Original Article

Comparison of Pregnancy Outcome in Infertile Women with Polycysticovarian Syndrome Using Letrozole Versus Clomiphene Citrate

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Abstract

Objective: To compare the efficacy of letrozole versus Clomiphene Citrate for successful pregnancy rate in patients with polycystic ovarian syndrome.

Study Design: Randomized Controlled Trial.

Place and Duration: Six months (10-08-2014 to 09-02-2015) at the department of obstetrics and Gynaecology Military Hospital Rawalpindi.

Methodology: A total of one hundred and eighty-four (n=184) female patients with age between 20-35 years who were diagnosed cases of the Polycystic ovarian syndrome with infertility of more than one-year duration were enrolled in the study. Patients were randomized into Group A, treated with Clomiphene Citrate and Group B treated with Letrozole and were assessed for positive pregnancy within next three menstrual cycles.

Results: Patients in both the groups were similar in their demographic characteristics. Patients treated with Letrozole showed significantly higher rates of successful pregnancies when compared with Clomiphene Citrate (46.7% vs 22.8%) (P<0.05). The rate of efficacy was significantly higher in the age group of 24-30 years and in women having infertility duration of 5-8 years. There was no successful induction in patients having more than 8 years duration of infertility

Conclusions: Letrozole was found to be more efficacious in terms of successful pregnancies rate in women with the Polycystic ovarian syndrome in this study.

Key Words: Letrozole, Clomiphene citrate, Polycystic ovarian syndrome.

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Introduction

Infertility is common in young females with Polycystic ovarian syndrome. Different treatment options are reported in the literature for ovulation induction. Polycystic ovarian syndrome is a quite frequently occurring complication of female Endocrinopathy. Its prevalence has greater variation with respect to diagnostic criteria used. The prevalence ranges from 3% to 20%.[1] There are many features showing the existence of Polycystic ovarian syndrome with most commonly presenting characteristics like elevated clinical and laboratory indices of androgen levels along with polycystic ovaries on ultrasound. The

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patients also present with abnormal ovulation symptoms. The clinical presentation includes irregularity in menstrual cycle, hirsuitism, infertility, abdominal obesity, hypertension as well as persistent acne and androgen-dependent alopecia. [2]

Recent literature has reported a quite high prevalence of pregnancy-related complications in women having Polycystic ovarian syndrome.[3] Adverse obstetric complications increase with different phenotypes of Polycystic ovarian syndrome patients. [4]

Due to the oligomenorrhea or anovulation these patients require assisted reproductive technology for induction of pregnancy. This procedure for the treatment of infertility often results in multiple births. [5] The insulin resistance is present in a large number of women ranging from 50% to 80% [6] and it's almost present in all obese women with having an incidence of 95%. [7]

Insulin resistance occurs independently and more frequently due to obesity. The combination of both Polycystic ovarian syndrome and obesity strongly disturb the insulin sensitivity. [8]

There are some drugs which are used as ovulation induction agents in women having the Polycystic ovarian syndrome. The most commonly and preferably used drug is clomiphene citrate (CC), which is an estrogen receptor modulator and very frequently used in Polycystic ovarian syndrome women from many years. it has many advantages of use like it has very less cost and has greater safety profile in contrast to other drugs used for this purpose. Another main advantage is it feasibility of oral administration. On another hand the alternative treatments like gonadotrophins are used for this purpose but this group has some disadvantages including the enhanced chance of serious complications as well as being very expensive. Similarly, it has a limitation of use through parenteral route. Many side effects are associated with this drug, most commonly effects on endometrial and cervical mucus due to antiestrogenic properties, which significantly affect the pregnancy and its outcome. [9] Many studies have proved the efficacy of Letrozole in comparison to Clomiphene citrate in terms of less side effects and more successful induction of pregnancy.[10] So this present study has been planned to investigate the efficacy of letrozole in comparison with Clomiphene citrate in our population.

Methodology

This prospective randomized controlled trial was conducted after taking necessary ethical approval from hospital ethical committee to conduct this study. The patients were taken informed written consent before randomization. A total of 184 patients with PCOS were included. The sample size was calculated by using WHO sample size calculator taking a level of significance 5%, Power of test 80%, the pregnancy rate for the Letrozole P1, 43.8%, and P2, the pregnancy rate for Clomiphene Citrate as 26.4%. The patients were selected from the outpatient department of Obstetrics and Gynecology by the researcher.

Rotterdam (2003) Diagnostic criteria for PCOS was used as two out of three of:

- Clinical Hyperandrogenism (Ferriman-Gallwey Score >8) or Biochemical Hyperandrogenism (Elevated Total/Free Testosterone) OR
- Oligomenorrhea (Less Than 6-9 Menses per Year) or Oligo-Ovulation OR
- Polycystic Ovaries on Ultrasound (>= 12 Antral Follicles in One Ovary or Ovarian Volume >= 10 cm3)

The inclusion criteria included patients in the age group of 20-35 years with PCOS and having infertility for more than one year. Patients with hyperprolactinemia, thyroid disorder, male factor, suspected tubal factor, endometriosis, unexplained infertility were not included in the study. Similarly, patients having Uterine and adnexal pathology e.g. leiomyomata, Hyperprolactinemia, FSH>9 ml U/ml (during early follicular phase), peritonitis, genital tuberculosis as per history and/ or having an abnormal pelvic anatomy were not selected in the study.

All the women were randomly divided into two equal groups of 92 patients by lottery method. In group, A clomiphene citrate 50 mg was given and in group B letrozole 2.5mg was given. Patients followed with follicle monitoring with Ultrasound on day 8 of the menstrual cycle, endometrial thickness was determined at the greatest diameter. Subcutaneous HCG 10,000iu was given to induce ovulation when one follicle of 18mm in diameter was noted. Each

woman was asked to have timed intercourse 24h to 36h after an ovulatory dose of HCG and was followed by serum beta HCG levels and Ultrasonography as soon as she misses her periods, up till three cycles of treatment. The final outcome measure or efficacy of the drug was measured in terms of conception within three cycles. Basic demographic information including name, age duration of marriage was recorded on a pre-designed proforma.

All the collected data was entered and analyzed through Statistical Package for social sciences (SPSS version 21). Quantitative variables were expressed as Mean ± SD. Qualitative variables were presented as frequency and percentages. Chi-square test was used to compare final outcome (efficacy) between two groups. *P*-value<0.05 was considered as statistically significant.

Results

The mean age in groups A was 27.2 ± 3.4 years and in the group, B was 26.7±3.3 years. In Group A, there were 26.1% (n=24) of patients who were between age 20-24 years, 53.3% (n=49) were between 25-29 years and 20.7% (n=19) were in age group 30-35 years. In Group B, there were 25.0% (n=23) of patients who were between age 20-24 years, 58.7% (n=54) were between 25-29 years and 16.3% (n=15) were in age group 30-35 years. The mean body mass index (BMI) in group A was 25.2±1.7 and in group B the mean BMI was 25.1±1.8. Similarly, the mean duration of infertility and mean testosterone levels were noted as 5.7±2.6 years and 2.5±0.18 nmol/L and in group B the mean values of duration of infertility and testosterone were recorded as 4.8±1.9 years and 2.7±0.32 nmol/L as elaborated in (table I). In Group A, there were 39.1% (n=36) of patients who had infertility duration between 1-4 years, 56.0% (n=46) had a duration of 5-9 years and 10.9% (n=10) had a duration of 9-12 years. In Group B, there were 55.4% (n=51) of patients who had infertility duration between 1-4 years, 38.0% (n=35) had duration of 5-9 years and 6.5% (n=6) had duration of 9-12 years.

Our study results showed that in group A (Clomiphene Citrate), the drug was found to be efficacious in 22.8% (n=21) of patients, while the percentage was 46.7% (n=43) in group B (Letrozole), implying significant (p-value < 0.05) difference in efficacy that is the patients treated with Letrozole (Group B) showed significantly higher rates of successful pregnancies when compared with Clomiphene Citrate (Group A).

Table I: Demographic Profile of the study Population (Age Distribution)

Clomiphene (A)		Letrozole (B)		P-value
Mean	SD	Mean	SD	
Age of Patient				
27.2	3.4	26.7	3.3	0.323
Body Mass Index (Kg/m2)				
25.2	1.7	25.1	1.8	0.933
Mean Duration of Infertility				
5.7	2.6	4.8	1.9	0.006
Mean Testosterone Levels (nmol/L)				
2.5	0.18	2.7	0.32	0.000

When the study sample was stratified with respect age it was found that there was no significant (p-value > 0.05) in the age group 20-24 years, when the efficacy of Clomiphene Citrate was compared with Letrozole group patients. In the age group 25-29 years, in group A (Clomiphene Citrate), treatment was found to be efficacious in 24.5% (n=12/49) patients, while it was efficacious in 48.1% (n=26/54) in group B (Letrozole) patients. Having a significant p-value 0.013 (<0.05), implying significant better results with Letrozole in terms of successful pregnancies. In the age group 30-35 years, in group A (Clomiphene Citrate), treatment was not efficacious in any patient, while it was efficacious in 20.0% (n=3/12) in group B (Letrozole) patients having a p-value of 0.041 (<0.05), implying significantly higher rates of successful pregnancies.

The stratification on the basis of infertility duration group 1-4 years, no significant difference was recorded in both groups with *P*-value of 0.186 (>0.05). In patients having infertility duration of 4-9 years, group A (Clomiphene Citrate), treatment was found to be efficacious in 10.9% (n=5/46) patients, while it was efficacious in 37.1% (n=13/35) in group B (Letrozole) patients. The *P*-value was found to be 0.005 (<0.05), implying a significant difference in patients treated with Letrozole (Group B) showed significantly higher rates of successful pregnancies. No patient showed efficacy in both groups having infertility duration of 9-12 years. (Table II).

Table II: Comparison of efficacy with respect to age and duration of infertility

Efficacy		Group		Total	P-value
		Clomiphene Citrate	Letrozole		
Overall Efficacy					
	Yes	21	43	64	0.001 *
	No	71	49	120	
Comparison of efficacy in different age groups					
20-24	Yes	9	14	23	0.148 **
	No	15	9	24	
25-29	Yes	12	26	38	0.015 *
	No	37	28	65	
30-35	Yes	0	3	3	0.076 **
	No	19	12	31	
Comparison of efficacy in different interval of duration of infertility					
1-4	Yes	16	30	46	0.186 **
	No	20	21	41	
5-8	Yes	5	13	18	0.007 *
	No	41	22	63	
9-12	Yes	0	0	0	Nil €
	No	10	6	16	
Total		10	6	16	

**Significant at 5% level of significance*

***Insignificant at 5% level of significance*

€ P-Value not calculated because there is no efficacy in this group

Discussion

In reproductive age, polycystic ovarian syndrome (PCOS) is one of the commonly occurring endocrinological disorder having an estimated prevalence of 4-8%.[11,12] There are many complications related to PCOS including reproductive and obstetric complications, psychological features and metabolic syndromes. The manifestations associated with obstetric and reproductive systems include menstrual dysfunction, infertility, hyperandrogenism and complication of pregnancy like early pregnancy loss, pregnancy-related hypertension, and diabetes. The PCOS also increases the chance of neonatal complications. [13]

In the literature, some studies showed the high efficacy of treatment for PCOS women in normal-weight women in contrast to overweight and obese women. The efficacy also has an inverse relation with age of the patient having PCOS. [14] but in this present study all the patients in both groups had mean BMI in normal ranges that is the mean body mass index (BMI) in group A was 25.2±1.7 and in group B the mean BMI was 25.1±1.8. Similarly, the mean age in groups A was 27.2 ± 3.4 years and in the group, B was 26.7±3.3 years.

Our study results showed that in Clomiphene Citrate group, the drug was found to be efficacious in 22.8% of patients, while the percentage was 46.7% in letrozole group, implying a significantly higher rate of successful pregnancies in letrozole group when compared with Clomiphene Citrate group. Results of our study support our hypotheses and show that letrozole is more effective as compared to clomiphene. Our finding are in line with other studies. [15]

A lower rate of multiple gestations has been found with use of Letrozole in comparison with CC. The main reason is that because embryo has no chance of exposure to letrozole due to short half-life of letrozole and timing of administration in early follicular phase. The clearance of drug takes place prior to the implantation occurs.[16] Letrozole inhibits selective aromatase which blocks the rate-limiting step of estrogen production from androstenedione and testosterone substrates. There are no active metabolites in letrozole. This drug has a short half-life the mean terminal half-life of this drug is from 30-60 hours having a mean value of 45 hours. [17]

The aromatization inhibiting from letrozole cause blockage of estrogen production from all sources,

which releases negative feedback of the hypothalamic-pituitary axis resulting in ovarian follicular stimulation and augmented gonadotropin secretion.[22] The accumulation of intraovarian androgens in ovary the follicular sensitivity to FSH increases due to aromatase inhibitors. [18]

No significant difference has been found in rates of miscarriage and ectopic pregnancy associated with pregnancies conceived in patients of PCOS after using letrozole and all other pregnancies together with spontaneous conceptions. [19] Clomiphene citrate has been a treatment of choice from a long time for induction of ovulation in PCOS patients having infertility. [20]

Along with being a very good choice for induction of ovulation in PCOS patients CC has some potential side effects like antiestrogenic effect on cervical mucus and endometrium which might avert the pregnancy even after successful induction of ovulation due to its longer half-life ranging from 5 days to 3 weeks. It stays in the body for longer duration and originate side effects. There are reported risk of ovarian hyperstimulation syndrome and multiple gestations due to augmentation of FSH by CC. [21, 22]

Accompanied by specific advantages and disadvantages the cost factor favors the CC because it has significantly lower cost in comparison to letrozole, especially when in the requirement of higher doses. In this situation, some studies have suggested that a combination of letrozole with FSH could be in comparison to FSH alone during intrauterine insemination cycles for ovarian stimulation. [23]

Conclusion

In conclusion, our study showed that letrozole was superior to clomiphene Citrate as a treatment for anovulatory infertility in women with the polycystic ovarian syndrome. The patients treated with Letrozole showed significantly higher rates of successful pregnancies when compared with Clomiphene Citrate. The rate of efficacy was significantly higher in the age group of 24-30 years and in women having infertility duration of 5-8 years. There was no successful induction in patients having more than 8 years duration of infertility.

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