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A PROSPECTIVE COMPARATIVE STUDY OF LETROZOLE AND CLOMIPHENE CITRATE IN OVULATION INDUCTION IN WOMEN HAVING PCOS

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Ovulation induction, PCOS, Clomiphene citrate, Letrozole, Prospective comparative study

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ABSTRACT: Introduction: Clomiphene citrate (CC) is the primary drug of choice for ovulation induction in PCOS but resistance to ovarian stimulation is frequent observation with CC. Letrozole (Let), an Aromatase Inhibitor (AI) induces folliculogenesis by releasing hypothalamo-pituitary axis from tonic inhibitory effect of estrogen. **Aim:** To compare the rate of folliculogenesis, number of follicle count, ovulation rate, conception rate and pregnancy outcome. **Materials & Methods:** This prospective comparative study was conducted in RGKMCH & NKIIC, Kolkata from July 2018 to June 2019. In this study 200 anovulatory PCO matched women of 20-40 years were divided into two groups, Group A-100 patients receiving CC 100 mg daily and Group B-100 patients receiving Letrozole 5 mg daily from Day 2 for 5 days. Follicular study started from D_9 of cycle and ovulation triggering by using Injection hCG was done as per standard protocol. Patients were evaluated in respect of terminal endocrinological profile, number of follicles, ovulation rate, pregnancy rate & outcome. **Results:** In Gr A & Gr B, mean no of follicles and terminal E_2 were 2.9 ±0.9 Vs 1.8 ± 0.6 ($p< 0.001$) and 486 ± 54 vs 266 ±46 pg ($p< 0.0001$) respectively. Ovulation and pregnancy rate in both groups were 84.6% Vs 90.2% ($p = 0.157$) and 18.5% vs 24.3% ($p<0.005$) in Gr A and Gr B respectively. **Conclusion:** Though the ovulation rate is comparable in both the groups, Letrozole group achieved more pregnancy than CC group.

INTRODUCTION: Infertility is a critical component of reproductive health [1]. The clinical definition of infertility used by the World Health Organization (WHO) is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [2].

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PCOS is the most common endocrine disorder affecting female fertility [3, 4, 5], originally described in 1935 by Stein and Leventhal and since then the subject of extensive analyses, although it's a etiology and pathophysiology are poorly understood even now [6, 7, 8].

The polycystic ovary syndrome is the most common cause of anovulatory infertility & characterised by ovulatory dysfunction and hyperandrogenism [9]. Infertility due to chronic anovulation is one of the commonest clinical manifestations of this syndrome [10, 11, 12]. The prevalence of infertility in women with PCOS

varies between 70 and 80%. Clomiphene citrate that antagonizes the negative feedback of estrogen at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin, has been used for ovulation induction for decades. Clomiphene citrate (CC) is a long-standing, standard drug for ovulation induction and is still considered as first-line option in PCOS women [13, 14]. However, clomiphene has certain well-defined disadvantages.

Clomiphene has drawbacks, including its over-all poor efficacy (only a 22% rate of live birth with up to six cycles of clomiphene), a relatively high multiple-pregnancy rate (3 to 8%) as compared with the rate associated with unassisted conception (<1%), and an undesirable side-effect profile, including mood changes and hot flushes. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population [15, 16] and 20-25% PCOS women are resistant to clomiphene [17, 18].

Anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus. Clomiphene resistance or clomiphene failure often results in the use of more expensive treatment options for infertility that may be associated with higher multiple pregnancy rates and an increased risk of the ovarian hyperstimulation syndrome (OHSS) [19]. The development of effective, simple, and safe treatments for infertility is an important public health goal [20].

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 [21, 22]. Aromatase inhibitors, which block estrogen synthesis, directly affect hypothalamic pituitary ovarian function and theoretically might increase pregnancy rates. Potential advantages of aromatase inhibitors include a more physiologic hormonal stimulation of the endometrium, a lower multiple pregnancy rate through single follicle recruitment, a better side-effect profile with fewer vasomotor and mood symptoms [23]. Letrozoleinhibits aromatase enzyme and prevents androgen to estrogen conversion thereby reducing estrogen production. Additionally, it has no adverse effect on endometrium and cervical mucus. A recent Systemic Review and Meta-analysis by Liu *et al* (2023) [24] letrozolehas been recommended over clomiphene citrate as an ovulation induction drug in women with infertility and PCOS. Letrozole has been shown to have good ovulation rate in CC-resistant PCOS women [25]. Indian PCOS women have high prevalence of insulin resistance [26] and thus are likely to have high CC resistance. Letrozole could prove to be a good alternative for ovulation induction in such women.

AIM: The aims of this study was to compare rate of folliculogenesis and number of follicle count, ovulation rate between Letrozole and Clomiphene citrate, endometrial morphology during the treatment period, the rate of conception and early pregnancy outcome and to assess whether Letrozole produces less side effects than Clomiphene citrate.

MATERIALS AND METHODS: This is a prospective comparative study conducted from July 2018 to June 2019 (12 months) in the department of Obstetrics and Gynaecology, R. G. Kar Medical College & Hospital, Kolkata, India in collaboration with North Kolkata Infertility & IVF Centre, Kolkata. A total of 200 PCOS women aged 20-40 years willing to conceive and attending OPD of Obstetrics & Gynaecology, R. G. Kar Medical College & Hospital were recruited for this study as per the inclusion and exclusion criteria. Ethical clearance was obtained through proper channels from the review and ethics committee of the institution. (Reference No- RMC/SS/5714 dated 07/12/2017).

Sample size/Design: According to the study conducted by Atay V. *et al* [27] letrozole produces higher rate of ovulation (82.4%) compared to Clomiphene Citrate (63.6%). Using these results as guidance data sample size of 100 in each group required for my study.

Sample size has been calculated using the following formula:

$$N = [Z\alpha \sqrt{\{2P (1-P)\}} + Z\beta \sqrt{\{P1 (1-P1) + P2 (1-P2\}}] 2 / (P1 - P2)2$$

Zα = 1.96 considering 95% confidence interval (CI), Zß = 0.84 considering power of the study as 80%, P1 = Proportion of Group-A patients receiving Letrozole (refer study), P2 = Proportion of Group-B patients receiving Clomiphene Citrate (refer study).

Inclusion criteria:

- Age: 20-40 years old
- Primary or secondary infertility
- Diagnosis of PCO as established by Rotterdam criteria (2004)
- Normal husband's semen analysis

Exclusion criteria:

- Age< 20 and > 40 years old
- Pelvic pathology e.g. uterine fibroid or ovarian cyst or any uterine congenital anomalies or endometriosis or PID
- UncorrectedHyperprolactinemia, Hypo or Hyperthyroidism (endocrinological disorder)
- Impaired hepatic or renal function
- Female with bilateral tubal block diagnosed by HSG or laparoscopy
- Any male factor of infertility

Informed written consent in their own language was taken from each patient. These 200 patients were divided in two groups alternatively, Group A (n=100) and Group B (n=100). Group A (Letrozole group) patient received 5 mg Letrozole daily in two divided doses from D2 to D6 for ovulation induction whereas Group B (Clomiphene citrate group) patients received 100 mg Clomiphene citrate daily in two divided doses from D2 to D6.

Serial folliculometry was started from D_9 of cycle to monitor ovulation status. Inj Human Chorionic Gonadotrophin (HCG) 5000 IU was given for ovulation triggering when at least one dominant follicle attained a size of ≥ 18 mm or two or more dominant follicles reached ≥16mm along with the Endometrial thickness ≥ 7mm. Folliculometry repeated after 48 hours of Inj HCG. If there was no ovulation then patient was called for Folliculometry after 72 hours of Inj HCG. After confirmation of ovulation, couple was advised for timed intercourse. Luteal phase support was given by Micronised Progesterone for 10 days following ovulation.

Pregnancy test was advised on D_{15} of ovulation or missed period. If pregnancy positive then TVS for confirmation of clinical pregnancy was done at 7 weeks of gestational age. Pregnancy was followed up in usual manner for final outcome.

Statistical Analysis: The data was compiled, tabulated and analysed by using SPSS version 20.

According to Medical statistics data was compared in this study in the following manner:

Data type	Continuous (Mean/Median)	Categorical (Proportion/Rate)
Statistic method	Mean: t-test	Chi-square
	Median: Mann-Whitney	Fisher's exact
Expression of statistical difference	p value	Odd ratio/ Relative risk/ Risk ratio/
	p <0.05 significant	Hazard ratio (95% confidence interval)
	p <0.01 very significant	
	p <0.001 extremely significant	

RESULTS: In the patient demography, **Table 1** shows the analysis of the age of the patients between the two study groups. All the patients were divided in three age groups i.e. <30 years, 30-35 years and 36-40 years. Most of the patients belonged to <30 years age group (80.5%). In the Letrozole group it was around 80% comparable to the CC group (81%).

TABLE 1: DEMOGRAPHIC PROFILE

Parameters	Letrozole	Clomiphene Citrate	p value
Age group (Years)			
< 30	80 (80%)	81(81%)	

30 - 35	15 (15%)	16 (16%)	
36 - 40	5 (5%)	3 (3%)	
Duration of infertility (Year)	3.5 (2,5)	3 (2, 5.75)	0.889
BMI			
Underweight (<18.5)	10 (10%)	5 (5%)	
Normal (18.5-24.9)	33 (33%)	35 (35%)	
Overweight (25-29.9)	49 (49%)	55 (55%)	
Obese (≥ 30)	8 (8%)	5 (5%)	
Type of infertility			
Primary	76 (76%)	73 (73%)	
Secondary	24 (24%)	27 (27%)	

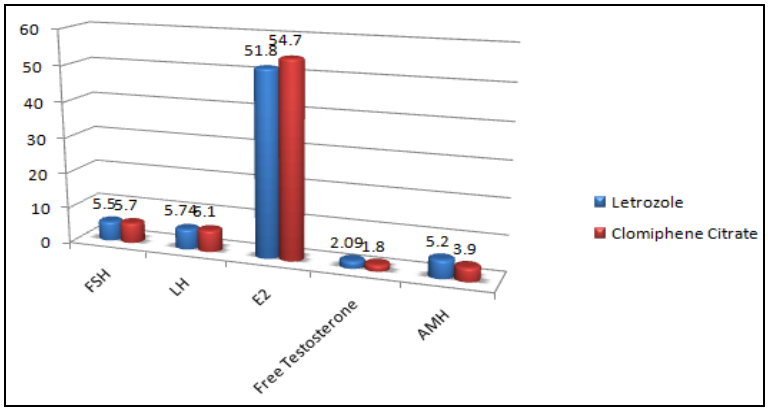

FIG. 1: BASELINE HORMONAL PROFILE IN BOTH GROUPS

In our study, **Fig. 1** shows that the baseline hormonal profile was comparable in both the study groups. Though AMH level was higher in Letrozole group but it was statistically insignificant.

TABLE 2: FOLLICULOGENESIS RATE

Folliculogenesis	Letrozole	Clomiphene Citrate	Total	Chi square value	P value (Fishers exact test)
No	2	6	8	2.08	0.279
Yes	98	94	192		

From **Table 2**, it is observed that in this study the rate of folliculogenesis was comparable in both groups (98% vs 94% in Letrozole and CC group respectively).

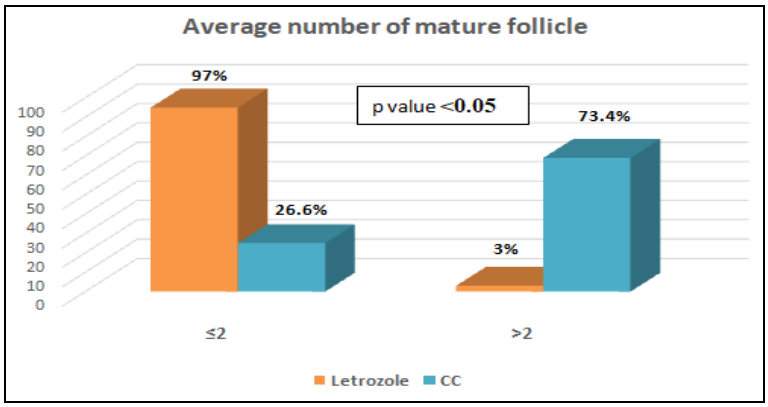

FIG. 2: DISTRIBUTION AS PER THE AVERAGE NUMBER OF MATURE FOLLICLE IN FOLLICULOMETRY PER CYCLE

Fig. 2 in this study shows that the average number of mature follicle was significantly more in CC group than Letrozole group. Another important finding we can observe in this study that more than 2 mature follicles were seen in 73.4% of patients receiving CC whereas it was only 3% in Letrozole group (Chi square value – 101.294, p value <0.05) which is statistically significant.

TABLE 3: MEAN SIZE OF DOMINANT FOLLICLE AND MEAN ENDOMETRIAL THICKNESS ON THE DAY OF hCG

Patient group	Size of DF (mean)	Mean ET on the day of hCG
Letrozole	18.96±1.5	9.6±1.8
Clomiphene Citrate	19.23±2.07	7.8±2.4
P value	0.293	0.04

In this study, from Table 3 it was observed that the average size of dominant follicle on the day of hCG was 18.9±1.5 mm in Letrozole group in comparison to 19.2±2.1 mm in CC group which is statistically insignificant. On contrary, it was observed that the mean endometrial thickness on the day of hCG was significantly more in Letrozole group than CC group (9.6±1.8 mm vs 7.8±2.4 mm respectively, p = 0.04).

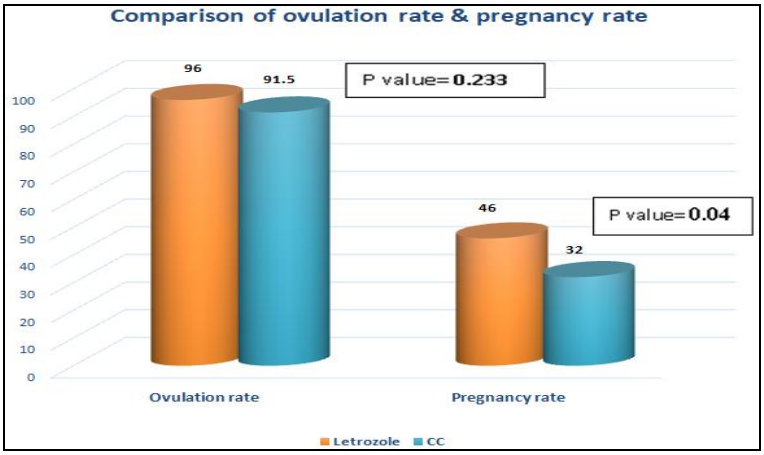

FIG. 3: COMPARISON OF OVULATION RATE AND PREGNANCY RATE

From **Fig. 3**, it is observed that the ovulation rate in Letrozole and CC group was 96% and 91.5% respectively which was not statistically significant (p= 0.233). In our study, the pregnancy rate was significantly more in Letrozole group than CC group (46% vs 32%, p= 0.04).

TABLE 4: COMPARISON OF PREGNANCY OUTCOME BETWEEN TWO GROUPS

Pregnancy outcome	Letrozole	Clomiphene Citrate	P value
Blighted ovum	2 (4.3%)	1(3.1%)	0.560
Live birth	23 (50%)	18 (56.2%)	0.38
Pregnancy continuation	16 (34.8%)	8 (25%)	0.08
Spontaneous abortion	4 (8.6%)	4 (12.5%)	1.0
Tubal ectopic	1 (2.2%)	1 (3.1%)	1.0
Total successful pregnancy	39 (84.8%)	26 (81.3%)	0.680
Total pregnancy	46	32	

From **Table 4**, it is observed that the total number of successful pregnancy was 39 out of 46 (84.8%) in case of Letrozole whereas it is 26 out of 32 (81.3%) in case of Clomiphene Citrate, and it is statistically not significant finding (p value is 0.680). Similarly the total number of pregnancy loss was also comparable in both Letrozole and CC group (15.2% vs 18.7% respectively).

TABLE 5: TREATMENT COMPLICATIONS BETWEEN TWO GROUPS

Pregnancy complication	Letrozole	Clomiphene Citrate	P value
Cycle cancellation	6	14	**0.045**
OHSS	0	1	0.747
Multiple pregnancy	1	2	0.357

It is observed in **Table 5** that the Cycle cancellation was significantly more in CC group than Letrozole group (14 vs 6 respectively, p= 0.045) but the other complications like OHSS and multiple pregnancy rate were comparable in both the groups.

DISCUSSION: The spectrum of PCOS ranges from infertility as a result of chronic an ovulation, menstrual irregularities, obesity and several dermatological features due to hyperandrogenism. The first-line pharmacological treatment consists of ovulation induction by clomiphene citrate. However, clomiphene has certain well-defined disadvantages such as discrepancy in ovulation and pregnancy rates (60-85% and 10-20% respectively), higher miscarriage rate than general population [15, 16] and 20-25% PCOS women are resistant to clomiphene [17, 18]. Anti-estrogenic effect of CC adversely affect endometrial growth and development as well as quantity and quality of cervical mucus. Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. Letrozole acts by reducing estrogen production by blocking androgens to estrogens conversion. Additionally, it has no adverse effect on endometrium and cervical mucus. In this study **Table 1** most of the patients belonged to <30 years age group (80.5%, Letrozole group - 80% & CC group - 81%) and comparable in both the groups. Age of the patient is a very important and independent determinant of female fertility and it declines with advancing age [28].

Table 1 also shows the Body Mass Index wise distribution between the two groups. While most of the patients i.e. 52% belonged to the overweight category (Letrozole 49% vs CC 55%) 34% patients were from the normal category (Letrozole 33% vs CC 35%). Few patients were underweight (7.5%) and few were obese (6.5%). Both of the groups were comparable in all the categories. **Table 1** shows the mean duration of infertility but it did not show any statistical significance between both the groups. In our study it is seen that most of the patients were suffering from primary infertility (74.5%) and it was comparable in both groups.

Table 2 & **Fig. 1** shows the comparison of baseline hormonal profile in between the two groups. In present study it has been seen that mean LH: FSH ratio is altered which is a usual finding in PCOS patients. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1 [29] or 3:1 [30] as tested on Day 3 of the menstrual cycle. The pattern is not very sensitive; a ratio of 2:1 or higher was present in less than 50% of women with PCOS in study by Banaszewska B. *et al* [28].

The mean AMH level was found to be slightly high according to the age group in our study population which corroborate with the observation of other studies among PCOS patients as it has been mentioned that Anti-Müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria [31, 32, 33]. Though the mean AMH level was slightly higher in the Letrozole group than the CC group but it was statistically insignificant.

In the present study it is observed that the folliculogenesis rate was 96% in overall study population and the rate was comparable in both study group **Table 3** though mono follicular development was significantly more in the Letrozole group than CC group (97% vs 26.6% respectively, **Fig. 2**. El Bigawy *et al.* [34] have demonstrated in their prospective randomized study the advantages of the use of letrozole in patients with PCOS, which is mono-ovulation and absence of antiestrogenic effect on endometrium, and higher pregnancy rate per cycle. These properties make letrozole a viable alternative to CC in patients with PCOS. Multifollicular development in CC is statistically significant in our study **Fig. 2**. This is expected and corroborated by number of studies [35, 36, 37].

It was observed in this study **Table 4** that the mean size of the dominant follicle on the day of hCG was comparable in both groups (18.96±1.5 vs 19.23±2.07 mm in Gr A & Gr B respectively, p value 0.293). Al-Fozan *et al.* (2004) [38] compared the effects of the Letrozole (7.5 mg/day) and CC (100 mg/day) in women undergoing ovulation induction and IUI. The pregnancy rate per cycle was similar in both groups, but the number of follicles of >14 mm and of ≥18 mm was higher in women treated with letrozole. On the contrary, in the study of Fatemi *et al.* (2003) [39] 15 patients undergoing IUI received from Day 3 to Day 7 of the cycle either letrozole 2.5 mg/day or CC 100 mg/day, significantly more follicles (>17 mm) developed in patients in the CC group compared with those in the letrozole group. In a retrospective analysis, Healey *et al.* (2003) [40] compared FSH alone or a combination of FSH and letrozole 5 mg/day and also showed that women co-treated with letrozole developed more follicles >14 mm.

From table 4 one of the important observation in our study was that the endometrial thickness on the day of hCG was significantly higher in Letrozole group than CC (9.6±1.8 vs 7.8±2.4 mm respectively, p = 0.04). Mitwally and Casper [17] foundletrozole associated with greater endometrial thickness. Cortinez *et al.* [41] found normal morphologic features of endometrium and full expression of pinopodes during implantation window when letrozole was used. Few studies have shown no significant difference between the two groups with regard to effect on endometrium [42, 43]. On contrary, Badawy *et al.* [35] 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 ± 0.7) vs. letrozole (8.1 ± 0.2, P = 0.021). They attributed this effect to greater number of mature follicles and higher serum E2 levels.

From **Fig. 3** it is seen that though the ovulation rate was comparable in both the groups (96% vs 91.5% in Letrozole and CC group respectively) but pregnancy rate was significantly more in Letrozole group than CC group [44] (46% vs 32% respectively, p = 0.04). Others reported similarly in ovulation rate, Badawy *et al* [35] (CC 70.9% vs Let 67.5%), Bayer *et al* [36] (CC 74.7% Vs Let 65.7%), and M. Zeinalzadeh *et al.* [37] (CC 72% vs Let 86%).

In majority of the studies, no statistically significant difference is found between CC and letrozole in ovulation rate. Misso *et al*. found comparable ovulation rates between CC and letrozole (RR, 0.94; 95% CI, 0.82–1.07; $I^2 = 0\%$) while the pregnancy rate was higher in the letrozole group. Badawy *et al* [35], with 438 women (1063 cycles), reported slightly better pregnancy rate in CC group (15.1% inletrozole and 17.9 % in CC group). Bayer *et al* [36] with 74 women, Zeinalzaden *et al* [37] with 107 women, both reported slightly better pregnancy rates with Letrozole but not statistically significant. A similar study by Begum *et al* [45] on 64 PCOS women who had failed to ovulate with CC 100 mg, showed a higher pregnancy rate of 40.63% with letrozole 7.5 mg compared to 15% with CC 150 mg. Atay *et al* [27] compared letrozole (2.5 mgs) with clomiphene citrate (100 mgs/day) in 106 women with PCOS and designated that the ovulation rate and the clinical pregnancy rate were significantly higher in the letrozole than clomiphene group. Moreover the authors advised letrozole as a better first line treatment in these patients [27]. These findings of significant higher clinical pregnancy rate with Letrozole corroborate with our study. The higher pregnancy rate in letrozole group can be explained by significant increase in endometrial receptivity as assessed by endometrial thickness. The lower pregnancy rate in CC may be due to antiestrogenic effects of CC on the endometrium and cervical mucosa. From **Table 5** it is observed that the number of successful pregnancy in term of live birth and ongoing pregnancy was comparable in both groups (84.8% vs 81.3% in Letrozole and CC respectively). It is seen that the overall pregnancy loss was 6.5% in my study population which is comparable in both groups.

A double-blind trial by Legro *et al* [46] found that letrozole is more effective than clomiphene in the treatment of infertility in PCOS. Based on treatment periods of up to five cycles, the study, which involved 750 anovulatory women with PCOS, found that the birth rates for letrozole and clomiphene were 27.5% and 19.1%, respectively. The rate of congenital abnormalities and the risk of pregnancy loss in the letrozole and clomiphene groups were found to be comparable, although the likelihood of twin births was lower with Letrozole [46].

Balen *et al.* reported that PCOS had a miscarriage rate of 36% when compared with 24% in women with normal ovaries [47]. PCOS women have a much higher risk of miscarriage compared with non-PCOS women. The risk has been estimated at 30–50% by Regan *et al* (1989) [48]. Among PCOS sufferers, high rates of miscarriage reaching threefold that of healthy women have been reported by Jakubowicz *et al (*2004) [49]. In our study **Table 5** the miscarriage rate was lower, this may be because of continuous follow up and better care at tertiary centre. **Table 6** shows that the cycle cancellation was significantly more in the CC group (14% vs 6%). In Letrozole group 1 patient and in CC group 2 patients had multiple pregnancy. Letrozole producing mono follicular development reduces the chances of multiple pregnancies compared to CC. Mitwally *et al* [50] reported low multiple gestation rates with aromatase inhibitors for ovulation

induction. Though in Letrozole group there was no incidence of Ovarian Hyper Stimulation Syndrome (OHSS) but 1 patient in CC group developed moderate degree of OHSS which was managed conservatively. The most dreaded complication of controlled ovarian stimulation is the occurrence of OHSS [51].

CONCLUSION: The present study titled "A Prospective Comparative Study of Letrozole and Clomiphene Citrate in Ovulation Induction in Momen having PCOS." shows that ovulation induction in infertile PCOS patients using Letrozole and Clomiphene Citrate has similar ovulation rate though Letrozole group had better endometrial thickness and less untoward effects in comparison to Clomiphene Citrate.

Our study showed statistically significant higher mono follicular development and significantly higher pregnancy rates when used as first line ovulation induction drug in infertile PCOS women. However there is need for a larger well designed randomized trials involving large number of patients to generate robust data in order to establish the true potential of Letrozole.

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CONFLICTS OF INTEREST: Nil

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