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Original Research Article

Pre-treatment with cyproterone acetate plus ethinylestradiol enhances ovarian response in women with polycystic ovary syndrome

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ABSTRACT

Background: Anti-mullerian hormone (AMH) and androgen levels are higher in women with polycystic ovary syndrome (PCOS) than norm-ovulatory women. Cyproterone acetate plus ethinylestradiol (CPA+EE) reduces AMH and free androgen level. The aim of the study was to determine if the pretreatment with CPA+EE before ovulation induction with letrozole improves ovarian response in PCOS women.
Methods: The study comprised of 100 infertile PCOS women with serum AMH>5 ng/ml. The study participants were randomly allocated into women given CPA+EE pretreatment cyclically for 3 months before ovulation induction with letrozole 5 mg from day 2-6 of a menstrual cycle, and women given only letrozole from day 2-6 without any pretreatment. Follicular growth was monitored by transvaginal sonography on day 12. Women who attained maximum follicular size (18-25 mm) were given 5000 IU HCG injection. Ovulation was confirmed by serum progesterone assay on day 21-23 and pregnancy was confirmed by serum β-hCG level or by pregnancy test kit.
Results: Ovulation rate was higher (82.4%) in pre treatment group compared in letrozole only group to (43.0%) with relative risk 1.92. Pregnancy rate was higher in (23.5%) in pre treatment group than letrozole only (8.8%) with relative risk 2.68.
Conclusions: Pretreatment with CPA+EE before ovulation induction with letrozole has better outcome in terms of ovulation and pregnancy than letrozole alone in PCOS women with high serum AMH.

Keywords: Anti-mullerian hormone, Cyproterone acetate plus ethinyl estradiol, Letrozole, Polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent female endocrinopathy in women of reproductive age and is a major cause of anovulatory infertility. It is a heterogeneous disease that affects around 5-10% of female populations.[1-3] It is characterized by defective follicular growth, maturation, and ovulation as well as hormonal dysregulation, including luteinizing hormone (LH), anti-mullerian hormone (AMH), and/or androgen hypersecretion.[4] The classic symptoms of the disease are due to hyperandrogenism and chronic anovulation.[5] Now-a-days letrozole is the recommended first line drug for ovulation induction in women with PCOS with anovulatory infertility.[6,7] Letrozole is a potent, reversible and highly selective aromatase inhibitor (AI).[8]

Anti-mullerian hormone (AMH), a dimeric glycoprotein, is a member of transforming growth factor beta (TGF-β) superfamily of regulatory protein.[9,10] It is exclusively produced by granulosa cells (GCs) of developing pre-antral and small antral follicles.[11] Serum AMH level is

correlated to the severity of PCOS symptoms.[12-14] There is association of high AMH level and lack of ovulation even after treatment with clomiphene citrate, letrozole, gonadotropins and also with laparoscopic ovarian drilling in PCOS women.[15-19] In addition, higher doses of ovulation induction drugs are needed to achieve ovulation in these women.[15-19] Oral contraceptive pills (OCP) can reduce the high AMH level.[20-22]

Cyproterone acetate plus ethinylestradiol (CPA+EE) is an OCP which contains synthetic estrogen 'ethinylestradiol' and a synthetic progestin 'cyproterone acetate' having anti-androgenic properties. This OCP can reduce serum AMH by suppressing the gonadotropins (LH and FSH) secretion. LH is responsible for the overexpression of AMH and AMH specific type 2 receptors (AMHR II) in lutein GCs in anovulatory PCOS.[23,24] So, reduced LH may directly impact on AMH secretion.[25] Moreover, reduced LH causes reduction in androgen level, which in turn decreases follicular excess and indirectly reduces AMH. On the other hand, suppression of follicle stimulating hormone (FSH) slows down the formation of pre-antral and small antral follicles that produces AMH.[25] A review article showed that short-term pre-treatment using OCP containing cyproterone acetate (CPA) may increase the fertility and improve pregnancy outcome, but proposed further studies to prove that.[26]

It is indeed a challenging matter to induce ovulation in anovulatory PCOS women. Sometimes clomiphene citrate and letrozole become resistant to some PCOS women. In this context, CPA+EE pre-treatment before letrozole ovulation induction may be a great hope both for the fertility expert and the anovulatory infertile PCOS women. Till date, there is no single study found to see the outcome of the ovulation induction with letrozole following pre-treatment with CPA+EE in PCOS women. So, this study was designed to evaluate the effectiveness of CPA+EE pre-treatment before letrozole ovulation induction in PCOS women with elevated serum AMH level.

METHODS

This randomized controlled trial was carried out in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from October, 2019 to September, 2021. It was approved by Institutional Review Board (IRB) (No. BSMMU/2020/6878). Diagnosed women of polycystic ovary syndrome (PCOS) with subfertility and with serum AMH level >5 ng/ml who attended the Department of Reproductive Endocrinology and Infertility at BSMMU were the study population.

Exclusion criteria

Exclusion criteria were age less than 18 years or more than 35 years, body mass index less than 18 kg/m^2 or more than 30 kg/m^2, bilateral tubal block, endocrine disorders i.e., hyperprolactinemia, diabetes mellitus (DM) or hypothyroidism, women having treatment with insulin sensitizer i.e., metformin, any contraindications to CPA+EE (i.e., history of thromboembolism or breast carcinoma), known cases of pulmonary, cardiac, liver or renal diseases and abnormal semen parameters of husband. The purpose and procedure of study, and possible side effects of the drugs were discussed with the participants. Informed written consent was obtained from those who were willing to participate in the study.

A total of 100 participants were enrolled according to eligibility criteria. After enrolment the participants were randomly allocated in 1:1 manner into two groups: group A (pre-treatment with CPA+EE followed by letrozole) and group B (letrozole alone). Group A patients received pre-treatment with tablets containing 2 mg cyproterone acetate and 35 µg of ethinyl estradiol (tablet Giane 35, Renata Pharmaceutical Limited, Dhaka) for three months in a sequential way i.e., one tablet daily for 21 days and 7 days tablet free interval. After that they received letrozole (tablet Ovazol, ACI Pharmaceuticals Limited, Dhaka) 5 mg daily for ovulation induction starting from the second day of menstruation for five days for three consecutive months. On the other hand, group B patients were given letrozole (tablet Ovazol) 5 mg daily for ovulation induction starting from the second day of menstruation for five days in three consecutive months without any pre-treatment. Participants were advised to consult before taking any other medication during the study period as they could interfere with the normal function of the hypothalamic-pituitary-gonadal axis. No women reported that they had taken such a drug during study period. Outcome variables are biochemical changes after pretreatment with CPA/EE (serum LH, serum testosterone, serum AMH), ovulation rate and pregnancy rate.

After three months of pretreatment with CPA/EE biochemical parameters i.e., serum luteinizing hormone (LH), total testosterone (T), and anti-Mullerian hormone (AMH) levels were tested and compared with baseline parameters in group A women. Blood sample were collected in the early morning during follicular phase (day 2-3). Serum LH and total testosterone level were measured by using chemiluminescent immunoassay (SEIMENS ADVIA Centaur Xp Immunoassay System). Serum AMH were measured by enzyme linked immunosorbent assay (ELISA) (Alinity ci-series, Abbott, USA).

In both groups, ovarian response (i.e., total number of developing follicles, mature follicles and also endometrial thickness) was assessed by folliculometry using transvaginal probe (Mindray DP-2200 plus ultrasound system). The folliculometry was carried out in both groups on day 12 of a menstrual cycle for each patient and treatment cycle. The HCG injection of 5,000 IU was given intramuscularly when at least one follicle became mature (18-25 mm). Timed intercourse was advised every other day for one week from 36 hours after HCG administration. Confirmation of ovulation was done by mid-luteal (day 21-23) serum progesterone measurement using

chemiluminescent immunoassay (SEIMENS ADVIA Centaur Xp Immunoassay System). Serum progesterone >3 ng/ml was considered ovulatory.

In case of ovulation without pregnancy in the initial cycle, letrozole were repeated in the same dose in next cycle. For each and every subject separate data collection sheet were used. Data were collected from the patients on different visits on variables of interest using interview observation.

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Mean±standard deviation (SD) values were calculated for continuous variables. For comparing the mean between the two study groups, unpaired t-test (Student's t-test) was used when data were normally distributed. Paired t-tests were used for comparing measurements before and after treatment. For comparing categorical data, the Chi-square test was performed. The p value <0.05 was considered as statistically significant.

RESULTS

A total of 100 participants were included and allocated into two groups by randomization. Figure 1 shows the drop outs and pregnancies in different cycles. After analysis of data of both groups, the results are displayed in tables and diagram.

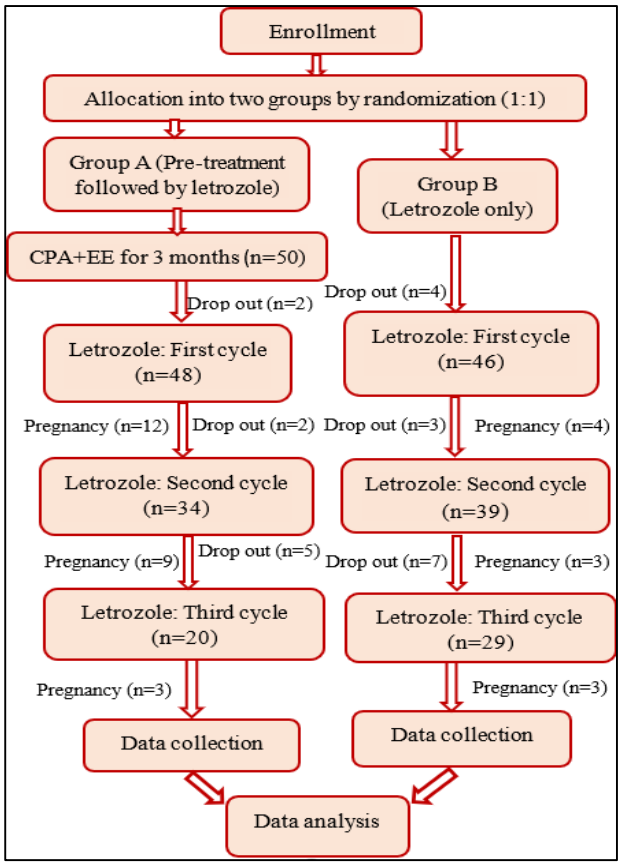

Figure 1: Flowchart showing the sequence of tasks.

Majority participants belonged to age group 22-25 years in both groups. The mean age was 25.2±4.0 years in group A and 24.6±3.8 years in group B. Mean BMI was 25.3±3.0 kg/m^2 in group A and 26.0±2.3 kg/m^2 in group B. Primary infertility was 86.0% and secondary infertility was 14% in both group A and group B. Age, BMI and fertility history were not statistically significant between two groups (p>0.05) (Table 1).

Table 1: Demographic characteristics of the study participants (n=100).

Variables	Group A (pre-treatment followed by letrozole) (n=50) (%)	Group B (letrozole alone) (n=50) (%)	P value
Age (years)			
18-21	22.0	22.0	0.411
22-25	32.0	38.0	
26-29	28.0	26.0	
30-35	18.0	14.0	
Mean±SD	25.2±4.0	24.6±3.8	
BMI (kg/m^2)			
18.5-24.9	38.0	28.0	0.202
25.0-29.9	62.0	72.0	
Mean±SD	25.3±3.0	26.0±2.3	
Infertility			
Primary	86.0	86.0	1.000
Secondary	14.0	14.0	

Table 2: Baseline hormonal parameters of study population (n=100).

Variables	Group A (pre-treatment followed by letrozole) (n=50)	Group B (letrozole alone) (n=50)	P value
	Mean±SD	Mean±SD	
Serum LH (mIU/ml)	11.67±10.64	8.84±5.83	0.102
Serum OCP (mIU/ml)	5.19±2.07	5.44±2.45	0.587
Serum testosterone (ng/dl)	59.65±53.05	59.93±59.31	0.981
Serum TSH (mIU/ml)	2.49±1.42	2.28±1.18	0.415
Serum AMH (ng/ml)	10.49±5.02	10.10±5.08	0.697
Serum prolactin (ng/dl)	11.93±4.99	11.17±4.04	0.409

The difference in mean serum luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, thyroid stimulating hormone (TSH), anti-mullerian hormone

(AMH) and prolactin were not statistically significant (p>0.05) between two groups (Table 2).

Table 3 shows that in group A patients, serum LH, testosterone and AMH level were significantly reduced after treatment with CPA/EE (p<0.005).

Table 3: Comparison of biochemical parameters before and after CPA/EE pre-treatment in group A.

Variables	Before treatment (n=50)	After treatment (n=48)	P value
	Mean±SD	Mean±SD	
Serum LH (mIU/ml)	11.67±10.64	6.30±2.81	0.001
Serum testosterone (ng/ml)	59.65±53.05	35.23±21.66	0.003
Serum AMH (ng/ml)	10.49±5.02	6.74±3.11	0.001

Table 4: Comparison of per cycle ovulation and pregnancy rate between two groups.

	Group A (pre-treatment followed by letrozole) (n=102 cycles)		Group B (letrozole alone) (n=114 cycles)		Relative risk (95% CI)	P value
	N	%	N	%		
Ovulation rate/cycle	84	82.4	49	43.0	1.92 (1.52-2.41)	0.001
Pregnancy rate/cycle	24	23.5	10	8.8	2.68 (1.35-5.34)	0.003

Table 4 illustrates that the per cycle ovulation rate was 1.92 times higher in group A (82.4%) than group B (43.0%) and the difference was statistically significant (p<0.05) between two groups. Additionally, Table 4 reveals that per cycle number of pregnancies was 2.68 times higher in group A (23.5%) than in group B (8.8%) and the difference was statistically significant (p<0.05) between two groups (Table 4).

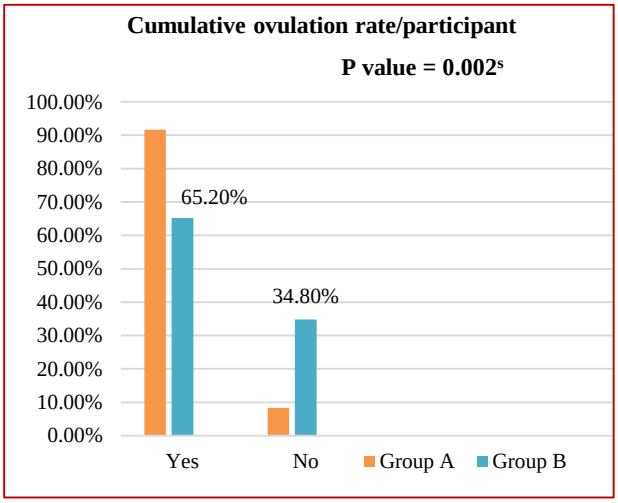

Figure 2: Comparison of cumulative ovulation rate/participant between the two groups.

The cumulative ovulation rate was significantly higher in group A (pretreatment followed by letrozole) (91.70%) than group B (letrozole alone) (65.20%) (Figure 2).

The cumulative pregnancy rate was significantly higher in group A (pretreatment followed by letrozole) (50%) than group B (letrozole alone) (21.7%) (Figure 3).

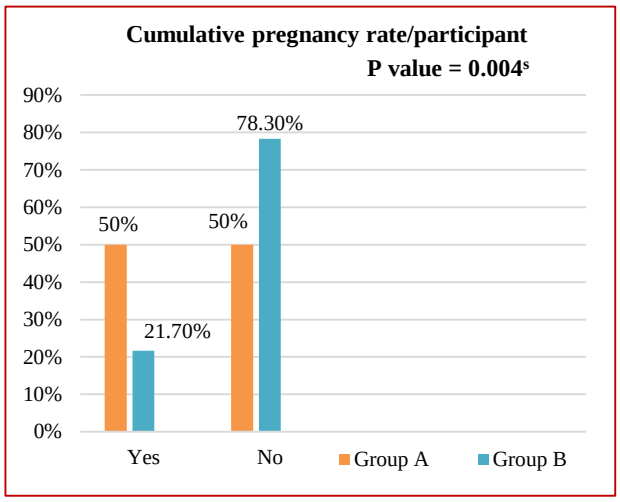

Figure 3: Comparison of cumulative pregnancy rate/participant between the two groups.

DISCUSSION

The focus of the current study was to evaluate the effectiveness of cyproterone acetate plus ethinyl estradiol (CPA+EE) pre-treatment before ovulation induction with letrozole in polycystic ovary syndrome (PCOS) women. The randomized controlled trial (RCT) by Branigan and Estes published in 2003 was the first to address the concept of pre-treatment with oral contraceptive pills before ovulation induction in PCOS women.[27] Although in their study they used drospirenone containing OCP as pretreatment, this study gives an idea to conduct the present study. There are many studies on the effect of pretreatment with combined hormonal pills in IVF cycles. But there are few studies on pre -treatment with OCP prior to ovulation induction in selected population of PCOS women with high AMH.

In this study the first major finding is improvement of biochemical parameters by CPA/EE pretreatment in PCOS women which is the major concern regarding its management. This current study shows that pre-treatment with cyproterone acetate-containing oral contraceptive pills (CPA/EE) for a period of three months in PCOS women with elevated AMH levels led to a significant decrease in serum AMH levels. In agreement with this work, Banu et al also reported a similar benefit of pretreatment with CPA/EE compared to metformin in Clomiphene citrate (CC) resistant PCOS women.[28] But the duration of treatment in the Banu et al study was extended to six months.[28] Additionally, Panidis et al in observed a similar outcome after six months of using cyproterone acetate-containing oral contraceptive pills, while comparing with drospirenone containing pills.[29]

However, it is important to note that, these findings were clearly contradictory to the conclusion drawn by Somunkiran et al.[30] Their study found no changes in serum AMH level after 6 months of CPA/EE treatment. Somunkiran et al reported that 80% of their participants had anovulation, whereas in our current study, all PCOS women were found to be anovulatory.[30] This could account for the discrepancy in the results. Again, in present study baseline serum AMH of recruited PCOS women were higher compared to the study conducted by Somunkiran et al.[30] This discrepancy in baseline AMH levels might also contribute to the differing outcomes observed between the two studies.

In terms of serum LH and serum testosterone, our current study demonstrated a significant decrease after three months of CPA/EE pretreatment. These findings are consistent with the results reported by Feng et al, who observed a similar reduction after three months of pretreatment.[31] Furthermore, Jing et al in and Panidis et al in also documented comparable outcomes in PCOS women, but their studies extended the treatment duration to six months.[29,31] Additionally, Bhattacharya and Jha reported a similar outcome when comparing cyproterone acetate containing OCP to drospirenone and desogestrel containing OCPs.[33] Notably, these effects were observed both after six and twelve months of treatment.

Second major finding of the study is pretreatment with CPA/EE before ovulation induction with letrozole are superior to letrozole alone in terms of ovulation and pregnancy.

In analyzing the ovulation rates of two groups, current investigation figured out that both the cumulative ovulation rate per participant and ovulation rate per cycle were significantly higher in the group that received three months of pre-treatment with CPA+EE before letrozole compared to the group that only received letrozole. In agreement with these work Salama and Hamza also observed a higher per cycle ovulation rate when using a similar drospirenone-containing OCP pre-treatment approach.[28] Moreover, Mumford et al concluded that high serum AMH is associated with lower ovulation rate, which clearly supports the findings of our study.[17] In our study, pre-treatment with CPA+EE before ovulation induction with letrozole reduced serum AMH level and resulted in greater ovulation rates in study group than letrozole alone group. Dewailly et al mentioned in a summary of presentations at a European Society of Human Reproduction and Embryology campus workshop on AMH held in French in May 2012 that decreased AMH in anovulatory PCOS women might enhance the transition of follicle to the growing stage.[9] This statement is clearly supported by our study. This study demonstrates that pre-treatment with CPA+EE before ovulation induction reduces serum AMH level and this in turn results in greater ovulation rates compared to using letrozole alone.

When comparing the pregnancy rates of two groups, it was discovered that the pregnancy rate in the pre-treatment group was much higher in current study. The pre-treatment group had a significantly greater cumulative pregnancy rate per participant and pregnancy rate per cycle. This result came in parallel with a study conducted by Salama and Hamza, which also reported that pre-treatment with drospirenone-containing oral contraceptive pills (OCP) followed by letrozole resulted in significantly higher cumulative pregnancy rates per participant and pregnancy rate per cycle compared to using letrozole alone.[28]

Lastly, both CPA/EE and letrozole are well tolerated drug and have better side effect profile when using as fertility treatment. In summary, pretreatment with CPA/EE appears promising in enhancing fertility outcomes for PCOS women undergoing ovulation induction by improving biological parameters.

However, it's important to acknowledge limitations identified in this study. Firstly, the study population was exclusively drawn from a single tertiary center in Dhaka city, potentially limiting the generalizability of the findings. Another limitation was the relatively small sample size employed in the study. Furthermore, both participants and investigators were not blinded to the treatment allocation after randomization, which could introduce bias into the results. Lastly, the study did not utilize serial transvaginal sonography for ovulation determination, a method that was omitted to reduce the risk of COVID-19 exposure. These limitations should be considered when interpreting the study's results and their applicability to a broader context.

CONCLUSION

The findings of the present study substantiate that pre-treatment with cyproterone acetate plus ethinyl estradiol (CPA+EE) before letrozole is more effective than letrozole alone in terms of higher ovulation and pregnancy rates without adding any serious side effects to the polycystic ovary syndrome women.

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Ethical approval: The study was approved by the Institutional Ethics Committee (No. BSMMU/2020/6878)

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