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Original Research Article

The Outcome of Two Different Ovulation Induction Regimes: A Randomized Control Trial

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Abstract

Aim: Comparison between two different drugs in treatment of infertility among PCOS patient.

Materials and Methods: The present Randomized control trial was conducted in the Department of Obstetrics and Gynaecology, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar among PCOS patients diagnosed on the basis of revised Rotterdam 2003 criteria. In this clinical trial out of 100 patients, 50 patients received Clomiphene Citrate 100 mg (group A) and rest 50 patients received Letrozole 2.5mg (group B) daily since day 2-6 or 3-7 of menstrual cycle.

Result: Monofollicular development was statistically significantly, greater in the group B. There was also statistically significant difference between the two groups in endometrial thickness (CC 7.16±1.05mm, Let 9.68±1.15mm). Similarly, the ovulation rate was 83% in group A and 90% in group B. The pregnancy rate was 21% in group A and 35% in group B.

Conclusion: The present study concluded that though Clomifen Citrate group showed good ovulation rate but final outcome was poor.

Keywords: Infertility, Letrozole, Clomifen, PCOS.

Introduction

Polycystic ovarian syndrome (PCOS) remains one of its leading etiology of infertility affecting 6% women within reproductive age & still increasing due to lifestyle changes and other familial factors and in India the prevalence is 3.7-22.5%.2.[1] It belongs to Group 2 ovulatory disorder according to WHO classification. PCOS diagnosis is routinely done clinically following Rotterdam's criteria. Ovulation induction is the mainstay of treatment for infertile couple after primary evaluation and failure of medical method seeks surgical intervention.

Clomiphene citrate is considered as the drug of choice for first line treatment of an ovulatory dysfunction for a variety of reasons. It is orally administered, has few side effects, is easily available and is inexpensive. Although ovulation rates are in the range of 70-80% the actual pregnancy rates are significantly lower at around 30-40%.[1,2] However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population,[3,4] and 20-25% PCOS

women are resistant to clomiphene.[5,6] The desire for an effective alternative persists.

Letrozole, an aromatase inhibitor, was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance.[7,8] Letrozole has found acceptance in various clinical situations and the indications for use have expanded.[9,10] However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population,[3,4] and 20-25% PCOS women are resistant to clomiphene.[5,6]

The most often asked question of whether Letrozole is better than clomiphene as a first line treatment option remains unanswered and a clear answer would have important clinical implications for infertility specialists. Hence the present study was conducted to compare the outcome of two different ovulation induction regimes in an Indian setup.

Materials and methods

Study Design

The present Randomized control trial was conducted in the Department of Obstetrics and Gynaecology, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar among PCOS patients diagnosed on the basis of revised Rotterdam 2003 criteria.[11]

The study protocol was reviewed by the Ethical Committee of the Hospital and granted ethical clearance. After explaining the purpose and details of the study, a written informed consent was obtained.

Inclusion Criteria

- Patients of an ovulatory PCOS
- Patients between 20-35 years of age
- Patients having infertility for more than one year.
- Patients who have signed the informed consent.

Exclusion criteria

- Patients who have not signed the informed consent.
- Patients having any kind of acute and chronic systemic illness.

Sample Selection

50 subjects in each arm to achieve 80% power of study and level of significance 0.05 were recruited for the study.

The minimum sample size for each group was calculated using the formula:

$n = (Z_{\alpha/2}+Z_{\beta})^2 *2*\sigma^2 / d^2$,

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$, Z_{β} is the critical value of the Normal distribution at β, σ^2 is the population variance], and d is the hypothesized difference between the two study groups. Assuming equal group sizes to achieve a power of 80% and a two-sided confidence level of 95%, the study required a sample size ranging from 16 to 50 for each group. Assuming a non-response rate of 10%, the minimum required sample size was 40. Therefore, a sample size of 50 for each group was included in the study.

Groups

Group A: Infertile patients with PCOS received 100 mg Clomifen Citrate.

Group B: Infertile patients with PCOS received 2.5 mg Letrozole.

Study protocol

In this trial 100 infertile patients with PCOS received either 100 mg Clomifen Citrate (n=50) or 2.5 mg Letrozole (n=50) daily since day 2-6 or day 3-7 of cycle. Serial follicular measurements were done by same observer from day 9 onwards and Human chorionic gonadotrophin was administered at a dose of 5,000 IU when at least 1 mature follicle (18-22 mm) was detected. Timed intercourse was advised to

the patients after 24-36 hrs of hCG. Then the number of follicles, endometrial thickness, ovulation rate & pregnancy rate were measured in both groups.

Statistical Analysis

The data was entered in the form of a data matrix in Microsoft Excel® and analysed statistically using IBM® SPSS® version 20.0.0. Descriptive statistics were calculated as frequencies for categorical variables and means and standard deviation for continuous variables. The association between the categorical variables was explored using Pearson chi-square test or fisher's exact test whereas applicable. The difference of continuous variables, among two groups was explored using independent samples t-test. P-value of <0.05 was considered statistically significant for the purpose of the study.

Results

Table 1: Demographic profile

Variables	Group A	Group B	p-value
Age (Years)	25.89±2.71	25.43±2.03	≥0.05
BMI	26.41±1.63	26.01±1.81	≥0.05
Mean Infertility Duration (Years)	5.38±1.79	5.94±1.74	≥0.05

Table 2: Comparison of outcome of ovarian stimulation

Variables	Group A	Group B	p-value
Mean Endometrial Thickness (mm) on the day of hCG administration	7.16±1.05	9.68±1.15	≤0.05
Mean No. of Follicles >18mm on the day of hCG administration	1.89±0.61	1.74±0.59	≥0.05
Mono follicular (%)	63.7	89.6	≤0.05
Multi-follicular (%)	36.3	10.4	

Table 3: Comparison of treatment outcome

Variables	Group A	Group B
Number of cycles (N)	**208**	**190**
Ovulation rate (%)	86.0	91.0
Pregnancy rate (%)	21.0	39.0
Multiple pregnancy (N)	29	1
Number of Miscarriage	6	2

Discussion

For many years, Clomifen Citrate has been used as the first treatment of choice for patients with PCOS. It is generally accepted that Clomifen Citrate reduces uterine receptivity, and thus reduces the chances of conception. It is associated with endometrial thinning in 15–50% of patients, probably due to estrogen receptor depletion. Furthermore, the use of CC may block estrogen receptors in the cervix, producing a negative effect on the quality and quantity of cervical mucus. Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss due to luteal phase defect.[12-14]

Aromatase inhibitors are non-steroidal compounds that suppress estrogen biosynthesis by blocking the action of the enzyme, aromatase, which converts androstenedione and testosterone to estrogens. Letrozole is a potent reversible oral aromatase inhibitor, which has been widely used in post-menopausal women with metastatic breast cancer.[15] It is given in a dose of 2.5–5 mg/day and has been shown to achieve optimal

suppression of serum estrogen level and is almost free of side effects.[15-17] The efficient estrogen-lowering property of letrozole could be utilized to temporarily release the hypothalamus from negative feedback effect of estrogen and thereby inducing an increased discharge of FSH. With letrozole, estrogen production is eventually advanced by the induced FSH discharge, but in contrast to the use of CC, the hypothalamus is able to respond to estrogen feedback with a negative feedback mechanism.[16] This helps in modulating an overzealous discharge of FSH, which in turn is more likely to result in a mono-follicular ovulation with moderate estrogen concentration.

Table 3: RCTs comparing letrozole versus clomiphene

Sl. no	Authors	Study design	Treatment arms	Numbers cycles	Endometrial thickness (mm)	Ovulation rates (%)	Pregnancy rates (%)
	Present study	**RCT**	Letrozole 2.5 mg vs. Clomiphene 100 mg	**190 Vs. 208**	**9.96±1.15 vs. 7.16±1.05**	**91.0 vs. 86.0**	**39.0 vs. 21.0**
1	Atay V et al.[18] Turkey, 2006	RCT	Letrozole 2.5 mg vs. Clomiphene 100 mg	51 vs. 55	8.4 ±1.8 vs. 5.2 ± 1.2	82.4 vs. 63.6	21.6 vs. 9.1
2	Bayar U et al.[19] Turkey, 2006	RCT	Letrozole 2.5 mg vs. Clomiphene 100 mg	99 vs. 95	8 (Median) vs. 8	65.7 vs. 74.7	9.1 vs. 7.4
3	Badawy A et al.[20] Egypt, 2009	RCT	Letrozole 5 mg vs. Clomiphene 100 mg	540 vs. 523	8.1±0.2 vs. 9.2±0.7	67.5 vs. 70.9	15.1 vs. 17.9
4.	Hegde R and Maitra C[21] 2020	RCT	Letrozole 2.5 mg vs. Clomiphene 100 mg	-	9.98±1.58 vs. 7.86±1.25	92.0 vs. 84.0	36.0 vs. 20.0

Conclusion

The present study concluded that though Clomifen Citrate group showed good ovulation rate but final outcome was poor which can be due to anti-estrogenic effect resulting poor endometrial response and negative effect on cervical mucus. However there is need for larger well designed randomized trials to generate robust data in order to establish the true potential of letrozole.

References

1. Homburg R. Clomiphene citrate - end of an era? A mini review. Hum Reprod. 2005; 20:2043-51.
2. Gysler M, March CM, Mishell DR Jr, Bailey EJ. A decade's experience with an individualized clomiphene treatment regimen including its effect on the post coital test. Fertil Steril. 1982; 37:161.
3. Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. Clin Obstet Gynecol. 1985; 12:605–632.
4. 7. Kistner RW. Induction of ovulation with clomiphene citrate (clomid). Obstet Gynecol Surv. 1965; 20:873–900.
5. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001; 75:305–309.

6. Wessman A, Mcardle CR, Achiron R. Ultrasound in infertility. In: MM, SM, editors. Infertility-a comprehensive text. Appleton and Lange. 1996; 447–492
7. Mitwally MFM, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001; 75:305-9.
8. Al-Omari WR, Sulaiman W, Al-Hadithi N. Comparision of two aromatase inhibitors in women with Clomiphene resistant polycystic ovary syndrome. Int J Gynecol Obstet. 2004; 85:289-91.
9. Azim A, Oktay K. Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma. Fertil Steril. 2007; 88:657-64.
10. Goswami SK, Das T, Chattopadhyay R, Sawney V, Kumar J, Choudhary K, Chakravarthy BN, Kabir SN. A randomized single - blind controlled trial of letrozole as a low-cost IVF protocol in women with poor ovarian response: a preliminary report. Hum Reprod. 2004; 19:2031-35.
11. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus worksho*p* group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004; 81:19-25.
12. Gonen Y, Casoer RF. Sonographic determination of an adverse effect of clomiphene citrate on endometrial growth. Hum Reprod. 1990; 5:670-4.
13. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationaship of endometrial thickness and pattern of fecundity in ovulation induction cycles: Effect of clomiphene citrate alone and with menopausal gonadotropin. Fertile Steril. 1993; 59:756-60.
14. Dickey RP, Holtkamp DE. Development, pharmacology and clinical experience with clomiphene citrate. Hum Reprod Update 1996; 2:248-506.
15. Lamb HM, Adkins JC. Letrozole: A review of its use in postmenopausal women with advanced breast cancer. Drugs. 1998; 56:1125-40.
16. Homburg R. Clomiphene citrate - end of an era? A mini review. Hum Reprod. 2005; 20:2043-51.
17. Dowsett M, Jones A, Johnston SR, Jacobs S, Trunet P, Smith IE. in vivo measurement of aromatase inhibitor by letrozole in postmenopausal women with breast cancer. Clin Cancer Res. 1995; 1:1511-5.
18. Atay V, Cam C, Muhcu M, Cam M, Karateke A: Comparision of Letrozole and Clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. J Int Med Res. 2006; 34:73-76.
19. Bayar U, Basavan M, Coskun A, Gezer S: Use of an aromatase inhibitors in patient with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril. 2006, 86:1447-51.
20. Badawy A, Abdul Aal I, Abulatta M: Clomiphene citrate or Letrozole in women polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril. 2009, 92:849-52.
21. Hegde R, Maitra C. Comparison of the role of letrozole & clomiphene citrate as a first line ovulation induction drug in infertile women with polycystic ovary syndrome. Indian J Obstet Gynecol Res. 2020;7(1):12-5.