ORIGINAL ARTICLE

Clomiphene Citrate Vs Latrozole in PCO's patient's for Ovulation induction

ASMA ASHFAQ, HUMA TAHSEEN, ZAHIDA NOREEN, *NASREEN ALAM*

ABSTRACT

Aim: To compare the efficacy of letrozole vs clomiphene Citrate for ovulation induction in PCOS.
Study Design: Randomized control trail.
Duration and Settings: Obstetrics & Gynecology Unit 1, Services hospital Lahore from January to December 2014.
Methods: 80 cases of pregnant women fulfilled the inclusion criteria were included. These selected patients were prescribed for 5 days either clomiphene or letrozole in two groups, each of 40 patients. All patients were examined with transvaginal scan for ovulation induction.
Results: The mean age of females was 23.76±2.41years. The mean duration of infertility was 2.45±0.62years. Letrozole was effective in 25(67.6%) of women while clomiphene showed effectiveness in just 12(32.4%) women, this was a difference in a p-value =0.004.
Conclusion: At the end, it was concluded that ovulation induction with letrozole should be taken as treatment of choice while treating young PCOS patients.
Keywords: Letrozole, Clomephine, PCOS, Ovulation

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrine disease and one of the main causes of infertility due to anovulation. It influences 20-33% of women in reproductive years[1]. PCOs are common among women of South Asia 50% and 50% of these are obese[2]. In Pakistan, infertility due ovulatory dysfunction is found in 21.9% women of reproductive PCOs were found 20.7%[3,4]. In PCOs, ovaries start secreting slightly more androgens and stops ovulation. There may be menstrual irregularity, features of hyperandrogenism and infertility[5].

Obesity, a feature among PCOS (60-70%) was a major contribution to the aggravation of insulin resistance. Women with this syndrome of chronic anovulation/oligo ovulation have hyper androgenism, both of these are important risk factors of obesity, diabetes mellitus, infertility, abortions[6]. Several strategies have been designed for induction of ovulation in PCOs women e.g.; weight reduction, laparoscopic ovarian drilling and metformin. The commonly used treatment of infertility is inducing ovulation by medications.[7] Ovarian excitation can be achieved by injecting of injectable gonadotrophins or by enhancing pituitary follicular stimulating hormone with clomiphene citrate and aromatase inhibitors[8].

It is accumulated in body with low clearance rate and long half-life i.e., 5-7 days[7]. Discrepancy between ovulation induction rate and pregnancy rate is related to anti-estrogenic effects on cervical mucus and endometrium and long acting gonadotrophins are more effective than clomiphene citrate[9]. Unlike clomiphene citrate gonadotrophins don't exert any peripheralanti-estrogenic effects[8]. When compared with clomiphene. Letrozole is associated with thicker endometrium and better pregnancyrate. Overall rates of congenital malformations among newborns conceived after treatment with letrozole and clomiphene citrate are similar[8].

Dept of Obs & Gynaecology, SIMS/Services Hospital, Lahore
Correspondence to Dr. Huma Tahseen
Email: humatahseen@hotmail.com

63.6% patients had successful ovulation induction with letrozole and 29.4%patients having clomiphene citrate showed successful ovulation induction[10]. Another study did not show any advantage to use of Letrozole over clomiphene citrate perovulation induction. In the study statistically greater endometrium in clomiphene citrate(6.8±0.3 mm Vs 4.4±0.4 mm).Without statistical difference ovulation rate in letrozole 67.5% and 70.9% inclomiphene[11].

The rationale of the study is to determine and compare of frequency of induction of ovulation in women with PCOs treated with letrozole versus clomiphenecitrate as published literature showed controversy. Moreover, there is no local study that was studied the ovulation after these two treatment methods. Only one local study available that was conducted in King Edward Medical University showing pregnancy but no magnitudes of ovulation induction[12]. So we planned to conduct this study to generate the results in our population and to resolve controversy.

The objective of the study was to compare the efficacy of letrozole vs clomiphenecitrate for ovulation induction in PCOS

MATERIAL AND METHODS

This randomized control trial was conducted in the Department of Obstetrics & Gynecology Unit-I, Services Hospital, Lahore from January to December 2014. Eighty cases (40 in each group) is calculated using 95% confidence interval. 80%power of test with an expected percentage of efficacies of letrozole group is 63.3% and29.4% in clomiphene citrate group. Non-probability, purposive sampling technique was used.

Inclusion criteria:

- age > 18 years but <30 years
- Diagnosed PCOS assessed by presence of any two of the following finding (peripherally arranged 2-9 follicles of 8-10mm), increase LH and FCH ratio >2
- History of oligomenorrhea i.e., <6cycles / years
- Serum testosterone >0.65 ng/ml

Exclusion criteria:

- Endocrine disorders like thyroid disorders assessed b TSH (0.5-5IU/L), T3 (4.3-8.6Pmol/l) and T4 (9-22Pmol/l), hyperprolactinemia assessed by serum prolectin levels (>400miu/l).
- Other causes of anovulatory infertility (kalmann‟s syndrome, stress, exercise, anorexia nervosa)

Data Collection: Eighty cases of PCOS women fulfilled the inclusion criteria were included from OPD. Informed consent was taken to include their data in study. Detailed demographic history including name, age, parity, were recorded. BMI was calculated and the patients were divided in two groups randomly by lottery method. ***Group 1(L):***40 women given letrozole, 5mg for 5 days of menstrual cycle. ***Group 2(C):***40 women given clomiphene citrate, 100mg for 5 days of menstrual cycle. All patients were passed through TVS so that efficacy can be evaluated (ovulation occurs on 14 day of menstrual cycle after a treatment of 5 days of both groups. Induction of ovulation is assessed by TVS. If follicle of >2cm is found on 12 days TVS and smaller/collapsed on 16 days TVS, ovulation induction was labeled). All the data was entered on a well-defined Performa.

Data Analysis: The collected data was entered and analyzed by SPSS version 16. Qualitative data like efficacy was presented by frequency and percentages. The quantitative data like age was presented in the form of mean±SD.

RESULTS

The mean age of females was 23.78±2.41years. The mean duration of infertility was 2.45±0.62 years. The mean BMI was 23.58±2.89kg/m^2. Table 1Efficacy was achieved in 25(67.6%) females with letrozole while in 12(32.4%) females with clomiphene citrate. The difference was significant (p-value=0.004) (Table 2).

Table 1: Baseline characteristics of patients (n=80)

Age (years)	23.78±2.41
Duration of infertility (years)	2.45±0.62
BMI (kg/m^2)	23.58±2.89

Table 2: Comparison of efficacy in both groups

Efficacy	Group		Total
	Letrozole	Clomiphene citrate	
Yes	25(67.6%)	12 (32.4%)	37(46.25%)
No	15(34.9%)	28 (65.1%)	43(53.75%)
Total	40 (100%)	40 (100%)	80 (100%)

P=0.004 (chi-square test)

DISCUSSION

Ovulation is an important prerequisite for a successful pregnancy. Anovulation accounts for 20% cases of infertility provided other factors are normal and PCOS is the main cause of anovulation. Clomiphene citrate is the most commonly prescribed drug for the treatment of women with infertility due to anovulation. Clomiphene citrate results in an ovulation rate of 60–85% but a conception rate of only about 20%.Clomiphene citrate is long acting (2 weeks) with low clearance rate, and this produces a negative impact on the cervical mucus and endometrial lining thickness, results to discrepancy between ovulation and conception rates.

Letrozole, an aromatase inhibitor, does not have the adverse antiestrogenic effectson endometrial receptivity of clomiphene and has been shown to its effectiveness with higher ovulation and conception rates. In patients with clomiphene resistance and failurethe success of previous results, its superior safety profile to clomiphene showing aromatase inhibitor Letrozole may be used as alternative treatment to clomiphene citrate for the first-linemedication of women with chronic anovulation and infertility[13]. The objective our clinical study was to compare efficacy of letrozole with Clomiphene Citrate in patients with PCOS. The results of my study suggest that there is an increased efficacy in letrozole group. In current study ovulation was observed in67.6% in letrozole group and 32.4% in clomiphene citrate group. P-value (0.004).

In the study of Begum MR 63.6% patient had successful ovulation induction with letrozole which is compare able to our results. P-Value (<0.05)[10]**.** In the study of Dehbashi et al ovulation with letrozole is 60% and with clomiphene citrate is 32%. P Value (0.009)[14]. In the clinical trial of Bayer et al ovulation per cycle inletrozole & clomiphene is comparable (65.7%vs74.7%) pvalue (0.17)[15].

On the basis of randomized control trails, the statistical -analysis for ovulationand ovulatory cycles and there was no any statistically significant difference between letrozole and clomiphene citrate noted. Different randomized trials have been observed the effectiveness of letrozole for ovulation induction in comparisons to clomiphene citrate. Results of different prospective randomized studies need to be commented. In all studies 2.5mg and 5mg dose of letrozole was given for 5 days daily. Difference between these studies is related to the inclusion criteria of patients.

In the study, 106 women with anovulation and PCOS were included. Results were more infavor of letrozole group than in clomiphene citrate group related to rates and numbers of ovulatory cycle (82.4% versus 63.6%, P-Value=0.016)[16]. In another study of Zeinalzadeh et al. (2010), 107 women with PCOS selected. Ovulation was highin letrozole group than clomiphene citrate (86% VS 75.5%). P-value (0.07). Above two studies having a high risk of bias[17]. Badway et al. (2007) conducted a study which included 438 women within fertility and PCOS. Patients were randomized to treatment with 5 mg letrozole and100mg clomiphene citrate. In the trial the benefit to the use of letrozole as an alternativeand first line medication to clomiphene citrate for inducing of ovulation in women with PCOS was notobserved, as a significant difference in ovulation was not found[11].

In the study of Roy et al. (2012) which was done in Dehli, the compare able ovulation rates and ovulatory cycle (66.6% in letrozole and 67.9% in clomiphene citrate group) and letrozole is as superior as clomiphene citrate in terms of ovulation. In the study no. of conception rates were increased in letrozole group (43.8%) compare able with clomiphene citrate group (26.4%), but there was no statistical difference in pregnancy rates. No any miscarriage and favorable pregnancy outcome was observed[18].

Abu Hashim et al reported that 15 to 14% of their PCOS women having a resistance to clomiphene. Letrozole has an advantage in inducing ovulation in 54.6% -84.4% of clomiphene resistant patients[19,20]. In the study of Hajishafiha (2014), it was hypothesis that in PCOS patients resistant to clomiphene and letrozole used a single agents, a combination of two drugs can be prescribed before using more extensive treatment that may produce severe complications or surgery. This combination can be administered in sever PCOS in order to save time and expenditures[21].

The second retrospective observational study which was done in Canada, found no difference in birth malformation between neonates of clomiphene citrate pregnancies that occur after stimulation in comparison to spontaneous induced and aromatase. Efficacy of letrozole inovulation with successful outcomes in assisted reproduction. Letrozole had superior efficacy in comparison with clomiphene in patients undergoing assisted reproduction. Letrozole have compare able results with recombinant FSH in stimulating ovulation in PCOS patients is found to be a as good as clomiphene and cost effective inducing drug.[22]

Despite the fact that gonadotrophins may be more effective in achieving higher pregnancy rates. Studies have shown the association of exaggerated ovarian response with letrozole and acceptable pregnancy rates in comparisons to gonadotrophin therapy. It could augment or even obviate the use of gonadotrophins in the treatment of women who have been failure in achieving pregnancy with clomiphene.

CONCLUSION

It is concluded from my study that an ovulatory PCOS patients can be successfully treated by ovulation inducing drug like letrozole. The other options of ovulation induction like gonadotrophins injections and laparoscopic ovarian drilling can be avoided. In our less developed country where monitoring expenses are high and laparoscopy facilities are limited. So an inexpensive Oral agent like letrozole can be used for ovulation with a high success rate. It would be an excellent therapy for ovulation induction in our patients.

REFERENCES

1. Balen A. Polycystic ovary syndrome and cancer. Human reproduction update 2001;7(6):522-5.
2. Jones GL, Palep-Singh M, Ledger WL, Balen AH, Jenkinson C, Campbell MJ, et al. Do South Asian women with PCOS have poorer health-related quality of life than Caucasian women with PCOS? A comparative cross-sectional study. Health and quality of life outcomes 2010;8(1):149.
3. Sadia S, Waqar F, Akhtar T, Sultana S. Characteristics of infertile patients with ovulatory dysfunction and their relation to body mass index. Journal of Ayub Medical College Abbottabad 2009;21(3):12-6.
4. Obaid-Ur-Rehman M. Polycystic ovary syndrome treatment of subfertilitywith insulin lowering medications. Pakistan Journal of Pharmacology 2005;22(1):35-9.
5. Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. Journal of international medical research 2006;34(1):73-6.
6. Fica S, Albu A, Constantin M, Dobri GA. Insulin resistance and fertility in polycystic ovary syndrome. Journal of medicine and life 2008;1(4):415.
7. Hussain NHN, Ismail M, Zain MM, Yeu PC, Ramli R, Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. Open Journal of Obstetrics and Gynecology 2013;3(05):11.
8. Kafy S, Tulandi T. New advances in ovulation induction. Topics in Obstetrics & Gynecology 2007;27(20):1-5.
9. Pritts EA. Letrozole for ovulation induction and controlled ovarian hyperstimulation. Current Opinion in Obstetrics and Gynecology 2010;22(4):289-94.
10. Begum MR, Ferdous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertility and sterility 2009;92(3):853-7.
11. Badawy A, Aal IA, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility and sterility 2009;92(3):849-52.
12. Yusuf L, Yaqub U, Hanif A. Efficacy of Clomiphene Citrate and Letrozole in Induction of Ovulation in Patients of PCOS: A Randomized Prospective Clinical Trial. Annals of King Edward Medical University 2013;18(2):133-.
13. Siddiqui M, Mahmud N, Chowdhury T. Letrozole for Induction of Ovulation in PCOS Patients: Resistant to Clomiphene Citrate. Journal of South Asian Federation of Obstetrics and Gynecology 2010;2(2):99-103.
14. Dehbashi S, Dehbashi S, Kazerooni T, Robati M et al. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. Iranian J Med Sciences 2015;34(1):23-8.
15. Bayar Ü, Basaran M, Kiran S, Coskun A, Gezer S. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertility and sterility 2006;86(5):1447-51.
16. Requena A, Herrero J, Landeras J, Navarro E, Neyro JL, Salvador C, et al. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Human reproduction update 2008;14(6):571-82.
17. Zeinalzadeh M, Basirat Z, Esmailpour M. Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. The Journal of reproductive medicine 2010;55(1-2):36-40.
18. Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, et al. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Journal of human reproductive sciences 2012;5(1):20.
19. Elnashar A, Fouad H, Eldosoky M, Saeid N. Letrozole induction of ovulation in women with clomiphene citrate–resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/follicle-stimulating hormone ratio. Fertility and sterility 2006;85(2):511-3.
20. Al-Omari W, Sulaiman W, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. International journal of gynecology & obstetrics 2004;85(3):289-91.
21. Hajishafiha M, Dehghan M, Kiarang N, Sadegh-Asadi N, Shayegh SN, Ghasemi-Rad M. Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug design, development and therapy 2013;7:1427.
22. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertility and sterility 2006;85(6):1761-5