International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 05|Issue 05 (September-October)|2022|Page: 682-687
SJIF: 5.782

Original Research Paper

A Comparative Study of Letrozole Versus Clomiphene Citrate in Ovulation Induction in Patients with the Polycystic Ovarian Syndrome

Authors:

[1]Dr. Shabina khan, MS Obstetrics & gynecology (Professor), [2]Dr. Padma Rao, MS Obstetrics & gynecology (Resident), [3]Dr. Sarita Kushwaha, MS obstetrics & gynecology (Resident)

[1,2,3]Department of Obstetrics & Gynecology, Rohilkhand Medical College & Hospital, Bareilly, UP, INDIA

Corresponding Author:- Dr Sarita Kushwaha JR3, Department of Obstetrics & Gynecology, Rohilkhand Medical College & Hospital, Bareilly, UP, INDIA.

Article Received: 15-08-2022 **Revised:** 04-09-2022 **Accepted:** 24-09-2022

Conflict of interest:- Nil

Funding:- Self

Ethical clearance:- Communication of Decision of the Institutional Ethics Committee (IEC) of Rohilkhand Medical College & Hospital, Pilibhit Bypass Road, Bareilly(U.P.) Pin- 243006

ABSTRACT:
Introduction: Polycystic ovarian syndrome (PCOS) is characterized by ovarian dysfunction. Ovulation was induced either by Selective estrogen receptor modulators (SERMS: Clomiphene citrate) or aromatase Inhibitors (Letrozole). Hence, the present study was conducted with an aim to assess the comparative efficacy and safety of Letrozole v/s Clomiphene Citrate in ovulation induction in patients with the polycystic ovarian syndrome. Methodology: A randomised trial was conducted in the department of Obstetrics and Gynecology, Rohilkhand Medical College and Hospital, Bareilly among 96 women with infertility in the age group of 21-35 years. All the eligible cases were randomly divided into two groups. Group A and group B were administered 50 mg Clomiphene Citrate and 2.5 mg Letrozole, respectively. Both groups were subjected to transvaginal ultrasonographic monitoring for detecting ovulation. The analysis was carried out on SPSS 24.0 version. Observations: Letrozole-treated patients (66.7%) had better ovulation rates than Clomiphene Citrate-treated patients (52.1%). With Letrozole, 52.1% of patients developed monofollicle and the mean endometrial thickness was 8.6 mm. However, the mean diameter of the largest follicle was more with clomiphene (21.15 mm). Conclusion: The results of this study suggested that aromatase inhibitors are safer and more effective in comparison to clomiphene citrate in terms of ovulation induction. With some limitations of the present study, we found that the advantages of administering Letrozole were more than clomiphene citrate for ovulation induction in women with PCOS.

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is a common endocrinological complication in women in the reproductively active age group with an average incidence of five to ten percent.[1] It is described as a heterogeneous syndrome complex characterized by the incidence of ovarian dysfunction (Oligo and/ or anovulation and polycystic ovaries), hyperandrogenic (clinical or biochemical) and polycystic ovaries in U/S without related problems.[2] Induction of ovulation is a beneficial restoration of one egg/period in a woman who has not yet fully matured egg or no egg at all. The limit of induction of ovulation was six ovulatory periods or twelve complete periods.[3] The commonly used drugs for ovulation induction are Selective estrogen receptor modulators (SERMS), i.e., Clomiphene citrate and aromatase Inhibitors, i.e., Letrozole. Other drugs which work as adjuncts are insulin sensitizers, gonadotrophins, GnRH agonists, dopamine agonists, and dexamethasone.3 Clomiphene Citrate is a nonsteroidal triphenylethylene component that is part of the SERM category. It binds to estrogen receptors (ER) in the hypothalamus and increases the frequency of pulsatile GnRH which leads to the rise in FSH. The antiestrogenic effects of clomiphene are seen in the cervix & endometrium.[4] It is associated with adverse effects namely egg enlargement, vasomotor

flare, abdominal pain or discomfort, constipation, nausea/vomiting, chest discomfort, visual symptoms, and headache. Additionally, it is contraindicated in hypersensitivity, Pregnancy, ovarian cyst, and uncontrolled adrenal or thyroid dysfunction.[5] On the other hand, aromatase inhibitors are oral, easy to use and inexpensive, with minimal side effects among which letrozole are third-generation aromatase inhibitors. It prevents negative estrogen response, without expanding receptors receptor. Both the estrogen in circulation and estrogen formed locally in the brain exert a negative response to gonadotropin release. Prevention of aromatization–Production of estrogen blocked in all sources. Remove the HP axis from the negative estrogenic response - increased Gonadotropin secretion - growth of follicles[6]. It is indicated in case of failure of ovulation induction by clomiphene citrate. It is associated with heartburn, nausea, vomiting, obesity, fatigue, dizziness, joint pain, unusual night sweats, a moderate decrease in lymphocyte count, transient depression, thrombocytopenia, and hyperactivity reactions are rare. Additionally, it has some benefits such as mono follicular ovulation and reduce multiple pregnancies, healthy endometrium, ease of management and low cost, reduction of the amount of FSH used for superovulation, and a good line of safety for the short half-life.[7] There are various views in favour of and against each drug. Hence, the present study was conducted with an aim to assess the comparative efficacy and safety of Letrozole v/s Clomiphene Citrate in ovulation induction in patients with the polycystic ovarian syndrome.

METHODOLOGY:

A prospective randomised, comparative trial was conducted in the department of Obstetrics and Gynecology, Rohilkhand and Medical College and Hospital, Bareilly from 1st November 2019 to 31st October 2020, among 96 women with ovarian factor infertility in the age group of 21-35 years. The sample size was calculated using the software Power and Sample Size Program. Necessary ethical permission was taken from the Institutional ethical committee; informed consent was obtained from each participant. Women in the age group of 21 to 35 years, with a duration of infertility of 2-3 years, presented with amenorrhea/oligomenorrhea, clinical features of hirsutism, acne with a USG evidence of polycystic ovary syndrome and normal bilateral tubal patency, with normal husband`s semen analysis and no history of ovulation induction drug treatment within six months were included in the study. While, women having adnexal pathology or uterine pathologies such as an ovarian cyst or fibroid uterus, having the clinical signs and symptoms of hypothyroidism and hyperthyroidism, having a previous history of any significant surgery which was related to genital tract or due to oligomenorrhea, and significant previous surgeries as surgery due to peritonitis or appendicitis were excluded.

Sampling: All cases that met the inclusion criteria were randomly divided into two groups- (A & B). Group A had given 50 mg Clomiphene Citrate (CC) for five days, while group B had given 2.5 mg Letrozole for five days. At first, most cases were explained about diet and lifestyle modification and drug therapy were given according to the group allotted.

Group A patients were administered Clomiphene Citrate 50 mg OD from D3-D7 of the menstrual cycle and Group B, Letrozole 2.5 mg from D3-D7 of the menstrual cycle. Both the group were subjected to transvaginal ultrasonographic monitoring of number of follicles, maximum diameter of the largest follicle, and endometrial thickness from D11 onwards. The serum progesterone levels were measured on Day 21 which indicates the definite occurrence of ovulation. On day two of the menstrual cycle measurement of hormones serum LH, serum FSH, fasting blood sugar level Serum LH/FSH Ratio, Serum TSH, Serum Prolactin, Serum Estradiol levels were studied the treatment was discontinued in both the groups, if patients developed ovarian enlargement

Clinical examination: Height (meters), weight (kilograms), blood pressure (mmhg), waist-hip ratio, and BMI (Ht/m^2) were measured along with hirsutism scoring.

Statistical Analysis

The analysis was carried out on SPSS 24.0 version. The results were presented in frequencies, percentages and mean ± SD. The Chi-square test and the unpaired t-was used to compare categorical variables and continuous variables, respectively. The p-value<0.05 was considered significant.

Observations:

The present study was conducted to compare the effect of Letrozole versus Clomiphene Citrate in PCOS women. A total of 96 patients were allocated equally in each group (**Group A:** Clomiphene Group and **Group B:** Letrozole group).

Table 1: Clinico-social profile of the cases

Variables		Group A (N=48) n (%)	Group B (N=48) n (%)	P-Value
Age Group (in years)	21-25	33 (68.8)	34 (70.8)	0.843
	26-30	12 (25.0)	10 (20.8)	
	31-35	03 (6.3)	04 (8.3)	
	Mean±SD	24.25±2.81	24.96±3.48	
Duration of infertility (in years)		2.42 ± 0.44	2.45 ± 0.42	0.733
BMI		23.68 ± 0.62	23.53 ± 0.84	0.322
Waist-hip ratio(WHP)		0.828 ± 0.12	0.838 ± 0.14	0.708
Presence of hirsutism		6 (12.5)	8 (16.7)	0.563
Oligomenorrhea		13 (27.1)	12 (25.0)	0.816
Amenorrhea		11 (22.9)	8 (16.7)	0.442
Ovulation		25 (52.1)	32 (66.7)	0.013

About three fourth of patients of group A (68.8%) and group B (70.8%) were between 21-25 years of age. The mean duration of infertility in Group A was 2.42 years and in Group B was 2.45 years. The mean body mass Index in Group A was 23.68 while it was 23.53 in group B. The mean WHR in Group A was 0.828 while in Group B it was 0.838. A meagre (12.5%) of the cases in Group A had clinical evidence of hirsutism while group B has a slightly higher proportion (16.7%) of clinical evidence of hirsutism. About one-fourth (27%) of the cases in Group A and 25% of the cases in Group B had oligomenorrhea. Group A had a slightly higher proportion of patients with amenorrhea (22%) than group B (16.7%). of the cases in Group B had a history of amenorrhea. After excluding pregnancy by urine gravindex method, these patients of PCOS were selected to study after progesterone withdrawal bleed. [Table 1]

Table 2: Response to treatment

Variables		Group A (N=48) n (%)	Group B (N=48) n (%)	P-Value
Ovulation		25 (52.1)	32 (66.7)	0.013
Numbers of follicles	No follicle	23 (47.9)	16 (33.3)	<0.001*
	One follicle	2 (4.2)	25 (52.1)	
	Two follicles	11 (22.9)	7 (14.6)	
	Three follicles	12 (25.0)	0 (0.0)	
Size of follicle (millimeter)#		21.15 ± 0.52	18.76 ± 0.68	<0.001
Endometrial thickness (millimeter)		7.1 ± 0.12	8.6 ± 0.14	<0.001
Serum progesterone level (ng/ml)		12.2 ± 0.32	13.4 ± 0.24	<0.001

Fisher`s exact test, #Cases with ovulation

There was a statistically significant difference in ovulation induction rate between the group of patients treated patients with Clomiphene Citrate and Letrozole. Letrozole-treated patients (66.7%) had better ovulation rates than Clomiphene Citrate-treated patients (52.1%). Out of 48 patients in the Clomiphene Citrate group, 4.2% of cases developed single follicles and 47.9% of the cases did not ovulate with Clomiphene Citrate therapy. However, with Letrozole, about half (52.1%) of patients developed a single follicle. The mean diameter of the largest follicle in group B was 18.76 mm in comparison with group A, where the mean diameter was 21.15 mm. The mean endometrial thickness in group A was 7.1 mm, while it was 8.6 mm in group B. The mean serum progesterone level in A and B group on 21 day of menses was 12.2 ng/ml and 13.4 ng/ml, respectively. [Table 2]

Table 3: Comparison of hormone levels in between group A and group B pre and post-treatment

Variables	Group A (N=48) n (%)	Group B (N=48) n (%)	Mean difference	P-Value
LH, FSH and LH: FSH				
LH	11.53±1.47	11.49±0.37	0.04	0.857
FSH	4.84±0.70	4.65±0.46	0.19	0.129
LH: FSH	2.43±0.46	2.49±0.27	0.06	0.381
LH*	9.34±1.11	11.88±0.35	2.54	<0.001
FSH*	4.56±0.51	5.92±0.71	1.36	<0.001
LH: FSH*	2.07±0.33	2.04±0.24	0.03	0.554
TSH, PRL AND serum estrogen				
TSH	1.68±0.32	1.81±0.27	0.138	0.026
PRL	11.31±0.57	12.50±0.97	1.190	<0.001
S/E2	57.23±4.71	57.06±2.50	0.167	0.829
TSH*	1.78±0.32	1.91±0.27	0.133	0.030
PRL*	11.41±0.57	12.60±0.97	1.190	<0.001
S/E2*	50.94±4.68	50.06±2.50	0.875	0.256

*LH: Luteinizing hormone, FSH: Follicle stimulating hormone, TSH: Thyroid stimulating hormone, PRL: Prolactin, S/E2: Serum estradiol, *post-treatment*

Even though the level of LH and FSH was more reduced after treatment with Clomiphene Citrate, however, there was no significant difference in the serum levels of LH and FSH after treatment. Similarly, there was no significant difference between the groups for thyroid stimulating hormone, prolactin and serum estradiol after treatment. [Table 3]

DISCUSSION:

The present study was conducted to compare the effect of Clomiphene citrate and Letrozole on ovulation induction which was assessed using ultrasonography and hormonal assay. A total of 96 patients were allocated equally in each group (Group A: Clomiphene Group and Group B: Letrozole group). The groups were compared for age, mean duration of reproduction, waist-hip ratio and body mass index and different parameters of hormones such as serum LH, Serum FSH, serum TSH, and serum Prolactin which had no statistically significant differences, suggesting that both the groups were comparable before initiating the treatment. Patients enrolled in both groups had no side effects with Letrozole and Clomiphene Citrate during the study period.

Rate of ovulation and thickness of the endometrium

In our study rate of ovulation and thickness of endometrium were more in the Letrozole group, 67% and 8.6 mm, respectively in comparison to the Clomiphene Citrate group where the rate of ovulation was 52% and the thickness of the endometrium was 7.1 mm. Aboubakr Elnashar et al.[viii] in their study confirmed the ovulation with Letrozole in more than half (55%) of the patients, while the thickness of the endometrium was 10.2 mm. In a study by Dehbashi S et al.[ix] after administering drugs letrozole and clomiphene citrate when the diameter of the follicle was more than 14 mm, the ovulation rate in the Letrozole group was 60% and in the Clomiphene Citrate group, it was 32%. Ray PB et al.,[x] studied one hundred and forty-seven infertile PCOS patients and confirmed the endometrial thickness of 8.7 mm with Letrozole similar to the present study. Sujata Kar et al.[xi] showed that ovulation rate and endometrial thickness were more in the Letrozole group (73%, 7.7 mm respectively) in comparison to the Clomiphene Citrate group (61%, 7.6 mm, respectively). Zeba D et al.[xii] conducted a study of 240 women and found that the effect of Letrozole was significantly better in endometrial thickness. Nambiar SS et al.xvii in their study reported that the thickness of endometrium was higher in the letrozole group. Gupta E et al.[xiii] committed a case that was expected to be heard in presence of 92 infertile women with PCOS. On the day when the follicle diameter size reached 18 mm, the thickness of the endometrium was higher in the letrozole group than in the Clomiphene Citrate group. Compared with the two drugs the ovulation rate was high in the letrozole group. These studies showed similar results to our study.

Conversely, Seyedoshohadaei F et al.[xiv] in their study on patients of infertility showed that Clomiphene citrate was a better drug than Letrozole for ovulation induction. They observed a better ovulation rate with Clomiphene citrate (73%) compared to Letrozole (68%). Angel M et al.[xv] showed that endometrial

thickness was more in clomiphene citrate. Liu C et al.[xvi] they conducted a study on 268 patients suffering from infertility of anovulation in PCOS. They concluded that the Clomiphene Citrate regimen was still better and recommended as the first-line therapy for induction of ovulation in patients of the polycystic ovarian syndrome.

Serum hormonal assay

Ray PB et al.x in their study found that on the day when the ovarian follicle was 18 mm in size, the serum estradiol level was significantly higher in the Clomiphene Citrate group compared to the letrozole group.

Monofollicular development and diameter of the follicle

Sujata Kar et al.xi showed that monofollicular development was more in the Letrozole group (80%) in comparison to the Clomiphene Citrate group (55%), the present study also confirmed that the monofollicular development was more in the Letrozole group (52.1%) compared to the Clomiphene Citrate group (4.2%). Similarly, Nambiar SS et al.[xvii] compared the two drugs Clomiphene Citrate and Letrozole for infertility treatment in form of ovulation induction in 200 women suffering the polycystic ovarian syndrome. The number of follicles was highly elevated in the clomiphene group. Patients treated with letrozole had higher monomolecular development. Angel M et al.xv showed that the diameter of the follicle was more in the letrozole group (20.76 mm) vs clomiphene citrate (20.67 mm).

Pregnancy rate

In our study and the pregnancy rate was higher in Letrozole group. Nambiar SS et al.xvii in their study showed that the total pregnancy rate was high in the letrozole group compared to the clomiphene group. In the clomiphene group there was one quadruplet and one twin pregnancy, in the letrozole group there were no twin pregnancies.

CONCLUSION:

The results of this study suggested that aromatase inhibitors, such as letrozole, were safer and more effective in comparison to clomiphene citrate in terms of ovulation induction. Along with this, letrozole might have benefits over clomiphene citrate in terms of thickness of the endometrium, the development of a single follicle and possibly predicting better pregnancy rates. With some limitations of the present study, we found that the advantages of administering Letrozole were more than clomiphene citrate for ovulation induction in women with PCOS.

REFERENCES:

1. Rasquin Leon LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. [Updated 2022 May 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459251/

2. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P T. 2013 Jun;38(6):336-55. PMID: 23946629; PMCID: PMC3737989.

3. Lindheim SR, Glenn TL, Smith MC, Gagneux P. Ovulation Induction for the General Gynecologist. J Obstet Gynaecol India. 2018 Aug;68(4):242-252. doi: 10.1007/s13224-018-1130-8. Epub 2018 May 12. PMID: 30065537; PMCID: PMC6046677.

4. Teramoto, Shokichi & Kato, Osamu. (2007). Minimal ovarian stimulation with clomiphene citrate: A large-scale retrospective study. Reproductive biomedicine online. 15. 134-48. 10.1016/S1472-6483(10)60701-8.

5. Yilmaz S, Yilmaz Sezer N, Gönenç İM, İlhan SE, Yilmaz E. Safety of clomiphene citrate: a literature review. Cytotechnology. 2018 Apr;70(2):489-495. doi: 10.1007/s10616-017-0169-1. Epub 2017 Nov 20. PMID: 29159661; PMCID: PMC5851961.

6. Peters A, Tadi P. Aromatase Inhibitors. [Updated 2022 Jul 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557856/

7. Gangadhara S, Bertelli G. Long-term efficacy and safety of anastrozole for adjuvant treatment of early breast cancer in postmenopausal women. Ther Clin Risk Manag. 2009 Aug;5(4):291-300. doi: 10.2147/tcrm.s3856. Epub 2009 May 4. PMID: 19753124; PMCID: PMC2690973.

8. 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.

9. Dehbashi S, Dehbashi S, Kazerouni T, Robati M, Alborzi S, Parsanezhad ME, Shadmand A. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. Iran J Med Sci. 2009;34(1):23-28.

10. Ray PB, Ray A, Chakraborti PS. Comparison

of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Archives of gynecology and obstetrics. 2012;285(3):873- 7.
11. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial. Journal of human reproductive sciences. 2012;5(3):262.
12. Zeba D, Biswas R, Fatema K, Khair MA, Zesmin F, Sharifa J. Letrozole or Clomiphene Citrate for Induction of Ovulation in Patients with Polycystic Ovarian Syndrome: A Prospective Randomized Trial. Faridpur Med. Coll. J. 2018;13(2):78-81.
13. Gupta E, Nayar K, Singh M, Gupta S, Bhattacharya R. To study the comparison of efficacy of letrozole versus clomiphene citrate for ovulation induction in infertile women with PCOS in Indian population. Fertility Science and Research. 2020;7(2):162.
14. Seyedoshohadaei F, Zandvakily F, Shahgeibi S. Comparison of the effectiveness of clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to isolated unovulation. Iranian journal of reproductive medicine. 2012;10(6):531.
15. Angel M, Ghose S, Gowda M. A randomized trial comparing the ovulation induction efficacy of clomiphene citrate and letrozole. Journal of natural science, biology, and medicine. 2014;5(2):450.
16. Liu C, Feng G, Huang W, Wang Q, Yang S, Tan J, Fu J, Liu D. Comparison of clomiphene citrate and letrozole for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial. Gynecological Endocrinology. 2017;33(11):872-6.
17. Nambiar SS. Clomiphene Citrate versus Letrozole for Ovulation Induction in PCOS: A Comparative Study. Journal of South Asian Federation of Obstetrics and Gynaecology. 2018;10(Suppl 2):384-399.