A COMPARATIVE STUDY OF LETROZOLE VS CLOMIPHENE CITRATE AS FIRST LINE FOR ANOVULATORY INFERTILITY– AN INSTITUTIONAL EXPERIENCE.

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Abstract

Background: Anovulatory infertility is a common problem and accounts for 40% of female infertility. In most of the cases, it further cannot be attributed to a specific treatable cause, thus ovulation induction becomes an empiric, organized and incremental titration intended to identify the successful treatment regimen associated with the least cost and risk. Clomiphene citrate has been traditionally used as the drug of choice. In the last decade letrozole has emerged as an alternative. However, its role as an alternative to clomiphene as first line therapy continues to be debated. **Objective**: To compare letrozole and clomiphene citrate in anovulatory infertility, with respect to ovulation rate and pregnancy rate. **Materials and methods:** 50 cases of primary infertility with anovulation were taken, in whom bilateral fallopian tubes were patent at laparoscopic chromopertubation, or hysterosalphingography or sonosalphingography. Their spouse had male factor fertility confirmed by adequate seminal parameters according to latest WHO guidelines. Patients were randomized into two groups. From day 3 – 7 of the menstrual cycle, patients (25 each) either received tablet letrozole 2.5mg OD orally or tablet clomiphene citrate 100mg OD orally. Transvaginal ultrasound on day 14 and 16 of the cycle were done for follow up. Advice for timed intercourse daily around the time of ovulation was given. Main outcomes measured were number of follicles, endometrial thickness, ovulation rate, pregnancy rate and miscarriage rates. **Results:** Letrozole was found to be more effective than clomiphene citrate in terms of monofollicular ovulation (98.70% vs 75.00%), significant improvement in endometrial thickness (9.5 ± 1.1 mm vs 8.3 ± 1.3 mm) and no cases with lag endometrium. All 25 cases in the letrozole group (100%) achieved ovulation in the first cycle of treatment out of which 6 cases (24.00%) became pregnant. There were no multiple pregnancies or miscarriages. We observed a statistically significant difference among both the groups in terms of outcome ($p<0.05$). There is a positive correlation ($\rho=0.7$) between letrozole and number of pregnancies in this study. **Conclusion:** Letrozole is a more effective drug; as a first line agent for ovulation induction in anovulatory infertility; alternative to clomiphene citrate.

Keywords: Letrozole, Clomiphene citrate, anovulation, infertility

Introduction

Female factor infertility accounts for 40-55%; out of which anovulation is the major cause.[2] Induction of ovulation in anovulatory women is a landmark achievement in the history of reproductive endocrinology. The last century has seen major advancement in the field of infertility and the discovery of various medical and surgical methods of ovulation induction has changed the face of treatment worldwide.

Clomiphene citrate has been traditionally used as the first line drug in all cases. Letrozole was introduced into infertility in the year 2000 and has been the second line treatment option, particularly in women with clomiphene resistance or failure.[3,4,5] But whether it is better than clomiphene as a first line regimen option is still debatable and unclear and a definite answer would have significant clinical implications for infertility experts.

Objective

This article aims at comparing role of letrozole vs clomiphene citrate in anovulatory infertility, with respect to ovulation rate and pregnancy rate.

Materials and Methods

- Health care setup – Tertiary care hospital
- Setting – JJM Medical College, Davangere, Karnataka.
- Duration of the study – 2015 to 2017 (2 years)
- Type of the study – Prospective cohort study
- Sample size – 50
- Level of evidence – Level IV
- Selection of cases – 50 cases of primary infertility with anovulation were taken who satisfied the inclusion and exclusion criteria of the study.

Inclusion criteria

a) All cases of primary infertility with anovulation
b) Patients with bilateral fallopian tubes patent observed at laparoscopic chromopertubation, or hysterosalphingography or sonosalphingography.
c) Their spouse should have male factor fertility confirmed by adequate seminal parameters according to latest WHO guidelines.

Exclusion criteria

a) Patients with regular menstrual cycles
b) Patients with secondary infertility
c) With tubal blockage identified at HSG, laparoscopic chromopertubation, or sonosalphingography
d) Clinical evidence of hyperprolactinemia, hypercortisolism, or thyroid dysfunction
e) Patients with unexplained infertility
f) Male infertility
g) Patients refused participation as per our protocol

After getting IEC clearance from the institute and informed written consent from the patients enrolled in our study, they were subjected for thorough examination for confirmation of anovulation [1,2] as the cause for infertility. These patients were either given oral contraceptive pill (OCPs) if they came within 5 days of their menses or progesterone pills if they had a history of previous amenorrhea after ruling out pregnancy. In next menstrual cycle, within 3 days of their menses, ovulation induction using two different regimens were started for them.

Randomization by coin-tossing method into two groups either letrozole or clomiphene citrate group was done. 25 women were given tablet letrozole 2.5mg/ day orally from day 3-7 of the menstrual cycle. Another 25 patients in clomiphene citrate group were given tablet clomiphene citrate 50 mg/ day orally from day 3 to day 7 of the menstrual cycle.

- Follow up – patients were asked to report back on 10^{th} to 14^{th} day of menstrual cycle. Transvaginal ultrasound for follicular development and endometrial thickness was done on day 14 and 16 of the cycle. Advice for timed intercourse daily around the time of ovulation was given. But if a dominant follicle was not found in both the ovaries and multiple small follicles were found less than 10mm, we considered that she would not ovulate in that cycle and was asked to review in the next cycle.
- Next menstrual cycle – In the absence of menstruation, as in most of our cases diagnosis of pregnancy was confirmed by either urine pregnancy test/ bimanual examination/ TVS. If not found to be pregnant, progesterone induced withdrawal bleeding was given and same regimen was given with stepped up dose. Stepped up dosage for clomiphene was 100mg/day and for letrozole was 5mg/day. Treatment was given for a maximum of 5 cycles.
- Main outcomes measured were number of follicles, endometrial thickness, ovulation rate, pregnancy rate and miscarriage rates.
- Statistical Analysis were reported as mean (SD) for continuous variables, frequencies (percentage) for categorical variables. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Chicago, IL.

Results

The patients who underwent treatment as per our study protocol were analysed statistically with student 't' test and chi square test and the results were tabulated.

A) Age of patients

Table 1 – Age group of patients

Age	Group L	Group CC
≤20 years	4	1
21 – 25 years	10	17
26 – 30 years	7	6
>31 years	4	1
Mean ± SD	25.4 ± 4.3	23.9 ± 3.21
Range	18 – 34	20 – 34

Group L vs Group CC t = 1.29, p = 0.20, statistically not significant

The majority of cases in both the groups were between 21 to 25 years of age. In group L, minimum age was 18 and maximum age was 34 years. In group CC, minimum age was 20 and maximum age was 34 years. The two groups were statistically matched

with respect to age. It shows that anovulation rate were high in the age group between 21 to 25 years which is the most common period of maximum fecundity.

B) Duration of infertility

Table 2 – Duration of infertility

Duration	Group L	Group CC
≤3 years	12	13
4 – 6 years	9	7
7 – 10 years	3	5
>10 years	1	0
Mean ± SD	4.30 ± 2.9	4.28 ± 2.29
Range	1 – 13	1.5 – 10

Group L vs Group CC – t = 0.03, p = 0.98, statistically not significant

The maximum duration of infertility observed in our study varied from 1 to 13 years. The maximum number of patients for ovulation induction in both groups belonged to 1 to 3 years group. The two groups were statistically matched in this regard.

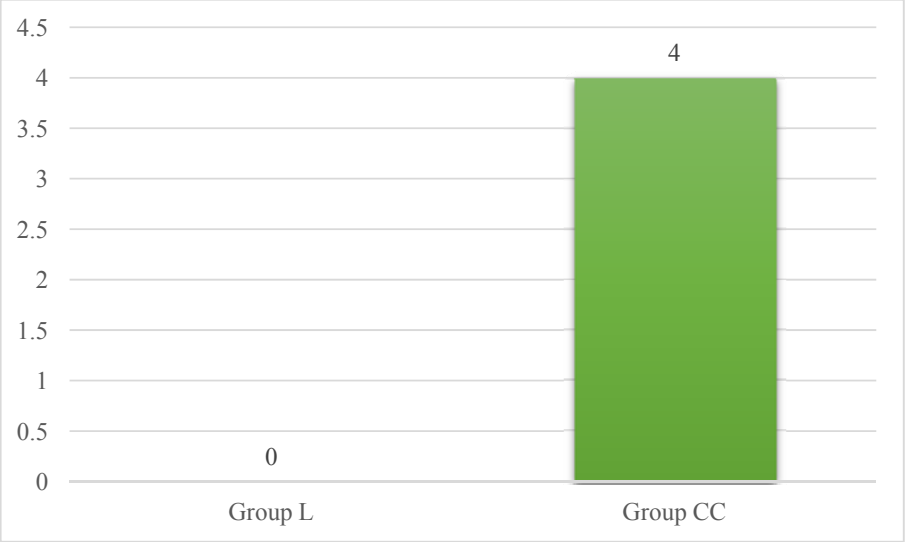
C) Diagnostic finding

The total number of cases undergoing laparoscopy was 14 [L (11) + CC (3)]. In group L, out of 11 cases, 10 cases revealed anovulatory ovaries. In group CC, out of 3 cases, 2 cases revealed anovulatory ovaries. In other 36 cases, HSG was done for 34 cases [L (16) + CC (18)] and SSG was done for 5 cases [L (1) + CC (4)].

D) Endometrial thickness

The endometrial thickness of cases in both the groups were measured in each cycle by USG. The mean endometrial thickness in group L was 9.5 ± 1.1 mm and in group CC was 8.3 ± 1.3 mm which was statistically significant.

E) Cases of lag endometrium



Graph 1 – Cases of lag endometrium

In group L, no cases of lag endometrium were reported whereas in group CC, 4 cases (16.00%) of lag endometrium were reported.

F) Monitoring number of follicles by USG

Table 3 – Monitoring number of follicles by USG

Category	No of follicles per cycle			Total no of cycles
	No of follicle	1 follicle	2 follicles	
Group L	0	78	1	79
Group CC	5	54	13	72

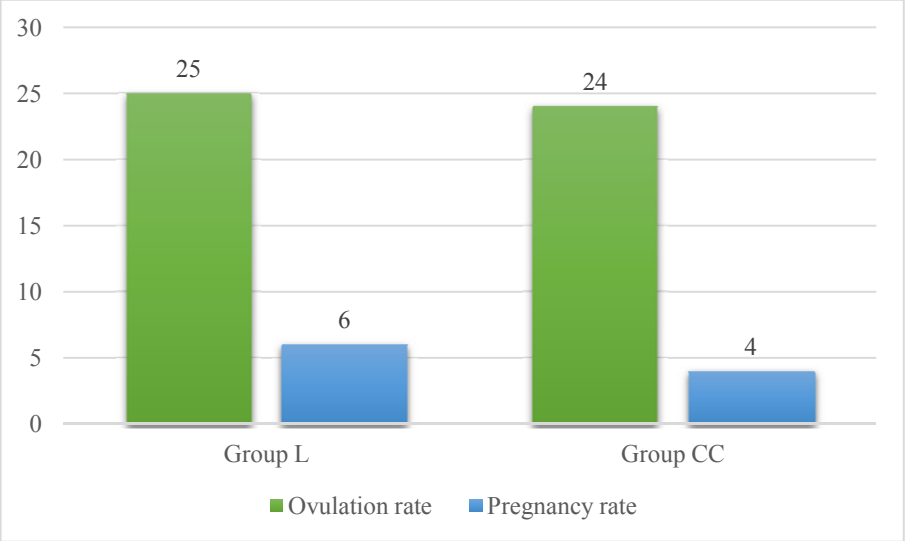
In group L – 98.70% cases had unifollicular development and only 1.3% cases had two follicle development. In group CC – 75.00% cases had unifollicular development and only 18.1% cases had two follicle development. The results are statistically significant ($p<0.05$)

G) Monitoring ovulation by USG

Table 4 – Monitoring ovulation by USG

Category	Group L	Group CC	P value
Ovulation in 1st cycle of treatment	25	23	0.14
Overall ovulation during treatment	25	24	0.13
Cases who failed to ovulate in 1st cycle	0	2	0.14
Case who all failed to ovulate during treatment	0	1	0.31
No of ovulated cases who achieved pregnancy	6	4	0.52
No of ovulated cases who failed to achieve pregnancy	19	20	0.52

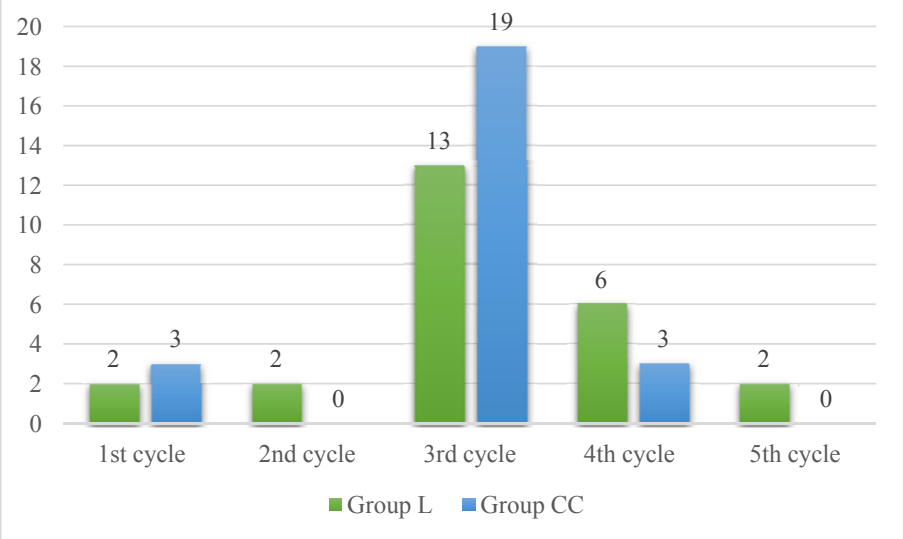
H) Ovulation and Pregnancy rates



Graph 2 – Ovulation and Pregnancy rates

Group L – 100% (n=25) of the cases ovulated during treatment and 24.00% (n=6) achieved pregnancy.
Group CC – 96.00% (n=24) of the cases ovulated during treatment and 16.00% (n=4) achieved pregnancy.

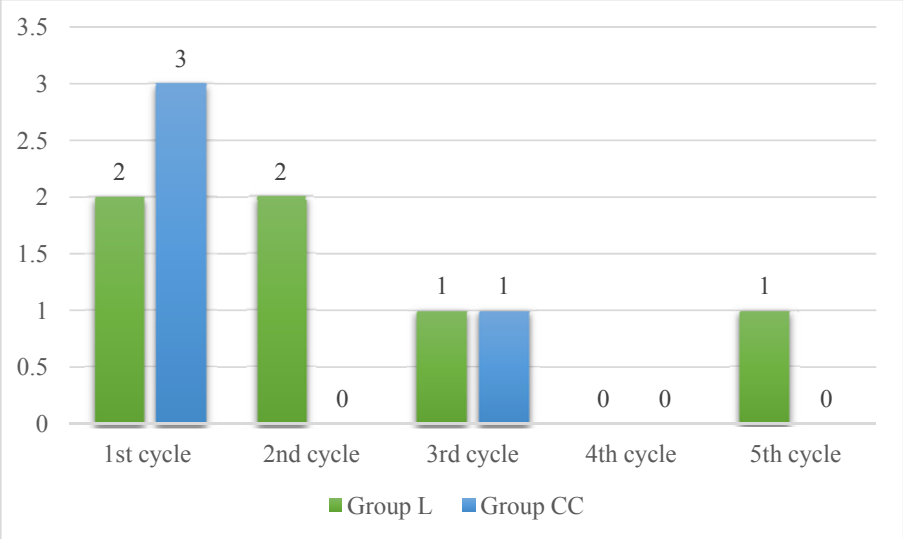
I) No of treatment cycles attended by patients



Graph 3 – No of treatment cycles attended by patients

Group L – 13 cases (52.00%) attended 3 cycles and were a total of 6 pregnancies (24.00%) in this group.
Group CC – 19 cases (76.00%) attended 3 cycles and were a total of 4 pregnancies (16.00%) in this group.

J) Conceived cycles



Graph 4 – Conceived cycles

From the above mentioned graph, it is noted that most of the cases conceived during first and second cycles of our treatment in both the groups.

K) Outcome of conception

Table 6 – Outcome of conception

Category	Group L	Group CC
Pregnancies continuing uneventfully	3	1
Delivering uneventfully	3	3
Total no of conceptions	6	4

In our study, a total of 6 cases (24.00%) got pregnant in letrozole group and 4 cases (16.00%) in clomiphene citrate group which is statistically significant ($p<0.05$). The Spearman's Rank correlation analysis were done which show highly positive correlation ($\rho=0.7$) between letrozole and number of pregnancies and weak correlation ($\rho=0.2$) between clomiphene citrate and number of pregnancies in our study.

Discussion

Conventionally, clomiphene citrate is the drug of choice for first line treatment of anovulatory dysfunction for various reasons. Clomiphene is a non-steroidal triphenylethylene derivative with both estrogen agonist and antagonist properties. Due to its structural similarity to estrogen, clomiphene competes for and binds nuclear estrogen receptors throughout the reproductive system. It causes reduced estrogen negative feedback and consequent increased pituitary gonadotropin release which in turn drives ovarian follicular development. It has convenient oral administration, few side effects, is inexpensive and easily available. But, clomiphene resistance together with various side effects like development of multiple follicles and increased miscarriage rates are areas of concern. It has prolonged accumulation in tissues due to its long half-life leading to prolonged depletion of estrogen receptors and further causing hot flushes and other perimenopausal symptoms. Even with high ovulation rates of 70-80%, the actual pregnancy rates are significantly lower (30 – 40%). This could be due to its peripheral anti-estrogenic action at the level of endometrium and cervical mucus.[6,7] Thus, the need for an effective alternative remains.

Letrozole, an aromatase inhibitor, since its introduction in infertility practice a decade ago has been used as a second line treatment, particularly in women with clomiphene resistance. Letrozole acts peripherally by blocking conversion of androgens to estrogens thus decreasing estrogen synthesis and releasing the HPO axis from estrogen negative feedback. This increases gonadotropin secretion and stimulation of ovarian follicle. It has noteworthy advantages over clomiphene. It does not deplete estrogen receptors throughout the body, keeps the HPO axis intact, facilitates monofollicular growth and ovulation and has a shorter half-life. Yet, in no country across globe is letrozole approved for ovulation induction. Mostly its use is off label and for research purposes. In India, it is banned for use in premenopausal infertile women.[8] Its use as a first line option for ovulation induction is still uncertain due to paucity of data backing its usefulness to do so.

Our study highlighted the effectiveness of letrozole as the primary inducing agent for anovulatory infertility. Ovulation rate and the consequent pregnancy rate was found to be 100% (n=25); 24% (n=6) in letrozole group vs 96% (n=24); 16% (n=4) in CC group. There

was significant improvement in endometrial thickness with no cases of lag endometrium in the letrozole group as compared to 16.00% (n=4) in CC group. Monofollicular stimulation and no cases of multiple gestation were seen in cases induced with letrozole.

ACOG in its current guidelines supports the recommendations that letrozole should be considered first line therapy for ovulation induction in women with polycystic ovary syndrome (PCOS) and a BMI> 30 because of increased live birth rate compared with clomiphene citrate.[9] Majority (80%) of cases of anovulatory infertility are due to PCOS,[9] others being stress related, Sheehan's syndrome, anorexia nervosa, Kallmann's syndrome, etc [10]; but in our study all cases of anovulatory infertility has been taken into account and further categorization into the specific causes for the same has not been done.

Legro and colleagues[11] in 2014 studied 750 women with anovulatory infertility receiving either clomiphene or letrozole concluded letrozole to be more effective. Ovulation rates for letrozole versus clomiphene were 61.7% and 48.3% respectively (P<0.001). the live birth rates for letrozole versus clomiphene were 27.5% and 19.1%, respectively (P= 0.007). An RCT on 106 women with PCOS to receive either letrozole(2.5mg) or clomiphene (100mg); Atay V et al [12] showed that the ovulation rate (82.4% vs 63.6%, P=0.01) and the clinical pregnancy rate (21.6% vs 9.1%, P= 0.03) were significantly higher with letrozole as compared to clomiphene group.

On the other hand, the numerous other studies have given conclusions contrary to our findings. In a large RCT involving 438 women with PCOS, Badawy et al [13] compared clomiphene with letrozole. Endometrial thickness with clomiphene was found to be significantly higher than with letrozole (9.2 ±0.7 vs 8.1 ± 0.2 mm, P=0.02) along with ovulation and pregnancy rates being comparable. Thus, no benefit was observed with letrozole being used as first line therapy.

A recent study done in 2016 makes us rethink about our options for the treatment. Al-Shaikh et al [14] studied 85 subfertile women with PCOS and found completely opposite findings in comparison to our study. Letrozole was better in regard to responded cycles and mean number of mature follicles whereas regarding to endometrial thickness, monofollicular cycles and pregnancy rate per cycle clomiphene citrate was better.

There were no cases of miscarriages in the present study. In 2009, Badawy et al [13] concluded miscarriage rates to be similar in both clomiphene and letrozole group (9.7% vs 12.1%). The administration of clomiphene or letrozole to pregnant rats have shown to have adverse fetal effects. [15,16] However, the recent study in 2014 by Sharma S et al [17] showed no significant difference in the overall rate of congenital malformations among children born to mothers who conceived naturally (2.9%) or after letrozole (2.5%) or clomiphene citrate (3.9%) treatment. Similarly, in our clinical setting, inducing drugs were discontinued many days before ovulation and conception and no anomalies were detected in any of the pregnancies in both the groups.

Conclusion

Letrozole can be used a mainstream drug for ovulation induction in anovulatory infertility. It is more effective than clomiphene citrate in terms of monofollicular ovulation, better endometrial thickness and no cases of lag endometrium. Hence, letrozole can be recommended as the first line drug for ovulation induction in anovulatory infertility.

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