Comparative study of Clomiphene Citrate and Letrozole in Ovulation Induction

Susanta Kumar Behera[1], Jyoti Ranjan Behera[2], Pankaj Kumar Sethy[3], Luzoo Prachishree[4*]

[1]Associate Professor, Department of Obstetrics and Gynecology, S.C.B. Medical College & Hospital, Cuttack; Odisha
[2]Associate Professor, Department of Pediatrics, M.K.C.G. Medical College & Hospital, Berhampur; Odisha, India.
[3]Assistant Professor, Department of Anesthesiology, M.K.C.G. Medical College & Hospital, Berhampur, Odisha, India.
[*4]Assistant Professor, Department of Obstetrics & Gynecology, M.K.C.G. Medical College & Hospital, Berhampur, Odisha, India

Corresponding Author: Dr Luzoo Prachishree, Assistant Professor, Department of Obstetrics & Gynecology, M.K.C.G. Medical College & Hospital, Berhampur, Odisha, India.

Abstract

Background: Infertility is a life crisis with invisible losses and its consequences are manifold. Infertility can threaten women's identity, status and economic security and consequently be a major source of anxiety, leading to lowered self-esteem and sense of powerlessness. For a couple without contraception the chances of conception are about 25% each month. So even ovulation happens, a couple is not guaranteed to conceive. Clomiphene citrate has been the most widely used treatment for fertility enhancement for the past 40 years. Clomiphene citrate (CC) is an anti estrogenic agent resulting in a 60-85% ovulation rate and 10-20% pregnancy rate / cycle. **Aims and Objectives:** The aim of the study was to compare the efficacy of ovulation induction by Clomiphene citrate and Letrozole in terms of no of maturing follicle, size of dominant follicle, ovulation (monofollicular or multifollicular), endometrial thickness and pregnancy and its outcome. **Method:** It was a prospective longitudinal study conducted in the Obstetrics & Gynecology Department of M.K.CG Medical College and Hospital. Berhampur; Odisha from October 2017 to October 2020. A careful & detailed history was elicited from the female as well as from male partner with special reference to certain specific history concerning the problem of infertility such as the age, duration, menstrual problem, past medical & surgical history, coital habits, use of contraceptive methods and treatment history. Subsequently thorough general & systemic examination was done to exclude any other organic disease in the female patient. Examination of breast, other secondary sexual characters, thyroid and presence of galactorrhea, hirsutism, and thorough pelvic examination was done. Patients randomized in to two groups out of 150 cases on anovulatory infertility: first group (CC group) of 75 cases was given Clomiphene citrate 50 mg starting from D3 to D7 of cycle and second group (Letrozole group) of 75 cases was given Letrozole 2.5 mg starting from D3 to D7 of cycle. In the both groups follicular study was done by serial transvaginal sonogram starting from D12 of cycle on alternate day till ovulation. The number of developing follicles, size of dominant follicle and endometrial thickness were observed serially by TVS. **Results:** Ovulatory factors contributing to primary infertility was 150 cases (49.83%) as majority where as tubal factors contribute to 81 cases (26.91%) and other factors contribute to 70 cases (23.26%). Most of the cases in both groups were of 2-4 year of infertility. Among

all cases, 60 cases (80%) of Clomiphene citrate group and 55 cases (74%) of Letrozole group were of 2-4 years of infertility as majority followed by 15 cases (20%) of CC group and 15 cases (20%) were of 5-7 years of infertility and 5 cases (6.7%) in Letrozole group were of > 7 years of infertility. In CC group, 56 cases (78.9%) and in Letrozole group, 60 cases (82.2%) had dominant follicle size of 18-20 mm as majority followed by 9 cases(12.7%) in CC group and 11 cases(15.1%) in Letrozole group had DF of size < 18mm and 4 cases (5.6%) in CC group and 2 cases (2.7%) had dominant follicle of size 21-25mm,. Only 2 cases (2.8%) in CC group had DF of size >25mm. The endometrial thickness (ET) varied from 5-12mm in all cases of both groups. In Clomiphene citrate group 39 cases (55%) had ET of 7-8 mm, 14 cases (19.7%) had ET of 9-10 mm, 6 cases (8.4%) had ET of 11-12mm and 12 cases (16.9%) had ET of 5-6mm. In Letrozole group, 44 cases (60.3%) had ET of 9-10mm, 21 cases (28.8%) had ET of 7-8 mm, 6 cases (8%) had ET of 5-6 mm and 2 cases (2.7%) had ET of 11-12mm. The ovulation occurred in 46 cases (64.8%) and 52 cases (71.2%) in Clomiphene citrate group and Letrozole group respectively. **Conclusion:** More number of DF was found in case of Letrozole as compared to Clomiphene citrate. Ovulation rate of letrozole is higher than that of Clomiphene citrate. More over pregnancy rate for Clomiphene citrate was lower than that of Letrozole. So Letrozole is found superior to Clomiphene citrate as an ovulation inducing agent in anovulatory infertility.

Keywords: Ovulation, Clomiphene Citrate, Letrozole, Dominant follicle.

Introduction

Infertility is a life crisis with invisible losses and its consequences are manifold. Infertility can threaten women's identity, status and economic security and consequently be a major source of anxiety, leading to lowered self-esteem and sense of powerlessness.[1] For a couple without contraception the chances of conception are about 25% each month. So even ovulation happens, a couple is not guaranteed to conceive.[2] Clomiphene citrate has been the most widely used treatment for fertility enhancement for the past 40 years. Clomiphene citrate (CC) is an anti estrogenic agent resulting in a 60-85% ovulation rate and 10-20% pregnancy rate / cycle. This disparity seems to be due to the anti estrogenic action of Clomiphene citrate which involves lasting estrogen receptor (ER) depletion. Because of its long half life (2 weeks), Clomiphene citrate accumulates in the body and may have a negative effect on the quality and quantity of cervical mucus, endometrial development, which may cause implantation failure, luteal phase defects and significant thinning of the endometrium, which is dose dependant.[3] Multifollicular development is relatively common with CC and the risk of multiple pregnancies is increased to approximately 5-8 %. Letrozole, an aromatase inhibitor has been investigated as potential ovulation induction agent who does not deplete estrogen receptors in central and peripheral target tissues, it typically results in mono follicular ovulation and it may have no negative impact on endometrium and cervical mucus. The aromatase inhibitors have a relatively shot half-life (45 hrs) and therefore would be eliminated from the body rapidly and used as an off line drug for ovulation induction.[4]

Aims and Objectives: The aim of the study was to compare the efficacy of ovulation induction by Clomiphene citrate and Letrozole in terms of no of maturing follicle, size of dominant follicle, ovulation (monofollicular or multifollicular), endometrial thickness and pregnancy and its outcome

Materials and Methods

It was a prospective longitudinal study conducted in the Obstetrics & Gynecology Department of M.K.CG Medical College and Hospital. Berhampur; Odisha from October 2017 to October 2020. Primary infertile patient with anovulation were included in this study basing on following criteria; inclusion criteria:(a) age < 35 years (b) semen parameters normal according to WHO criteria 1999 (c) normal pelvic USG and bilateral tubal patency confirmed by HSG and laparoscopy; exclusion criteria:(a) uterine adnexal pathology (b) ovarian cyst (c) medical illness like TB, STD, PID, DM, thyroid dysfunction, hepatic dysfunction and renal dysfunction (d) previous surgery related to genital tract. A careful & detailed history was elicited from the female as well as from male partner with special reference to certain specific history concerning the problem of infertility such as the age, duration, menstrual problem, past medical & surgical history, coital habits, use of contraceptive methods and treatment history. Subsequently thorough general & systemic examination was done to exclude any other organic disease in the female patient. Examination of breast, other secondary sexual characters, thyroid and presence of galactorrhea, hirsutism, and thorough pelvic examination was done. The male factors were excluded by doing clinical examination and seminal analysis. Basic investigations were performed like Hb%, DC, TLC, VDRL, FBS, HIV, HBsAg. Routine & microscopic examination of urine, Thyroid function test, X-ray chest, ECG & Cardiological check up. Patients randomized in to two groups out of 150 cases on anovulatory infertility: first group (CC group) of 75 cases was given Clomiphene citrate 50 mg starting from D3 to D7 of cycle and second group (Letrozole group) of 75 cases was given Letrozole 2.5 mg starting from D3 to D7 of cycle. In the both groups follicular study was done by serial transvaginal sonogram starting from D12 of cycle on alternate day till ovulation. The number of developing follicles, size of dominant follicle and endometrial thickness were observed serially by TVS. All couples advised timely intercourse during the time of ovulation and those having missed periods confirmed for pregnancy by urine pregnancy test & ultrasound. During antenatal period, there was follow up for ectopic pregnancy, miscarriage and fetal well being and the protocol was followed up for 3 cycles. Patients who do not ovulate after 3 treatment cycles registered resistant and those who do not get pregnant within 3 months registered as failure.

Results

Among 19380 gynecology cases seen during the above period of which 336 cases were found to have infertility giving rise to prevalence of 1.73%.Out of total 336 cases, primary and secondary infertility accounts for 301 cases(89.58%) and 35 cases(10.42%) respectively. Ovulatory factors contributing to primary infertility was 150 cases (49.83%) as majority where as tubal factors contribute to 81 cases (26.91%) and other factors contribute to 70 cases (23.26%)(Table-I).

Table-I: Causes of Primary Infertility

Factors	Cases(n=301)	Percentage
Ovulatory factors	150	49.83%
Tubal factors	81	26.91%
Others	70	23.26%

Total	301	100%

Most of cases in Clomiphene citrate and Letrozole group were in age group of 20-25 years. Among all cases, 40 cases (53.4%) in CC group and 39 cases (52%) in Letrozole group belonged to age group of 20-25 years and 28 cases (37.3%) in CC group and 28 cases (37.3%) in Letrozole group belonged to age group of 26-30 years and 7 cases (9.3%) in CC group and 8 cases (10.7%) in Letrozole group belonged to 31-35 years (Figure-I).

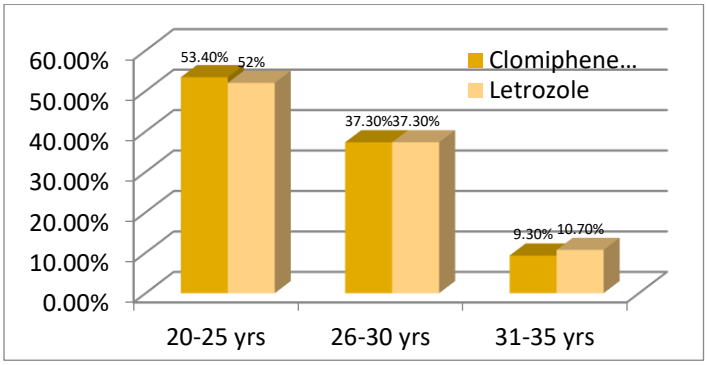

Figure-I: Age of Primary infertility cases in years

Most of the cases in both groups were of 2-4 year of infertility. Among all cases, 60 cases (80%) of Clomiphene citrate group and 55 cases (74%) of Letrozole group were of 2-4 years of infertility as majority followed by 15 cases (20%) of CC group and 15 cases (20%) were of 5-7 years of infertility and 5 cases (6.7%) in Letrozole group were of > 7 years of infertility (Table-II).

Table-II: Duration of Infertility

Duration of Infertility	CC(n=75)		Letrozole(n=75)	
	Number	Percentage	Number	Percentage
2-4 years	60	80%	55	73.3%
5-7 years	15	20%	15	20%
>7 years	Nil	NA	5	6.7%
Total	75	100%	75	100%

Body mass index of cases varied from 20-35 and most of cases in both groups had BMI in range of 20-30. In Clomiphene citrate group 40 cases (53.3%) and in Letrozole group 26 cases (34.7%) had BMI of 20-25 whereas 35 cases (46.7%) of CC group and 45 cases (60%) of Letrozole group had BMI of 26-30. Only 4 cases (5.3%) in Letrozole group had BMI of 31-35(Figure-II).

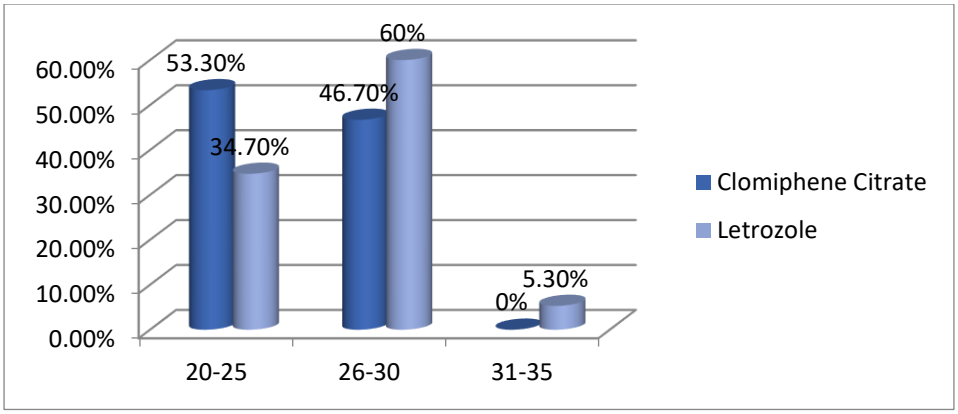

Figure-II: BMI of Ovulatory dysfunctional infertility Cases

Among the cases with normal ovary, 61 cases (81.3%) were given CC and 60 cases (77.3%) were given Letrozole whereas among 29 PCOD cases, Clomiphene citrate was given to 11 cases (14.6%) and Letrozole was given to 18 cases (24%).

Among CC groups after stimulation, maximum of 35 cases(49.4%) had follicle number of 9-10 followed by 18 cases(25.4%) had follicle number of 7-8, 7 cases(9.8%) each had follicle number of 11-12 and 5-6 and 4 cases(5.6%) had follicle number of 13-15. In Letrozole group after induction, maximum of 24 cases(32.8%) had follicle number of 5-6 followed by 20 cases(27.4%) had follicle number of 3-4, 13 cases(17.8%) had follicle number of 7-8, 11 cases(15%) had follicle number of 9-10, 3 cases(4.1%) had follicle number of 11-12 and 2 cases(2.8%) had follicle number of 13-15(Table-III).

Table-III: Number of Follicles on Stimulation

No of Follicles	CC(n=71)		Letrozole(n=73)	
	Number	Percentage	Number	Percentage
3-4	Nil	0%	20	27.4%
5-6	7	9.8%	24	32.9%
7-8	18	25.4%	13	17.8%
9-10	35	49.4%	11	15.0%
11-12	7	9.8%	3	4.1%
13-15	4	5.6%	2	2.8%
Total	71	100%	73	100%

In CC group, 56 cases (78.9%) and in Letrozole group, 60 cases (82.2%) had dominant follicle size of 18-20 mm as majority followed by 9 cases(12.7%) in CC group and 11 cases(15.1%) in Letrozole group had DF of size < 18mm and 4 cases (5.6%) in CC group and 2 cases (2.7%) had dominant follicle of size 21-25mm,. Only 2 cases (2.8%) in CC group had DF of size >25mm (Figure-III).

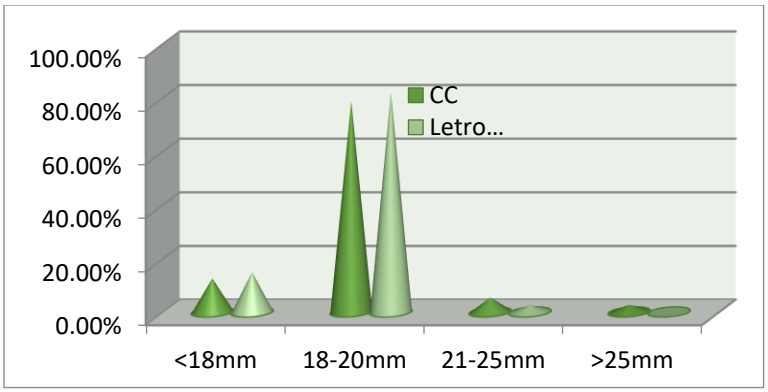

Figure-III: Size of Dominant Follicles on Stimulation

The endometrial thickness (ET) varied from 5-12mm in all cases of both groups. In Clomiphene citrate group 39 cases (55%) had ET of 7-8 mm, 14 cases (19.7%) had ET of 9-10 mm, 6 cases (8.4%) had ET of 11-12mm and 12 cases (16.9%) had ET of 5-6mm. In Letrozole group, 44 cases (60.3%) had ET of 9-10mm, 21 cases (28.8%) had ET of 7-8 mm, 6 cases (8%) had ET of 5-6 mm and 2 cases (2.7%) had ET of 11-12mm (Figure-IV).

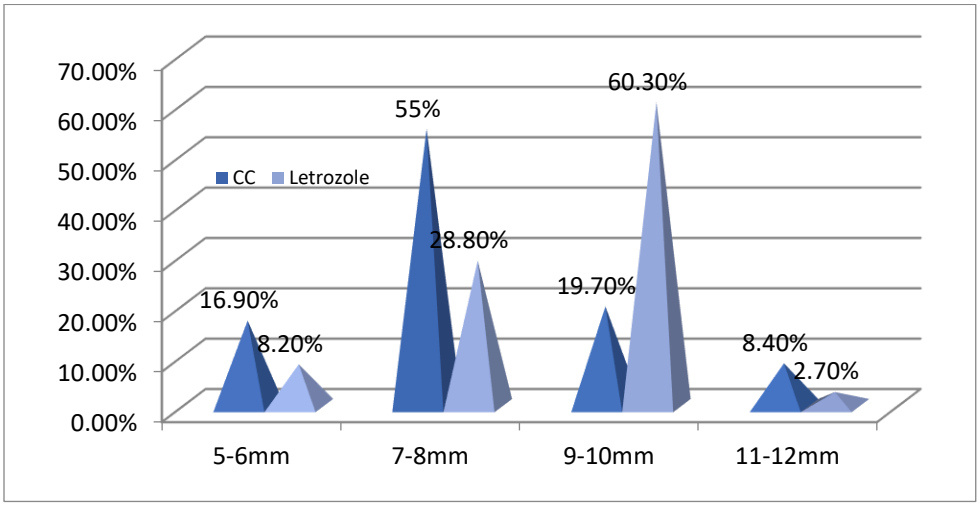

Figure-IV: Pattern of Endometrial thickness on ovulation induction

The ovulation occurred in 46 cases (64.8%) and 52 cases (71.2%) in Clomiphene citrate group and Letrozole group respectively. In Clomiphene citrate group 16 cases (34.7%) required 1 cycle, 19 cases (41.3%) required 2 cycle and 11 cases (23.9%) required 3 cycles for ovulation induction. In Letrozole group 17 cases (32.8%) required 1 cycle, 25 cases (48.0%) required 2 cycle and 10 cases (19.2%) required 3 cycles for ovulation induction (Table-IV).

Table-IV: No of Stimulated Cycles required for Ovulation

No of cycles	CC(n=46)		Letrozole(n=52)	
	Number	Percentage	Number	Percentage
One Cycle	16	34.8%	17	32.8%
Two Cycle	19	41.3%	25	48.0%

Three Cycle	11	23.9%	10	19.2%
Total(Ovulation rate)	46	64.8%	52	71.2%

Number of resistant cases has seen more in Clomiphene citrate group as compared to Letrozole group i.e 29 cases (38.7%) of CC vs 23 cases (30.6%) of Letrozole. Among all cases, 3 cases (5%) who received Clomiphene citrate and 2 case(2.5%) who received Letrozole got abdominal pain and 1 case(2.5%) who received Clomiphene citrate got vomiting for which cycles were cancelled. Cycle cancellation rate for Clomiphene citrate was 6.7% while the same was 4% for Letrozole. Pregnancy rate for Clomiphene citrate group and Letrozole group was 40 cases (53.3%) and 47 cases (62.6%) respectively (Table-V).

Table-V: Outcome of Ovulation Induction

Outcome	CC(n=75)	Letrozole(n=75)
Ovulation Rate	64.8%	71.2%
Cycle Cancellation Rate	6.7%	4%
Pregnancy Rate	53.3%	62.6%

Incidence of miscarriages was same in both group's i.e 7 cases (17.5%) of CC group and 6 cases (12.7%) of Letrozole group landed in miscarriages. The rate of ectopic pregnancies was comparable in both groups' i.e 3 cases (7.5%) of CC group and 3 cases (6.3%) of Letrozole group had ectopic pregnancies. Current study revealed 7 cases (17.5%) of CC group and 2 cases (4.3%) of Letrozole group had multiple pregnancies i.e multiple pregnancies more in Clomiphene citrate group than Letrozole group. It also included 23 cases (57.5%) and 36 cases (76.7%) of singleton pregnancies of CC group and Letrozole group respectively (Table-VI).

Table-VI: Pregnancy Outcomes after Ovulation Induction.

Pregnancy Outcome	CC(n=40)		Letrozole(n=47)	
	Number	Percentage	Number	Percentage
No of miscarriages	7	17.5%	6	12.7%
Ectopic Pregnancy	3	7.5%	3	6.3%
Singleton Pregnancy	23	57.5%	36	76.7%
Multiple Pregnancy	7	17.5%	2	4.3%
Total	40	53.3%	47	62.6%

In Clomiphene citrate group; out of 30 cases 23 cases (76.6%) were delivered by VD and 7 cases (23.3%) were delivered by caesarian section (CS). In Letrozole group; out of 38 cases, 30 cases (79%) were delivered by VD and 8 cases (21%) were delivered by CS. In Clomiphene citrate group, out of 30 cases that became pregnant 5 cases (16.6%) developed PIH, 2 cases (6.7%) developed PTL and 2 cases (6.7%) developed gestational diabetes mellitus (GDM). Out of 38 cases in Letrozole group, 6 cases (13.3%) developed PIH, 1 case (3.33%) developed preterm labor and 2 cases (6.67%) developed GDM (Figure-V).

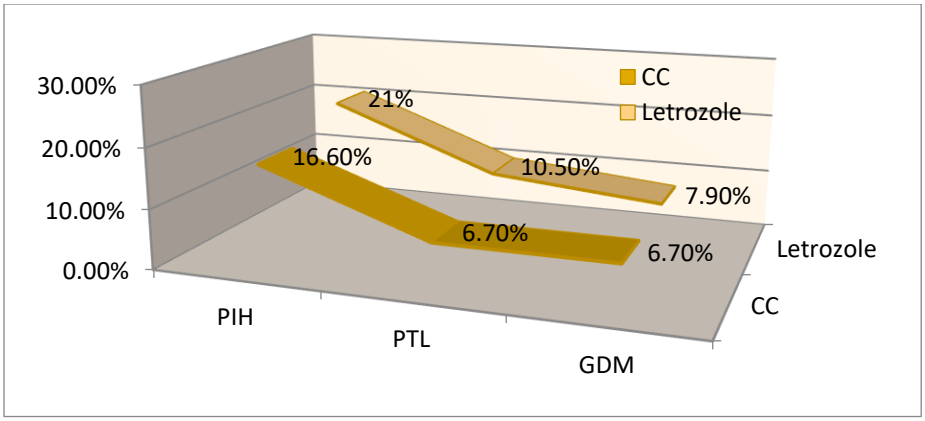

Figure-V: Obstetric Complications in Ovulation Induction

Discussion

In Clomiphene citrate group 53.4% cases are in age group of 20-25 years whereas in Letrozole group 52% cases were in age group of 20-25 years. A randomized trial by Al-Fozan et al and Begum et al on Letrozole versus Clomiphene citrate in women undergoing superovulation revealed mean age in both groups were similar concurrent to present study.[5,6] The duration of infertility in most of cases is 2-4 years in both groups. In Clomiphene citrate group maximum cases (53.3%) have B.M.I. of 20-25 whereas in Letrozole group maximum of cases (60%) have BMI of 26-30 which is similar to Begum et al (mean BMI of 25.60±2.80).In Clomiphene citrate group, 50% of cases had follicle numbers of 8-10 whereas in Letrozole gourp 16% of cases have follicle numbers as 8-10 i.emonofollicular development is significant in Letrozole which agreed with that of Sabnam SS.[7] In Clomiphene citrate group, 80% of cases had DF having size of 18-20 mm (cycles were cancelled in 4 cases) whereas in Letrozole group, 84% of cases had DF of size 18-20 mm (cycles were cancelled in 2 cases). So total of 6 cases were cancelled to prevent OHSS and multiple births. So no of mature follicles in both the groups were comparable which is concurrent to Barroso G et al.[8] This is not concurrent to Jee B C et al and Atay V et al showing no of mature follicles were comparatively low in Letrozole group.[9, 10] In Clomiphene citrate group; 55% cases, 19.7% cases, 16.9% cases and 8.4% cases had ET of 7-8mm, 9-10mm, 5-6 mm and 11-12mm respectively. In Letrozole group; 61.6% cases, 28.8% cases, 8.2% cases and 2.7% cases had ET of 9-10mm, 7-8mm, 5-6mm and 11-12mm. So maximum no of cases in Clomiphene citrate group had ET of 7-8mm and that of Letrozole group was of 9-10mm which is not similar to Al-Fozenet al showing no difference of ET in both the group. Bayar U et al also showed that median ET did not significantly differed between CC and Letozole group.[11] Study by Barroso G et al revealed significantly higher ET in Letrozole group (9.5±1.5mm vs 7.3 ±1.1mm). In study by Atay V et al, ET was found higher in Letrozole group. In study by Badawy et al, ET was significantly higher in Clomiphene citrate group.[12] Current study shows ovulation occurred in 64.8% of Clomiphene citrate group and in 71.2% of Letrozole group which is similar to Atay V et al having higher ovulation rate in Letrozole group than Clomiphene citrate group (82 4% vs 63.6%) but not similar to Bayar U et al (74.7% of CC and 65.7% of Letrozole). Similar study by Kar et al revealed higher ovulation rate among Letrozole group as compared to Clomiphene citrate group (73.0% Vs 60.7%).[13] In study by Begum et al, ovulation rate was significantly higher in Letrozole group than in Clomiphene citrate group (62 5% vs 37.5%). But Requena et al found comparable ovulation rate for Letrozole and Clomiphene citrate (OR1.7: 95% CI 0.66-2:09).[14] The number of resistant cases in Clomiphene citrate group (38.7%) was higher than that of Letrozole group (30.6%).The Pregnancy rate was 53.3% in Clomiphene citrate group whereas 62.6% in Letrozole group which does not talies to that of Sahu et al having

pregnancy rate of 24% in Letrozole group and 12% in Clomiphene citrate group[15] but similar to Atay V et al revealing higher pregnancy rate in Letrozole group compared to CC group (21.6% vs 9.1%). Among all cases studied, 3 cases of CC group and two case of Letrozole group had severe abdominal pain. Also one case from CC group had severe vomiting. So cycles were cancelled for all the 6 cases. The cycle cancellation rate for Clomiphene citrate was 6.7% and that of Letrozole was 4% which is not similar to Ashalata et al having cycle cancellation rate of 43.05% for CC group and 20.70% for Letrozole group.[16] In this study rate of miscarriage is same in both groups (10%) which is not agreed with that of Selvaraj et al having miscarriage between CC group and Letrozole group was 25% and 1.6% respectively.[17] Multiple births were found more in Clomiphene citrate as compared to Letrozole group (17.5% vs 4.3%). In Clomiphene citrate group; out of 30 cases, 23 cases (76.6%) were delivered by VD and 7 cases (23.3%) were delivered by caesarian section.In Letrozole group; out of 38 cases, 30 cases (79%) were delivered by by VD and 8 cases (21%) were delivered by caesarian section.In Clomiphene citrate group, 16.6% cases developed PIH, 6.7% cases developed preterm labor and 6.7% cases developed gestational diabetes mellitus (GDM). In Letrozole group, 21% cases developed PIH, 10.5% developed preterm labor and 7.9% cases developed GDM.

Conclusions

The numbers of follicles were more in Clomiphene citrate group as compared to Letrozole group. More number of DF was found in case of Letrozole as compared to Clomiphene citrate. Endometrial thickness is diminished due to anti estrogenic property of Clomiphene citrate as compared to Letrozole. Ovulation rate of letrozole is higher than that of Clomiphene citrate. More over pregnancy rate for Clomiphene citrate was lower than that of Letrozole. So Letrozole is found superior to Clomiphene citrate as an ovulation inducing agent in anovulatory infertility.

References

1. Inhorn MC. Global infertility and the globalization of new reproductive technologies: illustration from Egypt. Social Sciences and Medicines 2003; 56:1837-1851.
2. Cates W, Fairley T M M. Worldwide Pattern of Infertility: Is Africa Different? The Lancet 1985; 2(8455):596-598.
3. Greenblat R B, Barfield W E. Induction of Ovulation with Letrozole. JAMA 1990:178:101-105.
4. Dicky R P, Holtkamp D E. Development, Pharmacology and Clinical Experience with Clomiphene Citrate. Human Reprod Update 2:483-1996.
5. Haya Al-Fozan, Maha Al-Khadouri. A randomized trial of Letrozole versus Clomiphene citrate in women undergoing Superovulation. Fertility and Sterility 2004, 82(6):1561-1563.
6. Mosammat R Begum, Jannatul Ferdous. Comparison of efficacy of aromatase inhibitor and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertility and Sterility 2009, 92(3):853-857.
7. Nambiar Sabnam S. Clomiphene Citrate versus Letrozole for Ovulation Induction in PCOS: A Comparative Study. J South Asian Feder Obst Gynae 2018; 10(Suppl. 2): 384-399
8. Gerardo Barroso, Gerardo Menocal, Hector Felix. Comparison of the efficacy of the aromatase inhibitor Letrozole and Clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial.
9. Byung Chul Jee, LeeDayong. A retrospective analysis of the follicle-stimulating hormone starting dose in expected normal responders undergoing

their first in vitro fertilization cycle: proposed dose versus empiric dose. Clinical and Experimental Reproductive Medicine 2018; 45(4):183-188.
10. V Atay, C Cam, M Muhcu, M Cam. Comparison of Letrozole and Clomiphene Citrate in Women with Polycystic Ovaries Undergoing Ovarian Stimulation. The Journal of International Medical Research 2006; 34: 73–76.
11. U Bayar, Mustafa Basaran, Sibel Kiran. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertility and Sterility 2006; 86(5): 1447-1451.
12. Ahmed Badawy, Ibrahim Abdel Aal , Mohamed Abulatta. Clomiphene citrate or Letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril 2009 Sep; 92(3):849-852.
13. Sujata Kar. 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):262-265.
14. Antonio Requena, Julio Herrero, Jose Landeras, Esperanza Navarro. Use of Letrozole in assisted reproduction: a systematic review and meta-analysis. Human Reproduction Update 2008, 14(6): 571–582.
15. Mahija Sahu, Nihar Ranjan Rout. Comparative study of Clomiphene citrate versus Letrozole as first-line ovulation induction drug in infertile polycystic ovary syndrome women. Int J Reprod Contracept Obstet Gynecol. 2020 Jul; 9(7):2948-2952
16. A Ganesh & S K Goswami, K Chaudhury. Comparison of letrozole 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
17. Selvaraj Kamala, Selvaraj Priy. Comparison of Clomiphene Citrate and Letrozole for Ovulation of Induction and Resultant Pregnancy Outcome. J Obstet Gynecol Ind 2004; 54(6): 579-582.