

Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation

Maysoon Sharief, Najlaa Rasmee Nafee

Abstract

Objective: To compare the efficacy of letrozole in the induction of ovulation with clomiphene citrate in patients with polycystic ovary syndrome and primary infertility.

Methods: The prospective clinical trial was conducted at Basrah Maternity and Child Hospital, Basrah, Iraq, between January 2012 and April 2013, and comprised women with polycystic ovarian syndrome and primary infertility who were randomised into 2 groups. Group A received 100-200mg clomiphene citrate daily while group 2 received letrozole (2.5-5mg) daily. Both groups were followed by ultrasound until the dominant follicle reached a diameter >18mm, human chorionic gonadotropin 10,000 U/L was given and timed intercourse was advised.

Results: Of the 75 subjects in the study, 40 (53.3%) were in group A and 35 (46.6%) in group B. The mean age in group A was 25.3±2.1 years versus 26.1±1.3 years in group B ($p=0.05$). The number of mature follicles was significantly lower, but the endometrial thickness and ovulation were significantly higher in group B than in group A ($p<0.05$ each). There was no significant difference in pregnancy rate between the two groups ($p>0.05$).

Conclusion: Letrozole may have a role as the first-line treatment for ovulatory patients with polycystic ovary syndrome.

Keywords: Chemotherapy, Clomiphene, Letrozole, Infertility, Polycystic ovary. (JPMA 65: 1149; 2015)

Introduction

Infertility is a unique medical condition as it is a disorder that often involves a couple, not an individual. An infertile couple is one that has been unable to conceive in one year of unprotected intercourse. It is subdivided into primary and secondary.¹ Primary infertility applies to those who have never conceived, while secondary infertility is designated to those who have conceived at some time in the past.²

Polycystic ovary syndrome (PCOS) (Figure) is a common endocrine pathology in women in reproductive age.³ It is a heterogeneous disorder of unknown aetiology affecting 5-10% of women between late adolescence and early menopause.^{4,5} It involves women with obesity, excess hair growth and who have ovaries with multiple cysts. It is a disorder that affects the reproductive, endocrine and metabolic systems and it is the most common cause of an ovulatory infertility.⁶ It has eluded definitive description because of varied combination of clinical, biochemical and ultrasonographic features which may occur. The commonest association is of hyperandrogenism and chronic anovulation; recognition of characteristic ovarian ultrasound features together with clinical symptoms of oligomenorrhoea, hyperandrogenism, infertility or obesity is presently the preferred diagnosis.⁷

Well-recognised clinical presentation included menstrual cycle disturbances (oligo/amenorrhoea), obesity and hyperandrogenism manifesting as hirsutism, acne or androgen-dependent alopecia. However, clinical features vary considerably between women and indeed some women with PCOs do not appear to display any of the common symptoms.^{5,8}

PCOS is characterised by ovulatory dysfunction. Menstrual periods do not necessarily have to be absent. Many women with PCOS continue to ovulate, but do so either irregularly or with compromised progesterone production. Many women with PCOS are not obese, and many women with PCOS do not have excess hair growth, but to some extent virtually all women with PCOS have some degree of insulin resistance.

The current study was planned to compare the use of letrozole with clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation, and to evaluate the pregnancy rate between the two groups.

Patients and Methods

The prospective clinical trial was conducted at Basrah Maternity and Child Hospital, Basrah, Iraq, between January 2012 and April 2013, and comprised women with PCOS and primary infertility.

The subjects were selected from among those who were attending the infertility centre with primary infertility,

.....
Department of Gynecology & Obstetrics, University of Basrah, Basrah, Iraq.

Correspondence: Maysoon Sharief. Email: maysoonsharief60@yahoo.com

which was defined as inability of a couple to obtain pregnancy after 1-2 years of unprotected intercourse. The sample size depended on the availability and willingness of patients.

All subjects were diagnosed as having an ovulation due to PCOS.

PCOS was diagnosed when the ultrasonographic (USG) findings of the ovaries were >10 follicles 2-8 mm in diameter scattered either around or through an echodense thickened central stroma. In addition, there had to be one or more of the following: oligomenorrhoea, positive progesterone, withdrawal bleeding, hirsutism/acne, obesity, and Luteinizing hormone/Follicle-stimulating hormone (LH/FSH) ratio >2 or raised circulating androgen, normal thyroid stimulating hormone (TSH).

All patients having had patent tubes by either hysterosalpingiogram or laparoscopy, history of pelvic surgery with tubal blockage were excluded from the study.

Those included were aged between 18 and 36 years, period of infertility was more than 2 years, serum prolactin level was normal, serum FSH <12u/L, normal thyroid function, and hirsutism, which was diagnosed when the Ferriman and Gallwey score was >8.⁹ Besides, the male partners had to have a normal seminal analysis by World Health Organisation (WHO) criterion.¹⁰

After approval was obtained from the ethical committee of the College of Medicine, University of Basrah, Iraq, the patients were examined clinically, their weight, height, waist circumference (WC), body mass index (BMI) were estimated, transvaginal USG was done to exclude any pelvic pathology before treatment.

The patients were randomised into two groups. Group A received clomiphene citrate for six months with a dose between 100-200 mg for five days beginning on day three of the menstrual cycle. Group B received aromatase inhibitor (letrozole) 2.5-5mg daily for 5 days starting from the third day of a spontaneous or progesterone-induced menstrual bleeding.

Follicular development was monitored using transvaginal ultrasound from day 10 onward. When at least one mature follicle (mean diameter >18 mm) was observed, 10,000 IU of human chorionic gonadotropin (HCG) was given subcutaneously to trigger ovulation. The second transvaginal ultrasound was done after 48 hours of HCG injection to observe the release of ova. Ovulation was ascertained by observing the rupture of follicle by

transvaginal ultrasound and day 21 serum progesterone.

A progesterone level >20ng/ml was considered ovulatory. The main outcome measure was rate of ovulation and detection of pregnancy by beta HCG (BHCG) level obtained 2 weeks after timed intercourse and ultrasound was performed 2-4 weeks after the missed period by the presence of cardiac activity.

For statistical analysis, T-test was carried out for quantitative data and Z-test for qualitative data. P<0.05 was considered significant.

Result

Of the 75 subjects in the study, 40(53.3%) were in group A and 35(46.6%) in group B. The mean age in group A was 25.3±2.1 years versus 26.1±1.3 years in group B (p=0.05) (Table-1). The basal hormonal status on day 3 of the cycle, such as FSH, LH, TSH and prolactin, was not statistically significant (p>0.05 each).

The number of mature follicles was significantly lower in group B, but the endometrial thickness and ovulation were significantly higher in that group (p<0.05 each) (Table-2).

Pregnancy rate was not significantly different between the two groups (p>0.05). The day on which HCG was given did not differ between the two groups (p>0.05). One (2.5%) twin pregnancy occurred in group A.

Table-1: Demographic characteristic.

	Clomiphene Citrate N:40	Letrozole N:35	P value
Mean age (years)	25.3±2.1	26.1±1.3	T=1.949, df=73, P=0.055, NS
Mean infertility period	2.3±0.4	2.4±0.6	T=0.858, df=73, P=0.393, NS
Mean Body mass index (Kg/m ²)	27.8±1.7	28.1±1.91	T=0.719, df=73, P=0.474, NS
Mean FSH	6.82±1.22	7.23±2.1	T=1.049, df=73, P=0.299, NS
Mean LH	6.39±2.12	5.92±3.1	T=0.774, df=73, P=0.441, NS
Mean E2	62.25±18.1	63.42±1.5	T=0.381, df=73, P=0.704, NS
Mean TSH	2.85±1.35	3.1±2.1	T=0.620, df=73, P=0.536, NS
Mean Prolactin	24.86±8.37	25.38±7.1	T=0.287, df=75, P=0.774, NS

NS= Not significant.

FSH: Follicle-stimulating hormone

LH: Luteinizing hormone

E2: Estradiol

TSH: Thyroid stimulating hormone

Table-2: Response to ovarian stimulation.

	Clomiphene Citrate N:40 Mean ± SD	Letrozole N:35 Mean ± SD	P value
Follicular development by day 14 (mm)	22.3±1.0	21.5±2.6	T=1,801, df=73, P=0.075, NS
No. of follicles > 18 mm on day of HCG administration	2.4±1.1	1.3±0.31	T=5.71, df=73, P=0.0001, HS
Serum E2 on day of HCG (PG/ml)	415±1.3	325±1.25	T=304.5, df=73, P=0.0001, HS
Endometrial thickness (mm) at 14 day	52±1.2	84±1.8	T=91.59, df=73, P=0.0001, HS
Day of HCG administration	12.9±1.6	12.8±1.8	T=0.254, df=73, P=0.799, NS
Ovulation (%)	25 (62.5%)	29 (82.9%)	Z=1.9589, P=0.05, S
Pregnancy (%)	7 (17.5%)	10 (28.6%)	Z=1.1425, P=0.25428, NS

NS= Not significant.

HS= Highly significant.

HCG: Human chorionic gonadotropin.

**Figure:** Ultrasonographic Picture of polycystic ovarian syndrome (PCOS).

Discussion

Fertility and child-bearing is a complex process and ovulation is the first step to be identified towards the conquest of infertility. Ovulation is the result of well-synchronised balance among central nervous system, hypothalamus, pituitary axes and ovary.

Clomiphene citrate, which is the most commonly prescribed medication, initiates ovulation by blocking the negative feedback on endogenous oestrogen at the level of hypothalamus-pituitary promoting an increase in the pulsatile release of LH and FSH in anovulatory POCS

patients.¹¹

For many years the first treatment of choice for ovulation induction in POCS was clomiphene citrate,¹² but up to 58% of such patients are resistant to it and do not ovulate.¹³ The pregnancy rate per cycle remain relatively low.¹³ It has also been demonstrated that clomiphene citrate has an antagonistic effect on the endometrium and may reduce endometrial thickness.¹⁴ Clomiphene citrate may block oestrogen receptors in the cervix, producing a negative effect on the quality and quantity of cervical mucus.¹⁵ Therefore, there is a discrepancy between the ovulation and conception rates associated with clomiphene citrate use.¹⁶

Although not all patients behave in a similar manner, but 50% of women on clomiphene citrate develop a thin endometrium <8mm with a tendency toward a non-trileminar pattern at mid-cycle. By additional supplemental oestrogen, the phenomena cannot be improved, suggesting that it is a result of oestrogen receptor depletion.¹⁶

Inappropriate development of endometrium is associated with a low implantation rate and early pregnancy loss caused by luteal phase defect.¹⁵

Some patients (20%-28%) do not respond to clomiphene citrate in spite of high dose as the anti-oestrogenic effect is dose-dependent; a daily dose of clomiphene citrate >150mg is not recommended.¹⁶

To produce a good ovulation after clomiphene citrate regimen, induction with gonadotropins is essential which increase both the cost and risk associated with treatment.¹⁷

Letrozole, an aromatase inhibitor, has the same role as clomiphene citrate in initiating gonadotropin release by withdrawing negative feedback to the pituitary by reducing the blood oestrogen level by blocking the conversion of androgen to oestrogen. So the initial release of FSH may be more than with clomiphene citrate.¹⁸

Multiple developing follicles appear on day 7 but because of the letrozole dose not deplete oestrogen receptors. Unlike clomiphene citrate,¹⁹ normal negative feedback occurs centrally as the dominant follicle grows and oestrogen levels increase.¹⁸

This result in FSH suppression and atresia of smaller follicles, and mid cycle mono-ovulation occurs in most patients.¹⁸ Single follicle is the major advantage of using aromatase inhibitors for ovulation induction, particularly

desirable in patients with PCOS who are often hyper-responsive to gonadotropins.²⁰

One double-blind randomised trial comparing the use of an aromatase inhibitor with clomiphene citrate for stimulation in 49 women with infertility found increased endometrial thickness compared to those receiving clomiphene citrate because 3-fold increase in pregnancy rate was observed in patients who received aromatase inhibitor compared to those on clomiphene citrate treatment; 16.7% versus 5.6% respectively.²¹

In women with PCOS who did not have an adequate response to clomiphene citrate, ovulation occurred in 75% of the letrozole treatment cycles and clinical pregnancy was achieved in 17% of the cycles.¹³

In the present study the day of HCG administration did not differ in those treated with clomiphene citrate compared with letrozole. Although the ovulation is significantly lower in letrozole group, but the rate of clinical pregnancy was significantly lower in letrozole group in comparing with clomiphene citrate group.

However, the small sample size is a limitation of the study whose results may not be generalised.

Conclusion

Letrozole may be preferable in certain groups of patients with infertility. However, due to sample size limitations, further studies are needed.

References

- Dor J, Lerner-Geva L, Rabinovici J, Chetrit A, Levran D, Lunenfeld B, et al. cohort of infertile women who underwent in vitro fertilization. *FertilSteril*. 2002; 77:324-7.
- Nieschlag E, Hertle L, Fishedick A, Abshagen K, Behre HM: Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. *Hum Reprod*. 1998; 13:2147-50.
- Dunaif A. *The polycystic ovary syndrome..* Cambridge MA, USA: Black well scientific publication, 1992; pp377-84.
- Hull MGR. Epidemiology of infertility and polycystic ovarian disease: and ocrinological and demographic studies. *GynecolEndocrinol*. 1987; 1:235-45.
- Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries-a common finding in normal woman. *Lancet*. 1988; 1:870-2.
- Dunaif A, Insulin resistance and the polycystic ovary syndrome, mechanisms and implication for pathogenesis. *Endocrine Rev* 1997; 18: 774-800.
- Kyei-Mensah AA, LinTan S, Zaidi J, Jacobs HS. Relationship of ovarian stromal volume to serum androgen concentrations in patients with polycystic ovary syndrome. *Hum Reprod*. 1998; 13:1437-41.
- Michelmores KF, Balen AH, Dunger DB, Vassey. Polycystic ovaries and associated clinical and biochemical features in young women *ClinEndocrinol (Oxf)*. 1999; 51:779-86.
- Balen AH. Secondary amenorrhoea. In: Edwards D. Keith eds. *Dewhurst's text book of Obsteteic and Gynecology* 6th edition. Black well science LTD, 1999; pp 42-60.
- World Health Organization, WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Geneva: WHO, 2010.
- Kettel LM, Roseff SJ, Berga SL. Hypothalamus-pituitary-ovarian response to Clomiphene citrate in women with polycystic ovary syndrome, *FertilSteril*. 1993; 59:532-8.
- Franks S. Polycystic ovary syndrome. *N Engl J Med*. 1995; 333:853-61.
- Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to Clomiphene citrate. *FertilSteril*. 2001; 75:305-9.
- Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H. Effect of Clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. *FertilSteril*. 1997; 67:256-60.
- Randall JM, Templeto A. Cervical mucus score and in vitro sperm sperm mucus interaction in spontaneous and Clomiphene citrate cycles. *FertilSteril*. 1991; 56:465-8.
- Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. *ClinObstetGynaecol*. 1985; 12:605-32.
- Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome *Cochrane Database Syst Rev*. 2000; CD000410.
- Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgen stimulate early stages of follicular growth in the primate ovary. *J Clin Invest*. 1998; 101:2622-9.
- Ohno Y, Fujimoto Y. Endometrial oestrogen and progesterone receptors and their relationship to sonographic appearance of the endometrium. *Hum Reprod Update*. 1998; 4:560-4.
- Casper RF. Letrozole ovulation or super-ovulation. *FertilSteril*. 2003; 80:1335-7.
- Sammour A, Biljan MM, Tan SL. Iulandi: prospective randomized trial comparing the effect of Letrozole and Clomiphene citrate on follicular development, endometrial thickness, and pregnancy rate in patient undergoing superovulation prior to intrauterine insemination. *FertilSteril* 2001; 76: 110.