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COMPARISON OF ANASTROZOLE VERSUS CLOMIPHENE CITRATE IN INFERTILE WOMEN WITH ANOVULATORY POLYCYSTIC OVARIAN SYNDROME: A PROSPECTIVE RANDOMISED TRIAL

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ABSTRACT **Objective:** To compare the effects of anastrozole and clomiphene citrate (CC) for ovulation induction in infertile women with polycystic ovary syndrome (PCOS). **Materials and Methods:** This prospective, randomized clinical trial included 80 patients of infertile women with PCOS, comprised of two groups. Group A comprised 40 patients who received anastrozole (oral 1 mg) daily and the group B 40 patients who received (oral 100 mg) CC daily for 5 days starting on day 3 of menses. Both the groups were followed by ultrasound until the dominant follicle reached a diameter ≥18 mm, human chorionic gonadotropin (hCG) 10,000 IU was given, and timed intercourse was advised. The treatment continued for five cycles in both the groups. **Results:** The mean age, duration of infertility, body mass index, and endocrine status in both the groups were similar at baseline. The mean number of follicles with size >18 mm during stimulation, though statistically not significant, was higher in the anastrozole group (0.95±0.99 vs 0.73±0.85; p=0.277). There was no statistically significant difference in pretreatment endometrial thickness between the two groups, but endometrial thickness at the time of hCG administration was statistically significantly greater in the anastrozole group (10.78±1.09 mm vs. 9.69±1.07 mm; p< 0.001). Ovulation occurred in 12 subjects (30%) in the anastrozole group and 6 (15%) in the CC group. Conception rate was 25% in anastrozole group as compared to 10% in CC group. For both the outcomes, the success rate was higher in anastrozole group; however, difference was not significant statistically (p>0.05). **Conclusion:** Anastrozole showed superiority over Clomiphene citrate in enhancing the endometrial thickness and consecutively in achieving higher conception rates apart from higher ovulation rates, though they were not significant statistically. Anastrozole may have a role as a first-line treatment for anovulatory patients with PCOS.

KEYWORDS : : Anastrozole, Clomiphene Citrate, Anovulatory infertility, Polycystic ovarian syndrome

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies that affect women of reproductive age group and the most common cause of anovulatory infertility. PCOS has been defined using various criteria; namely Rotterdam criteria, endorsed by the National Institutes of Health (NIH) and Androgen Excess Society (AES) guidelines. The diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries.1 Prevalence of PCOS varies 7-10% worldwide using above criterias.2

PCOS represents 70-80% of anovulatory infertility cases. Clomiphene citrate (CC), a selective estrogen receptor modulator; is considered as first line therapy for ovulation induction in PCOS women, with overall ovulation rate of 73%, pregnancy rate of 36% and live birth rate of 29% over 6 months.3 However, ~20%–25% of anovulatory women with PCOS do not respond to CC and are considered to be "clomiphene-resistant.4 The reason may be a high intraovarian androgen environment affecting the oocyte quality as well as ovulation, tenacious cervical mucus and unfavorable endometrium because of continuous accumulation of CC due to long half-life.

Considering this limitation of CC, attempts to find out alternative pharmacological management of PCOS are being explored. Aromatase inhibitiors, have been used in women with PCOS as an alternative method to avoid the anti-estrogenic effect of CC on the endometrium. Traditionally, Letrozole, an aromatase inhibitor, is being used as an alternative to CC with promising results and sometimes better than clomiphene citrate in achieving ovulation and conception.5 Recently, Anastrozole, another aromatase inhibitor, has also been proposed to be used for ovulation induction in women with polycystic ovary syndrome and has been shown comparable results.6 However, supportive clinical evidence is not strong enough to advocate its use as the first choice pharmacological treatment modality in place of CC.

With this background, the present study is being planned to compare the efficacy of Clomiphene Citrate and Anastrozole for ovulation induction in patients with polycystic ovarian syndrome (PCOS).

MATERIAL AND METHODS:

The present study was a prospective randomized controlled trial carried out in Department of Obstetrics and Gynecology, Command Hospital, Lucknow, between June 2017 to June, 2019. The study was done on women with Polycystic Ovarian syndrome presenting with infertility. The inclusion Criteria for study was women diagnosed as PCOS, having at least 1 year of infertility with patent bilateral tubes demonstrated by HSG or laparoscopy, having husband's normal semen analysis according to WHO criteria (2010) within 3 months of study period.

Exclusion criterias for study were tubal factor infertility, male factor infertility, severe endometriosis (revised American Fertility Society Stage III/ IV), lack of patient consent, patient having contraindication to CC and anastrozole such as – uncontrolled thyroid or adrenal dysfunction/ organic intracranial lesion such as pituitary tumor/ undiagnosed uterine bleeding/ ovarian cyst/ prior hypersensitivity to CC or anastrozole/ sex hormone dependent tumor of reproductive tract and accessory.

The study was approved by Institutional Ethics Committee, Command Hospital, Lucknow. Informed consent was obtained from all the participants.

A total of 80 patients with confirmed diagnosis of PCOS as per revised 2003 consensus diagnostic criteria by the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group; satisfying inclusion and exclusion criteria were enrolled in study after taking informed consent. All patients had normal serum PRL, TSH, and 17a-hydroxyprogesterone. Withdrawal bleeding was achieved by using medroxyprogesterone acetate (10-mg tablets) for 5-10 days before stimulation when menses were irregular.

The patients were randomly allocated by computer generated table to one of the following two groups:

Group A (n=40): consisted of patients who received Anastrozole 1 mg tablet orally, daily, starting on day 3 of the menses, for 5 days.

Group B (n=40): consisted of patients who received Clomiphene Citrate (100 mg) orally daily, for 5 days, starting on day 3 of menses.

All patients were monitored by transvaginal ultrasound for mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle. Injection of human chorionic gonadotropin (hCG 5,000–10,000 IU, IM) was given when at least one follicle measured >18 mm. Patients were advised to have intercourse 24–36 hours after hCG injection. For diagnosis of pregnancy, serum hCG was determined 2 weeks after hCG injection if menstruation is absent. The primary outcome measures were - number of growing and mature follicles, serum E2 (pg/mL), serum P (ng/mL), and endometrial thickness (mm). The secondary outcome measure were occurrence of pregnancy and miscarriage. The process was repeated upto 5 cycles. Data so collected was entered into MS-Excel.

Data Analysis: The data was analyzed using Statistical Package for Social Sciences, version 21.0. Chi-square test and Independent samples 't'-test was used. A 'p' value less than 0.05 indicated a statistically significant association.

RESULTS:

Baseline demographic, clinical and endocrine characteristics of the two trial groups were similar (Table1). There were no statistically significant differences between the two groups in age, duration of infertility, BMI, and endocrine status at baseline level.

Table 1: Baseline characteristics of patients in both groups

SN	Characteristic	Group A (n=40)		Group B (n=40)		Statistical significance	
		Mean	SD	Mean	SD	't'	'p'
1	Mean age (Years)	25.03	2.62	25.40	3.50	0.535	0.594
2	Mean BMI	22.60	2.86	22.63	2.79	0.038	0.970
3	Infertility duration (Years)	2.85	2.35	2.83	2.30	0.048	0.962
4	No. of follicles	6.23	2.13	6.34	2.20	0.206	0.837
5	FSH (mIU/ml)	5.94	1.19	5.94	1.25	0.007	0.994
6	LH (mIU/ml)	11.70	2.69	12.39	4.72	0.810	0.421
7	Prolactin (mIU/ml)	20.74	5.02	21.01	3.40	0.282	0.779
8	E2 (pmol/l)	330.43	97.61	319.90	104.03	0.467	0.642
9	Endometrial thickness (mm)	4.74	1.12	4.63	1.27	0.428	0.670

Mean total number of completed cycles till successful ovulation/ completion of study were 4.05±1.11 in Group A and 4.33±0.80 in Group B. Statistically, there was no significant difference between two groups with respect to total number of completed cycles.

There was no significant difference between two groups in respect of mean number of follicular size >18 mm, mean FSH, LH, prolactin and estradiol levels post treatment .

Mean endometrial thickness was 10.78±1.09 mm in Group A as compared to 9.69±1.07 mm in Group B. Statistically, there was a significant difference between two groups ($p<0.001$).

Table 2: Comparison of Outcome parameters between two groups

SN	Variable	Group A (n=40)		Group B (n=40)		Statistical significance	
		Mean	SD	Mean	SD	't'	'p'
1.	Total number of completed cycles	4.05	1.11	4.33	0.80	1.274	0.206
2.	No. of follicles with size >18 mm	0.95	0.99	0.73	0.85	1.095	0.277
3.	FSH (mIU/ml)	7.82	2.62	7.08	2.82	1.225	0.224
4.	LH (mIU/ml)	8.35	3.76	7.90	4.35	0.492	0.624
5.	Prolactin (mIU/ml)	15.20	4.10	14.05	4.16	1.246	0.216
6.	E2 (pmol/l)	1351.8	452.9	1520.3	443.8	1.680	0.097
7.	Endometrial thickness (mm)	10.78	1.09	9.69	1.07	4.677	<0.001

Ovulation success was achieved in 12 (30%) of Group A and 6 (15%) of Group B cases. Conception rate was 25% in Group A as compared to 10% in Group B. Though for both the outcomes, the success rate was higher in Group A as compared to that in Group B yet this difference was not significant statistically ($p>0.05$). No serious side effect needing intervention was noticed in either of two groups.

Table 3: Comparison of Ovulation and Pregnancy rates between two groups

SN	Outcome	Group A (n=40)		Group B (n=40)		Statistical significance	
		No.	%	No.	%	2	'p'
1.	Ovulation	12	30.0	6	15.0	2.581	0.108
2.	Pregnancy	10	25.0	4	10.0	3.117	0.077

DISCUSSION

In present study, mean total number of completed cycles till successful ovulation/ completion of study were 4.05±1.11 in Anastrozole and 4.33±0.80 in CC Group. Mean number of follicles with size >18 mm was 0.95±0.99 in Anastrozole as compared to 0.73±0.85 in CC Group, thus showing no significant difference between two groups. Compared to present study, Sipe et al.7 in their study reported the number of follicles >15 mm as 0.6±0.7 in Anastrozole group as compared to 1.6±1.5 in CC group and found the difference between two groups to be significant. The difference from the present study could be attributable to difference in follicle size taken as the criteria. The results in present study are in agreement with the findings of Tredway et al.8 who found no significant difference in mean number of follicles with >17 mm size between Clomiphene citrate 50 mg/day and Anastrozole 1 mg/day groups and showed it to be 0.8 between day 11-13 of cycle.

In present study, mean FSH values showed an increase from 5.94±1.19 and 5.94±1.25 mIU/ml in Anastrozole and CC groups to 7.82±2.62 and 7.08±2.82 mIU/ml following treatment, thereby showing a % increase of 31.9% and 19.3% respectively in the corresponding groups. On the other hand, the LH values showed a change from 11.70±2.69 and 12.39±4.72 mIU/ml respectively in Anastrozole and Clomiphene citrate groups to 8.35±3.76 and 7.90±4.35 mIU/ml respectively thus showing a % decline of 28.6% and 32.6% respectively. It was interesting to note that while prior to treatment, the LH/FSH ratio was nearly 2 or above, following treatment it was much lower than 2 and in proximity with 1. There is limited data regarding change in hormonal profile in studies comparing clomiphene citrate to Anastrozole. However, the increase in FSH in Anastrozole group could be attributable primarily to its estrogen lowering effect which stimulates the pituitary gland to secrete the FSH. It is also evident by the nature of change in estradiol levels, which showed relatively lesser incline in Anastrozole group (3 times) as compared to CC group (4 times). Despite this explanation, post-treatment hormonal profile in general did not show a significant difference between two groups. Thus, it could be inferred that while the pathway of change in FSH in two groups could be different yet both the groups achieved almost similar outcome, as far as hormonal profile was concerned.

In present study, endometrial thickness showed an increase from baseline 4.74±1.12 and 4.63±1.27 mm in Anastrozole and Clomiphene citrate groups to 10.78±1.09 and 9.69±1.07 mm in corresponding groups, thus showing a % increase of 127.4% and 109.3% respectively. Post-treatment endometrial thickness values were significantly higher in Anastrozole group as compared to Clomiphene citrate group. The positive effect of third generation aromatase inhibitors on endometrial thickness has been extensively reported in different studies.9,10 In studies comparing CC to Anastrozole too11 , it has been shown to be thicker in Anastrozole as compared to CC as observed in present study.
In present study, ovulation success was achieved in 12 (30%) of Anastrozole and 6 (15%) of CC Group cases. Conception rate was 25% in Anastrozole as compared to 10% in CC Group. Statistically, there was no significant difference between two groups with respect to ovulation and pregnancy rates. Compared to present study, Gupta et al.11 in their study reported cumulative ovulation rate of 59.4% and 43.6% for CC and Anastrozole groups. Sipe et al.7 also reported pregnancy rates in two groups to be similar, however, in their study, the pregnancy rate was higher in clomiphene (20%) as compared to anastrozole (12%) group.

The present study is one of the only few studies that has evaluated

Anastrozole to Clomiphene citrate as the first-line of therapy and has showed almost comparable results of two. In present study, no significant side effect needing intervention was noted in either of two groups and shows no other benefit of using Anastrozole except for a thicker post-treatment endometrium. The present study was limited for number of samples and number of cycles. As such there are limited studies addressing the issue from the perspective raised by us, further studies to corroborate the findings are recommended.

CONCLUSION:

In present study, anastrozole, had edge over clomiphene citrate in enhancing the endometrial thickness and consecutively in achieving higher conception rates apart from higher ovulation rates, though they were not significant statistically. The results of present study are path breaking and need further corroboration with more clinical trials on a larger sample size for use of astrozole as a first-line treatment modality for ovulation induction in comparison to clomiphene citrate.

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