 75.2% in group A (letrezole group) (P = 0.35), the endometrial thickness was statistically significant difference in the letrzole group on day of HCG administration (6.6_$^{+}$1.69 mm in the letrezole group, 5.4_$^{+}$1.61 mm in the clomide group, P < 0.001). Serum estradiol was significantly lower in letrezole group (456_$^{+}$150 versus 922_$^{+}$301 pg/ml, P < 0.001). While the rate of multiple follicular development was greater in the group B (clomide 55.15%, letrezole 25.41%, P=0.025), which was statistically significant. The pregnancy occurred in 36 out 100 (36%) in letrezole group and 12 out 100 (12%) in clomide group, the difference was highly statistically significant (P < 0.025).

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

Conclusion:

Letrezole had a good efficacy and may be regard as first line treatment in patients with unexplained infertility in comparison with clomiphene citrate.

Introduction:

Infertility is define as inability to conceive after one year of regular unprotected intercourse. The three most common causes of infertility are an ovulation, tubal blockage and semen fluid abnormality. Unexplained infertility is common problem and is responsible for about (25-30 %) of couples in which they will have no cause for their sub fertility following routine investigations [(1)]. The diagnosis of unexplained infertility is done after finding normal semen analysis, patent fallopian tubes and normal ovulation [(2)]. The absence of an abnormal finding does not preclude the presence of an obstacle to normal reproduction. Therefore , the treatment for unexplained infertility is empiric because it does not imply a precise impairment or functional defect [(3)]. Clomiphene citrate and intrauterine insemination, controlled ovarian hyper stimulation with IUI, IVF, expectant observation with timed inter course and life style changes are the most frequent optional treatment in patient with unexplained infertility [(4,5)].

For the last couple of decades, Clomiphene citrate remain the most common drug used for ovulation induction in infertile patients with an ovulation and unexplained infertility either alone or in combination with HMG or recombinant FSH [(6)]. Several hypotheses explain the mode of action of Clomiphene citrate but the exact mechanism and sit of action need to be clarified, the overall action can be due to its effect on hypothalamus, pituitary and ovary [(7)]. Clomiphene citrate is a non steroidal triphenylethylene derivative that has both estrogen agonist and antagonist properties [(8)].

Clomiphene citrate binds to estrogen receptors in the hypothalamus, this prolonged binding interrupts the negative feedback of increasing estrogen level and results in continued production of FSH which stimulate follicular growth and development. The rate of ovulation in previous experiences was 60%-80% and the rate of pregnancy per cycle was 10%-20% per cycle [(9)]. The gap between ovulatory and pregnancy rates had variously attributed to its anti-estrogenic effects on endometrial, cervical mucus and high LH, resulting in luteal phase dysfunction. Several modification have been tried to overcome the unwanted effects by clomiphene plus therapy. So maximum cumulative pregnancy rate was around 30% through 3-6 consecutive cycles, the conception rate was the same 10%-15% [(10)]. However clomiphene resistance occurs on 15-20%, moreover

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

it may affect cervical mucus and endometrium hence result in this difference between ovulation rates and pregnancy rates [11].Letrezole is a third generation aromatase inhibitor that acts by inhibiting estrogen synthesis so cause negative feedback inhibition on hypothalamus-pituitary axis thus stimulate more FSH release from pituitary gland lead to more follicular growth and development [12].

It also known to increase intrafollicullar androgen which is thought to up regulate and sensitize FSH receptors in the ovary [13]. Letrezole unlike clomiphene citrate does not decrease estrogen receptors or thin the endometrial lining [14]. letrezole' s short half life (44 hours) certain its clearance before implantation occur and this unlike to that of clomiphene citrate.

Letrezole was introduce in practice in the year of 2000 and it is regarded as second line option specially in patients with clomiphene resistance. Letrezole at the customary dose of 2.5mg induce mono follicular response and does not adversely affect the endometrial or cervical mucus due to absence of peripheral estrogen receptor blockage. The estradiol level during ovulation induction with letrezole is significantly lower when compared other stimulation protocols. Such a reduction may be contributory, in part, to pregnancy rates. In this study we try to compare the effect of letrezole to clomiphene citrate in patients with unexplained infertility.

Methods:

A prospective randomized study that attend at the outpatient clinic of bint al huda teaching hospital and at the privet clinic in Thiqar city from the period of 1st June 2012 to the period of 1st June 2014 in which 200 patients with unexplained infertility were included in our studies, all patients were reviewed for their past medical and surgical history and clinical examination were done for them, they were counseled about the study and the benefit and side effect of each drugs and informed consent have been taken for each patients. Inclusion criteria include: age of patients between (20-40) years old, infertility for > 2 years, patients consider to have unexplained infertility when they fulfill the following points: normal hormonal assays in the (2-4) days of menstrual cycle which include (FSH, LH, testosterone and DHEAS), normal prolactin and TSH at any time of menstrual cycle, normal ovulation by measuring midluteal progesterone level which is > 5 ng/l, patent both tubes on hystrosalpangiography and normal semen parameters according to WHO criteria[15]. Our exclusion criteria were patients with irregular cycles, ovarian cyst in early follicular phase, FSH > 12 mlU/ ml, age less than 15 years and more than 40 years, tubal blockage, hormonal abnormalities (hyper or

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

hypothyroidism and high prolatin level).

The patients then randomized to two group the letrozole group and the clomiphene citrate. Ultrasounds examination was performed at early follicular phase as basic first examination and to exclude any ovarian cyst. The group A included 100 patients were received letrozole (5 mg) orally twice daily from days (3-7) of the cycle, while the group B included 100 patients were received clomiphene citrate (50 mg) orally twice daily from days (2-6) of the cycle. Ultrasound were performed on day 12 of menstrual cycle in both groups to pick up follicular growth and endometrial thickness.

Human chorionic gonadotropin (10000 IU/IM) were giving when one follicle reach 18 mm or more in diameter and when endometrial thickness exceeding 7 mm in diameter and estradiol level also measured at day of HCG injection . HCG injection was cancelled if patients have > 3 follicles (15-18) mm. Sexual intercourse was advise on day of HCG injection and every other day for 3 days after the injection. Pregnancy test was done 5 days after missed period to confirm the pregnancy, ultrasound was done 5 weeks after last menstrual period to confirm fetal cardiac activity and exclude ectopic pregnancy. The primary outcome was the clinical pregnancy rate (presence of gestational sac in the uterus detected by U/S). the secondary outcome was the number of follicles with diameter > 18 mm, serum estradiol and endometrial thickness on the day of HCG injection, ongoing pregnancy rate (pregnancy beyond 20 weeks gestation), miscarriage rate (natural loss of pregnancy before 20 weeks gestations), ectopic pregnancy and multiple pregnancy rate.

Data analyses were performed using SPSS for Windows. Means (SD) and proportions were compared between the two groups using Student, s t-test and chi square tests, respectively. Between-group differences were regarded as significant when $P < 0.05$.

Result:

A total of 200 patients were randomly divided into two groups [group A letrezole (n=100), group B clomide (n=100)]. There were no statically significant differences between the two groups regarding the age, BMI, duration of infertility as shown in (table 1). The rate of multiple follicular development was greater in the group B (clomide 55.15%, letrezole 25.41%, P=0.025), which was statistically significant while the rate of single follicular development was greater in the group A (letrezole 75.38%, clomide 52.73%, P=0.028), which also was statistically significant.The ovulation rate was 62.5% in the group B (clomid group)

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

and 75.2% in group A (letrezole group) (P = 0.35). There was statistically significant difference between the two groups regarding endometrial thickness on day of HCG administration (6.6_$^{+}$1.69 mm in the letrezole group, 5.4_$^{+}$1.61 mm in the clomide group, P < 0.001). Serum estradiol was significantly lower in letrezole group (456_$^{+}$150 versus 922_$^{+}$301 pg/ml, P < 0.001). The pregnancy occurred in 36 out 100 (36%) in letrezole group and 12 out 100 (12%) in clomide group, the difference was highly statistically significant (P < 0.025). There is 10 cases of abortions in group A and 12 cases of abortion in group B, there were 6 twin cases in the 1st group and 5 twin cases in the 2nd group. One case in the clomide group have ectopic pregnancy, no cases of ovarian hyperstimulation syndrome have been identified in both groups.

Discussion:

clomiphene citrate has been used for ovulation induction for anovulatory infertility and unexplained infertility since 1967. It still used as first line treatment, but it associated with resistance in (15% - 20%) of cases, poor cervical mucus and endometrial thickness in (20%- 40%) of cases due to prolong depletion in estrogen receptors in the endometrium and in the cervix [16,17]. Other drug that can be used for induction of ovulation is the aromatase inhibitor, letrezole, but evidence of it efficacy is conflicting.

Letrezole inhibit aromataization so prevent conversion of androsterone to estrogen so enhance FSH production from anterior pituitary gland leading to follicular growth and development also recently they found that letrezole enhance the sensitivity of follicle to FSH action through amplification of FSH receptors gene expression [18].

In our study ovulation rate was 62.5% in the clomiphene citrate and 75.2% in the letrezole group which was statistically not significant (P=0.35) and this was correspond to other studies , Sujata et al [19] , Badway et al [20], Bayer et al [21]. In the present study multiple follicles development was greater in group B which was statistically significant and this was the same result for other studies Sujata et al [19] , Badway et al [20], and in contrast to the result of the other studies Haqnawaz et al [22], Fouda et al [23]. There was statistically significant difference between the two groups regarding endometrial thickness on day of HCG administration (6.6_$^{+}$1.69 mm in the letrezole group, 5.4_$^{+}$1.61 mm in the clomide group, P < 0.001). Serum estradiol was significantly lower in letrezole group (456_$^{+}$150 versus 922_$^{+}$301 pg/ml, P < 0.001), the results of our study are in agreement with the result of Fouda et al [23], Metwally et al [24], Sh Tehrani Nejad et al [25], but other studies reveal the endometrial thickness was comparable between the two groups [26,27].

The pregnancy occurred in 36 out 100 (36%) in letrezole group and 12 out

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

100 (12%) in clomide group, the difference was highly statistically significant (P < 0.025). This result of our study was similar to the result of other studies Hendawy et al [28], who stated that pregnancy rate was higher in letrezole group comparable with clomide this difference was statistically significant could be attributed to the effect of letrezole on endometrial thickness which is better than clomide. The majority of studies that compare between those two drugs in patients with unexplained infertility revealed that letrezole produced few numbers of mature follicles compared with clomide but the pregnancy rate was similar or the same between the two drugs [29]. We suppose that letrezole resulted in comparable pregnancies rate despite few numbers of follicles because it has no side effect on endometrium. However, Cortinez reported letrezole treatment in infertile ovulatory women was associated with in-phase histological dating of endometrium and normal pinopode expression [30]. So in our study highlights the need for the larger randomized controlled studies to determine whether the letrezole group is the first choice for the patients with unexplained infertility.

The result of our study reveal no increase incidence of congenital anomalies which was same to that of Foman et al [31].

Conclusion:

Letrezole had a good efficacy and may be regard as first line treatment in patients with unexplained infertility in comparison with clomiphene citrate.

Table (1): Demographic criteria for both groups.

Variables	Group A (letrezole)	Group B(clomide)	P value
Age (years)	26.22-+3.32	27.41-+ 3.41	0.233
Parity	0.3 -+ 0.1	0.4 -+ 0.2	0.11
BMI(kg/m^2)	26.78 -+2.24	26.67_+ 2.01	0.34
Duration of infertility	4.39_+ 1.96	4.45_+19.4	0.076

*BMI: body mass index.

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

Table (2). Ovulation induction cycle characteristic.

Variable	Group A	Group B	P value
No of cycles completed	220	230	
Rate of single follicle development	75.38%	52.73%	0.028
Rate of multiple follicles development	25.41%	55.15%	0.025
Endometrial thickness on day HCG(mm).	6.6_$^{+}$1.69	5.4_$^{+}$1.61	0.001
Serum estradiol (pg/ml)	456_$^{+}$150	922_$^{+}$301	0.001
Ovulation rate	75.2%	62.5%	0.35

Table (3). Pregnancy outcomes.

Variable	Group A	Group B	
Pregnancy rate	36%	12%	0.025
Abortion	10%	12%	0.926
Multiple pregnancy	5%	6%	0.756

References :

1-Kamath MS, Bhattacharya S. Demographics of infertility and management of unexplained infertility. Best Pract Res Clin Obstet Gynaecol 2012.

2-Quaas, A. and Dokras, A. Diagnosis and Treatment of Unexplained Infertility. Reviews in Obstetrics Gynecology I, 2008, 69-76.

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

3-The Practice Committee of the American Society for Reproductive Medicine. Effectiveness and treatment for unexplained infertility. Fertli Steril 2006; 86:111-4.

4-Stephen EH, Chandra A. Updated projections of infertility in the United states: 1995-2025. Fertil Steril 1998; 70:30-4.

5- The Practice Committee of the American Society for Reproductive Medicine, Optimal evaluation of infertile female. Fertli Steril 2006; 86: 264-7.

6-Badawy A, El Nashar A, EI Totongy M. Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmentation ovulation in the management of unexplained infertility : a randomized double-blind controlled trial. Fertli Steril 2006; 86: 647-70.

7-Adashi EY. Clomiphene citrate: mechanism and site of action : hypotheses revisited. Fertli Steril, 1984; 42: 331-42.

8- Practice Committee of the American Society for Reproductive Medicine. Use of Clomiphene citrate in women. Fertli Steril, 2006; 86(5 suppl 1):S 187-93.

9-Dicky RP, Holtkamp DE. Development, pharmacology and clinical experience with clomiphene citrate. Hum Reprod Update 1996;2:483-506.

10-Mukheriee S, Sharma S and Chakravarty BN. Comparative in Polycystic Ovarian Syndrome and Unexplained Infertility –A Prospective Clinical Trial. Journal of Human Reproductive Sciences,3,80-84.

11-Homburg R. Clomiphene citrate-end of an era? A mini-review. Hum Reprod 2005; 8: 2043-51.

12-Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006; 85: 277-284.

13- Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interaction in primate ovarian follicle development. J Clin Endocrinol Metab 1999; 84:2951-2956.

14-Topipat C, Choktanasiri W, Jultanmas R, et al. A comparison of the effects of clomiphene citrate and the aromatase inhibitor letrezole on superovulation in Asian women with normal ovulatory cycles. Gynecol Endocrinol 2008; 24: 145-150.

15-Menkveld, R. Clinical significance of the low normal sperm morphology value as proposed in the fifth edition of the WHO laboratory manual for the examination and processing of human semen. Asian Journal of andrology, 2010; 12: 47-58.

16-Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Hum Reprod 1990; 5:670-4.

17- Eden JA, Place J, Carter GD, Jones J, Alaghband-Zadeh J, Pawson ME. The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. Obstet Gynecol. 1989;73:187-90.

18-Weil SJ, Vendola K, Zhou J, Adesanya OO, Wang J, Okafor J, et al.

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

Androgen receptor controlled ovarian hyperstimulation in the primate ovary: cellular localization, regulation, and functional correlation. J Clin Endocrinol Metab. 1998;83:2479-85.

19- Sujata Kar. Clomiphene citrate or letrezole as first line ovulation induction drug in infertile PCOS women: A prospective randomized trial . J Hum. Reprod. Sci. 2012; 5(3): 262-265.

20-Badawy A, Aal IA, Abulalta M. Clomiphene citrate or Letrezole for ovulation induction in women with poly cystic ovarian syndrome: A prospective randomized trial. Fertil Steril. 2009; 92:849-52.

21-Bayar U, Tanriverdi HA, Aykut B, Ayoglu F, Ozcan O, Erdal K. Letrezole vs clomiphene citrate in patients with ovulatory infertility. Fertil Steril. 2006;85:1045-8.

22-HaqNawas F, Virk S, Qadir T and Imam S. Comparison of letrezole and clomiphene citrate efficacy along with gonadotrophins in controlled ovarian hyperstimulation for intrauterine insemination cycles. Journal of reproduction and infertility, 2013;14:138-142.

23-Usama M Fouda, Ahmed M Sayed. Extended regimen versus clomiphene citrate for super ovulation in patients with unexplained infertility undergoing intrauterine insemination: A randomized controlled trial. Reproductive biology and endocrinology 2011, 9:84.

24-Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an adequate response to clomiphene citrate. Fertil Steril. 2001, 75(2): 305-309.

25-Sh Tehrani Nejad E, Abediasl Z, Rashidi BH, Azimi Nekoo E, Shariat M, Amirchagh maghi E. Comparison of the efficacy of the aromatase inhibitor letrezole and clomiphene citrate gonadotropins in controlled ovarian hyper stimulation:A prospective, simply randomized, clinical trial. J Assist Reprod Genet 2008, 25(5): 187-190.

26 -Badawy A, El Nashar A, EI Totongy M. Clomiphene citrate or aromatase inhibitors for super ovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized clinical trial. Fertil Steril. 2009, 92(4): 1355-135.

27-Al-Fozan H, Al-Khadouri M, Tang SL, Tulandi T: A randomized trial of letrezole versus clomiphene citrate in women undergoing super ovulation. Fertil Steril 2004, 82(6): 1561-1563.

28-Sherif F, Hendawy, Hanan E, Samaha and Mohamed F, Elkholy: letrezole versus clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome undergoing intrauterine insemination. Clinical Medicine Insight: Reproductive Health 2011:511-16.

29-Requena A, Herrero J, Landeras J, Navarro E, Neyro JL, Savador C, Tur R, Callejo J, Checa MA, Farre M, et al: use of letrezole in assisted reproduction: a systematic review and

Web Site: https://jmed.utq.edu.iq Email:utjmed@utq.edu.iq
ISSN (Print):1992-92 18, ISSN (Online):1992-92 18
DOI: https://doi.org/10.32792/utq/utjmed/15/1/6

meta-analysis. Hum Reprod Update 2008, 14(6):571-582.

30-Cortinez A, De Carvalho I, Vantman D, Gabler F, Iniguez G, Vega M: Hormonal profile and endometrial morphology in letrezole-controlled ovarian hyper stimulation in ovulatory infertile patients. Fertil Steril 2005, 83(1):110-115.

31 -Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R: Fetal safety of letrezole and clomiphene citrate for ovulation induction. J Obstet Gynecol Can 2007, 29(8):668-671

.

ليتريزول اوكلوميفين سيتريت لتحفيز التبويض للمرضى الذين يعانون من العقم غي معروف السبب

نادية صدام الاسدي

الخلاصة:

المقدمة:

هدف الدراسة مقارنة فعالية اليتريزول للكلوميفين سيتريت للمرضى الذين يعانون من العقم كعلاج مساعد

طريقة العمل:

شملت الدراسة (٢٠٠) مريضة من اللواتي يعانون من عقم غير معروف السبب قسمت بطريقة عشوائية إلى مجموعتين، المجموعة الأولى استلمت (٥ ملغم ليتريزول من اليوم الثالث إلى اليوم السابع من الدورة الشهرية) المجموعة الثانية استلمت (١٠٠ ملغم كلوميفين سيتريت من اليوم الثاني إلى اليوم السادس من الدورة الشهرية) نمو الحويصلة تمت مراقبته عن طريق السونار، تم تسريع التبويض عن طريق حقن الhCG عند وجود واحدة أو أكثر بحجم أكثر من ١٨ ملم. فحص الحمل عمل بعد ٥ أيام عن موعد تأخر الدورة. النتائج الأولية هي معدل الحمل والنتائج الثانوية هي نمو الحويصلة وسماكة بطانة الرحم.

النتائج:

كلا المجموعتين متقاربتين من ناحية معدل التبويض (٦٢,٥%) في مجموعة ب (كلوميفين سيتريت) و (٧٥,٥%) في مجموعة ا (ليتريزول) (P = 0.35)، بينما كان معدل سماكة بطانة الرحم إحصائيا أكثر في مجموعة ا (ليتريزول) في يوم اعطاء ال hCG، (1.69 $^{+}$_6.6 ملم في مجموعة ا (ليتريزول) و 1.61 $^{+}$_5.4 ملم في مجموعة ب (كلوميفين سيتريت). مستوى هرمون الايسترادايول كان إحصائيا اقل في مجموعة ا (ليتريزول) (150 $^{+}$_456 مقابل 301 $^{+}$_922 بيكوغم/ مل) (P< 0.001) . بينما كان معدل نمو الحويصلات المتعددة كان أكثر في مجموعة ب (كلوميفين سيتريت)(كلوميفين ٥٥,١٥%)، (ليتريزول ٢٥,٤١%) (P =0.025) وهذا إحصائيا أكثر فائدة . وكان هنالك اختلاف إحصائي واضح من حيث معدل الحمل (٣٦%) في مجموعة ا (ليتريزول) و (١٢%) في مجموعة ب (كلوميفين سيتريت) (P < 0.025).

الاستنتاج :

ليتريزول لديه فعالية جيدة وبلامكان اعتباره الخط الأول للمرضى الذين يعانون من العقم غي معروف السبب بالمقارنة مع الكلوميفين سيتريت .