Content available at: iponlinejournal.com

Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.innovativepublication.com



Original Research Article

Comparison of the role of letrozole & clomiphene citrate as a first line ovulation induction drug in infertile women with polycystic ovary syndrome

Rashmi Hegde¹, Camelia Maitra^{1,*}

¹Dept. of Obstetrics and Gynaecology, S. S. Institute of Medical Sciences & Research Centre, Davanagere, Karnataka, India



ARTICLE INFO	ABSTRACT	
Article history: Received 15-11-2019 Accepted 04-12-2019 Available online 21-02-2020 Keywords: Letrozole Clomiphene citrate PCOS Infertility	 Aim: To compare the role between Clomiphene Citrate & letrozole for infertile patients with Polycystic Ovary Syndrome as an ovulation induction agent & which drug can be chosen as a first line ovulation induction agent in future. Materials and Methods: This prospective study was carried at SSIMS & RC OBG OPD. Total 50 patients of PCOS (diagnosed by Rotterdam criterion) were included in this study. In this clinical trial out of 50 	
	 patients, 25 patients received Clo miphene Citrate 100mg (n=25) and rest 25 patients received Letrozole 2.5mg (n=25) daily since day 2-6 or3-7 of menstrual cycle. Follicular respose was carried out from day 9 by trans-vaginal sonogram till atleast 1 mature follicle (18-22mm) was detected & hCG was administered at a dose of 5000 IU. Timed intercourse was advised 24-36 hours after hCG injection. The number of Follicles, Endometrial Thickness, Ovulation rate & Pregnancy rate were measured in both groups. Result: Monofollicular development was statistically significantly, greater in the Let group (CC 61.9%, Let 86.9%). There was also statistically significant difference between the two groups in endometrial thickness (CC 7.86±1.25mm, Let 9.18±1.49mm). Similarly, The ovulation rate was 84%% in CC group and 92% in Let group. The pregnancy rate was 20% in CC group and 36% in Let group. Conclusion: Letrozole might be an acceptable alternative to clomiphene citrate to induce ovulation and pregnancy in PCOS patients. © 2020 Published by Innovative Publication. This is an open access article under the CC BY-NC-ND 	
	license (https://creativecommons.org/licenses/by/4.0/)	

1. Introduction

80% of the couples achieve conception within 1 year of having regular unprotected intercourse with adequate frequency (4-5times/ week). According to the Indian Society of Assisted Reproduction, infertility currently affects about 10-14 percent of the Indian population, in which male is directly responsible in about 30-40% and female in about 40-55% and both are responsible in 10% cases. PCOS is one of the most common cause of infertility affecting 6% women within reproductive age & still increasing due to lifestyle changes and other familial factors.¹ In India the prevalence is 3.7-22.5%.² It is characterised by a combination of hyperandrogenism (either Clinical or Biochemical), chronic anovulation & polycystic ovaries. It is frequently associated with insulin resistance & obesity.³ It belongs to group 2 ovulatory disorder (hypothalamic pituitary dysfunction) 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 (CC) is till date a first line ovulation induction agent. It is long-standing, standard drug for ovulation induction.^{4,5} 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,^{6,7} and 20-25% PCOS women are resistant to clomiphene.^{8,9} Anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors,

https://doi.org/10.18231/j.ijogr.2020.003 2394-2746/© 2020 Innovative Publication, All rights reserved.

^{*} Corresponding author. E-mail address: cameliamaitra22@gmail.com (C. Maitra).

adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus. So, though ovulation rate is really good with this drug but final outcome in respect to a successful pregnancy is still a doubt.

Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. It has been in use for few years now, and numbers of researchers have studied this molecule as an option for ovulation induction.^{8,10} Its mode of action is by reducing estrogen production by blocking androgens to estrogens conversion. Additionally, it has no adverse effect on endometrium and cervical mucus. In India, letrozole was approved for ovulation induction from 2006 to 2011 by the Drug controller general of India (DCGI). Letrozole has been shown to have good ovulation rate in CC-resistant PCOS women.¹¹ Indian PCOS women have high prevalence of insulin resistance.¹² and thus are likely to have high CC resistance. Letrozole could prove to be a good alternative for ovulation induction in such women.

2. Materials and Methods

This clinical trial was carried out at OBG OPD SSIMS & RC from 1st June to 31st December 2018. Total 50 patients of PCOS were included in the study. Diagnosis of PCOS was made on Rotterdam criteria. Exclusion criteria were patients with renal, liver or thyroid diseases. In this trial 50 infertile patients with PCOS received either 100 mg CC (n=25) or 2.5 mg Letrozole (n=25) 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. In relation to side effects- in Letrozole group only 4% patients had OHSS whereas Clomiphene Citrate group had 12%. Similarly, 40% of patients receiving Clomiphene Citrate had multiple pregnancy, whereas in Letrozole group it was nil.

3. Results

Total 50 patients with infertility due to PCOS were included in the study. There were 25 patients in the CC group and remaining 25 patients were in the letrozole group. Patient Characteristics like age, duration of infertility, BMI, presenting signs and symptoms were kept similar in both groups, which is depicted in Table 1 below.

In Table 2, it shows 84% patients ovulated in first cycle of treatment in group 1, whereas in group 2 it was 92%.

Monofollicular development is statistically significant in group 2 (letrozole group) as compared to group 1 (Clomiphene citrate group), i.e. 61.9% in group 1 and 86.9% in group 2. This study shows that Multifollicular development was greater in patients who received Clomiphene citrate (38.1%) as compared to those who received Letrozole (13.1%).

Endometrial response was statistically significant in Letrozole group (group 2) i.e. 9.18 + 1.49mm, as compared to Clomiphene group (group 1) i.e. 7.86 + 1.25mm.

This study also showed that the rate of OHSS was higher in patients who received Clomiphene citrate (group 1) i.e. 12%, as compared to patients who received Letrozole (group 2) i.e. 4%.

Table 3 depicts the outcome of treatment observed in our study, where ovulation rate was higher in group 2(92%) as compared to group 1(84%). Similarly the pregnancy rate was also higher in group 2(36%) as compared to group 1(20%).

It was observed that rate of multiple pregnancy was higher in Group 1 i.e. 40%, whereas none of the subjects in Group 2 developed multiple pregnancies.

4. Discussion

Since 1960, Clomiphene Citrate was considered to be the sole first line ovulation induction agent. However, clomiphene resistance (15-20%), endometrial thinning, and poor cervical mucus (15-50% of cases) makes it ineffective in many situations. Letrozole, which is an aromatase inhibitor, has been explored as a good alternative by many researchers, but the evidence about its efficacy as compared to clomiphene is conflicting.

Clomiphene citrate (*CC*) is a non-steroidal tri-phenyl ethylene derivative. It has both estrogen agonist & antagonist properties, depending on prevailing levels of endogenous estrogen. CC is a racemic mixture of 2 distinct stereo-isomers, enclomiphene (62%) and zuclomiphene (38%). Because of its structural similarity to estrogen, CC probably induces ovulation primarily through the effects on hypothalamic GnRH pulse generator. During CC treatment, Levels of LH & FSH rise then fall again after typical 5 day course of therapy. In normal cycling women, CC increases GnRH pulse frequency. In anovulatory women with PCOS, in whom GnRH pulse frequency is already very high, CC increases pulse amplitude but not the frequency. It can also be used in males with oligospermia.

4.1. Clomiphene Resistance

It is defined as absent of ovulation (absence of follicular development on TVS with concomitant failure of E2 levels to raise) after treatment with CC (100mg for 5 days in 3 cycles). It is seen in 20-25% of the cases.

Known side effects are vasomotor flushes, breast tenderness, pelvic discomfort, nausea, visual disturbances, rarely OHSS (Ovarian hyper-stimulation syndrome).

Letrozole is third generation aromatase inhibitor used for treatment of breast cancer in post menopausal women for

Age (years)	Group-1 Clomiphene Citrate 24.96 + 3.51	Group 2 Letrozol e 27.72 + 4.89
BMI (kg/m2) Married Life (years)	24.8 + 3.13 4.42 + 2.44	24.62 + 3.13 5.12 + 3.65
Married Life (years)	4.42 + 2.44	5.12 + 5.05
Table 2: Outcome of ovarian stimulation		
	Group-1 Clomiphene Citrate	Group-2 Letrozolo
Ovulation in First Cycle of Treatment %	84.0	92.0
Monofollicular development %	61.9	86.9
Multifollicular development %	38.1	13.1
Endometrial thickness (mm)	7.86 + 1.25	9.18 + 1.49
OHSS %	12.0	04.0
Table 3: Outcome of treatment		
	Group-1 Clomiphene Citrate	Group-2 Letrozole
Ovulation rate (%)	84.0	92.0
Pregnancy rate (%)	20.0	36.0
Multiple pregnancy (%)	40	None

Table 1: Patient Characteristics

several years, later it was approved for ovulation induction. It is a category B drug.

Aromatase inhibitors release the HPO axis from the estrogenic negative feedback, increase gonadotrophin secretion, and stimulate ovarian follicular development. Locally in the ovary they increase the follicular sensitivity to FSH. Advantages of letrozole over CC are: 1) Rapid elimination from the body (half life-45 hrs), 2) no adverse anti-estrogenic effects on endometrium or cervical mucus, 3) absence of estrogen receptor depletion and, 4) limited number of mature follicles(decrease incidence of OHSS & multiple pregnancy).

In our study, CC group shows statistically significant multi-follicular development (CC 38.1%, Let 13.1%). This is expected and corroborated by number of studies. Letrozole resulted in mono- folliculogenesis in 86.9% of cases, which is optimal for ovulation induction in PCOS women. However, where multiple follicular development is needed, letrozole may be inadequate.

In our study, the mean endometrial thickness was slightly higher in letrozole group, 9.18 + 1.49 compared to CC 7.86 ± 1.25 . In a recent study by Banerjee *et al* 147 Indian women with PCOS were compared between letrozole (2.5 mg) Vs. clomiphene (100 mg). Mean endometrial development was 8.72 ± 11.41 mm in letrozole and 8.78 ± 1.16 mm in CC group (P = 0.004). Mitwally and Casper found letrozole associated with greater endometrial thickness.¹³

Badawy *et al.*¹⁴ in their study of 438 patients with 1063 cycles, one of the largest studies comparing CC and letrozole, reported statistically significantly higher endometrial thickness in CC group (9.2 \pm 0.7) vs. letrozole (8.1 \pm 0.2,*P* = 0.021). Few studies have shown no significant

difference between the two groups with regard to effect on endometrium. ^{15,16}

Pregnancy rate per cycle was astonishingly high with letrozole in our study (36.0%) Vs. (20.0%). Requena et al in their literature review looked at randomized trials comparing letrozole versus clomiphene as first line therapy and included four studies (Atay et al 2006; Bayar et al 2006; Sorabvand et al 2006; Badawy et al 2007).^{14,17–19}

The ovulation rate for letrozole in comparison with clomiphene did not differ significantly, being 84% with CC vs 92% with letrozole.

In a meta-analysis by He and Jiang,²⁰ the clinical efficacy of letrozole was compared with clomiphene for ovulation induction in PCOS women. This is one of the largest meta-analysis of the subject published. Six RCTs involving 841 patients were analyzed. There were no significant differences in pregnancy rate, abortion rate, and multiple pregnancy rate between the two groups. The evidence from ovulation rate was not enough to support either of the drugs.

5. Conclusion

Our study showed statistically significantly higher monofollicular development and pregnancy rates when letrozole was used as ovulation induction drug in infertile PCOS women. Whereas, though CC group showed good ovulation rate but final outcome was poor which can be due to antiestrogenic 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.

6. Source of funding

None.

7. Conflict of interest

None.

References

- Hussain NH, Ismail M, Zain MM, Yeu PC, Ramli R, et al. Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. *Open J Obstet Gynecol.* 2013;3(05):11.
- 2. Saxena P, Kaur M. Standards of Care in Diagnosis and Management of Adolescent PCOS. AOGD BULLETIN ;.
- 3. 3.Recommendations from the international evidence based guideline for the assessment & management of Polycystic ovarian syndrome ;.
- Casper RF. Letrozole versus clomiphene citrate: Which is better for ovulation induction? *Fertil Steril*. 2009;92:858–859.
- Amsterdam E. Sponsored 3rd PCOS consensus workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod.* 2012;27:14–24.
- Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. *Clin Obstet Gynecol*. 1985;12:605–632.
- Kistner RW. Induction of ovulation with clomiphene citrate (clomid). *Obstet Gynecol Surv.* 1965;20:873–900.
- 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.
- Wessman A, Mcardle CR, Achiron R. Ultrasound in infertility. In: MM, SM, editors. Infertility-a comprehensive text. vol. 1996. Appleton and Lange ;. p. 447–492.
- Sammour A, Biljan MM, Tan SL, Tulandi T. Prospective randomized trial comparing the effects of letrozole and clomiphene citrate (CC) on follicular development, endometrial thickness and pregnancy rate in patients undergoing superovulation prior to intrauterine insemination. 57th Annual Meeting of the American Society for Reproductive Medicine. Orlando, FL: 2001. (Abstract O-291). . *Fertil Steril.* 2001;76:S110.
- Ganesh A, Goswami SK, Chattopadhyay R, Choudhury K, Chakravarty B. Comparison of letroz with continuous gonadotropins and clomiphene gonadotropin combination for ovulation induction. In

1387 PCOS women after clomiphene citrate failure: A randomized prospective clinical trial. *J Assist Reprod Genet*. 2009;26:19–24.

- Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Insulin resistance in metabolic syndrome in Indian PCOS South Asians. *Indian J Endocrinal Metab.* 2012;16:44–55.
- 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;75:305–309. Available from: 10.1016/S0015-0282(00)01705-2.
- Badaway A, Aal IA, Abulalta M. Climiphene Citrate or Letrozole for ovulation induction in women with polycystic ovarian syndrome: A prospective randomized trial. *Fertil Steril.* 2009;92:849–852.
- Fisher SA, Reid RL, Vugt DAV, Casper RF. A randomized doubleblind comparison of the effects of clomiphene citrate and the aromatase inhibitor on ovulatory function in normal women. *Fertil Steril.* 2002;78:280–285.
- Kilic-Okman T, Kucuk M, Altaner S. Comparison of the effects of letrozole and clomiphene citrate on ovarian follicles, endometrium, and hormone levels in the rat. *Fertil Steril*. 2003;80:1330–1332.
- 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.
- Bayar U, Tanriverdi HA, Aykut B, Ayoglu F, Ozcan O, et al. Letrozole vs clomiphene citrate in patients with ovulatory infertility. *Fertil Steril.* 2006;85:1045–1048.
- Sohrabvand F, Ansari S, Bagheri M. Efficacy of combined metformin - letrozole in comparison with metformin - clomiphene citrate in clomiphene resistant infertile women with polycystic ovarian disease. *Hum Reprod.* 2006;21:1432–1435.
- He D, Jiang F. Meta analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome. *Reprod Biomed Online*. 2011;23:91–96.

Author biography

Rashmi Hegde Professor

Camelia Maitra Post Graduate

Cite this article: 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):12-15.